Reviews in
Mutation Research

Review

DNA repair/pro-apoptotic dual-role proteins in five major DNA repair pathways: fail-safe protection against carcinogenesis

Carol Bernstein [a,*], Harris Bernstein [a], Claire M. Payne [a], Harinder Garewal [b,1]

[a] *Department of Microbiology and Immunology, College of Medicine, University of Arizona, Tucson, AZ 85724, USA*
[b] *Tucson Veterans Affairs Hospital, Tucson, AZ 85723, USA*

Abstract

Two systems are essential in humans for genome integrity, DNA repair and apoptosis. Cells that are defective in DNA repair tend to accumulate excess DNA damage. Cells defective in apoptosis tend to survive with excess DNA damage and thus allow DNA replication past DNA damages, causing mutations leading to carcinogenesis. It has recently become apparent that key proteins which contribute to cellular survival by acting in DNA repair become executioners in the face of excess DNA damage.

Five major DNA repair pathways are homologous recombinational repair (HRR), non-homologous end joining (NHEJ), nucleotide excision repair (NER), base excision repair (BER) and mismatch repair (MMR). In each of these DNA repair pathways, key proteins occur with dual functions in DNA damage sensing/repair and apoptosis. Proteins with these dual roles occur in: (1) HRR (BRCA1, ATM, ATR, WRN, BLM, Tip60 and p53); (2) NHEJ (the catalytic subunit of DNA-PK); (3) NER (XPB, XPD, p53 and p33[ING1b]); (4) BER (Ref-1/Ape, poly(ADP-ribose) polymerase-1 (PARP-1) and p53); (5) MMR (MSH2, MSH6, MLH1 and PMS2). For a number of these dual-role proteins, germ line mutations causing them to be defective also predispose individuals to cancer. Such proteins include BRCA1, ATM, WRN, BLM, p53, XPB, XPD, MSH2, MSH6, MLH1 and PMS2. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: DNA repair; Apoptosis; Carcinogenesis

1. Introduction

A widely held view is that the initial reaction of a cell to DNA damage is to repair the damage. However, with increasing levels of DNA damage the cell switches to cell cycle arrest or to apoptosis. Cell cycle arrest is sometimes permanent, but ordinarily reversible, allowing time for further DNA repair. The maintenance of a switching mechanism that shifts the cell from DNA repair to apoptosis, as appropriate in the presence of excessive DNA damage, appears to be of central importance for avoiding progression to cancer. The default mechanism of apoptosis prevents clonal expansion of cells in which unrepaired damage would lead to mutation and to carcinogenesis (Fig. 1).

During progression to cancer, the capability of cells to undergo apoptosis is often reduced, suggesting that the normal ability to undergo apoptosis is protective
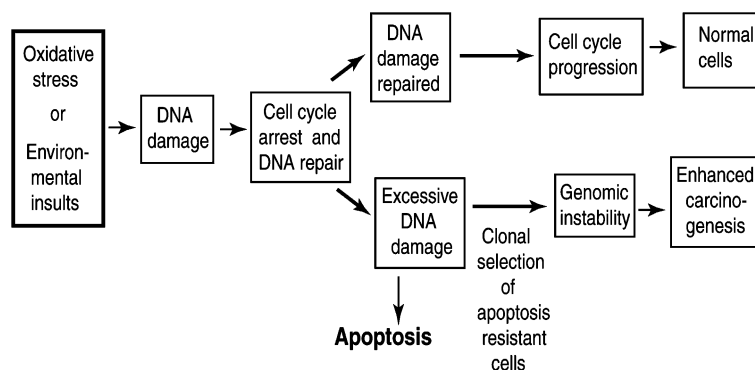
Fig. 1. Roles of DNA damage, DNA repair, cell cycle arrest and apoptosis in carcinogenesis.

against cancer. For example, loss of the capacity to undergo apoptosis occurs early in the progression to adenocarcinoma of the colon [1–3] and esophagus [4,5]. Apoptosis capability may be reduced in three ways: by mutation, by silencing or loss of genes encoding required components of the apoptosis pathway (e.g. *p53* and *bax*) [6,7], or by persistent activation of genes encoding apoptosis suppressors (e.g. *bcl-2*) [8]. Failure to undergo apoptosis in the face of unrepaired damage leads to enhanced mutation [9–11], including chromosome aberrations, and can be a cause of the genomic instability that is a general characteristic of cancer progression [12].

In the following sections, we discuss the various specific DNA repair processes, how these processes recognize and repair DNA damage, and how they switch from repair to apoptosis when DNA damage presumably overwhelms repair capacity. One should keep in mind, however, that of necessity most of the mechanistic information provided is based on in vitro or purified enzyme studies and, thus, may or may not reflect processes in vivo in man. Similarly, biochemical events observed in cultured cells or with purified enzymes may provide valuable clues to in vivo processes, but may not be exactly correct.

There are two distinct types of cell death in vivo, apoptosis and necrosis [13–15]. Apoptosis is a controlled form of cell death, in which the cell undergoes "cellular suicide". The cell shrinks, dehydrates, fragments its nucleus, and is phagocytized by macrophages [16]. Necrosis, on the other hand, is a traumatic, but passive, form of cell death, in which ion pumps fail, the cell swells and then undergoes lysis with the release of inflammatory mediators [13,17].

A cell will first try to repair any DNA damage and survive; however, if DNA damages are excessive, the preferred mode of cell death in a multicellular organism is apoptosis, a process which does not elicit an inflammatory response. How does a cell ensure that its death will occur by apoptosis, rather than necrosis? Given that both DNA repair and apoptosis are energy-demanding processes, the answer may lie in the proper utilization of the available ATP in the cell (Fig. 2) [18–20]. Energy is required for both DNA repair [21–35] and apoptosis [18,36–40]. In addition, during both DNA repair and apoptosis, the ATP-dependent ion pumps that keep Ca^{++} [41] at a low cytosolic concentration and sustain a critical internal K^+ concentration [42] need to be maintained.

If the repair of DNA damage is prolonged in any given cell, an "energy catastrophe" [43] will occur (Fig. 2). The considerable investment of energy to repair DNA was particularly noted by Roca and Cox [25] in bacteria, where they pointed out the "profligate" chemical energy invested in the degradation and replacement of a strand of DNA, 1000 bases or more in length, to repair one DNA mismatch. Therefore, in mammalian cells, a large amount of ATP may be similarly directed toward the repair of DNA and diverted away from the ATP-dependent steps required for the execution phase of apoptosis. In particular, the formation of the apoptosome [44–49], the multimeric complex consisting of dATP, Apaf-1 and cytochrome c necessary for the formation of active caspase-9 [50], and the activation of downstream
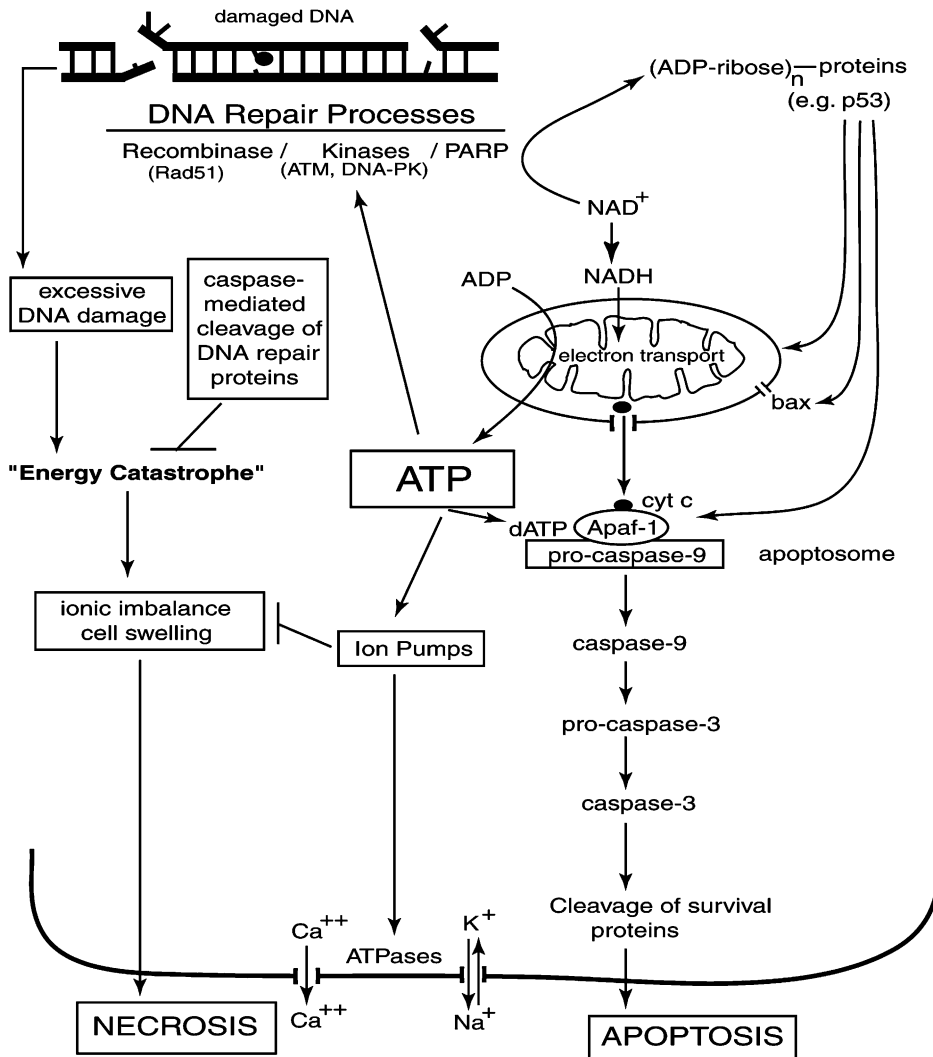
Fig. 2. Demands on the ATP pool to ensure the repair of DNA, the completion of the effector phase of apoptosis and the maintenance of ion pumps. Excessive DNA damage may result in an "energy catastrophe" if the apoptosome (dATP, Apaf-1, pro-caspase-9) fails to form, resulting in necrosis. The cleavage of key DNA repair proteins (e.g. hsRad51, ATM, DNA-PK, PARP) that consume a significant amount of ATP, will divert ATP toward apoptosis and the maintenance of ion pumps.

effector caspases (e.g. caspase-3, -6 and -7) during the demolition phase of apoptosis [46,49,51], require dATP or ATP [36,37]. In addition, in the face of excessive DNA damage, ATP is diverted from maintaining the ion pumps (Fig. 2). In the case of the Ca^{++}-ATPase, energy depletion prevents Ca^{++} ions from being extruded from the cell, thereby increasing the intracellular Ca^{++} concentration from nanomolar to lethal micromolar concentrations. The influx of excessive Ca^{++} activates calcium-dependent phospholipases, nucleases and proteases, which dramatically injure the cell. Failure of the Na^+, K^+-ATPase causes excessive amounts of Na^+ to enter the cell, followed by a large influx of water, resulting in cellular swelling and lysis. Since K^+ normally prevents apoptosis [52] by inhibiting the Apaf-1 oligomerization

Table 1
Proteins with a dual role in DNA repair and apoptosis

Protein	Repair pathway	DNA lesions or damaging agent	Activities promoting repair	Apoptotic pathway(s)
BRCA1	HRR [76,79]; TCR [277,278]	Double-strand break (DSB) [76]; crosslinks [77]; oxidative damage [277,278]	Interacts with Rad51 [75]; induces GADD45, causing cell cycle arrest [81]	Induces (non-p53) H-Ras, MEKK4, JNK, FAS pathway [86]
ATM	HRR [99]	DSB [99,101]; ionizing radiation [100]	Activates BRCA1 [107]; activates H2AX [34]; activates p53, causing cell cycle arrest [110,111]; inhibits MDM2, preventing degradation of p53 [115]; activates hChk2, causing cell cycle arrest [118]	ATM $\rightarrow$ E2F1 $\rightarrow$ p73 [122–124]; ATM $\rightarrow$ c-Abl $\rightarrow$ p73 [105]; activates BRCA1 [107]; activates p53 [110,111,125]
ATR	HRR [108]	Ionizing radiation [108]; UV [108]	Activates BRCA1 [108]; activates p53 [130]; activates hChk1, causing cell cycle arrest [130]	Activates BRCA1 [108]; activates p53 [130]
WRN	HRR [140]	DSB [140]; crosslinks [141]	DNA helicase [139]; exonuclease [139]	p53 mediated [143–145]
BLM	HRR [74,139]	Ionizing radiation [139]	DNA helicase [139]; interacts with Rad51 [139,143–145]	p53 mediated [143–145]
TIP60	HRR [146]	DSB [146]	DNA helicase [146]	Pathway unknown [146]
p53	HRR [96,147,148]; BER [219,280]; NER [185]	Ionizing radiation [279]; ionizing radiation, alkylating agents, oxidative damage [219]; pyrimidine dimers [281,282]; bulky adducts [166]	Binds Holliday junctions and facilitates cleavage [147]; interacts with BRCA2 [96] and Rad51 [148]; stabilizes DNA polβ [219]; interacts with Ref-1 [219]; binds DNA ends [283]; interacts with XPD and XPB [185]; activates GADD45 [242]	Two p53 apoptosis pathways after DNA damage: (1) transactivation-dependent p53AIP1 [194]; XPE [171]; APAF-1 [180]; PERP [284]; (2) non-transcription-dependent XPB and XPD [179]; BLM DNA helicase [143]; caspase-8 [285]
XPB	NER [187]	UV, bulky adducts [188]	Helicase [167]	Acts with p53 [179]
XPD	NER [178]	UV, bulky adducts [178]	Helicase [178]	Acts with p53 [179]
P33[ING1b]	NER [195]	UV lesions [195]	Interacts with p53 in repair [195]	Interacts with PCNA [196]
Ref-1	BER [281]	AP sites, oxidative damage [197]	AP endonuclease [286]	Stimulates DNA binding by p53 [200]
PARP	BER [207]	Alkylating agents [204]; ionizing radiation [204]; oxidative damage [204]; SSB, DSB ionizing radiation [217]	Recruits BER enzymes to sites of damage [207]	Depletion of NAD$^+$ [68]; induces p53 [214,215]
DNA-PK$_{cs}$	NHEJ [154]	DSB [154]	Joins DNA ends [154]	Activates p53 [158]
MLH1; PMS2; MSH2; MSH6	MMR [224]; HRR [74]	Alkylating damages [225]; oxidative damages [223]; mispairs during recombination [74]	Excises mismatched bases [225]	Pathway involving the mitochondria [223]; decrease in Bcl-2 [226]

step in the formation of the apoptosome [53], the efflux of K^+ from the cell will help shift the mode of cell death from apoptosis to necrosis. It may be that, in order to ensure that apoptosis occurs instead of necrosis in the face of excessive DNA damage, key proteins involved in DNA repair that are consumers of energy are cleaved and inactivated during apoptosis, such as ATM [54,55], DNA-PK [56], hsRad51 [57–59] and PARP [60–63]. Inactivation of these proteins diverts ATP from DNA repair, and may also prevent confusing pro-survival signals. In addition to the formation of the apoptosome, ATP is also necessary for the accumulation and stabilization of p53 [27], a DNA damage-responsive transcription factor that increases the expression of pro-apoptotic proteins [64] (e.g. bax) which damage the mitochondrial outer membrane with the release of cytochrome c (Fig. 2) [65]. p53 also increases the expression of Apaf-1 [66,67], which is part of the apoptosome. During DNA damage-induced apoptosis, p53 has also been reported to directly target the mitochondria [47].

The cleavage of PARP during apoptosis appears to be an especially critical step, since PARP rapidly consumes NAD^+, the pyridine nucleotide, which, in its reduced form, contributes electrons to complex I of the mitochondrial electron transport chain (Fig. 2). The NAD^+ precursors, nicotinic acid and nicotinamide, in fact, can protect against apoptosis induced by the multiple stress-inducer, deoxycholate [68]. Since PARP also poly(ADP) ribosylates and inhibits p53 [69], PARP cleavage will result in the activation of p53 (Fig. 2). The cleavage of PARP also results in a gain-of-function, which augments the loss of PARP activity [70]. After cleavage by caspase-3, the N-terminal apoptotic fragment of PARP retains a strong DNA binding activity and totally inhibits the catalytic activity of uncleaved PARP [70]. Fig. 2 outlines a mechanism whereby the cell senses the presence of too much DNA damage, and shunts the available ATP toward apoptosis, while at the same time, maintaining ion pumps that prevent cellular lysis. In vivo, cell fate will culminate with the phagocytosis of the apoptotic cell and/or apoptotic bodies. In vitro, cell fate will culminate in the eventual loss of ion pumps, a fate termed "secondary necrosis" of apoptotic cells. Since phagocytes are usually absent from most in vitro culture systems, phagocytosis of early apoptotic cells does not occur.

Over time, a high level of apoptosis can lead to clonal selection of apoptosis-resistant cells. The generation of mutations as a consequence of increased unrepaired DNA damage in apoptosis-resistant, proliferating cells appears to be an important aspect of the development of cancer at numerous sites within the body. This is exemplified by the natural progression of follicular lymphoma to high-grade lymphoma [71]. The constitutive presence of bcl-2 confers apoptosis resistance on follicular lymphoma cells, which then allows mutations and chromosomal aberrations to increase. As reviewed next, the mechanism of apoptosis resistance involves, in part, the loss of key bi-functional proteins which are necessary for initiation of both apoptosis and DNA repair. Loss of apoptosis competence coupled with loss of capability to repair DNA damage increases genomic instability which in turn accelerates progression to cancer (Fig. 1) [72].

Five major DNA repair pathways are homologous recombinational repair (HRR); non-homologous end joining (NHEJ); nucleotide excision repair (NER); base excision repair (BER); and mismatch repair (MMR) [73]. We review evidence that key proteins associated with these five major forms of DNA repair also have a role in triggering cell cycle arrest and apoptosis (Table 1).

2. Homologous recombinational repair (HRR)

In HRR, sequence information that is lost due to damage in one double-stranded DNA molecule is accurately replaced by physical exchange of a segment from an homologous intact DNA molecule. We focus on seven genes directly involved in HRR that are also involved in apoptosis (Table 1, Fig. 3). These are breast cancer-associated gene 1 (*BRCA1*), *ATM*, ATM-related (*ATR*), Werner syndrome gene (*WRN*), Bloom syndrome gene (*BLM*), *Tip60* and *p53*. We also discuss *Rad51* and *BRCA2* because of their role in the HRR process and *c-Abl* which has a clear role in apoptosis and a possible role in DNA repair.

2.1. Activities of BRCA1 in HRR

BRCA1 protein acts as part of a large multimeric complex referred to as the BRCA1-associated genome
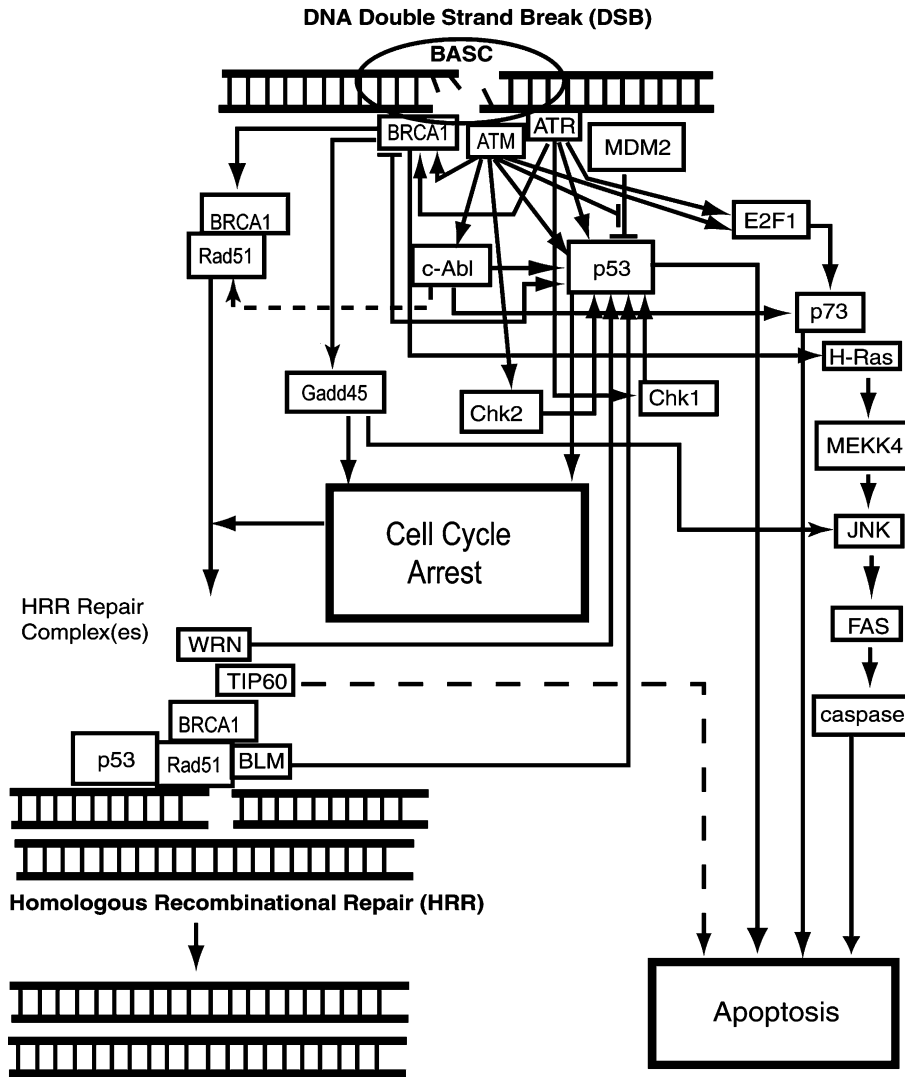
Fig. 3. Involvement of gene products in HRR and apoptosis. The dashed lines indicate uncertainty due to differing results in different reports or less clear results.

surveillance complex (BASC, shown at the top of Fig. 3) [74]. BASC is thought to act as a sensor for DNA damage [74]. BRCA1 has an interaction domain for Rad51, and participates with Rad51 in HRR of double-strand breaks (shown at the bottom left of Fig. 3) [75,76]. BRCA1 and Rad51 also participate in HRR of interstrand crosslinks caused by *cis*-diamine-dichloroplatinum(II) [77]. Mutations in BRCA1 cause reduced HRR of double-strand breaks and of DNA crosslinks, and increase genomic instability [78,79].

