Cell Death and Differentiation (2018) 25, 114–132
Official journal of the Cell Death Differentiation Association
www.nature.com/cdd

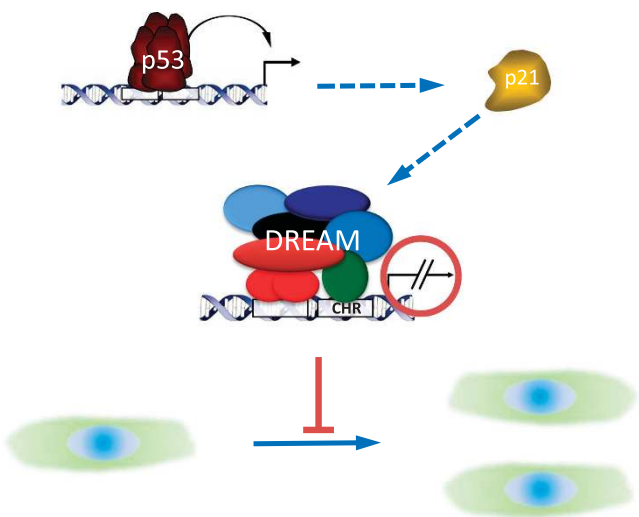
OPEN

Review

Cell cycle arrest through indirect transcriptional repression by p53: I have a DREAM

Kurt Engeland[1]

Activation of the p53 tumor suppressor can lead to cell cycle arrest. The key mechanism of p53-mediated arrest is transcriptional downregulation of many cell cycle genes. In recent years it has become evident that p53-dependent repression is controlled by the p53–p21–DREAM–E2F/CHR pathway (p53–DREAM pathway). DREAM is a transcriptional repressor that binds to E2F or CHR promoter sites. Gene regulation and deregulation by DREAM shares many mechanistic characteristics with the retinoblastoma pRB tumor suppressor that acts through E2F elements. However, because of its binding to E2F and CHR elements, DREAM regulates a larger set of target genes leading to regulatory functions distinct from pRB/E2F. The p53–DREAM pathway controls more than 250 mostly cell cycle-associated genes. The functional spectrum of these pathway targets spans from the G_1 phase to the end of mitosis. Consequently, through downregulating the expression of gene products which are essential for progression through the cell cycle, the p53–DREAM pathway participates in the control of all checkpoints from DNA synthesis to cytokinesis including G_1/S, G_2/M and spindle assembly checkpoints. Therefore, defects in the p53–DREAM pathway contribute to a general loss of checkpoint control. Furthermore, deregulation of DREAM target genes promotes chromosomal instability and aneuploidy of cancer cells. Also, DREAM regulation is abrogated by the human papilloma virus HPV E7 protein linking the p53–DREAM pathway to carcinogenesis by HPV. Another feature of the pathway is that it downregulates many genes involved in DNA repair and telomere maintenance as well as Fanconi anemia. Importantly, when DREAM function is lost, CDK inhibitor drugs employed in cancer treatment such as Palbociclib, Abemaciclib and Ribociclib can compensate for defects in early steps in the pathway upstream from cyclin/CDK complexes. In summary, the p53–p21–DREAM–E2F/CHR pathway controls a plethora of cell cycle genes, can contribute to cell cycle arrest and is a target for cancer therapy.
Cell Death and Differentiation (2018) **25,** 114–132; doi:10.1038/cdd.2017.172; published online 10 November 2017



Graphical Abstract

Facts

- p53 causes cell cycle arrest
- p21/CDKN1A is required for indirect transcriptional repression by p53
- The DREAM protein complex is a transcriptional repressor
- CHR and E2F promoter elements bind the DREAM complex
- p21/CDKN1A initiates a switch from activating B-MYB- and FOXM1-containing complexes to the repressing DREAM complex
- p53 indirectly downregulates many cell cycle genes

Open Questions

- How do p63, p73 and p53 variants influence the p21–DREAM–E2F/CHR (p53–DREAM) pathway?
- Are cellular kinase inhibitors other than p21/CDKN1A regulating this pathway?
- Which clinical benefits can be achieved in cancer treatment with small-molecule CDK inhibitors by compensating for defects in the p53–DREAM pathway?
- What are the overlaps or differences in pRB and DREAM function?