2.2. Cell cycle arrest activities of BRCA1

When BRCA1 and p53 are co-transfected into cells, their interaction stimulates *p53*-mediated transcription from promoters containing p53-responsive elements, indicating that BRCA1 functions as a p53 transcriptional coactivator [80]. BRCA1 induces the growth arrest and DNA damage inducible gene 45 (*GADD45*) [81] which activates the G_2M cell cycle checkpoint [82].

BRCA1 has a protein interaction domain for p53 [75], and BRCA1 expression is modulated by p53 [83]. BRCA1 levels are down-regulated in response to p53 induction by DNA damage in cells that undergo either growth arrest or apoptosis (Fig. 3) [83]. Since BRCA1 plays a role in DNA repair, one can ask why it disappears shortly after DNA damage has been produced. A possible explanation, suggested by Arizti et al. [83], is that BRCA1, once phosphorylated, acts synergistically with p53 to activate the p53 pathways of cell cycle arrest and DNA damage response, and then is repressed and/or degraded in a p53-dependent manner when it is no longer needed. MacLachlan et al. [84] also suggested on the basis of their findings that, upon treatment with DNA damaging agents, BRCA1 initially participates in accumulation of p53 protein, but later p53 acts to reduce BRCA1 expression, forming a feedback loop.

2.3. Role of BRCA1 in apoptosis

BRCA1 acts as a transcriptional regulator, and a major target of BRCA1 is the DNA damage-responsive gene *GADD45* [85]. This indicates that BRCA1 triggers apoptosis through activation of c-Jun N-terminal kinase/stress-activated kinase (JNK/SAPK, Fig. 3), a signaling pathway potentially linked to *GADD45* gene family members [85]. This also indicates that the p53-independent induction of GADD45 by BRCA1 and its activation of JNK/SAPK might provide a pathway for BRCA1-induced apoptosis [85].

Under conditions of excessive DNA damage BRCA1 is necessary for the induction of apoptosis [86]. BRCA1 modulates stress-induced apoptotic signaling through a pathway that sequentially involves the H-Ras proto-oncogene, mitogen and extracellularly activated protein kinase 4 (MEKK4), JNK, Fas (CD95)/Fas ligand interactions, and activation of procaspase-8. This Fas-dependent signaling pathway is independent of p53 function (Fig. 3) [86].

2.4. Defects in BRCA1 are associated with cancer

Germ-line mutations in genes involved in repair predispose to cancer (Table 2). Germline mutations in BRCA1 and BRCA2 confer a high risk of breast

Table 2
Human genes encoding DNA repair proteins which predispose to cancer when mutated in the germ line

Gene	Repair pathway	Cancer site(s) associated with defective or reduced gene product
BRCA1	HRR	Breast, ovarian [75,106]
BRCA2	HRR	Breast, ovarian [75,106]
ATM	HRR	Leukemia, lymphoma, breast [99]
WRN	HRR?	Increase in cancer incidence, mainly sarcomas [139]
BLM	HRR	Early development of cancers seen in normal population [139]
RTS (*RECQ4*)	DNA repair but type unknown	Increased cancer incidence, mainly osteogenic sarcomas [139]
NBS	HRR	Increased malignancy, AT-like [287]
Mre11	HRR	AT-like [288]
FANCA, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*	HRR?	Acute myeloid leukemia; squamous cell carcinomas of head and neck [289]
XPC, *XPE*	GGR	Skin [172]
XPA, *XPB*, *XPD*, *XPF*, *XPG*	GGR and TCR	Skin [172]
XPV	Polymerase η postreplication repair	Skin [290]
hMSH2, *hMSH6*, *hMLH1*, *hPMS2*	MMR, HRR, TCR	Hereditary non-polyposis colon cancer [221,291]

HRR: homologous recombinational repair; GGR: global genomic repair (a form of nucleotide excision repair); TCR: transcription coupled repair (a form of nucleotide excision repair); MMR, mismatch repair; *XPA*, *XPB*, *XPC*, *XPD*, *XPF*, *XPG*: xeroderma pigmentosum complementation groups A, B, C, D, F and G, respectively; *hMSH2* and *hMSH6*: human *MutS* homologs 2 and 6, respectively; *hMLH1*: human *MutL* homolog 1; *hPMS2*: human post-meiotic segregation 2; *FANCA*, *FANCC*, *FANCD2*, *FANCE*, *FANCF*, *FANCG*: Fanconi anemia complementation groups A, C, D2, E, F and G, respectively; RTS: Rothmund–Thomson syndrome; *NBS*: Nijmegen breakage syndrome; AT-like: ataxia telangiectasia-like.

and ovarian tumors [87] and may also be associated with adenocarcinoma of the colon [88,89]. In sporadic, non-inherited breast cancer, the majority of high-grade ductal carcinomas have reduced or undetectable levels of BRCA1 [90]. This reduced expression of BRCA1 may be due, in part, to epigenetic silencing by methylation of the BRCA1 promoter [91] and, in part, to loss of heterozygosity [92].

2.5. Role of BRCA1 in avoiding genetic instability

Most cancers exhibit genetic instability. This instability occurs at two levels [12]. In some cancers, instability is observed mainly at the nucleotide level and results in base substitutions or deletions or insertions of a few nucleotides. In most cancers, instability is observed at the chromosome level resulting in loss and gain of whole chromosomes (or large portions thereof) and chromosomal translocations. BRCA1 acts to regulate centrosome duplication and the G_2M checkpoint [93]. In BRCA1-defective cells, improper amplification of functional centrosomes leads to the formation of multiple spindle poles within a single cell. These abnormalities directly result in the unequal segregation of chromosomes, abnormal nuclear division and aneuploidy. Loss of BRCA1 function causes genetic instability (including frequent numerical and structural chromosomal aberrations) which leads to further alterations including inactivation of tumor suppressor genes and/or activation of oncogenes and ultimately to increased tumorigenesis [94]. In general, defective *BRCA1* can enhance cancer progression by allowing excessive DNA damage through insufficient DNA repair, improper centrosome duplication, loss of the ability to undergo cell cycle arrest, and loss of the ability to undergo apoptosis in the presence of increased unrepaired DNA damage.

2.6. BRCA2 in HRR

BRCA2 appears to be needed for the nuclear localization of RAD51 as well as for cell cycle checkpoint regulation [95]. BRCA1, BRCA2 and RAD51 interact and co-localize in a punctuate pattern, called foci (identified by immunofluorescence), in the nucleus during the S-phase of the cell cycle, indicating coordinated function [75,76,96]. Mutations in *BRCA2* give rise to phenotypic effects similar to those of mutations

in BRCA1, suggesting that they have related functions [96]. Despite the similarity in function of BRCA1 and BRCA2, the two genes are not related by sequence. BRCA2, in contrast to BRCA1, associates in vivo with a significant portion of the endogenous pool of RAD51 [97], suggesting that BRCA2 may have a more direct role in the strand exchange reactions of HRR. BRCA2-deficient cells are defective in HRR of double-strand breaks and DNA crosslinks [98].

2.7. Activities of ATM in HRR

ATM is a serine/threonine protein kinase, and in response to DNA damage phosphorylates, and thus activates a number of proteins. ATM is a component of the BASC complex (top of Fig. 3) and plays a central role in signaling DNA damage, particularly double-strand breaks in DNA [99] (Table 1). ATM acts as a cellular gatekeeper and is a key initiating factor in the cascade of events leading to activation of at least the six DNA damage-responsive signaling pathways and cell cycle checkpoints shown in Fig. 3 as well as its interaction with H2AX, discussed in the following sections. It is not clear which of the activities of ATM are of most importance in its role in DNA repair.

Cells derived from patients defective in ATM are hypersensitive to ionizing radiation (IR), bleomycin, restriction endonucleases, and inhibitors of topoisomerase, all agents that induce double-strand breaks [100]. For example, the topoisomerase inhibitor, camptothecin, induces double-strand breaks predominantly in replication forks, and ATM mutant cells are defective in repair of this particular subclass of double-strand breaks [101].

Although in some cell lines there is evidence that ATM acts, in part, through activation of c-Abl, in another cell line this was not found, so in Fig. 3, the arrow indicating c-Abl-activating DNA repair through Rad51 is drawn with a dashed line. On the one hand, Chen et al. [102] showed that IR induces RAD51 tyrosine phosphorylation, which depends on both ATM and c-Abl tyrosine kinase. ATM is required for the activation of the tyrosine kinase c-Abl [103], probably by phosphorylating c-Abl on serine 465 [104]. c-Abl phosphorylates RAD51 in vitro and in vivo enhancing complex formation between RAD51 and RAD52, and RAD51 and RAD52 cooperate in HRR [102,105,106]. On the other hand, a recent report by

Takao et al. [103], using a chicken B lymphocyte cell line, indicated that ATM was essential for DNA repair after IR, but that c-Abl was not.

In response to IR, ATM also phosphorylates and activates BRCA1, which may be critical for proper responses to IR-induced DNA damage [107,108]. C-terminal binding protein interacting protein (CtIP) inhibits BRCA1 by binding to the BRCA1 C-terminal (BRCT) domain repeats of BRCA1. Upon IR, ATM directly phosphorylates CtIP, dissociating it from BRCA1 [109]. Failure of this dissociation results in persistent repression of BRCA1-dependent induction of GADD45. Another possible way in which ATM may be active in repair is through the phosphorylation and activation of H2AX, which opens up chromatin to allow DNA repair enzymes access to double-strand breaks [34].

2.8. Cell cycle arrest activities of ATM

In response to DNA damage and replication blocks, cells prevent cell cycle progression through the control of critical cell cycle regulators. Cells deficient in ATM exhibit defective cell cycle checkpoints at the G_1S transition, during S phase, and at the G_2M boundary. The G_1S cell cycle checkpoint is mediated primarily by activation and accumulation of the p53 protein, which in turn activates the gene encoding p21, an inhibitor of the cell cycle machinery [105]. In response to double-strand breaks, ATM acts upstream of p53 (Fig. 3) and controls its activity through phosphorylation of a single residue, serine 15, thought to act by decreasing binding of p53 to its inhibitor MDM2 [110,111]. A later report, however, indicated that serine 15 phosphorylation contributes to p53 activation by causing increased binding of the phosphorylated p53 to the transcription factor CBP/p300 (and in this report, serine 15 phosphorylation did not influence the interaction of p53 with MDM2) [112]. The p300/CBP protein acetylates lysine 382 at the C-terminus of p53, which promotes p53 binding to specific DNA sequences [113]. Serine 15 is located in the nuclear export signal sequence of p53, and phosphorylation of serine 15 after DNA damage results in p53 not being exported from the nucleus [114]. This increases its transactivation function. In response to DNA damage, ATM also phosphorylates the p53 inhibitory protein MDM2, reducing its binding to p53 and preventing the rapid degradation of p53 [115]. In addition, JNK, activated by ATM phosphorylation, can in turn phosphorylate p53 on ser 37 to block MDM2 binding [116].

Checkpoint kinase 2 (Chk2) is the mammalian homolog of the *S. cerevisiae* Rad53 and *S. pombe* Cds1 protein kinases required for the DNA damage and replication checkpoints. The *Chk2* gene encodes a G_2M checkpoint kinase. Chk2 is rapidly phosphorylated and activated in response to replication blocks and DNA damage; the response to DNA damage occurs in an ATM-dependent manner (Fig. 3) [117]. When activated by DNA damage, hChk2 phosphorylates p53 on serine 20 blocking binding to MDM2 and thereby stabilizing p53 [118]. The Nijmegen breakage syndrome 1 gene (*NBS1*), encodes a component of the BASC complex, which interacts with ATM and is phosphorylated by it after exposure to IR. When the *NBS1* gene is mutated, the resulting syndrome appears to be caused by defective responses to double-strand breaks. The ATM-dependent activation of the checkpoint kinase hChk2 by IR also requires NBS1 [119], suggesting that NBS1 has a role in cell cycle arrest. In general, ATM both directly and indirectly mediates a series of p53 modifications aimed at creating structural configurations that stabilize and activate p53 [105].

2.9. Role of ATM in apoptosis

Xu and Baltimore [120] found that mouse ATM−/− embryonic stem cells are hypersensitive to IR and defective in cell cycle arrest following radiation. However, in contrast to mouse ATM−/− embryonic stem cells, mouse ATM−/− thymocytes are more resistant to apoptosis induced by IR than normal thymocytes, implying a role for wild-type ATM in inducing apoptosis [120]. Bhandoola et al. [121] presented evidence that mature T cells are signaled to die by ATM-dependent, but p53-independent, apoptosis. Following IR, c-Abl is phosphorylated in an ATM-dependent manner, and activated c-Abl can, in turn activate p73 (Fig. 3), a p53-like protein, which has a role in DNA damage-induced apoptosis [103].

The transcription factor, E2 promoter binding factor 1 (E2F1) protein, has a role in regulating cell cycle progression, particularly at the G_1S transition. Lin et al. [122] showed that, in response to DNA damage of mouse thymocytes, E2F1 protein is phosphorylated by ATM and ATR kinases at a site in its amino

terminus. This stabilizes E2F1, which transcriptionally activates the p73 promoter (Fig. 3). Accumulation of p73 leads, in turn, to induction of apoptosis [123,124]. ATM is also required for IR-induced apoptosis in differentiated neurons. This occurs through a pathway that depends on ATM-induced phosphorylation of two sites on p53 [125], and is also largely dependent on BAX [126], a member of the Bcl-2 family of cell death regulators, which promotes apoptosis. In response to double-strand break damage, ATM is involved in DNA repair, entry into cell cycle arrest, and apoptosis. Defects in ATM lead to loss of these abilities, causing increased genomic instability [99].

2.10. ATM cleavage upon commitment to apoptosis

Upon commitment to apoptosis, caspases (cysteine aspartic acid proteases) are activated in a proteolytic cascade. In this cascade, initiator caspases (e.g. caspase-8 and -9) activate downstream caspases such as caspase-3, -6 and -7, which are responsible for dismantling cellular proteins as part of the execution phase of apoptosis. During IR-induced apoptosis, ATM is cleaved by a caspase-3-like apoptotic protease [54,127]. The cleavage of ATM during apoptosis generates a truncated protein devoid of kinase activity. This truncated protein nevertheless retains its DNA binding ability suggesting that it may act in a trans-dominant-negative fashion to prevent DNA repair and DNA damage signaling [127]. These findings support the hypothesis of Section 1 (illustrated in Fig. 2) that upon commitment to apoptosis, DNA repair is counterproductive.

2.11. Defects in ATM are associated with cancer

Inherited mutations of the *ATM* gene cause increased susceptibility to T-cell pro-lymphocytic leukemia, and B-cell chronic lymphocytic leukemia. Defective ATM may also predispose to sporadic colon cancer in tumors with microsatellite instability [128]. Epidemiological studies also indicate an excess of breast cancer in the relatives of individuals with ataxia telangiectasia. Loss of heterozygosity of ATM frequently occurs at an early stage of development of breast cancer [92].

2.12. ATR (ATM-related) kinase

Like ATM, ATR is a member of a family of high molecular weight protein kinases occurring in a variety of eukaryotes and involved in DNA damage responses. Brown and Baltimore [129] have suggested that ATR and ATM may have both overlapping and non-redundant roles in regulating p53. ATM is responsive to IR but not UV, hydroxyurea or MMS-induced DNA damage, whereas ATR is responsive to both IR- and UV-induced damage. ATR activates p53 in response to DNA damage by phosphorylating p53 on serines 15 and 37. In response to DNA damage, ATR also phosphorylates and activates Chk1, a protein kinase that phosphorylates p53 on serine 20 [130] and regulates cell cycle progression [131]. ATR kinase also mediates phosphorylation of BRCA1 in response to UV, but at sites that are both distinct and overlapping with those phosphorylated by ATM in response to IR [108]. Thus, BRCA1 is activated by ATM and ATR and acts downstream of them. As noted by Shiloh [105], ATM and ATR are sentries at the gate of genome stability.

2.13. c-Abl activity in HRR

There have been several reports on the activity of c-Abl in HRR. In one report, upon activation, c-Abl phosphorylated RAD51 (on tyr 54), inhibiting its binding to DNA and the function of RAD51 in strand exchange reactions [132]. In a second report, activation of c-Abl resulted in phosphorylation of Rad51 at other tyrosine residues, and enhanced the interaction between Rad51 and Rad52, thought to stimulate strand exchange activity [102]. In a third report, c-Abl deficiency had little effect on tested functions of HRR, though it was clearly necessary for apoptosis [133].

2.14. c-Abl activity in growth arrest and apoptosis

c-Abl is a tyrosine kinase that is phosphorylated and activated in cells exposed to IR and other DNA damaging agents by DNA-PK [134] and ATM (Fig. 3) [104]. Activation of c-Abl by ATM prevents the nuclear export of p53 [135] and can induce growth arrest in a p53-dependent and Rb-dependent manner [136]; c-Abl, through its Src-homology (SH3) domain, binds to p73 in vivo through a p73 PXXP domain [137,138].

IR-induced activation of c-Abl (through ATM) then allows c-Abl to phosphorylate p73 at tyrosine residues, and this, in turn, activates the p73-dependent apoptosis pathway (Fig. 3) [137,138].

2.15. Werner syndrome and Bloom syndrome

Two further genes, which may be involved in HRR, are the genes responsible for Werner syndrome (*WRN*) and Bloom syndrome (*BLM*). These two genes each encode a RecQ family DNA helicase [139]. Homozygous mutations in each of these genes are associated with genomic instability and cancer predisposition. WRN is unique within this family in that it also has an exonuclease activity. WRN protein forms distinct nuclear foci (identifiable by immunofluorescence) that partially overlap with RAD51 nuclear foci formed in response to DNA damages (including double-strand breaks), suggesting that WRN takes part in HRR [140]. The finding that WRN defective cells are sensitive to DNA crosslinking drugs [141] also suggests a defect in HRR, since DNA crosslinks are ordinarily repaired by HRR. BLM protein is a component of the BASC complex (described earlier), which includes BRCA1 and ATM, suggesting that BLM is also involved in HRR [74]. BLM interacts directly with RAD51 [139]. Both BLM and WRN interact functionally with p53, and p53-mediated apoptosis is defective in BLM and WRN mutant cells [142–145]. Although the evidence indicates that BLM and WRN participate in both HRR and p53-mediated apoptosis, their specific roles in these processes are not yet understood.

2.16. TIP60 and p53

Histone acetylases are important chromatin modifiers and play a central role as chromatin transcription activators. TIP60 histone acetylase is part of a multimeric protein complex. Besides histone acetylase activity, TIP60 also acts as a DNA helicase and binds specifically to Holliday-like structures in DNA (three- and four-way junctions) that are intermediates in HRR. Ectopic expression of mutated TIP60 lacking histone acetylase activity results in cells with defective double-strand DNA break repair and with loss of apoptotic competence [146]. The defect in double-strand break repair may reflect a role of TIP60 in resolving Holliday junctions during HRR. The loss of apoptotic

competence suggests a defect in the cell's ability to signal the existence of DNA damage to the apoptotic machinery.

p53 binds strongly and with high specificity to Holliday junctions and facilitates their cleavage, which is an important step in the HRR pathway [147]. In addition, p53 interacts physically and functionally with BRCA2 [96] and RAD51 [148]. These findings are consistent with a role of p53 in HRR. p53 also exhibits a 3′ to 5′ exonuclease activity indicating a direct role in DNA repair [149]. Marmorstein et al. [96] presented evidence that BRCA2 and RAD51 cooperate to down-regulate p53, which decreases p53 transactivation activity and limits the length or severity of p53-mediated cell cycle arrest after DNA damage. Thus, in response to DNA damage, p53 fulfills multiple roles. It not only participates in HRR, but also, when activated, signals cell cycle arrest to allow for further repair, and apoptosis if repair is insufficient.

2.17. Rad51 has a central role in HRR (but no pro-apoptotic role)

The human form of Rad51 (HsRad51) binds to DNA and promotes ATP-dependent homologous pairing and strand exchange, the central reactions of HRR [150,151]. HsRad51 is a homolog of, and functionally similar to, the extensively studied RecA protein of *E. coli* and the Rad51 protein of yeast, where the basic mechanism of HRR is understood in detail. Antisense inhibition of mouse Rad51 enhances radiosensitivity [152] and Rad51 homozygous mutant mouse embryos are hypersensitive to IR [153]. The underlying basis for this sensitivity appears to be the loss of ability to repair double-strand breaks. Loss of heterozygosity of RAD51 is associated with progression toward sporadic breast carcinoma [92]. Upon commitment to apoptosis, Rad51 is cleaved by caspase-3 [59]. The cleavage of both ATM and Rad51 by caspase-3 suggests that inhibition of HRR may be part of the apoptotic response in cells suffering from excessive DNA damage.

3. Non-homologous end-joining (NHEJ)

There are two distinct mechanisms for repairing double-strand breaks, HRR and NHEJ. HRR is thought to be largely accurate by analogy with this process

in microorganisms. NHEJ is regarded as largely inaccurate because it involves end-joining reactions with junctions containing deletions back to regions of microhomology of 1–10 bases within 20 base pairs of the ends [154]. Mammalian cells repair the majority of double-strand breaks by NHEJ [154], although there is evidence that NHEJ may be coupled to HRR to generate accurate repair of double-strand breaks [155].

3.1. Role of DNA-PK in repair

NHEJ is carried out, in part, by DNA-PK, a holoenzyme consisting of a catalytic subunit (DNA-PK$_{cs}$) and a DNA binding and regulatory subunit, Ku. NHEJ is initiated by Ku (a heterodimer of Ku70 and Ku86), binding to both DNA ends of a double-strand break (Fig. 4). Ku then recruits DNA-PK$_{cs}$, a quiescent protein kinase which is only activated by association with Ku at DNA ends. The complex of Ku and DNA-PK$_{cs}$, now an active heterodimer protein kinase called DNA-PK, is able to align the ends of the double-strand break (Fig. 4) and allow their ligation by DNA ligase IV, which, among one or more other factors and activities, completes NHEJ DNA repair [156]. The two pathways, HRR and NHEJ, appear to be complementary since double mutant cells defective in both HRR and NHEJ are profoundly more sensitive to IR than either mutant alone [157].

3.2. Role of DNA-PK in apoptosis

Studies involving different mouse strains or different cell lines have different results with respect to DNA-PK involvement in apoptosis, so the arrows in Fig. 4 that deal with apoptosis are drawn with dashed lines. On the one hand, one study indicates that upon exposure to IR, DNA-PK phosphorylates p53 at serines 15 and 37. This activation of p53 then leads to apoptosis in response to DNA damage [158]. Along the same line, another study indicates that DNA-PK also phosphorylates MDM2, preventing its inhibitory action on p53 and allowing p53 to transactivate downstream target genes [159]. Further, DNA-PK and p53 were shown to form a protein complex that interacts with gemcitabine-containing DNA and plays a role in signaling apoptotic pathways [160]. In addition, mice defective in DNA-PK$_{cs}$ had significantly suppressed IR-induced apoptosis and BAX expression, indicating that DNA-PK$_{cs}$ serves as an upstream effector for p53 activation in response to IR, linking DNA damage to apoptosis [161].
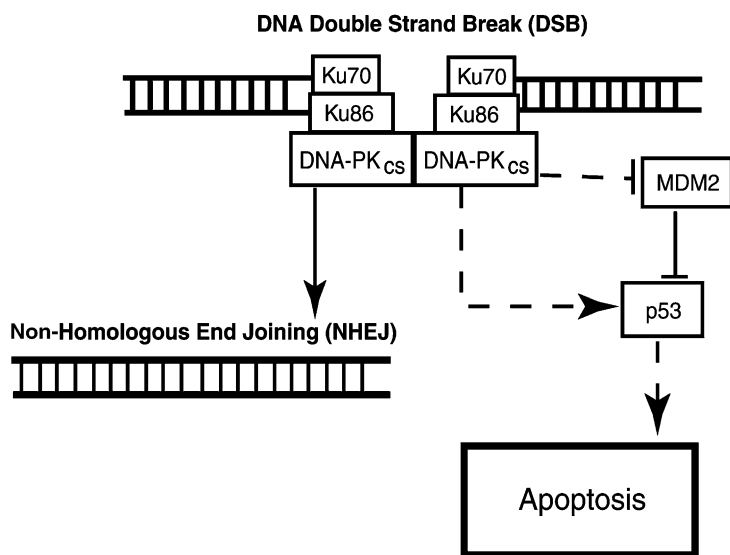

Fig. 4. Involvement of gene products in NHEJ and apoptosis. The dashed lines relating to apoptosis indicate differences in results in different organisms and cell lines in these reactions (see text).

On the other hand, studies by Jhappan et al. [162], using IR on another strain of DNA-PK$_{cs}$-defective mice, and by Jimenez et al. [163] on another cell line defective in DNA-PK, found that the p53-mediated apoptosis response was intact. In addition, the restriction enzyme PvuII forms blunt end double-strand breaks and such damages are ordinarily repaired by NHEJ catalyzed by DNA-PK. Such blunt end double-strand breaks were found to induce apoptosis in p53-deficient cells, indicating that apoptosis can be induced by these damages in a p53-independent fashion [164]. The mechanism appears to involve a decline in Bcl-2 levels.

It is not clear whether the different findings are due to mouse strain or cell line differences, or different conditions of the assays. But once cells become committed to apoptosis, DNA-PK is specifically cleaved by caspase-3 [165].

4. Nucleotide excision repair (NER)

NER repairs DNA with helix-distorting damages, including the damages of cyclobutane pyrimidine dimers and 6–4 photoproducts produced by UV light, and adducts produced by the chemotherapeutic agents cisplatin and 4-nitroquinoline oxide [166,168]. About 30 polypeptides are involved in NER, and the NER process has been reconstituted with purified components (summarized in [167]). Key steps of NER (see Fig. 5 for some of these steps) include: (i) recognition of a DNA defect; (ii) recruitment of a repair complex; (iii) preparation of the DNA for repair through action of helicases; (iv) incision of the damaged strand on each side of the damage, with release of the damage in a single-strand fragment about 24–32 nucleotides long; (v) filling in of the gap by repair synthesis; (vi) ligation to form the final phosphodiester bond [168,169]. Two subpathways of NER are global genomic repair (GGR) and transcription coupled repair (TCR). These pathways are initiated somewhat differently, with GGR acting on damages in non-transcribed regions of DNA and TCR acting on damages in actively transcribed DNA. However, after initiation, most enzymatic steps utilize the same enzymes and enzyme complexes [168,169]. The initiation step, the rate-limiting step of NER, can involve one of the three different pairs of proteins (see Fig. 5), depending in part on which helix-distorting, or transcription-blocking damage is involved [170–172]. Rates of initiation depend on how much the helix is distorted and can vary by more than 1000-fold [166,172].

As shown by Li and Ho [173], when lower levels of helix-distorting damages are produced by UV, p53 protein is increased, which in turn promotes participation in NER. After high doses of UV, cells are inefficient at NER. NER is also activated at an early stage of apoptosis before apoptosis becomes irrevocable, after which NER is greatly reduced [174]. p53-regulated NER and apoptosis occur at different levels depending on the state of cellular differentiation [175,176].

Four genes of the NER pathways, *XPD*, *XPB*, *p53* and *p33^{ING1b}*, as described below are required for both efficient NER and for apoptosis in response to UV-induced damages.

4.1. The role of XPD in NER, apoptosis and disease

Alterations at specific sites within the XPD protein have been identified as affecting one of two different primary functions of XPD: stabilization of the transcription factor complex TFIIH, and a $5' \rightarrow 3'$ helicase function most strongly expressed when XPD is part of the TFIIH complex [177]. The helicase function of XPD is essential for NER. When XPD helicase function is defective due to an alteration in its ATP hydrolysis region, neither $5'$ nor $3'$ incisions in defined positions around a DNA adduct can be detected [178]. XPD function is also required for p53-mediated apoptosis [179,180].

Different alterations in XPD cause different defects in DNA repair, RNA transcription and in apoptosis. Identified defects at specific sites within XPD cause defects in transcription and NER, and also cause one of three different major diseases, xeroderma pigmentosum, Cockayne's syndrome or trichothiodystrophy [177]. Other mutations in XPD cause more subtle effects. An XPD substitution at amino acid 312 (a minority variant polymorphic form of the protein) increases protection from lung cancer [181]. In addition, an alteration at amino acid 751 gives some protection against basal cell carcinoma [182], but possibly increases risk among smokers and drinkers for squamous cell carcinoma of the head and neck [183].
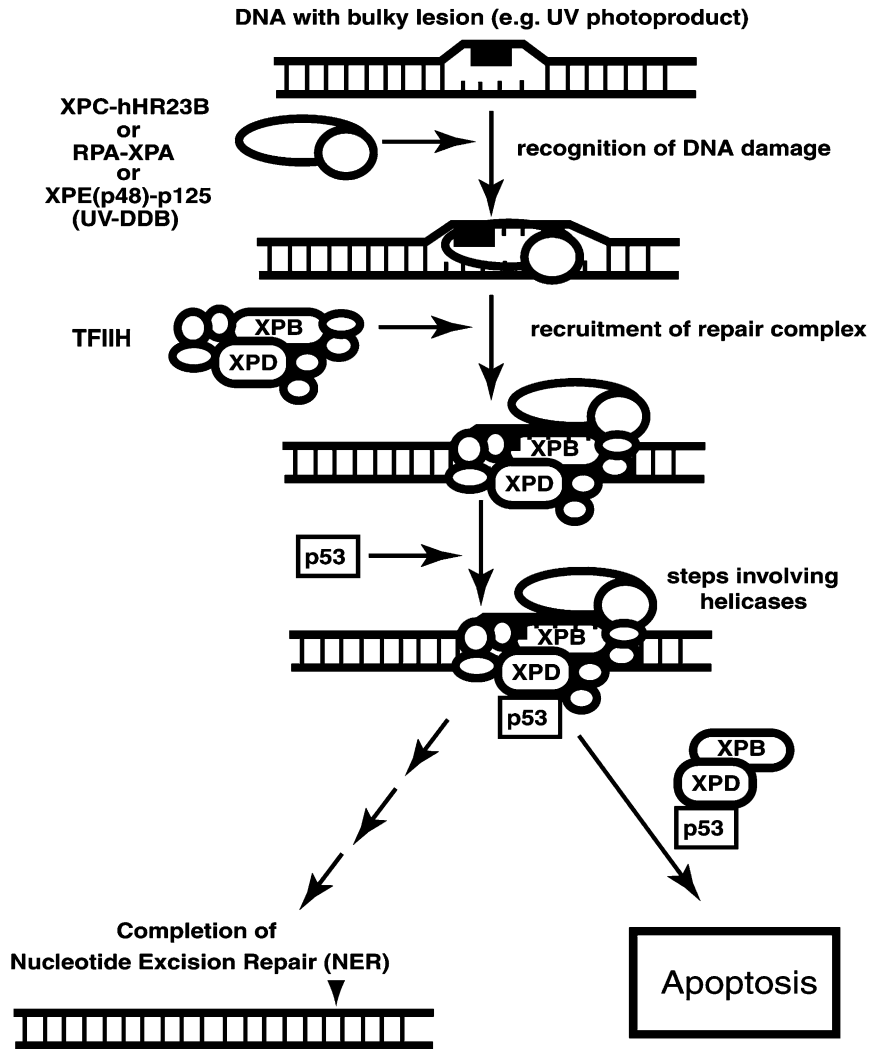
Fig. 5. Involvement of gene products in NER and apoptosis.

TFIIH is a nine subunit complex which acts in NER (Fig. 5). XPD and XPB are members of this complex whose helicase activities are required for NER, as they allow the opening of DNA around the DNA damage during the GGR subpathway of NER [184]. During the TCR subpathway of NER, it is thought that stalling of RNA pol II at a site of DNA damage recruits the TFIIH complex, with its XPD subunit, to participate in NER [184].

The XPD protein binds with p53 in vitro, and p53 binding to XPD within the TFIIH complex inhibits the helicase activity of XPD [185]. Binding of XPD to p53 occurs at the carboxy terminal domain of XPD [186]. While transfer of a wild-type *p53* expression vector into primary normal human fibroblasts results in apoptosis, primary fibroblasts from individuals with a defect in XPD have a deficiency in the apoptotic response [179]. The XPD polymorphic variant at amino acid 312 did not have an altered binding efficiency for p53. However, when present in lymphoblastoid cell lines, this XPD variant produced a 2.5-fold higher apoptotic response to UV-induced damage than that shown by

the majority type of XPD [186]. This higher apoptotic response may account for the protective effect of this variant against lung cancer.

4.2. The role of XPB in NER and apoptosis

The XPB protein is a $3' \rightarrow 5'$ helicase acting within the TFIIH complex (Fig. 5) [167] and XPB is necessary for transcription and NER [187] as well as for p53-dependent apoptosis [179]. The few XPB mutations known each have different levels of deficiency with respect to repair of cyclobutane pyrimidine dimers and pyrimidine(6–4)pyrimidine dimers, two different types of UV lesion [188]. XPB (also known as ERCC3) has been shown to bind to p53 in vitro [189] and to the C-terminal domain of p53 in vivo [185].

4.3. The role of p53 in NER and in apoptosis after DNA damage usually repaired by NER

The induction of NER and apoptosis after UV damage in mouse fibroblasts is observed only in $p53^{+/+}$ and not in $p53^{-/-}$ cells, indicating that both stress response functions are dependent on wild-type p53 function [173]. Both NER subpathways, GGR and TCR, in human fibroblasts depend on p53 [190]. In $p53^{+/+}$ fibroblasts, NER only requires low levels of p53 induction, but a large amount of p53 induction is required for triggering apoptosis [173]. However, wild-type p53 activity was not required for apoptosis in undifferentiated murine keratinocytes, although p53 was needed for apoptosis of differentiated keratinocytes [191]. p53 directly interacts with three components of the TFIIH complex, which is at the center of the NER response (Fig. 5). As reviewed by Frit et al. [184], the amino terminal transactivation domain of p53 interacts with p62, a component of TFIIH, and the carboxy terminus of p53 binds to the amino-terminal half of XPD and to helicase motif III of XPB. These interactions inhibit the helicase activity of TFIIH without affecting its ATPase activity. The p53 mutants frequently found in tumor cells are less efficient helicase inhibitors. Mutant p53 affects NER in a dominant negative manner. This implies that wild-type p53 undergoes protein–protein interactions which are important in NER [192]. UV-induced apoptosis is dependent on p53, but this UV-induced apop-

tosis requires active XPB and XPD proteins as well [179].

In addition to direct interaction with components of TFIIH, p53 also functions in NER by transcriptional activation of XPE (p48, involved in damage detection). This effect of p53 occurs through the basal level of p53 present before UV damage occurs plus the newly induced level of p53 after irradiation [171]. In addition to its role in NER, the transactivation activity of p53 was found to be needed for p53-dependent apoptosis [193]. Recently, one particular p53 transactivation activity needed for apoptosis after UV-induced damage has been elucidated by Oda et al. [194]. This transactivation occurs after phosphorylation of the ser46 of p53, changing the conformation of p53 so that it now transactivates p53-regulated apoptosis-inducing protein 1 (*p53AIP1*). p53AIP1 localizes to mitochondria where it causes dissipation of the mitochondrial membrane potential ($\Delta\psi_\mathrm{m}$). The downstream cytotoxic effects of this perturbation are not known.

4.4. The role of p33^{ING1b} in NER and apoptosis

p33^{ING1b} is one of four isoforms of the tumor suppressor gene *ING1*, coded for by alternative splicing of *ING1*. p33^{ING1b} expression is induced by UV-irradiation and enhances repair of UV-damaged DNA through a mechanism which requires the participation of p53, and a possible interaction with GADD45 [195]. p33^{ING1b}, through an octapeptide motif called the proliferating cell nuclear antigen (PCNA)-interacting-protein domain (PIP), also strongly binds PCNA in a UV-inducible manner. This binding apparently correlates with the ability of p33^{ING1b} to induce apoptosis [196].

5. Base excision repair (BER)

BER is a major DNA repair pathway protecting mammalian cells against single-base DNA damage caused by methylating and oxidizing agents, other genotoxicants, and a large number (about 10,000 per cell per day) of spontaneous depurinations [197]. BER is mediated through at least two subpathways, one involving single nucleotide BER and the other involving
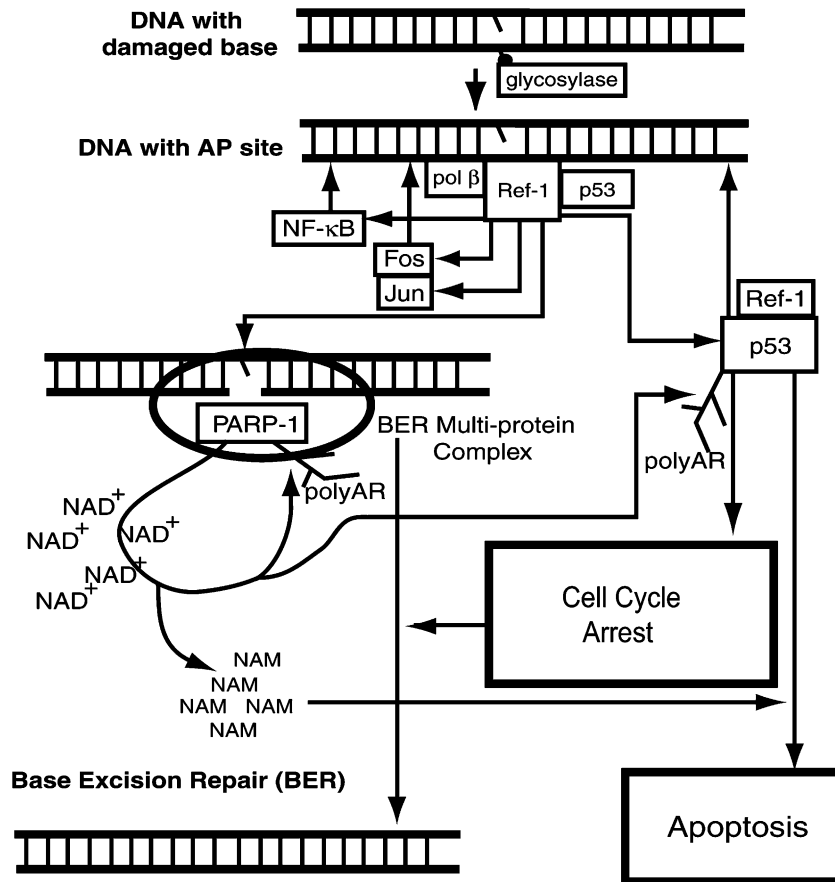
Fig. 6. Involvement of gene products in BER and apoptosis.

longer patch BER of 2–15 nucleotides. BER can be initiated through removal of a damaged base by a DNA glycosylase, which binds the altered deoxynucleoside in an extrahelical position and catalyzes cleavage of the base–sugar bond. This generates an apurinic/apyrimidinic site (AP site). BER can also occur at a site of spontaneous depurination. Ref-1, an AP endonuclease, then makes a 5′ nick in the DNA backbone. This is followed by poly(ADP-ribose) polymerase-1 (PARP-1) acting as a nick surveillance protein, binding to the nicked DNA (Fig. 6). PARP-1 binds even more strongly if there is a stalled single nucleotide BER block at the excision step. Subsequently, repair patch synthesis and DNA ligation complete the process [197,198] (some steps shown in Fig. 6).

5.1. Role of Ref-1 in BER and cancer

Ref-1 is a multifunctional protein that serves as the AP endonuclease in BER (see Fig. 6) [197]. Ref-1 is dramatically elevated in prostate cancer [199] and a variety of other cancers [197], indicating that during progression to prostate cancer enhanced BER may provide a growth advantage.

5.2. Role of Ref-1 in apoptosis

Ref-1 associates with p53 and is a potent activator of p53 binding in vivo, enhancing the ability of p53 to transactivate a number of p53 target promoters [200]. Ref-1 overexpression increases the ability of p53 to stimulate p21 and cyclin G expression. Up-

regulation of p21 leads to cell cycle arrest by inhibiting cyclin-dependent kinase function [201] and cyclin G has pro-apoptotic activity [202]. Down-regulation of Ref-1 (by antisense strategies) causes a reduction in the ability of p53 to transactivate the p53 and Bax promoters. Thus, Ref-1 not only plays a key role in BER, but also is a key regulator of p53 and, hence, of cell cycle arrest and apoptosis. Ref-1 is induced by oxidative agents and in turn stimulates the DNA binding activity of several transcription factors including Fos, Jun and NF-κB [197]. When cells become committed to apoptosis, presumably due to excessive DNA damage, Ref-1 expression is down-regulated [203].

5.3. The role of poly(ADP-ribose) polymerase (PARP) in BER

One of the immediate cellular responses to DNA damage by alkylating agents, IR, oxidants [204] and hydrophobic bile acids [205] is the activation of PARP-1. PARP-1 is a member of a family of enzymes which includes the DNA damage-responsive members PARP-1 and PARP-2 [206]. PARP-1 is activated upon binding to single- or double-strand breaks in DNA, and is involved especially in long patch BER, probably by recruiting DNA repair enzymes to the vicinity of a DNA lesion [198] (see left side of Fig. 6). PARP-1 is part of the BER multi-protein complex (also includes XRCC1 and possibly DNA ligase III and DNA polymerase β), which detects DNA interruptions and carries out efficient repair [207]. PARP-1 catalyzes the synthesis of poly(ADP-ribose) from the respiratory coenzyme NAD^+ with the release of nicotinamide (NAM, Fig. 6). The branched linear ADP polymer is attached (see Fig. 6) to PARP-1 itself, p53, the Ca^{++}/Mg^{++} endonuclease [208], and to other nearby DNA binding proteins such as histones [209]. Because of its negative charges, the attachment of ADP-ribose polymers to acceptor proteins creates a region of negative charge around the break, thereby opening up the chromatin and allowing access of repair proteins to the site of DNA damage.

5.4. The role of PARP in apoptosis

Treatment of cells with 3-aminobenzamide, an effective PARP inhibitor, sensitized Jurkat cells to apoptosis, suggesting that, at lower levels of DNA damage, PARP activity protects against apoptosis [205]. Since PARP inhibits the pro-apoptotic Ca^{++}/Mg^{++} endonuclease through poly(ADP) ribosylation [208], this may be one mechanism of its protective action. Also Beneke et al. [213] found that, in the presence of single-strand breaks, the rate of apoptosis in PARP-1 defective cells was strongly increased compared to cells with intact PARP-1 activity. p53 expression was also drastically increased in the PARP-1 defective cells, suggesting that PARP activity may delay apoptosis by inhibiting the increase in pro-apoptotic p53 levels.

Since PARP-1 consumes NAD^+ and ultimately, ATP, excessive DNA damage will eventually lead to cell death through excessive PARP-1 activity (see Fig. 2). The addition of the NAD^+ precursors, nicotinic acid and nicotinamide, can however, effectively increase intracellular levels of NAD^+ [210–212], thereby protecting cells against excessive DNA damage, ATP depletion and cell death. We recently reported that both nicotinic acid and nicotinamide dramatically protect cells against apoptosis induced by the DNA-damaging agent, deoxycholate [68], suggesting that the drain on NAD^+ levels may be responsible for the induction of apoptosis. Thus, depletion of NAD^+ by PARP-1 utilization may provide a linkage between excessive DNA damage and the triggering of apoptosis or necrosis, depending upon the severity of the ATP drain (see Fig. 2).

PARP-1 also enhances induction of p53 in response to DNA damage [214,215]. Furthermore, p53 undergoes extensive poly(ADP) ribosylation (Fig. 6) early in the apoptotic program prior to commitment to cell death [69]. These findings suggest that PARP-1 may activate p53 function, and thus influence entry into apoptosis.

As an essential early event in apoptosis, PARP-1 is cleaved by caspase-3 [216], suggesting that PARP-1-mediated BER is counterproductive once a cell is committed to apoptosis.

5.5. The role of PARP in cancer prevention

Inactivation of p53 in mice results in spontaneous development of tumors which are mainly lymphomas, soft tissue sarcomas, and rare carcinomas, but overall the spectrum of tumors in p53-deficient mice is narrower than in p53-deficient humans (Li–Fraumini

syndrome). However, mice deficient for both p53 and PARP-1 have a high frequency of carcinomas in the mammary gland, lung, prostate and skin, as well as brain tumors, reminiscent of Li–Fraumini syndrome in humans [176]. These findings suggest that PARP-1 and p53 may interact to maintain genome integrity by promoting effective repair of DNA damage and/or induction of apoptosis in the face of excessive DNA damage, thereby suppressing tumorigenesis in mice.

Individuals with familial adenomatous polyposis (FAP) are predisposed to colon cancer. Cristovao et al. [217] showed that cells from healthy individuals have a marked stimulation of PARP-1 activity upon IR, whereas this response is absent in FAP patients. These authors proposed that a deficiency of PARP-1-mediated BER might contribute to FAP-associated colon cancer. They suggested that in FAP patients there might be a defect in NAD^+ consumption in relation to PARP activity in DNA repair.

5.6. The role of p53 in BER

Offer et al. [218] have shown that p53 acts directly in BER, as a DNA repair protein, and not through its transactivation role. They showed that a transactivation-deficient p53 mutant, p53-22-23, was more efficient in BER than wild type p53. Zhou et al. [219] showed that stimulation of BER by p53 is correlated with its ability to interact directly with Ref-1 and DNA polymerase β, and that p53 stabilizes the interaction between polymerase β and abasic DNA. Offer et al. [220] also showed that p53 modulates BER in a cell cycle specific manner after exposure to IR.

6. Mismatch repair (MMR)

A highly conserved set of MMR proteins in humans is primarily responsible for the post-replication correction of nucleotide mispairs and extra-helical loops. Mutational defects in *MMR* genes in humans give rise to a mutator phenotype, microsatellite instability, and a predisposition to cancer. MMR mutations are implicated in the etiology of hereditary non-polyposis colorectal cancer (HNPCC) syndrome [221] and a wide variety of sporadic tumors. The MMR system is also involved in the cellular response to a variety of DNA damaging agents. Although mutants defective in *MMR* genes might be expected to exhibit increased cytotoxicity upon treatment with DNA damaging agents, they are observed to be resistant to the normally cytotoxic effects of several genotoxic methylating agents [222]. Mouse embryonic fibroblast and human epithelial cell lines lacking the MMR protein MLH1 are more resistant than wild-type cells to two inducers of oxidative stress, hydrogen peroxide and *tert*-butyl hydroperoxide [223]. Analysis of this resistance indicates that it results from a defect in apoptosis, as the consequence of a requirement for wild-type MLH1 in the transduction of apoptotic signals by a mitochondrial pathway, although the details of this pathway are currently unknown.

6.1. The roles of MLH1, PMS2, MSH2 and MSH6 in MMR repair

The MMR system includes hMLH1 and hPMS2, which form a heterodimer (hMutLα), and hMSH2 and hMSH6, which form another heterodimer (hMutSα) (Fig. 7). When methylated bases of the type O^6-methylguanine (O^6MeG) are paired in duplex DNA with a C or a T, these altered pairs are corrected by MMR. The MMR repair process involves the detection of the mispair by hMutSα, the recruitment of hMutLα, and the replacement of the mispaired base (left side of Fig. 7) [224]. The hMSH2/hMSH6 heterodimer is also part of the BASC complex [74] and thus it may be employed in HRR to correct base mispairs or other abnormalities that can arise from the strand exchange reactions of HRR.

6.2. The roles of MLH1, PMS2, MSH2 and MSH6 in apoptosis

Cells impaired in MMR are unable to remove O^6MeG and are less sensitive to induction of apoptosis by methylating agents [225]. O^6-alkylguanine is considered the preponderant toxic lesion formed by several anticancer alkylating agents [226]. Methylation-induced apoptosis appears to be MMR dependent and to be triggered by secondary lesions, possibly double-strand breaks [226]. Induction of apoptosis by methylation is preceded by a decrease in Bcl-2, hypophosphorylation of Bad, cytochrome c release from the mitochondria, and activation of caspase-9 and -3 (right side of Fig. 7). The ultimate
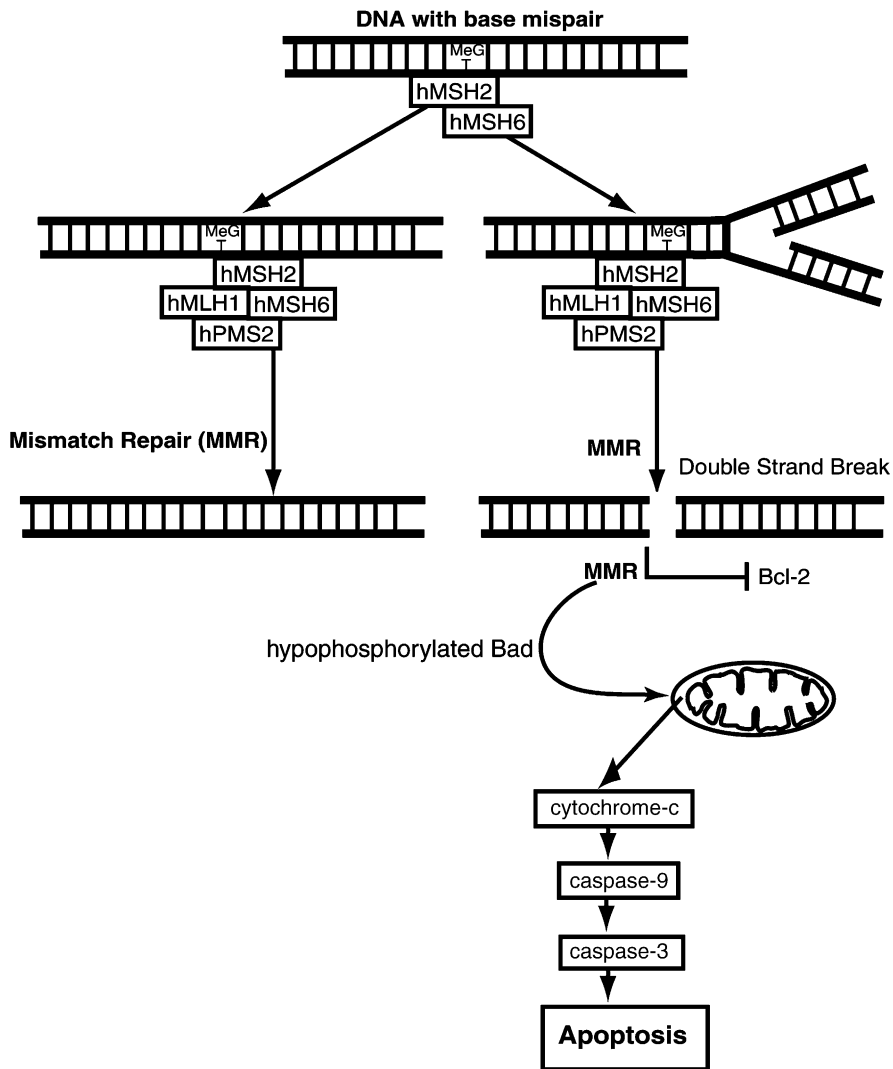
Fig. 7. Involvement of gene products in MMR and apoptosis.

O^6MeG-derived lesions that trigger apoptosis are probably DNA double-strand breaks formed during the process of MMR (e.g. by nuclease attack at gaps and stalled replication forks) [226]. Agents which introduce methylations in DNA, to form adducts such as O^6MeG, cause p53 phosphorylation on serine residues 15 and 392, and these phosphorylation events depend on the presence of functional hMutLα and hMutSα [225]. Upon exposure to alkylating agents that generate O^6MeG, induction of apoptosis was found to require MutSα but, surprisingly, was largely

p53-independent [227]. These results implicate the MMR system in the initial step of a damage-signaling cascade that can lead to p53-independent apoptosis in response to methylation-induced DNA damage.

6.3. The role of O^6-methylguanine methyl transferase in MMR and cancer

Although the DNA-methylated base O^6MG can be removed by MMR (see the previous section), it can also be repaired specifically by O^6-methylguanine

methyl transferase (MGMT) which removes the methyl group and restores the guanine base to its original undamaged state. MGMT defective cells are hypersensitive to killing by methylating agents, and this killing is due to apoptosis. Presumably, apoptosis is induced by the MMR system which can act as a backup for MGMT repair of O^6MG [226].

MGMT plays an important role in the resistance of pancreatic tumors to chemotherapeutic DNA alkylating agents [228]. MGMT activity is upregulated in dysplastic pancreatic epithelium, and its expression increases during tumor progression, reaching the highest levels in the invasive components of the tumor. On the other hand, epigenetic silencing of *MGMT* by promoter hypermethylation can lead to G:C to A:T transition mutations in the *p53* gene [229].

7. Induction of apoptosis by DNA damage: role of p53

7.1. Activation of p53 through increased stability

p53, in unstressed cells, is present in a latent state and is maintained at low levels by targeted degradation. Different genotoxic stresses, including double-strand breaks produced by IR and lesions resulting from UV irradiation or chemical damage to DNA, initiate signaling pathways that transiently stabilize p53, causing it to accumulate in the nucleus and activate it as a transcription factor [230]. After DNA damage, the level of p53 increases largely because the half-life of the protein is increased and also because of increased translation of p53 mRNA [7]. The increase in p53 is ordinarily proportional to the extent of damage, but the kinetics of p53 increase differs for different types of DNA damage. The cellular level of p53 can dictate the response of the cell such that lower levels of p53 result in growth arrest, whereas higher levels result in apoptosis [231]. Growth arrest and apoptosis are two genetically separable functions of p53. A transactivation-incompetent p53 can induce apoptosis but not growth arrest, whereas induction of p21/WAF1, a major transcription target of p53, can induce growth arrest but not apoptosis [231].

p53 can be activated or induced in response to DNA damage by specific DNA repair proteins (e.g. BRCA1, ATM, ATR, DNA-PK, Ref-1, PARP-1, as described earlier). Normally, the p53 protein is unstable with a half-life ranging from 5 to 40 min, depending on the cell type [232]. Upon exposure to DNA damaging agents, p53 becomes metabolically stable and transcriptionally activated. This activation results from post-translational modifications on some of 18 different sites, including phosphorylations, acetylations or sumoylations (covalent attachments of small ubiquitin-like proteins) [230]. p53 instability is due to its ubiquitination and proteosomal degradation in vivo. Both of these processes are transiently suppressed after DNA damage [233].

Interaction of p53 with sites of DNA damage has also been shown to induce selective proteolytic cleavage of p53, resulting in fragments of 40 and 35 kDa molecular weight. The interaction of p53 with single-stranded DNA also gives rise to a novel p50 kDa protein [234]. Okorokov and Milner [234] have proposed that the cleaved forms may also be a means to activate functions of p53 that are cryptic in the intact protein.

7.2. Transactivation by p53

p53 degradation is mediated by MDM2, a nuclear protein induced by p53 that binds to the p53 transactivation domain and promotes p53 degradation [235,236]. MDM2 directly suppresses p53 transactivation and p53-mediated growth arrest and apoptosis [237]. MDM2 is a member of a novel class of E3 ubiquitin ligases which can ubiquitinate p53 in the nuclear compartment [238], presumably preparing p53 for export from the nucleus to the cytoplasm and for proteosome degradation in the cytosol. c-Abl protein tyrosine kinase can enhance the expression level of p53 by inhibiting MDM2-mediated degradation of p53 [239].

p300/CBP transcriptional coactivators play an important role in enhancing the transcriptional functions of p53. They bind directly to the p53 transactivation domain, thereby enhancing p53 activation of the p21 promoter. This results in an increase in p21 which carries out the p53-dependent checkpoint function [240]. p300, through its acetyl transferase activity, acetylates lys-382 in the carboxy terminus of p53, which enhances its sequence-specific binding and activity as a transcription factor [113]. p300 also plays a pivotal role in regulating MDM2-mediated p53 degradation. Normal p53 turnover requires specific and indepen-

dent interaction of p300 with both p53 and MDM2 [241]. Therefore, post-translational acetylation enhances p53 stability and transcriptional activity.

7.3. Cell cycle arrest induced by p53

Increase of p53 by DNA damage leads to cell cycle arrest in G_1 and/or G_2, allowing time for DNA repair to take place, and then induces apoptosis if excess DNA damage is present [7]. Cell cycle arrest involves the transcriptional activation of p21WAF1/Cip1, a cyclin-dependent kinase inhibitor. In the early phase of the p53 response to DNA damage, p53 is stabilized by phosphorylation of specific residues which impedes the inhibitory effect of MDM2 binding. This allows p53 to activate cell cycle checkpoints giving further time for DNA repair. If the damage is not excessive, the cell cycle can resume because p53 activation also induces MDM2 synthesis, which then inhibits p53 as part of an autoregulatory loop. Another protein transcriptionally activated by p53 is GADD45 which binds to PCNA and can arrest the cell cycle, and is also involved in NER [242].

7.4. Induction of apoptosis by p53

Both a p53-mediated transcriptional activity and a p53 activity not requiring transcription appear to play a role in apoptosis, and the relative importance of each type of activity depends on the cell type and experimental situation [7,116]. Two distinct mechanisms by which p53 contributes to apoptosis are the transcriptional up-regulation of Bax [243] and direct interaction of p53 with mitochondria [47,244]. Regulation of Bax by p53 appears to influence the decision to commit to apoptosis in at least some cell types. Overexpression of Bcl-2 can block p53-mediated apoptosis, presumably because Bcl-2 binds to Bax, antagonizing Bax's ability to promote apoptosis. Thus, p53-dependent Bax synthesis tips the scales toward apoptosis. The association of p53 with mitochondria results in the opening of the mitochondrial permeability transition pore, release of cytochrome c, activation of caspases, degradation of survival proteins and induction of apoptosis [47]. Another gene induced by DNA damage in a p53-dependent manner is killer/death receptor 5 (*DR5*), a member of the tumor necrosis factor receptor family [245]. Overexpression of *killer/DR5* leads to

apoptosis. Mutation in this gene leads to loss of apoptotic function and is associated with head and neck cancer [246].

8. Induction of apoptosis by DNA damage: role of Bcl-2 family proteins

The Bcl-2 family of cell death regulators plays a crucial role in determining cell fate in the apoptotic pathway. The anti-apoptotic members of the Bcl-2 family include Bcl-x_L, Bfl-1 and Mcl-1, and the pro-apoptotic members include Bax, Bcl-xS, Nbk, Bak, Bad and Bid. Both Bcl-2 and Bax are associated with the outer membrane of mitochondria, the endoplasmic reticulum and the nuclear envelope [247]. Bax forms channels in lipid membranes and the pro-apoptotic effect of Bax appears to be elicited through an intrinsic pore-forming activity [8], thus leading to leakage of cytochrome c from the mitochondrial intermembrane compartment into the cytosol. Cytosolic cytochrome c initiates the apoptotic program by activating caspases, leading to degradation of specific survival proteins. Bcl-2 overexpression prevents the release of cytochrome c and ensuing events and thus mediates anti-apoptotic effects [248,249]. An inhibitory effect of Bcl-2 on Bax channel-forming activity seems likely [8]. Onset of apoptosis appears to be controlled by the ratio of death promoters (like Bax) to antagonists (like Bcl-2). This death–life rheostat is mediated, at least in part, by competitive dimerization: when Bax is in excess, Bax homodimer formation will dominate, and apoptosis occurs. As Bcl-2 increases, Bax/Bcl-2 heterodimers predominate, and cells are protected from apoptosis [250,251]. An excess of Bcl-2, for example, is normally found in memory cells of the B-cell lineage, thereby contributing to long-term survival. Bax also forms heterodimers with Bcl-x_L and Mcl-1. In some cell types, c-Myc is necessary for DNA damage-induced apoptosis in the G_2 phase of the cell cycle [252]. The pro-apoptotic function of c-Myc may occur by stimulating Bax activity at the mitochondria [253].

The DNA damaging agent, cisplatin, induces the pro-apoptotic conformation of Bak [254]. Cisplatin is a widely used anticancer drug and its action presumably depends on Bak-mediated induction of apoptosis in cancer cells.

9. Reduction of apoptosis capability during progression to cancer

We now discuss evidence indicating that defects in the recognition of excess damage and/or failure of the apoptotic machinery to act on this information leads to genomic instability and progression to cancer.

9.1. p53 defects reduce apoptosis capability and increase cancer risk

Since p53 plays a key role in apoptosis induced by DNA damaging agents, mutant embryonic stem cells defective in *p53* have greater clonogenic survival than *p53* wild-type cells upon exposure to increasing doses of UV-irradiation [255]. Among surviving p53-defective clones, mutation frequency is higher than in *p53* wild-type clones, as expected if loss of an appropriate apoptosis response and reduction in NER capability (see the previous sections) causes genomic instability. Human germline mutations in the *p53* gene have been found to cause Li–Fraumini syndrome (heterozygous *p53* mutant), which is characterized by the development of various tumor types including soft tissue sarcomas, osteosarcoma, breast carcinomas, brain tumors, leukemia and lymphomas [256]. In addition, *p53* mutations have been found in about half of human cancers [257]. Thus, loss of the ability to appropriately respond to DNA damage by inducing apoptosis contributes to progression of a wide range of cancers.

In most cases, Li–Fraumini syndrome results from inheritance of a mutant *p53* allele, followed by somatic loss of the remaining wild-type allele. However, some cases of Li–Fraumini do not exhibit a *p53* genetic defect, but instead exhibit heterozygous germ line mutations in the *hCHK2* gene [258]. Thus, hChk2 and p53 respond similarly to DNA damage in that both are activated by ATM and both block entry into mitosis; furthermore, when mutant, both give rise to the Li–Fraumini syndrome involving increased risk of several types of cancer.

9.2. Overexpression of Bcl-2 reduces apoptosis capability and increases cancer risk

Suppression of apoptosis by overexpression of *Bcl-2* or *Bcl-x*$_L$ markedly elevates the levels of IR-induced mutations [9]. Overexpression of Bcl-2

increases chromosome instability [11,259]. This suggests that inability of cells to undergo apoptosis when excess DNA damage is present leads to an increase in errors of replication and repair in surviving cells, and thus an increase in mutation. NER of UV-induced cyclobutane pyrimidine dimers is attenuated in cells that overexpress Bcl-2 [260]. Two possible explanations were proposed for this effect: (a) Bcl-2 might block the nuclear trafficking needed for NER; or (b) the possible antioxidant function of Bcl-2 might attenuate NER. The increased mutation promoted by Bcl-2 overexpression could be due, in part, to the persistence of DNA damages, that would otherwise be repaired by NER, and inaccurate DNA synthesis past these damages in template DNA. The increase in mutation may contribute to cancer progression as evidenced by the findings that Bcl-2 is frequently overexpressed in colon, breast, and skin cancers [261–263]. In addition, for over 50% of non-Hodgkin's lymphoma cases, the *bcl-2* gene is markedly overexpressed due to a t(14;18)(q32;q21) translocation [264,265], which places *bcl-2* gene expression under control of the immunoglobulin enhancer [266].

9.3. Genes with a dual role in DNA repair and apoptosis

The genes encoding proteins which are listed in Table 1 have a dual role in DNA repair and apoptosis. Mutation, epigenetic silencing, or dysregulation of each of these genes could, in principle, lead to loss of both DNA repair capability and apoptosis capability. Loss of either of these capabilities would be expected to increase genomic instability and predispose to cancer. Therefore, it is not surprising that many of the genes encoding proteins listed in Table 1, when defective, strongly predispose to cancer (e.g. *BRCA1*, *ATM*, *WRN*, *BLM*, *p53*, *XPB*, *XPD*, *hMLH1*, *hPMS2*, *hMSH2*, *hMSH6*, see Table 2).

10. Conclusions

10.1. The switch from repair to apoptosis

A key unresolved issue is how a cell "determines" when DNA damage is "excessive" and how this determination triggers the shift from repair to apoptosis.

It seems plausible that proteins employed in recognition of DNA damage in order to initiate repair may also use this recognition capability to help trigger cell cycle arrest followed by apoptosis when damage is excessive. Altogether, about 130 genes have been identified in the human genome whose products are employed in DNA repair [73]. As described in detail in previous sections, a subset of DNA repair proteins appear to serve a triggering function for DNA repair initiation, cell cycle arrest and for apoptosis. These include ATM, ATR, BRCA1 (and perhaps BLM, WRN and NBS1) employed in HRR; DNA-PK employed in NHEJ; XPB, XPD, p53 and ING[ING1b] in NER; Ref-1/Ape and PARP employed in BER; MLH1, PMS2, MSH2 and MSH6 proteins in MMR.

ATM, a component of the BASC DNA damage sensing complex, plays a key role in activating multiple responses to DNA damage, particularly double-strand breaks. Through its kinase activity it phosphorylates BRCA1 and c-Abl to promote HRR, particularly of double-strand breaks. ATM also phosphorylates and thus activates p53, MDM2, hChk2 and JNK promoting cell cycle arrest. Thus, it appears that ATM promotes HRR, initiates the switch from HRR to cell cycle arrest, and by its action on E2F1 induces apoptosis. ATR may have a parallel role to ATM in response to a partially non-overlapping set of DNA damages. BRCA1, another component of the BASC DNA damage sensing complex, participates in HRR and induction of p53-independent apoptosis (Fig. 3). Other components of the BASC complex, BLM and NBS1 may also have a role in cell cycle arrest and/or induction of apoptosis. DNA-PK has a role in both NHEJ and in induction of p53 leading to growth cycle arrest and apoptosis.

The helicases XPB and XPD, and the p53 and p33[ING1b] proteins are needed for both NER and apoptosis in response to excess DNA damages. Ref-1 functions in BER as an AP endonuclease and also regulates the transactivation and pro-apoptotic functions of p53 in vivo. MMR gene products both act to repair DNA mispairs, and to signal apoptosis.

10.2. Short term consequences of DNA damage

1. The DNA of the human cell is subjected to high levels of damage, especially from endogenous reactive oxygen species. The average rate is estimated to be from about 10^4 damages per cell per day [267] to as high as 10^6 damages per cell per day [268]. For cells exposed to extrinsic genotoxic agents, this rate is much higher.
2. The initial reaction of the cell to incident damage is to employ DNA repair processes to remove the damage. Five major repair pathways in humans are HRR, NER, BER, MMR and NHEJ, each specialized for certain types of DNA damage.
3. When incident DNA damage overwhelms repair capabilities, some damages persist.
4. DNA damages that remain unrepaired can cause mutation when the cell replicates inaccurately past the altered bases in template DNA, or when the damage is repaired inaccurately (e.g. by NHEJ).
5. To avoid such errors, certain DNA-repair proteins (e.g. ATM, ATR, BRCA1, DNA-PK, Ref-1, PARP and MMR proteins) detect high levels of DNA damage and induce growth arrest (e.g. by activating p53) to allow time for further DNA repair. If this fails they induce apoptosis (for example, through the action of p53 on Bax, or through p53-independent pathways).
6. When a cell becomes committed to apoptosis, DNA repair is counter-productive and so repair enzymes are cleaved (e.g. ATM, Rad51, PARP-1 and DNA-PK$_{cs}$) or down-regulated (e.g. BRCA1, Ref-1). Since DNA repair is a very energy-consuming process, a dramatic drop in ATP due to repair can trigger necrosis, a mode of cell death that usually does not occur in vivo, since it elicits an inflammatory process. The cleavage of DNA repair enzymes, such as ATM [54,127], Rad51 [59], PARP-1 [60], and DNA-PK$_{cs}$ [56] may conserve a damaged cell's remaining energy to ensure that the physiologic process of cellular attrition, apoptosis, occurs [269].

One particular example of when damages are "excessive" for the repair capabilities available is when an individual gets a sunburn. Another example is when ingestion of high fat meals cause an increased release of bile acids into the intestinal tract. Physiological levels of total bile acids in the aqueous portion (the portion in contact with colonic epithelial cells) of the feces after a series of high fat meals can go up to 1960 μM [270]. It was shown by Booth et al.

[271] that 300 μM of the bile salts deoxycholate or lithocholate cause moderate to extensive levels, respectively, of DNA damage, measured by the comet assay, in HT29 cells. We showed [3] that treatment of normal colon epithelial cells, obtained in biopsies, with 1000 μM deoxycholate caused about 60% of the goblet cells within the biopsy to undergo apoptosis. Thus, for at least two tissues, the skin and the colonic epithelium, there are acute circumstances when cells receive DNA damages at levels in excess of the ability of cells to repair them. These two tissues, in particular, are susceptible to carcinogenesis.

However, in some in vitro studies, genotoxicity is observed (i.e. chromosome aberration, micronuclei) after the use of a DNA-damaging agent but no apoptotic cells are found. Although these observations apparently contradict the hypothesis that excessive DNA damage leads to apoptosis, these in vitro cell lines are usually transformed or neoplastic. Neoplastic cells have developed mechanisms to avoid apoptosis, such as failure to adequately form the apoptosome [272], up-regulation of anti-apoptotic transcription factors, e.g. NF-κB [205,273], up-regulation of anti-apoptotic molecules that protect against mitochondrial loss of cytochrome c, e.g. bcl-2 [248], or up-regulation of the inhibitors of apoptosis proteins (IAPs), which inhibit the downstream caspases [274], to name a few. Ultimately, non-apoptotic modes of cell death may result after genotoxic stress and failure of homeostasis.

10.3. Long term consequences of DNA damage in relation to cancer

Mutations arise in large part from inaccurate replication of a damaged template strand or inaccurate repair of damaged DNA. Although excessive rates of cell division were originally thought to be responsible for cancer, this concept alone does not explain why cancers of hematopoietic cells are not the most prevalent cancers, and why cancers of the colon are more frequent than those of the small intestine. Also, although basal cell carcinoma of the skin has a high mitotic rate, it has a very favorable prognosis and rarely metastasizes. In addition, follicular lymphoma cells with a mitotic rate less than that of a reactive germinal center progress to high-grade lymphoma whereas a reactive germinal center does not. These conundrums can be explained by taking into consideration the basal rate of apoptosis and the mutation–induction capabilities of environmental toxins and dietary factors.

Deleterious mutations in genes encoding proteins employed in DNA repair and/or apoptosis (e.g. *p53* and *hChk2*, Li–Fraumini syndrome) increase genomic instability. Genomic instability increases the occurrence of new mutations including those affecting oncogenes and tumor suppressor genes. Genomic instability appears to be the engine of both tumor progression and tumor heterogeneity [92]. Mutations affecting oncogenes or tumor suppressor genes ordinarily convey growth advantages leading to selective proliferation of cells harboring them. Such cell lineages may progress to malignancy. During progression to malignancy and tumor cell invasion, cells with new mutations that promote survival and proliferative vigor are selected. Thus, there may be a constitutive increase in the levels of some pro-survival proteins, such as phosphatidyl inositol 3′-kinase (PI3-K) [275] and NF-κB [276], and DNA repair enzymes such as Ref-1 [199] and MGMT [228], in progression to cancer.

Acknowledgements

References

[1] C.M. Payne, H. Bernstein, C. Bernstein, H. Garewal, Role of apoptosis in biology and pathology: resistance to apoptosis in colon carcinogenesis, Ultrastruct. Pathol. 19 (1995) 221–248.

[2] H. Garewal, H. Bernstein, C. Bernstein, R. Sampliner, C.M. Payne, Reduced bile acid-induced apoptosis in normal colorectal mucosa: a potential biological marker for cancer risk, Cancer Res. 56 (1996) 1480–1483.

[3] C. Bernstein, H. Bernstein, H. Garewal, P. Dinning, R. Jabi, R. Sampliner, M.K. McCuskey, M. Panda, D. Roe, L. L'Heureux, C.M. Payne, A bile acid-induced apoptosis assay for colon cancer risk and associated quality control studies, Cancer Res. 59 (1999) 2353–2357.

[4] N. Katada, R.A. Hinder, T.C. Smyrk, N. Hirabayashi, G. Perdikis, R.J. Lund, T. Woodward, P.J. Klinger, Apoptosis

is inhibited early in the dysplasia-carcinoma sequence of Barrett esophagus, Arch. Surg. 132 (1997) 728–733.

[5] C.E. Whittles, L.R. Biddlestone, A. Burton, H. Barr, J.A. Jankowski, P.J. Warner, N.A. Shepherd, Apoptotic and proliferative activity in the neoplastic progression of Barrett's oesophagus: a comparative study, J. Pathol. 187 (1999) 535–540.

[6] L. Mullauer, P. Gruber, D. Sebinger, J. Buch, S. Wohlfart, A. Chott, Mutations in apoptosis genes: a pathogenetic factor for human disease, Mutat. Res. 488 (2001) 211–231.

[7] A. Levine, p53, the cellular gatekeeper for growth and division, Cell 88 (1997) 323–331.

[8] B. Antonsson, F. Conti, A. Ciavatta, S. Montessuit, S. Lewis, I. Martinou, L. Bernasconi, A. Bernard, J.-J. Mermod, G. Mazzei, K. Maundrell, F. Gambale, R. Sadoul, J.-C. Martinou, Inhibition of Bax channel-forming activity by Bcl-2, Science 277 (1997) 370–372.

[9] C. Cherbonnel-Lasserre, S. Gauny, A. Kronenberg, Suppression of apoptosis by Bcl-2 or Bcl-x_L promotes susceptibility to mutagenesis, Oncogene 13 (1996) 1489–1497.

[10] G.T. Williams, M.R. Critchlow, V.L. Hedge, K.B. O'Hare, Molecular failure of apoptosis: inappropriate cell survival and mutagenesis, Toxicol. Lett. 102/103 (1998) 485–489.

[11] M.-L. Kuo, S.-G. Shiah, C.-J. Wang, S.-E. Chuang, Suppression of apoptosis by Bcl-2 to enhance benzene metabolites-induced oxidative DNA damage and mutagenesis: a possible mechanism of carcinogenesis, Mol. Pharmacol. 55 (1999) 894–901.

[12] C. Lengauer, K.W. Kinzler, B. Vogelstein, Genetic instabilities in human cancers, Nature 396 (1998) 643–649.

[13] J. Searle, J.F.R. Kerr, C.J. Bishop, Necrosis and apoptosis: distinct modes of cell death with fundamentally different significance, Pathol. Annu. 17 (1982) 229–259.

[14] C.M. Payne, C. Bernstein, H. Bernstein, Apoptosis overview emphasizing the role of oxidative stress, DNA damage and signal-transduction pathways, Leuk. Lymphoma 19 (1995) 43–93.

[15] M. Leist, P. Nicotera, The shape of cell death, Biochem. Biophys. Res. Commun. 236 (1997) 1–9.

[16] J.F.R. Kerr, J. Searle, B.V. Harmon, C.J. Bishop, Apoptosis, in: C.S. Potten (Ed.), Perspectives on Mammalian Cell Death, Oxford University Press, New York, 1987, pp. 93–128.

[17] J.J. Lemasters, A.L. Nieminen, T. Qian, L.C. Trost, B. Herman, The mitochondrial permeability transition in toxic, hypoxic and reperfusion injury, Mol. Cell Biochem. 174 (1997) 159–165.

[18] Y. Eguchi, S. Shimizu, Y. Tsujimoto, Intracellular ATP levels determine cell death fate by apoptosis or necrosis, Cancer Res. 57 (1997) 1835–1840.

[19] M. Leist, B. Single, A.F. Castoldi, S. Kuhnle, P. Nicotera, Intracellular adenosine triphosphate (ATP) concentration: a switch in the decision between apoptosis and necrosis, J. Exp. Med. 185 (1997) 1481–1486.

[20] H.C. Ha, S.H. Snyder, Poly(ADP-ribose) polymerase is a mediator of necrotic cell death by ATP depletion, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 13978–13982.

[21] J.L. Sims, S.J. Berger, N.A. Berger, Poly(ADP-ribose) polymerase inhibitors preserve nicotinamide adenine dinucleotide and adenosine 5′-triphosphate pools in DNA-damaged cells: mechanism of stimulation of unscheduled DNA synthesis, Biochemistry 22 (1983) 5188–5194.

[22] S.K. Das, N.A. Berger, Alterations in deoxynucleoside triphosphate metabolism in DNA damaged cells: identification and consequences of poly(ADP-ribose) polymerase dependent and independent processes, Biochem. Biophys. Res. Commun. 137 (1986) 1153–1158.

[23] M.M. Cox, Relating biochemistry to biology: how the recombinational repair function of RecA protein is manifested in its molecular properties, Bioessays 15 (1993) 617–623.

[24] J. Radons, B. Heller, A. Burkle, B. Hartmann, M.L. Rodriguez, K.D. Kroncke, V. Burkart, H. Kolb, Nitric oxide toxicity in islet cells involves poly(ADP-ribose) polymerase activation and concomitant NAD^+ depletion, Biochem. Biophys. Res. Commun. 199 (1994) 1270–1277.

[25] A.I. Roca, M.M. Cox, RecA protein: structure, function, and role in recombinational DNA repair, Prog. Nucl. Acid Res. Mol. Biol. 56 (1997) 129–223.

[26] Y. Habraken, P. Sung, L. Prakash, S. Prakash, ATP-dependent assembly of a ternary complex consisting of a DNA mismatch and the yeast MSH2–MSH6 and MLH1–PMS1 protein complexes, J. Biol. Chem. 273 (1998) 9837–9841.

[27] F. Brockhaus, B. Brune, p53 accumulation in apoptotic macrophages is an energy demanding process that precedes cytochrome c release in response to nitric oxide, Oncogene 18 (1999) 6403–6410.

[28] T.T. Paull, M. Gellert, M, Nbs1 potentiates ATP-driven DNA unwinding and endonuclease cleavage by the Mre11/Rad50 complex, Genes Dev. 13 (1999) 1276–1288.

[29] J.P. Braybrooke, K.G. Spink, J. Thacker, I.D. Hickson, The RAD51 family member, RAD51L3, is a DNA-stimulated ATPase that forms a complex with XRCC2, J. Biol. Chem. 275 (2000) 29100–29106.

[30] E. Citterio, V. Van Den Boom, G. Schnitzler, R. Kanaar, E. Bonte, R.E. Kingston, J.H. Hoeijmakers, W. Vermeulen, ATP-dependent chromatin remodeling by the Cockayne syndrome B DNA repair-transcription-coupling factor, Mol. Cell. Biol. 20 (2000) 7643–7653.

[31] K.P. Hopfner, A. Karcher, D.S. Shin, L. Craig, L.M. Arthur, J.P. Carney, J.A. Tainer, Structural biology of Rad50 ATPase: ATP-driven conformational control in DNA double-strand break repair and the ABC-ATPase superfamily, Cell 101 (2000) 789–800.

[32] S.L. Oei, M. Ziegler, ATP for the DNA ligation step in base excision repair is generated from poly(ADP-ribose), J. Biol. Chem. 275 (2000) 23234–23239.

[33] L.J. Blackwell, K.P. Bjornson, D.J. Allen, P. Modrich, Distinct MutS DNA-binding modes that are differentially modulated by ATP binding and hydrolysis, J. Biol. Chem. 276 (2001) 34339–34347.

[34] S. Burma, B.P. Chen, M. Murphy, A. Kurimasa, D.J. Chen, ATM phosphorylates histone H2AX in response to DNA double-strand breaks, J. Biol. Chem. 276 (2001) 42462–42467.

[35] R. Kato, M. Kataoka, H. Kamikubo, S. Kuramitsu, Direct observation of three conformations of MutS protein regulated by adenine nucleotides, J. Mol. Biol. 309 (2001) 227–238.

[36] X. Liu, C.N. Kim, J. Yang, R. Jemmerson, X. Wang, Induction of apoptotic program in cell-free extracts: requirement for dATP and cytochrome c, Cell 86 (1996) 147–157.

[37] P. Li, D. Nijhawan, I. Budihardjo, S.M. Srinivasula, M. Ahmad, E.S. Alnemri, X. Wang, Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade, Cell 91 (1997) 479–489.

[38] L.M. Leoni, Q. Chao, H.B. Cottam, D. Genini, M. Rosenbach, C.J. Carrera, I. Budihardjo, X. Wang, D.A. Carson, Induction of an apoptotic program in cell-free extracts by 2-chloro-2′-deoxyadenosine 5′-triphosphate and cytochrome c, Proc. Natl. Acad. Sci. U.S.A. 95 (1998) 9567–9571.

[39] D. Ferrari, A. Stepczynska, M. Los, S. Wesselborg, K. Schulze-Osthoff, Differential regulation and ATP requirement for caspase-8 and caspase-3 activation during CD95- and anticancer drug-induced apoptosis, J. Exp. Med. 188 (1998) 979–984.

[40] P. Nicotera, M. Leist, E. Fava, L. Berliocchi, C. Volbracht, Energy requirement for caspase activation and neuronal cell death, Brain Pathol. 10 (2000) 276–282.

[41] E. Carafoli, Intracellular calcium homeostasis, Annu. Rev. Biochem. 56 (1987) 395–433.

[42] C.D. Bortner, F.M. Hughes Jr., J.A. Cidlowski, A primary role for K$^+$ and Na$^+$ efflux in the activation of apoptosis, J. Biol. Chem. 272 (1997) 32436–32442.

[43] J.C. Martinou, D.R. Green, Review: breaking the mitochondrial barrier, Nat. Rev. Mol. Cell. Biol. 2 (2001) 63–67.

[44] A.M. Chinnaiyan, The apoptosome: heart and soul of the cell death machine, Neoplasia 1 (1999) 5–15.

[45] H. Zou, Y. Li, X. Liu, X. Wang, An APAF-1 cytochrome c multimeric complex is a functional apoptosome that activates procaspase-9, J. Biol. Chem. 274 (1999) 11549–11556.

[46] S. Desagher, J.C. Martinou, Mitochondria as the central control point of apoptosis, Trends Cell Biol. 10 (2000) 369–377.

[47] N.D. Marchenko, A. Zaika, U.M. Moll, Death signal-induced localization of p53 protein to mitochondria. A potential role in apoptotic signaling, J. Biol. Chem. 275 (2000) 16202–16212.

[48] C. Adrain, S.J. Martin, The mitochondrial apoptosome: a killer unleashed by the cytochrome seas, Trends Biochem. Sci. 26 (2001) 390–397.

[49] S.H. Kaufmann, M.O. Hengartner, Programmed cell death: alive and well in the new millennium, Trends Cell Biol. 11 (2001) 526–534.

[50] S.M. Srinivasula, M. Ahmad, T. Fernandes-Alnemri, E.S. Alnemri, Autoactivation of procaspase-9 by Apaf-1-mediated oligomerization, Mol. Cell 1 (1998) 949–957.

[51] E.A. Slee, C. Adrain, S.J. Martin, Executioner caspase-3, -6, and -7 perform distinct, non-redundant roles during the demolition phase of apoptosis, J. Biol. Chem. 276 (2001) 7320–7326.

[52] G.J. Thompson, C. Langlais, K. Cain, E.C. Conley, G.M. Cohen, Elevated extracellular [K$^+$] inhibits death-receptor- and chemical-mediated apoptosis prior to caspase activation and cytochrome c release, Biochem. J. 357 (2001) 137–145.

[53] K. Cain, C. Langlais, X.M. Sun, D.G. Brown, G.M. Cohen, Physiological concentrations of K$^+$ inhibit cytochrome c-dependent formation of the apoptosome, J. Biol. Chem. 276 (2001) 41985–41990.

[54] X. Tong, B. Liu, Y. Dong, Z. Sun, Cleavage of ATM during radiation-induced apoptosis: caspase-3-like apoptotic protease as a candidate, Int. J. Radiat. Biol. 76 (2000) 1387–1395.

[55] A. Hotti, K. Jarvinen, P. Siivola, E. Holtta, Caspases and mitochondria in c-Myc-induced apoptosis: identification of ATM as a new target of caspases, Oncogene 19 (2000) 2354–2362.

[56] Q. Song, S.P. Lees-Miller, S. Kumar, Z. Zhang, D.W. Chan, G.C. Smith, S.P. Jackson, E.S. Alnemri, G. Litwack, K.K. Khanna, M.F. Lavin, DNA-dependent protein kinase catalytic subunit: a target for an ICE-like protease in apoptosis, EMBO J. 15 (1996) 3238–3246.

[57] J. Flygare, R.C. Armstrong, A. Wennborg, S. Orsan, D. Hellgren, Proteolytic cleavage of HsRad51 during apoptosis, FEBS Lett. 8 (1998) 247–251.

[58] Y. Huang, S. Nakada, T. Ishiko, T. Utsugisawa, R. Datta, S. Kharbanda, K. Yoshida, R.V. Talanian, R. Weichselbaum, D. Kufe, Z.-M. Yuan, Role for caspase-mediated cleavage of Rad51 in induction of apoptosis by DNA damage, Mol. Cell. Biol. 19 (1999) 2986–2997.

[59] J. Flygare, D. Hellgren, A. Wennborg, Caspase-3 mediated cleavage of HsRad51 at an unconventional site, Eur. J. Biochem. 267 (2000) 5977–5982.

[60] S.H. Kaufmann, S. Desnoyers, Y. Ottaviano, N.E. Davidson, G.G. Poirier, Specific proteolytic cleavage of poly(ADP-ribose) polymerase—an early marker of chemotherapy-induced apoptosis, Cancer Res. 53 (1993) 3976–3985.

[61] Z. Herceg, Z.Q. Wang, Failure of poly(ADP-ribose) polymerase cleavage by caspases leads to induction of necrosis and enhanced apoptosis, Mol. Cell. Biol. 19 (1999) 5124–5133.

[62] X. Li, Z. Darzynkiewicz, Cleavage of poly(ADP-ribose) polymerase measured in situ in individual cells: relationship to DNA fragmentation and cell cycle position during apoptosis, Exp. Cell Res. 255 (2000) 125–132.

[63] K.A. O'Brien, D.E. Muscarella, S.E. Bloom, Differential induction of apoptosis and MAP kinase signaling by mitochondrial toxicants in drug-sensitive compared to drug-resistant B-lineage lymphoid cell lines, Toxicol. Appl. Pharmacol. 174 (2001) 245–256.

[64] M. Schuler, D.R. Green, Mechanisms of p53-dependent apoptosis, Biochem. Soc. Trans. 29 (2001) 684–688.

[65] B.M. Polster, K.W. Kinnally, G. Fiskum, Bh3 death domain peptide induces cell type-selective mitochondrial outer membrane permeability, J. Biol. Chem. 276 (2001) 37887–37894.

[66] A.I. Robles, N.A. Bemmels, A.B. Foraker, C.C. Harris, APAF-1 is a transcriptional target of p53 in DNA damage-induced apoptosis, Cancer Res. 61 (2001) 6660–6664.

[67] K. Kannan, N. Kaminski, G. Rechavi, J. Jakob-Hirsch, N. Amariglio, D. Givol, DNA microarray analysis of genes involved in p53 mediated apoptosis: activation of Apaf-1, Oncogene 20 (2001) 3449–3455.

[68] C.L. Crowley, C.M. Payne, H. Bernstein, C. Bernstein, D. Roe, The NAD$^+$ precursors, nicotinic acid and nicotinamide protect cells against apoptosis induced by a multiple stress inducer, deoxycholate, Cell Death Diff. 7 (2000) 314–326.

[69] C.M. Simbulan-Rosenthal, D.S. Rosenthal, R. Luo, M.E. Smulson, Poly(ADP-ribosyl)ation of p53 during apoptosis in human osteosarcoma cells, Cancer Res. 59 (1999) 2190–2194.

[70] D. D'Amours, F.R. Sallmann, V.M. Dixit, G.G. Poirier, Gain-of-function of poly(ADP-ribose) polymerase-1 upon cleavage by apoptotic proteases: implications for apoptosis, J. Cell Sci. 114 (2001) 3771–3778.

[71] S.J. Korsmeyer, Bcl-2 initiates a new category of oncogenes: regulators of cell death, Blood 80 (1992) 879–886.

[72] C. Bernstein, H. Bernstein, C.M. Payne, H. Garewal, Field defects in progression to adenocarcinoma of the colon and esophagus, Electronic J. Biotechnol. 3 (3) (2000) 1–17 (Available on the Web: http//www.ejb.org/content/vol13/issue3/full/1).

[73] R.D. Wood, M. Mitchell, J. Sgouros, T. Lindahl, Human DNA repair genes, Science 291 (2001) 1284–1289.

[74] Y. Wang, D. Cortez, P. Yazdi, N. Neff, S.J. Elledge, J. Qin, BASC, a super complex of BRCA1-associated proteins involved in the recognition and repair of aberrant DNA structures, Genes Dev. 14 (2000) 927–939.

[75] M.A. Brenneman, BRCA1 and BRCA2 in DNA repair and genome stability, in: J.A. Nickoloff, M.F. Hoekstra (Eds.), DNA Damage and Repair, Advances from Phage to Humans, Vol. 3, Humana Press, Totowa, NJ, 2001, pp. 237–267.

[76] J.J. Chen, D. Silver, S. Cantor, D.M. Livingston, R. Scully, BRCA1, BRCA2 and RAD51 operate in a common DNA damage response pathway, Cancer Res. 59 (1999) 1752s–1756s.

[77] A. Husain, G. He, E.S. Venkatraman, D.R. Spriggs, BRCA1 upregulation is associated with repair-mediated resistance to *cis*-diamminedichloroplatinum (II), Cancer Res. 58 (1998) 1120–1123.

[78] M.E. Moynahan, J.W. Chiu, B.H. Koller, M. Jasin, BRCA1 controls homology-directed DNA repair, Mol. Cell 4 (1999) 511–518.

[79] M.E. Moynahan, T.Y. Cui, M. Jasin, Homology-directed DNA repair, mitomycin-C resistance, and chromosome stability is restored with correction of a *Brca1* mutation, Cancer Res. 61 (2001) 4842–4850.

[80] T. Ouchi, A.N.A. Monteiro, A. August, S.A. Aaronson, H. Hanafusa, BRCA1 regulates p53-dependent gene expression, Proc. Natl. Acad. Sci. U.S.A. 95 (1998) 2302–2306.

[81] S. Jin, H. Zhao, F. Fan, P. Blanck, W. Fan, A.B. Colchagie, A.J. Fornace Jr., Q. Zhan, BRCA1 activation of the GADD45 promoter, Oncogene 19 (2000) 4050–4057.

[82] X.W. Wang, Q. Zhan, J.D. Coursen, M.A. Khan, H.U. Kontny, L. Yu, M.C. Hollander, P.M. O'Connor, A.J. Fornace Jr., C.C. Harris, GADD45 induction of a G2/M cell cycle checkpoint, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 3706–3711.

[83] P. Arizti, L. Fang, I. Park, Y. Yin, E. Solomon, T. Ouchi, S.A. Aaronson, S.W. Lee, Tumor suppressor p53 is required to modulate BRCA1 expression, Mol. Cell. Biol. 20 (2000) 7450–7459.

[84] T.K. MacLachlan, B.C. Dash, D.T. Dicker, W.S. El-Deiry, Repression of BRCA1 through a feedback loop involving p53, J. Biol. Chem. 275 (2000) 31869–31875.

[85] D.P. Harkin, J.M. Bean, D. Miklos, Y.-H. Song, V.B. Truong, C. Englert, F.C. Christians, L.W. Ellisen, S. Maheswaran, J.D. Oliner, D.A. Haber, Induction of GADD45 and JNK/SAPK-dependent apoptosis following inducible expression of BRCA1, Cell 97 (1999) 575–586.

[86] M. Thangaraju, S.H. Kaufmann, F.J. Couch, BRCA1 facilitates stress-induced apoptosis in breast and ovarian cancer lines, J. Biol. Chem. 275 (2000) 33487–33496.

[87] A.J. Alberg, K.J. Helzlsouer, Epidemiology prevention, and early detection of breast cancer, Curr. Opin. Oncol. 9 (1997) 505–511.

[88] E. Garcia-Patino, B. Gomendio, M. Lleonart, J.M. Silva, J.M. Garcia, M. Provencio, R. Cubedo, P. Espana, S. Ramon y Cajal, F. Bonilla, Loss of heterozygosity in the region including the BRCA1 gene on 17q in colon cancer, Cancer Genet. Cytogenet. 104 (1998) 119–123.

[89] L. Drucker, R. Stackievitz, B. Shpitz, S. Yarkoni, Incidence of BRCA1 and BRCA2 mutations in Ashkenazi colorectal cancer patients: preliminary study, Anticancer Res. 29 (2000) 559–562.

[90] C.A. Wilson, L. Ramos, M.R. Villasenor, K.H. Anders, M.F. Press, K. Clarke, B. Karlan, J.J. Chen, R. Scully, D. Livingston, R.H. Zuch, M.H. Kanter, S. Cohen, F.J. Calzone, D.J. Slamon, Localization of human BRCA1 and its loss in high-grade, non-inherited breast carcinomas, Nat. Genet. 21 (1999) 236–240.

[91] A. Catteau, W.H. Harris, C.-F. Xu, E. Solomon, Methylation of the BRCA1 promoter region in sporadic breast and ovarian cancer: correlation with disease characteristics, Oncogene 18 (1999) 1957–1965.

[92] C.Y. Shen, J.C. Yu, Y.L. Lo, C.H. Kuo, C.T. Yue, Y.S. Jou, C.S. Huang, J.C. Lung, C.W. Wu, Genome-wide search for loss of heterozygosity using laser capture microdissected tissue of breast carcinoma: an implication for mutator phenotype and breast cancer pathogenesis, Cancer Res. 60 (2000) 3884–3892.

[93] X. Xu, Z. Weaver, S.P. Linke, C. Li, J. Gotay, X.-W. Wang, C.C. Harris, T. Ried, C.-X. Deng, Centrosome amplification and a defective G2-M cell cycle checkpoint induce genetic instability in BRCA1 exon 11 isoform-deficient cells, Mol. Cell 3 (1999) 389–395.

[94] C.X. Deng, F. Scott, Role of the tumor suppressor gene Brca1 in genetic stability and mammary gland tumor formation, Oncogene 19 (2000) 1059–1064.

[95] M. Kraakman-van der Zwet, W.J.I. Overkamp, R.E.E. van Lange, J. Essers, A. van Duijn-Goedhar, I. Wiggers, S. Swaminathan, P.P.W. van Buul, A. Errami, R.T.L. Tan, N.G.J. Jaspers, S.K. Sharan, R. Kanaar, M.Z. Zdzienicka,

Brca2 (XRCC11) deficiency results in radioresistant DNA synthesis and a higher frequency of spontaneous deletions, Mol. Cell. Biol. 22 (2002) 669–679.

[96] P.L. Welcsh, K.N. Owns, M.-C. King, Insights into the functions of BRCA1 and BRCA2, TIG 16 (2000) 69–74.

[97] L.Y. Marmorstein, T. Ouchi, S.A. Aaronson, The BRCA2 gene product functionally interacts with p53 and RAD51, Proc. Natl. Acad. Sci. U.S.A. 95 (1998) 13869–13874.

[98] F. Xia, D.G. Taghian, J.S. DeFrank, Z.-C. Zeng, H. Willers, G. Itiakis, S.N. Powell, Deficiency of human BRCA2 leads to impaired homologous recombination but maintains normal nonhomologous end joining, Proc. Natl. Acad. Sci. U.S.A. 98 (2001) 8644–8649.

[99] K.K. Khanna, Cancer risk and the ATM gene: a continuing debate, J. Natl. Cancer Inst. 92 (2000) 795–802.

[100] J. Thacker, Cellular radiosensitivity in ataxia-telangiectasia, Int. J. Radiat. Biol. 66 (1994) S87–S96.

[101] R.T. Johnson, E. Gotoh, A.M. Mullinger, A.J. Ryan, Y. Shiloh, Y. Ziv, S. Squires, Targeting double-strand breaks to replicating DNA identifies a subpathway of double-strand break repair that is defective in ataxia-teleangiectasia cells, Biochem. Biophys. Res. Commun. 261 (1999) 317–325.

[102] G. Chen, S.S. Yuan, W. Liu, Y. Xu, K. Trujillo, B. Song, F. Cong, S.P. Goff, Y. Wu, R. Arlinghaus, D. Baltimore, P.J. Gasser, M.S. Park, P. Sung, E.Y.-H.P. Lee, Radiation-induced assembly of Rad51 and Rad52 recombination complex requires ATM and c-Abl, J. Biol. Chem. 274 (1999) 12748–12752.

[103] Y. Shaul, c-Abl: activation and nuclear targets, Cell Death Diff. 7 (2000) 10–16;
N. Takao, R. Mori, H. Kato, A. Shinohara, K. Yamamoto, c-Abl tyrosine kinase is not essential for ataxia telangiectasia mutated functions in chromosomal maintenance, J. Biol. Chem. 275 (2000) 725–728.

[104] R. Baskaran, L.D. Wood, L.L. Whitaker, C.E. Canman, S.E. Morgan, Y. Xu, C. Barlow, D. Baltimore, A. WynshawBoris, M.B. Kastan, J.Y.J. Wang, Ataxia telangiectasia mutant protein activates c-Abl tyrosine kinase in response to ionizing radiation, Nature 387 (1997) 516–519.

[105] Y. Shiloh, ATM and ATR: networking cellular responses to DNA damage, Curr. Opin. Genet. Dev. 11 (2001) 71–77.

[106] A.R. Venkitaraman, Breast cancer genes and DNA repair, Science 286 (1999) 1100–1102.

[107] D. Cortez, Y. Wang, J. Qin, S.J. Elledge, Requirement of ATM-dependent phosphorylation of Brca1 in the DNA damage response to double-strand breaks, Science 286 (1999) 1162–1166.

[108] M. Gatei, B.B. Zhou, K. Hobson, S. Scott, D. Young, K.K. Khanna, Ataxia telangiectasia mutated (ATM) kinase and ATM and Rad3 related kinase mediate phosphorylation of Brca1 at distinct and overlapping sites. In vivo assessment using phospho-specific antibodies, J. Biol. Chem. 18 (2001) 17276–17280.

[109] S. Li, N.S. Ting, L. Zheng, P.L. Chen, Y. Ziv, Y. Shiloh, E.Y. Lee, W.H. Lee, Functional link of BRCA1 and ataxia telangiectasia gene product in DNA damage response, Nature 406 (2000) 210–215.

[110] S. Banin, L. Moyal, S.-Y. Shieh, Y. Taya, C.W. Anderson, L. Chessa, N.I. Smorodinsky, C. Prives, Y. Reiss, Y. Shiloh, Y. Ziv, Enhanced phosphorylation of p53 by ATM in response to DNA damage, Science 281 (1998) 1674–1677.

[111] C.E. Canman, D.-S. Lim, K.A. Cimprich, Y. Taya, K. Tamai, K. Sakaguchi, E. Apella, M.B. Kavtan, J.D. Siliciano, Activation of the ATM kinase by ionizing radiation and phosphorylation of p53, Science 281 (1998) 1677–1679.

[112] N. Dumaz, D.W. Meek, Serine 15 phosphorylation stimulates p53 transactivation but does not directly influence interaction with MDM2, EMBO J. 18 (1999) 7002–7010.

[113] K. Sakaguchi, J.E. Herrera, S. Saito, T. Miki, M. Bustin, A. Vassilev, C.W. Anderson, E. Appella, DNA damage activates p53 through a phosphorylation–acetylation cascade, Genes Dev. 12 (1998) 2831–2841.

[114] Y. Zhang, Y. Xiong, A p53 amino-terminal nuclear export signal inhibited by DNA damage-induced phosphorylation, Science 292 (2001) 1910–1915.

[115] R. Khosravi, R. Maya, T. Gottlieb, M. Oren, Y. Shiloh, D. Shkedy, Rapid ATM-dependent phosphorylation of MDM2 precedes p53 accumulation in response to DNA damage, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 14973–14977.

[116] M. Ljungman, Dial 9-1-1 for p53: mechanisms of p53 activation by cellular stress, Neoplasia 2 (2000) 208–225.

[117] S. Matsuoka, M. Huang, S.J. Elledge, Linkage of ATM to cell cycle regulation by the Chk2 protein kinase, Science 282 (1998) 1893–1897.

[118] A. Hirao, Y.Y. Kong, S. Matsuoka, A. Wakeham, J. Ruland, H. Yoshida, D. Liu, S.J. Elledge, T.W. Mak, DNA damage-induced activation of p53 by the checkpoint kinase Chk2, Science 287 (2000) 1824–1827.

[119] G. Buscemi, C. Savio, L. Zannini, F. Micciche, D. Masuada, M. Nakanishi, H. Tauchi, K. Komatsu, S. Mizutani, K.K. Khanna, P. Chen, P. Concannon, L. Chessa, D. Delia, Chk2 activation dependence on Nbs1 after DNA damage, Mol. Cell. Biol. 21 (2001) 5214–5222.

[120] Y. Xu, D. Baltimore, Dual roles of ATM in the cellular response to radiation and in cell growth, Genes Dev. 10 (1996) 2401–2410.

[121] A. Bhandoola, B. Dolnick, N. Fayad, A. Nussenzweig, A. Singer, Immature thymocytes undergoing receptor rearrangements are resistant to an ATM-dependent death pathway activated in mature T cells by double-stranded DNA breaks, J. Exp. Med. 192 (2000) 891–897.

[122] W.-C. Lin, F.-T. Lin, J.R. Nevins, Selective induction of E2F1 in response to DNA damage, mediated by ATM-dependent phosphorylation, Genes Dev. 15 (2001) 1833–1844.

[123] N.A. Lissy, P.K. Davis, M. Irwin, W.G. Kaelin, S.F. Dowdy, A common E2F-1 and p73 pathway mediates cell death induced by TCR activation, Nature 407 (2000) 642–645.

[124] M. Irwin, M.C. Marin, A.C. Phillips, R.S. Seelan, D.I. Smith, W. Liu, E.R. Flores, K.Y. Tsal, T. Jacks, K.H. Vousden, W.G. Kaelin, Role for the p53 homologue p73 in E2F-1-induced apoptosis, Nature 407 (2000) 645–648.

[125] Y. Lee, P.J. McKinnon, ATM dependent apoptosis in the nervous system, Apoptosis 5 (2000) 523–529.

[126] M.J. Chong, M.R. Murray, E.C. Gosink, H.R. Russell, A. Srinivasan, M. Kapsetaki, S.J. Korsmeyer, P.J. McKinnon, ATM and Bax cooperate in ionizing radiation-induced apoptosis in the central nervous system, Proc. Natl. Acad. Sci. U.S.A. 97 (2000) 889–894.

[127] G.C.M. Smith, F. d'Adda di' Fagigna, N.D. Lakin, S.P. Jackson, Cleavage and inactivation of ATM during apoptosis, Mol. Cell. Biol. 19 (1999) 6076–6084.

[128] Y. Ejima, L. Yang, M.S. Sasaki, Aberrant splicing of the ATM gene associated with shortening of the intronic mononucleotide tract in human colon tumor cell lines: a novel mutation target of microsatellite instability, Int. J. Cancer 86 (2000) 262–268.

[129] E.J. Brown, D. Baltimore, ATR disruption leads to chromosomal fragmentation and early embryonic lethality, Genes Dev. 14 (2000) 397–402.

[130] S.T. Shieh, J. Ahn, K. Tamai, Y. Taya, C. Prives, The human homologs of checkpoint kinases Chk1 and Cds1 (Chk2) phosphorylate p53 at multiple DNA damage-inducible sites, Genes Dev. 14 (2000) 289–300.

[131] H. Zhao, H. Piwnica-Worms, ATR-mediated checkpoint pathways regulate phosphorylation and activation of human Chk1, Mol. Cell. Biol. 21 (2001) 4129–4139.

[132] Z.-M. Yuan, Y. Huang, T. Ishiko, S. Nakada, T. Utsugisawa, S. Kharbanda, R. Wang, P. Sung, A. Shinohara, R. Weichselbaum, D. Kufe, Regulation of Rad51 function by c-Abl in response to DNA damage, J. Biol. Chem. 273 (1998) 3799–3802.

[133] N. Takao, R. Mori, H. Kato, A. Shinohara, K. Yamamoto, c-Abl tyrosine kinase is not essential for ataxia telangiectasia mutated functions in chromosomal maintenance, J. Biol. Chem. 275 (2000) 725–728.

[134] S. Kharbanda, P. Pandey, S.F. Jin, S. Inoue, A. Bharti, Z.-M. Yuan, R. Weichselbaum, D. Weaver, D. Kufe, Functional interaction between DNA-PK and c-Abl in response to DNA damage, Nature 386 (1997) 732–735.

[135] R.V. Sionov, S. Coen, Z. Goldberg, M. Berger, B. Bercovich, Y. Ben-Neriah, A. Ciechanover, Y. Haupt, c-Abl regulates p53 levels under normal and stress conditions by preventing its nuclear export and ubiquitination, Mol. Cell. Biol. 21 (2001) 5869–5878.

[136] S.-T. Wen, P.K. Jackson, R.A. van Etten, The cytostatic function of c-Abl is controlled by multiple nuclear localization signals and requires the *p53* and *Rb* tumor suppressor gene products, EMBO J. 15 (1996) 1583–1595.

[137] R. Agami, G. Blandino, O. Oren, Y. Shaul, Interaction of c-Abl and p73α and their collaboration to induce apoptosis, Nature 399 (1999) 809–813.

[138] Z.-M. Yuan, H. Shioya, T. Ishiko, X. Sun, J. Gu, Y.Y. Huang, H. Lu, S. Kharbanda, R. Weichselbaum, D. Kufe, p73 is regulated by tyrosine kinase c-Abl in the apoptotic response to DNA damage, Nature 399 (1999) 814–817 (correction: Nature 400 (1999) 792).

[139] P. Mohaghegh, I.D. Hickson, DNA helicase deficiencies associated with cancer predisposition and premature aging disorders, Hum. Mol. Genet. 10 (2001) 741–746.

[140] S. Sakamoto, K. Nishikawa, S.J. Heo, M. Goto, Y. Furuichi, A. Shimamoto, Werner helicase relocates into nuclear foci in response to DNA damaging agents and co-localizes with RPA and Rad51, Genes Cell 6 (2001) 421–430.

[141] M. Poot, J.S. Yom, S.H. Whang, J.T. Kato, K.A. Gollahon, P.S. Rabinovitch, Werner syndrome cells are sensitive to DNA crosslinking drugs, FASEB J. 15 (2001) 1224–1226.

[142] E.A. Spillare, A.I. Robles, X.W. Wang, J.-C. Shen, C.-E. Yu, G.D. Schellenberg, C.C. Harris, p53-mediated apoptosis is attenuated in Werner syndrome cells, Genes Dev. 13 (1999) 1355–1360.

[143] X.W. Wang, A. Tseng, N.A. Ellis, E.A. Spillare, S.P. Linke, A.I. Robles, H. Seker, Q. Yang, P. Hu, S. Berenstan, N.A. Bemmels, S. Garfield, C.C. Harris, Functional interaction of p53 and BLM DNA helicase in apoptosis, J. Biol. Chem. 276 (2001) 32948–32955.

[144] G. Blander, J. Kipnis, J.F. Leal, C.E. Yu, G.D. Schellenberg, M. Oren, Physical and functional interaction between p53 and the Werner's syndrome protein, J. Biol. Chem. 274 (1999) 29463–29469.

[145] G. Blander, N. Zalle, J.F. Leal, R.L. Bar-Or, C.E. Yu, M. Oren, Werner syndrome protein contributes to induction of p53 by DNA damage, FASEB J. 14 (2000) 2138–2140.

[146] T. Ikura, V.V. Ogryzko, M. Grigoriev, R. Groisman, J. Wang, M. Horikoshi, R. Scully, J. Qin, Y. Nakatani, Involvement of the TIP60 histone acetylase complex in DNA repair and apoptosis, Cell 102 (2000) 463–473.

[147] S. Lee, L. Cavallo, J. Griffith, Human p53 binds Holliday junctions strongly and facilitates their cleavage, J. Biol. Chem. 272 (1997) 7532–7539.

[148] H.W. Sturzbecher, B. Donzelmann, W. Henning, U. Knippschild, S. Buchhop, p53 is linked directly to homologous recombination processes via RAD51/RecA protein interaction, EMBO J. 15 (1996) 1992–2002.

[149] T. Mummenbrauer, F. Janus, B. Muller, L. Wiesmuller, W. Deppert, F. Grosse, p53 exhibits 3′-to-5′ exonuclease activity, Cell 85 (1996) 1089–1099.

[150] P. Baumann, F.E. Benson, S.C. West, Human Rad51 protein promotes ATP-dependent homologous pairing and strand transfer reactions in vitro, Cell 87 (1996) 757–766.

[151] R.C. Gupta, L.R. Bazemore, E.I. Golub, C.M. Radding, Activities of human recombination protein Rad51, Proc. Natl. Acad. Sci. U.S.A. 94 (1997) 463–468.

[152] T. Taki, T. Ohnishi, A. Yamamoto, S. Hiraga, N. Arita, S. Izumoto, T. Hayakawa, T. Morita, Antisense inhibition of the RAD51 enhances radiosensivity, Biochem. Biophys. Res. Commun. 223 (1996) 434–438.

[153] D.S. Lim, P. Hasty, A mutation in mouse rad51 results in an early embryonic lethal that is suppressed by a mutation in p53, Mol. Cell. Biol. 16 (1996) 7133–7143.

[154] G. Chu, Double-strand break repair, J. Biol. Chem. 272 (1997) 24097–24100.

[155] C. Richardson, M. Jasin, Coupled homologous and nonhomologous repair of a double-strand break preserves genomic integrity in mammalian cell, Mol. Cell. Biol. 20 (2000) 9068–9075.

[156] P. Karran, DNA double strand break repair in mammalian cells, Curr. Opin. Genet. Dev. 10 (2000) 144–150.

[157] M. Takata, M.S. Sasaki, E. Sonoda, C. Morrison, M. Hashimoto, H. Utsumi, Y. Yamaguchi-Iwai, A. Shinohara,

S. Takeda, Homologous recombination and non-homologous end-joining pathways of DNA double-strand break repair have overlapping roles in the maintenance of chromosomal integrity in vertebrate cells, EMBO J. 17 (1998) 5497–5508.

[158] S.Y. Shieh, M. Ikeda, Y. Taya, C. Prives, DNA damage-induced phosphorylation of p53 alleviates inhibition by MDM2, Cell 91 (1997) 325–334.

[159] L.D. Mayo, J.J. Turchi, S.J. Berberich, Mdm-2 phosphorylation by DNA-dependent protein kinase prevents interaction with p53, Cancer Res. 57 (1997) 5013–5016.

[160] G. Achantha, H. Pelicano, L. Feng, W. Plunkett, P. Huang, Interaction of p53 and DNA-PK in response to nucleoside analogues: potential role as a sensor complex for DNA damage, Cancer Res. 61 (2001) 8723–8729.

[161] S. Wang, M. Guo, H. Ouyang, X. Li, C. Cardon-Cardo, A. Kurimasa, D.J. Chen, Z. Fuks, C.C. Ling, G.C. Li, The catalytic subunit of DNA-dependent protein kinase selectively regulates p53-dependent apoptosis but not cell cycle arrest, Proc. Natl. Acad. Sci. U.S.A. 97 (2000) 1584–1588.

[162] C. Jhappan, T.M. Yusufzai, S. Anderson, M.R. Anver, G. Merlino, The p53-response to DNA damage in vivo is independent of DNA-dependent protein kinase, Mol. Cell. Biol. 20 (2000) 4075–4083.

[163] G.S. Jimenez, F. Bryntesson, M.I. Torres-Arzayus, A. Priestly, M. Beeche, S. Saito, K. Sakaguchi, E. Appella, P.A. Jeggo, G.E. Taccioli, G.M. Wahl, M. Hubank, DNA-dependent protein kinase is not required for the p53-dependent response to DNA damage, Nature 400 (1999) 81–83.

[164] J. Lips, B. Kaina, DNA double-strand breaks trigger apoptosis in p53-deficient fibroblasts, Carcinogenesis 22 (2001) 579–585.

[165] T. Itoh, T. Horio, DNA-dependent protein kinase catalytic subunit is cleaved during UV-induced apoptosis, J. Dermatol. Sci. 25 (2001) 72–77.

[166] D. Gunz, M.T. Hess, H. Naegeli, Recognition of DNA adducts by human nucleotide excision repair, J. Biol. Chem. 271 (1996) 25089–25098.

[167] G.S. Winkler, W. Vermeulen, F. Coin, J.-M. Egly, J.H.J. Hoeijmakers, G. Weeda, Affinity purification of human DNA repair/transcription factor TFIIH using epitope-tagged xeroderma pigmentosum B protein, J. Biol. Chem. 273 (1998) 1092–1098.

[168] A.S. Balajee, V.A. Bohr, Genomic heterogeneity of nucleotide excision repair, Gene 250 (2000) 15–30.

[169] R.D. Wood, Nucleotide excision repair in mammalian cells, J. Biol. Chem. 272 (1997) 23465–23468.

[170] S.M. Patrick, J.J. Turchi, Stopped-flow kinetic analysis of replication protein A-binding DNA, J. Biol. Chem. 276 (2001) 22630–22637.

[171] B.J. Hwang, J.M. Ford, P.C. Hanawalt, G. Chu, Expression of the *p48* xeroderma pigmentosum gene is p53-dependent and is involved in global genomic repair, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 424–428.

[172] D.P. Batty, R.D. Wood, Damage recognition in nucleotide excision repair of DNA, Gene 241 (2000) 193–204.

[173] G. Li, V.C. Ho, p53-dependent DNA repair and apoptosis respond differently to high- and low-dose ultraviolet radiation, Br. J. Dermatol. 139 (1998) 3–10.

[174] F.J. Geske, A.C. Nelson, R. Lieberman, R. Strange, T. Sun, L.E. Gerschenson, DNA repair is activated in early stages of p53-induced apoptosis, Cell Death Diff. 7 (2000) 393–401.

[175] G. Li, V.C. Ho, D.L. Mitchell, M.J. Trotter, V.A. Tron, Differentiation-dependent p53 regulation of nucleotide excision repair in keratinocytes, Am. J. Pathol. 150 (1997) 1457–1464.

[176] V.C. Tron, M.J. Trotter, L. Tang, M. Krajewska, J.C. Reed, V.C. Ho, G. Li, p53-regulated apoptosis is differentiation dependent in ultraviolet B-irradiated mouse keratinocytes, Am. J. Pathol. 153 (1998) 579–585.

[177] A.R. Lehmann, The xeroderma pigmentosum group D (*XPD*) gene: one gene, two functions, three diseases, Genes Dev. 15 (2001) 15–23.

[178] G.S. Winkler, S.J. Araujo, U. Fiedler, W. Vermeulen, F. Coin, J.-M. Egly, J.H.J. Hoeijmakers, R.D. Wood, H.T.M. Timmers, G. Weeda, TFIIH with inactive XPD helicase functions in transcription initiation but is defective in DNA repair, J. Biol. Chem. 275 (2000) 4258–4266.

[179] X.W. Wang, W. Vermeulen, J.D. Coursen, M. Gibson, S.E. Lupold, K. Forrester, G. Xu, L. Elmore, H. Yeh, J.H.J. Hoeijmakers, C.C. Harris, The XPB and XPD DNA helicases are components of the p53-mediated apoptosis pathway, Genes Dev. 10 (1996) 1219–1232.

[180] A.I. Robles, X.W. Wang, C.C. Harris, Drug-induced apoptosis is delayed and reduced in XPD lymphoblastoid cell lines: possible role of TFIIH in p53-mediated apoptotic cell death, Oncogene 18 (1999) 4681–4688.

[181] D. Butkiewicz, M. Rusin, L. Enewold, P.G. Shields, M. Chorazy, C.C. Harris, Genetic polymorphisms in DNA repair genes and risk of lung cancer, Carcinogensis 22 (2001) 593–597.

[182] M. Dybdahl, U. Vogel, G. Frentz, H. Wallin, B.A. Nexo, Polymorphisms in the DNA repair gene *XPD*: correlations with risk and age at onset of basal cell carcinoma, Cancer Epidemiol. Biomarkers Prev. 8 (1999) 77–81.

[183] E.M. Sturgis, R. Zheng, L. Li, E.J. Castillo, S.A. Eicher, M. Chen, S.S. Strom, M.R. Spitz, Q. Wei, *XPD/ERCC2* polymorphisms and risk of head and neck cancer: a case-control analysis, Carcinogenesis 21 (2000) 2219–2223.

[184] P. Frit, E. Bergmann, J.-M. Egly, Transcription factor IIH: a key player in the cellular response to DNA damage, Biochemie 81 (1999) 27–38.

[185] X.W. Wang, H. Yeh, L. Schaeffer, R. Roy, V. Moncollin, J.M. Egly, Z. Wang, E.C. Friedberg, M.K. Evans, B.G. Taffe, V.A. Bohr, G. Weeda, J.H.J. Hoeijmakers, K. Rorrester, C.C. Harris, p53 modulation of TFIIH-associated nucleotide excision-repair activity, Nat. Genet. 10 (1995) 188–195.

[186] H. Seker, D. Butkiewicz, E.D. Bowman, M. Rusin, M. Hedayati, L. Grossman, C.C. Harris, Functional significance of XPD polymorphic variants: attenuated apoptosis in human lymphoblastoid cells with the XPD 312 Asp/Asp genotype, Cancer Res. 61 (2001) 7430–7434.

[187] J.R. Hwang, V. Moncollin, W. Vermeulen, T. Seroz, H. van Vuuren, J.H.J. Hoeijmakers, J.M. Egly, A $3' \rightarrow 5'$

XPB helicase defect in repair/transcription factor TFIIH of xeroderma pigmentosum group B affects both DNA repair and transcription, J. Biol. Chem. 271 (1996) 15898–15904.

[188] L. Riou, L. Zeng, O. Chevallier-Lagente, A. Stary, O. Nikaido, A. Taieb, G. Weeda, M. Mezzina, A. Sarasin, The relative expression of mutated *XPB* genes results in xeroderma pigmentosum/Cockayne's syndrome or trichothiodystrophy cellular phenotypes, Hum. Mol. Genet. 8 (1999) 1125–1133.

[189] X.W. Wang, K. Forrester, H. Yeh, M.A. Feitelson, J. Gu, C. Harris, Hepatitis-B-virus-x protein inhibits p53 sequence-specific DNA-binding, transcriptional activity, and association with transcription factor ERCC3, Proc. Natl. Acad. Sci. U.S.A. 91 (1994) 2230–2234.

[190] J.-P. Therrien, R. Drouin, C. Baril, E.A. Drobetsky, Human cells compromised for p53 function exhibit defective global and transcription-coupled nucleotide excision repair, whereas cells compromised for pRb function are defective only in global repair, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 15038–15043.

[191] V.C. Tron, M.J. Trotter, L. Tang, M. Krajewska, J.C. Reed, V.C. Ho, G. Li, p53-regulated apoptosis is differentiation dependent in ultraviolet B-irradiated mouse keratinocytes, Am. J. Pathol. 153 (1998) 579–585.

[192] Q. Zhu, M.A. Wani, M. El-mahdy, A.A. Wani, Decreased DNA repair efficiency by loss or disruption of p53 function preferentially affects removal of cyclobutane pyrimidine dimers from non-transcribed strand and slow repair sites in transcribed strand, J. Biol. Chem. 275 (2000) 11492–11497.

[193] C. Chao, S. Saito, J. Kang, C.W. Anderson, E. Appella, Y. Xu, p53 transcriptional activity is essential for p53-dependent apoptosis following DNA damage, EMBO J. 19 (2000) 4967–4975.

[194] K. Oda, H. Arakawa, T. Tanaka, K. Matsuda, C. Tanikawa, T. Mori, H. Nishimori, Y. Nakamura, Y. Taya, *p53AIP1*, a potential mediator of p53-dependent apoptosis, and its regulation by ser-46-phosphorylated p53, Cell 102 (2000) 849–862.

[195] K.-J. Cheung Jr., D. Mitchell, P. Lin, G. Li, The tumor suppressor candidate p33[ING1] mediates repair of UV-damaged DNA, Cancer Res. 61 (2001) 4974–4977.

[196] M. Scott, P. Bonnefin, D. Vieyra, F.-M. Boisvert, D. Young, D.P. Bazett-Jones, K. Riabowol, UV-induced binding of ING1 to PCNA regulates the induction of apoptosis, J. Cell Sci. 114 (2001) 3455–3462.

[197] A.R. Evans, M. Limp-Foster, M.R. Kelley, Going APE over ref-1, Mutat. Res. 461 (2000) 83–108.

[198] R. Prasad, O.I. Lavrik, S.-J. Kim, P. Kedar, X.-P. Yang, B.J. Vande Berg, S.H. Wilson, DNA polymerase β-mediated long patch base excision repair, J. Biol. Chem. 276 (2001) 32411–32414.

[199] M.R. Kelley, L. Cheng, R. Foster, R. Tritt, J. Jiang, J. Broshears, M. Koch, Elevated and altered expression of the multifunctional DNA base excision repair and redox enzyme Ape1/ref-1 in prostate cancer, Clin. Cancer Res. 7 (2001) 824–830.

[200] C. Gaiddon, N.C. Moorthy, C. Prives, Ref-1 regulates the transactivation and pro-apoptotic functions of p53 in vivo, EMBO J. 18 (1999) 5609–5621.

[201] J. Brugarolas, C. Chandrasekaran, J.I. Gordon, D. Beach, T. Jacks, G.J. Hannon, Radiation-induced cell cycle arrest compromised by p21 deficiency, Nature 377 (1995) 552–557.

[202] K. Okamoto, C. Prives, A role of cyclin G in the process of apoptosis, Oncogene 18 (1999) 4606–4615.

[203] K.A. Robertson, D.P. Hill, Y. Xu, L. Liu, S. Van Epps, D.M. Hockenbery, J.R. Park, T.M. Wilson, M.R. Kelley, Down-regulation of apurinic/apyrimidinic endonuclease expression is associated with the induction of apoptosis in differentiating myeloid leukemia cells, Cell Growth Diff. 8 (1997) 443–449.

[204] A. Burkle, Poly(ADP-ribosyl)ation, a DNA damage-driven protein modification and regulator of genomic instability, Cancer Lett. 163 (2001) 1–5.

[205] C.M. Payne, C. Crowley, D. Washo-Stultz, M. Briehl, H. Bernstein, C. Bernstein, S. Beard, H. Holubec, J. Warneke, The stress-response proteins poly(ADP-ribose) polymerase and NF-κB protect against bile salt induced apoptosis, Cell Death Differ. 5 (1998) 623–636.

[206] J.P. Gagne, R.G. Shah, G.G. Poirier, Analysis of ADP-ribose polymer sizes in intact cells, Mol. Cell. Biochem. 224 (2001) 183–185.

[207] M. Masson, C. Niedergang, V. Schreiber, S. Muller, J. Menissier-deMurcia, G. deMurcia, XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage, Mol. Cell. Biol. 18 (1998) 3563–3571.

[208] A.G. Yakovlev, G. Wang, B.A. Stoica, H.A. Boulares, A.Y. Spoonde, K. Yoshihara, M.E. Smulson, A role of the Ca^{2+}/Mg^{2+}-dependent endonuclease in apoptosis and its inhibition by poly(ADP-ribose) polymerase, J. Biol. Chem. 275 (2000) 21302–21308.

[209] G. de Murcia, A. Huletsky, D. Lamarres, A. Gaudreau, J. Pouyet, M. Daune, G.G. Poirier, Modulation of chromatin superstructure induced by poly(ADP-ribose) synthesis and degradation, J. Biol. Chem. 261 (1986) 7011–7017.

[210] R.S. Grant, V. Kapoor, Murine glial cells regenerate NAD, after peroxide-induced depletion, using either nicotinic acid, nicotinamide, or quinolinic acid as substrates, J. Neurochem. 70 (1998) 1759–1763.

[211] A.B. Weitberg, Effect of nicotinic acid supplementation in vivo on oxygen radical-induced genetic damage in human lymphocytes, Mutat. Res. 216 (1989) 197–201.

[212] T.M. Jackson, J.M. Rawling, B.D. Roebuck, J.B. Kirkland, Large supplements of nicotinc acid and nicotinamide increase tissue NAD^+ and poly(ADP-ribose) levels but do not affect diethylnitrosamine-induced altered hepatic foci in Fischer-344 rats, J. Nutr. 125 (1995) 1455–1461.

[213] R. Beneke, C. Geisen, B. Zevnik, T. Bauch, W.-U. Muller, J.-H. Kupper, T. Moroy, DNA excision repair and DNA damage-induced apoptosis are linked to poly(ADP-ribosyl)ation but have different requirements for p53, Mol. Cell. Biol. 20 (2000) 6695–6703.

[214] M.L. Agarwal, A. Agarwal, W.R. Taylor, Z.-Q. Wang, E.F. Wagner, G.R. Stark, Defective induction but normal

activation and function of p53 in mouse lacking poly-ADP-ribose polymerase, Oncogene 15 (1997) 1035–1041.

[215] J. Wesierska-Gadek, Z.-Q. Wang, G. Schmid, Reduced stability of regularly spliced but not alternatively spliced p53 protein in PARP-deficient mouse fibroblasts, Cancer Res. 59 (1999) 28–34.

[216] D.W. Nicholson, A. Ali, N.A. Thornberry, J.P. Vaillancourt, C.K. Ding, M. Gallant, Y. Gareau, P.R. Griffin, M. Labelle, Y.A. Lazebnik, N.A. Munday, S.M. Raju, M.E. Smulson, T.T. Yamin, V.L. Yu, D.K. Miller, Identification and inhibition of the ICE/CED-3 protease necessary for mammalian apoptosis, Nature (London) 376 (1995) 37–43.

[217] L. Cristovao, M.C. Lechner, P. Fidalgo, C.N. Leitao, F.C. Mira, J. Rueff, Absence of stimulation of poly(ADP-ribose) polymerase activity in patients predisposed to colon cancer, Br. J. Cancer 77 (1998) 1628–1632.

[218] H. Offer, M. Milyavsky, N. Erez, D. Matas, I. Zurer, C.C. Harris, V. Rotter, Structural and functional involvement of p53 in BER in vitro and in vivo, Oncogene 20 (2001) 581–589.

[219] J. Zhou, J. Ahn, S.H. Wilson, C. Prives, A role for p53 in base excision repair, EMBO J. 20 (2001) 914–923.

[220] H. Offer, I. Zurer, G. Banfalvi, M. Reha'k, A. Falcovitz, M. Milyavski, N. Goldfinger, V. Rotter, p53 modulates base excision repair activity in a cell cycle-specific manner after genotoxic stress, Cancer Res. 61 (2001) 88–96.

[221] H.T. Lynch, T. Smyrk, J.F. Lynch, Overview of natural history, pathology, molecular genetics and management of HNPCC (Lynch syndrome), Int. J. Cancer 69 (1996) 38–43.

[222] O. Humbert, S. Fiumicino, G. Aquilina, P. Branch, S. Oda, A. Zijno, P. Karran, M. Bignami, Mismatch repair and differential sensitivity of mouse and human cells to methylating agents, Carcinogenesis (London) 20 (1999) 205–214.

[223] R.A. Hardman, C.A. Afshari, J.C. Barrett, Involvement of mammalian MLH1 in the apoptotic response to peroxide-induced oxidative stress, Cancer Res. 61 (2001) 1392–1397.

[224] J. Jiricny, M. Nystrom-Lahti, Mismatch repair defects in cancer, Curr. Opin. Genet. Dev. 10 (2000) 157–161.

[225] D.R. Duckett, S.M. Bronstein, Y. Taya, P. Modrich, hMutSα- and hMutLα-dependent phosphorylation of p53 in response to DNA methylator damage, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 12384–12388.

[226] K. Ochs, B. Kaina, Apoptosis induced by DNA damage O^6-methylguanine is Bcl-2 and caspase-9/3 regulated and Fas/caspase-8 independent, Cancer Res. 60 (2000) 5815–5824.

[227] M.J. Hickman, L.D. Samson, Role of DNA mismatch repair and p53 in signaling induction of apoptosis by alkylating agents, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 10764–10769.

[228] D.M. Kokkinakis, M.M. Ahmed, R. Delgado, M.M. Fruitwala, M. Mohiuddin, J. Albores-Saavedra, Role of O^6-methylguanine-DNA methyltransferase in the resistance of pancreatic tumors to DNA alkylating agents, Cancer Res. 57 (1997) 5360–5368.

[229] M. Esteller, R.A. Risques, M. Toyota, G. Capella, V. Moreno, M.A. Peinado, S.B. Baylin, J.G. Herman, Promoter hypermethylation of the DNA repair gene O^6-methyl guanine-DNA methyltransferase is associated with the presence of G:C to A:T transition mutations in human colorectal mutagenesis, Cancer Res. 61 (2001) 4689–4692.

[230] E. Appella, C.W. Anderson, Post-translational modifications and activation of p53 by genotoxic stresses, Eur. J. Biochem. 268 (2001) 2764–2772.

[231] X. Chen, L.J. Ko, L. Jayaraman, C. Prives, p53 levels, functional domains, and DNA damage determine the extent of the apoptotic response of tumor cells, Genes Dev. 10 (1996) 2438–2451.

[232] E. Reihsaus, M. Kohler, S. Kraiss, M. Oren, M. Montenarh, Regulation of the level of the oncoprotein p53 in non-transformed and transformed cells, Oncogene 5 (1990) 137–145.

[233] C.G. Maki, P.M. Howley, Ubiquitination of p53 and p21 is differentially affected by ionizing and UV radiation, Mol. Cell. Biol. 17 (1997) 355–363.

[234] A.L. Okorokov, J. Milner, Proteolytic cleavage of p53: a model for the activation of p53 in response to DNA damage, Oncol. Res. 9 (1997) 267–273.

[235] Y. Haupt, R. Maya, A. Kazaz, M. Oren, MDM2 promotes the rapid degradation of p53, Nature 387 (1997) 296–299.

[236] M.H.G. Kubbutat, S.N. Jones, K.H. Vousden, Regulation of p53 stability by MDM2, Nature 387 (1997) 299–303.

[237] J. Chen, X. Wu, J. Lin, A.J. Levine, Mdm-2 inhibits the G1 arrest and apoptosis functions of the p53 tumor suppressor protein, Mol. Cell. Biol. 16 (1996) 2445–2452.

[238] R. Honda, H. Tanaka, H. Yasuda, Oncoprotein MDM2 is a ubiquitin ligase E3 for tumor suppressor p53, FEBS Lett. 420 (1997) 25–27.

[239] R.V. Sionov, E. Moallem, M. Berger, A. Kazaz, O. Gerlitz, Y. Ben-Neriah, M. Oven, Y. Haupt, c-Abl neutralizes the inhibitory effect of Mdm2 on p53, J. Biol. Chem. 274 (1999) 8371–8374.

[240] D.M. Scolnick, N.H. Chehab, E.S. Stavridi, M.C. Lien, L. Caruso, E. Moran, S.L. Berger, T.D. Halazonetis, CREB-binding protein and p300/CBP-associated factor are transcriptional coactivators of the p53 tumor suppressor protein, Cancer Res. 57 (1997) 3693–3696.

[241] S.R. Grossman, M. Perez, A.L. Kung, M. Joseph, C. Mansur, Z.-X. Xiao, S. Kumar, P.M. Howley, D.M. Livingston, p300/MDM2 complexes participate in MDM2 mediated p53 degradation, Mol. Cell 2 (1998) 405–415.

[242] M.L. Smith, J.M. Ford, M.C. Hollander, R.A. Bortnick, S.A. Amundson, Y.R. Seo, C.-X. Deng, P.C. Hanawalt, A.J. Fornace, p53-mediated DNA repair responses to UV radiation: studies of mouse cells lacking p53, p21, and/or gadd45 genes, Mol. Cell. Biol. 20 (2000) 3705–3714.

[243] T. Miyashita, J.C. Reed, Tumor suppressor p53 is a direct transcriptional activator of the human Bax gene, Cell 80 (1995) 293–299.

[244] P.-G. Li, R. Dietz, R. vonHarsdorf, p53 regulates mitochondrial membrane potential through reactive oxygen species and induces cytochrome c-independent apoptosis blocked by Bcl-2, EMBO J. 18 (1999) 6027–6036.

[245] G.S. Wu, T.F. Burns, E.R. McDonald, W. Jiang, R. Meng, I.D. Krantz, G. Kao, J.-D. Gan, J.-Y. Zhou, R. Muschel, S.R. Hamilton, N.B. Spinner, S. Markowitz, G. Wu, W.S. El-Deiry, Killer/DR5 is a DNA damage-inducible p53-regulated death receptor gene, Nat. Genet. 17 (1997) 141–143.

[246] S.I. Pai, G.S. Wu, N. Ozoren, L. Wu, J. Jen, D. Sidransky, W.S. El-Deiry, Rare loss-of-function mutation of a death receptor gene in head and neck cancer, Cancer Res. 58 (1998) 3513–3518.

[247] S. Krajewski, S. Tanaka, S. Takayama, M.J. Schibler, W. Fenton, J.C. Reed, Investigation of the subcellular-distribution of the Bcl-2 oncoprotein-residence in the nuclear-envelope, endoplasmic-reticulum and outer mitochondrial-membranes, Cancer Res. 53 (1993) 4701–4714.

[248] J. Yang, X. Liu, K. Bhalla, C.N. Kim, A.M. Ibrado, J. Cai, T.-L. Peng, D.P. Jones, X. Wang, Prevention of apoptosis by Bcl-2: release of cytochrome c from mitochondria blocked, Science 275 (1997) 1129–1132.

[249] R.M. Kluck, E. Bossy-Wetzel, D.R. Green, D.D. Newmeyer, The release of cytochrome c from mitochondria: a primary site for Bcl-2 regulation of apoptosis, Science 275 (1997) 1132–1136.

[250] T.W. Sedlak, Z.N. Oltavi, E. Yang, K. Wang, L.H. Boise, C.B. Thompson, S.J. Korsmeyer, Multiple Bcl-2 family members demonstrate selective dimerizations with Bax, Proc. Natl. Acad. Sci. U.S.A. 92 (1995) 7834–7838.

[251] Z.N. Oltavi, C.L. Milliman, S.J. Korsmeyer, Bcl-2 hetero-dimerizes in vivo with a conserved homolog, Bax, that accelerates programmed cell death, Cell 74 (1993) 609–619.

[252] S. Adachi, A.J. Obaya, Z. Han, N. Ramos-Desimone, J.H. Wyche, J.M. Sedivy, c-Myc is necessary of DNA damage-induced apoptosis in the G2 phase of the cell cycle, Mol. Cell. Biol. 21 (2001) 4929–4937.

[253] E.L. Soucie, M.G. Annis, J. Sedivy, J. Filmus, B. Leber, D.W. Andrews, L.Z. Penn, Myc potentiates apoptosis by stimulating Bax activity at the mitochondria, Mol. Cell. Biol. 21 (2001) 4725–4736.

[254] A. Mandic, K. Viktorsson, M. Molin, G. Adusjarvi, H. Eguchi, S.-I. Hayashi, M. Toi, J. Hannson, S. Linder, M.C. Shoshan, Cisplatin induces the proapoptotic conformation of Bak in a ΔMEKK1-dependent manner, Mol. Cell. Biol. 21 (2001) 3684–3691.

[255] S.W. Corbet, A.R. Clarke, S. Glidhill, A.H. Wyllie, p53-dependent and -independent links between DNA-damage apoptosis and mutation frequency in ES cells, Oncogene 18 (1999) 1537–1544.

[256] D. Malkin, The Li–Fraumini syndrome, in: B. Vogelstein, K.W. Kinzler (Eds.), The Genetic Basis of Human Cancer, McGraw-Hill, New York, NY, 1998, pp. 393–407.

[257] M. Hollstein, K. Rice, M.S. Greenblatt, T. Soussi, R. Fuchs, T. Sorlie, E. Hovig, B. Smithsorensen, R. Montesano, C.C. Harris, Database of p53 gene somatic mutations in human tumors and cell-lines, Nucl. Acids Res. 22 (1994) 3551–3555.

[258] D.W. Bell, J.M. Varley, T.E. Szydlo, D.H. Kang, D.C.R. Wahrer, K.E. Shannon, M. Lubratovich, S.J. Verselis, K.J. Isselbacher, J.F. Fraumini, J.M. Birch, F.P. Li, J.E. Garber, D.A. Haber, Heterozygous germ line hCHD2 mutations in Li–Fraumini syndrome, Science 286 (1999) 2528–2531.

[259] M. Taga, K. Shiraishi, T. Shimura, N. Uematsu, M. Oshimura, O. Niwa, Increased frequencies of gene and chromosome mutations after X-irradiation in mouse embryonal carcinoma cells transfected with the bcl-2 gene, Jpn. J. Cancer Res. 91 (2000) 994–1000.

[260] Y. Liu, L. Naumovski, P. Hanawalt, Nucleotide excision repair capacity is attenuated in human promyelocytic HL60 cells that overexpress BCL2, Cancer Res. 57 (1997) 1650–1653.

[261] L. Kaklamanis, A. Savage, N. Mortensen, P. Tsiotos, I. Doussis-Anagnostopoulou, S. Biddolph, R. Whitehouse, A.L. Harris, K.C. Gatter, Early expression of bcl-2 protein in the adenoma-carcinoma sequence of colorectal neoplasia, J. Pathol. 179 (1996) 10–14.

[262] C. Binder, D. Marx, R. Overhoff, L. Binder, A. Schauer, W. Hiddemann, Bcl-2 protein expression in breast cancer in relation to established prognostic factors and other clinic-opathological variables, Ann. Oncol. 61 (1996) 1005–1010.

[263] A.N. Crowson, C.M. Magro, M.E. Kadin, M. Stranc, Differential expression of the bcl-2 oncogene in human basal cell carcinoma, Hum. Pathol. 27 (1996) 355–359.

[264] A. Bakhshi, J.P. Jensen, P. Goldman, J.J. Wright, O.W. McBride, A.L. Epstein, S.J. Korsmeyer, Cloning the chromosomal breakpoint of t(14;18) human lymphomas: clustering around JH on chromosome 14 and near a transcriptional unit on 18, Cell 47 (1985) 899–906.

[265] M.L. Cleary, S.D. Smith, J. Sklar, Cloning and structural analysis of cDNAs for bcl-2 and a hybrid bcl-2/immuno-globulin transcript resulting from the t(14;18) translocation, Cell 47 (1986) 19–28.

[266] Y. Tsujimoto, L.R. Finger, J. Yunis, P.C. Nowell, C.M. Croce, Cloning of the chromosome breakpoint of neoplastic B cells with the t(14;18) chromosome translocation, Science 226 (1984) 1097–1099.

[267] B.N. Ames, L.S. Gold, Endogenous mutagens and the causes of aging and cancer, Mutat. Res. 250 (1991) 3–16.

[268] G.P. Holmquist, Endogenous lesions, S phase-independent spontaneous mutations and evolutionary strategies, Mutat. Res. 400 (1998) 59–68.

[269] A.H. Boulares, A.J. Zoltoski, F.J. Contreras, A.G. Yakovlev, K. Yoshihara, M.E. Smulson, Regulation of DNAS1L3 endonuclease activity by poly(ADP-ribosyl)ation during etoposide-induced apoptosis, J. Biol. Chem. 277 (2002) 372–378.

[270] J. Stadler, H.S. Stern, K.S. Yeung, V. McGuire, R. Furrer, N. Marcon, W.R. Bruce, Effect of high fat consumption on cell proliferation activity of colorectal mucosa and on soluble faecal bile acids, Gut 29 (1988) 1326–1331.

[271] L.A. Booth, I.T. Gilmore, R.F. Bilton, Secondary bile acid induced DNA damage in HT29 cells: are free radicals involved? Free Radic. Res. 26 (1997) 135–144.

[272] J.R. Liu, A.W. Opipari, L. Tan, Y. Jiang, Y. Zhang, H. Tang, G. Nunez, Dysfunctional apoptosome activation in ovarian cancer: implications for chemoresistance, Cancer Res. 62 (2002) 924–931.

[273] Y.-H. Chen, Y. Lu, I.G. De Plaen, L.-Y. Wang, X.-D. Tan, Transcription factor NF-κB signals antianoikic function of trefoil factor 3 on intestinal epithelial cells, Biochem. Biophys. Res. Commun. 274 (2000) 576–582.

[274] C.Y. Wang, M.W. Mayo, R.G. Korneluk, D.V. Goeddel, A.S. Baldwin Jr., NF-κB antiapoptosis: induction of TRAF1 and TRAF2 and c-IAP1 and c-IAP2 to suppress caspase-8 activation, Science 281 (1998) 1680–1683.

[275] S. Fan, Y.X. Ma, J.-A. Wang, R.-Q. Yuan, Q. Meng, Y. Cao, J.L. Lattera, I.D. Goldberg, E.M. Rosen, The cytokine hepatocyte growth factor/scatter factor inhibits apoptosis and enhances DNA repair by a common mechanism involving signaling through phosphatidyl inositol 3′ kinase, Oncogene 19 (2000) 2212–2213.

[276] V. Bours, M. Bentires-Alj, A.-C. Hellin, P. Viatour, P. Robe, S. Delhalle, V. Benoit, M.-P. Merville, Nuclear factor-κB, cancer, and apoptosis, Biochem. Pharm. 60 (2000) 1085–1090.

[277] L.C. Gowen, A.V. Avrutskaya, A.M. Latour, B.H. Koller, S.A. Leadon, BRCA1 required for transcription-coupled repair of oxidative DNA damage, Science 281 (1998) 1009–1012.

[278] F. Le Page, V. Randrianarison, D. Marot, J. Cabannes, M. Perricaudet, J. Feunteun, A. Sarasin, BRCA1 and BRCA2 are necessary for the transcription-coupled repair of the oxidative 8-oxoguanine lesion in human cells, Cancer Res. 60 (2000) 5548–5552.

[279] Q. Zhan, F. Carrier, A. Fornace, Induction of cellular p53 activity by DNA-damaging agents and growth arrest, Mol. Cell. Biol. 13 (1993) 4242–4250.

[280] H. Offer, R. Wolkowicz, D. Matas, S. Blumenstein, Z. Livneh, V. Rotter, Direct involvement of p53 in the base excision repair pathway of the DNA repair machinery, FEBS Lett. 450 (1999) 197–204.

[281] J.M. Ford, P.C. Hanawalt, Li–Fraumini syndrome fibroblasts homozygous for p53 mutations are deficient in global DNA repair but exhibit normal transcription-coupled repair and enhanced UV resistance, Proc. Natl. Acad. Sci. U.S.A. 92 (1995) 8876–8890.

[282] J.M. Ford, P.C. Hanawalt, Expression of wild-type p53 is required for efficient global genomic nucleotide excision repair in UV-irradiated human fibroblasts, J. Biol. Chem. 272 (1997) 28073–28080.

[283] S. Lee, B. Elenbaas, A.J. Levine, J. Griffith, p53 and its 14 kDa C-terminal domain recognize primary DNA damage in the form of insertion/deletion mismatches, Cell 81 (1995) 1013–1020.

[284] L.D. Attardi, E.E. Reeczek, C. Cosmas, E.G. Demicco, M.E. McCurrach, S.W. Lowe, T. Jacks, PERP, an apoptosis-associated target of p53, is a novel member of the PMP-22/gas family, Genes Dev. 14 (2000) 704–718.

[285] H.-F. Ding, Y.-L. Lin, G. McGill, P. Juo, H. Zhu, J. Blenis, J. Yuan, D.E. Fisher, Essential role for caspase-8 in transcription-independent apoptosis triggered by p53, J. Biol. Chem. 275 (2000) 38905–38911.

[286] B. Demple, T. Herman, D.S. Chen, Cloning and expression of APE, the cDNA encoding the major human apurinic endonuclease: definition of a family of DNA repair enzymes, Proc. Natl. Acad. Sci. U.S.A. 88 (1991) 11450–11454.

[287] I. Van der Burgt, K.H. Chrzanowska, D. Smeets, C. Weemaes, Nijmegen breakage syndrome, J. Med. Genet. 33 (1996) 153–156.

[288] G.S. Stewart, R.S. Maser, T. Stankovic, D.A. Bressan, M.I. Kaplan, N.G.J. Jaspers, A. Raams, P.J. Byrd, J.H.H. Petrini, A.M.R. Taylor, The DNA double-strand break repair gene hMre11 is mutated in individuals with an ataxia telangiectasia-like disorder (ATLD), Cell 99 (1999) 577–587.

[289] I. Garcia-Higuera, T. Taniguchi, S. Ganesan, M.S. Meyn, C. Timmers, J. Hejna, M. Grompe, A.D. D'Andrea, Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway, Mol. Cell 7 (2001) 249–262.

[290] C.L. Limoli, E. Giedzinski, W.F. Morgan, J.E. Cleaver, Polymerase η deficiency in the xeroderma pigmentosum variant uncovers an overlap between the S phase checkpoint and double-strand break repair, Proc. Natl. Acad. Sci. U.S.A. 97 (2000) 7939–7946.

[291] I. Mellon, D.K. Rajpal, M. Koi, C.R. Boland, G.N. Champe, Transcription-coupled repair deficiency and mutations in human mismatch repair genes, Science 272 (1996) 557–560.