Prologue

One central role of the tumor suppressor p53 is to arrest the cell cycle. p53 indirectly downregulates the expression of many genes which are essential for progression through the cell division cycle. The detailed mechanism of indirect transcriptional repression by p53 has only recently become

[1]Molecular Oncology, Medical School, University of Leipzig, Leipzig, Germany
*Corresponding author: K Engeland, Molecular Oncology, Medical School, University of Leipzig, Semmelweisstr. 14, Leipzig 04103, Germany. Tel: +49 341 97 259 00. E-mail: engeland@medizin.uni-leipzig.de
Received 21.7.17; revised 10.9.17; accepted 13.9.17; Edited by F Pentimalli; published online 10.11.17

clear. p53 employs a protein complex named DREAM to downregulate gene expression. DREAM functions as a transcriptional repressor complex. With the advent of genome-wide experimental and bioinformatic analyses, we are now in the position to assess the wide spectrum of genes controlled through the newly defined p53–DREAM pathway.

p53 Downregulates Expression of Cell Cycle Genes

p53 is at the heart of several fundamental cellular signaling pathways.[1–4] The most important of these pathways for p53's tumor-suppressive role are induction of apoptosis and cell cycle arrest.[5,6]

Cell cycle arrest can be achieved by depleting regulatory proteins required for cell cycle progression. Upon p53 activation, genes for many central cell cycle proteins are transcriptionally downregulated. Key examples for genes repressed after induction of p53 are *cyclin A*,[7] polo-like kinase 1 (*PLK1*),[7] *cyclin B1*,[8–10] *cyclin B2*,[10] cyclin-dependent kinase 1 (*CDK1*),[11] *CDC20*,[12] cell cycle phosphatases *CDC25A*[13] and *CDC25C*,[14] DNA replication licensing factor *MCM5*,[7,15] *CKS1*[16] and antiapoptotic *Survivin* (*BIRC5*).[7] Even such a small selection of genes exemplifies that p53-dependent downregulation of expression affects many aspects of cell cycle regulation.

Transcriptional Repression by p53 is Indirect

Transcriptional regulation is essential to the function of p53 as a tumor suppressor.[2] Interestingly, the number of genes downregulated after p53 activation (approximately 2700) is larger than the number of genes activated by p53 (approximately 2200).[17] Before this enigma was finally solved, several mechanisms had been proposed to explain how p53 can serve as a transcriptional activator as well as a repressor.[2,4,18] However, experimental data obtained for particular genes were often not consistent with the suggested mechanism or results published for certain genes by different groups were contradictory.[17–19] Furthermore, different models for p53-dependent repression require direct binding of p53 to the downregulated gene. However, genome-wide mRNA expression and chromatin immunoprecipitation (ChIP) results demonstrated that this requirement is not fulfilled for most repressed genes. Only about 3% of the genes downregulated by p53 are also bound by p53.[17] Thus, essentially all genes are downregulated by p53 indirectly.

Prior to the availability of genome-wide ChIP data on binding of p53 and other factors potentially involved in transcriptional repression, it was not evident by which mechanism p53 downregulates a plethora of cell cycle genes. This changed when the mammalian DREAM complex together with its target genes was discovered[20,21] and the observation was made that DREAM is formed following p53 induction.[22]

DREAM is a Transcriptional Repressor

The DREAM transcriptional complex displays two remarkable features. It changes its composition to exert opposing functions in gene regulation and it contains two subunits that bind to distinct DNA elements.

DREAM is composed of the MuvB core complex, E2F4-5/DP, and p130 or p107 proteins, which are related to the retinoblastoma tumor suppressor pRB[20,21] (Figure 1). E2F4, E2F5 and p130/p107 had long been implicated in transcriptional repression via E2F sites.[23] Consistently, DREAM was initially identified as a complex which binds promoters through E2F sites.[20,21,24] However, DREAM loses its E2F/pRB-related components to associate with the transcriptional activators B-MYB and FOXM1 during the cell cycle.[20,22,25–27] Thus, these MuvB-based complexes cannot bind E2F sites. DREAM as all other MuvB-derived complexes binds DNA through cell cycle genes homology regions (CHRs).[28–30] CHR transcriptional elements are distinct from E2F sites and are bound by the LIN54 component of MuvB[31,32] (Figure 1).

MuvB-based complexes can switch their function. Association of MuvB with B-MYB or FOXM1 switches DREAM to B-MYB-MuvB (MMB), FOXM1-MMB or FOXM1-MuvB complexes and turns the MuvB core from repressor to activator. This change in protein composition of MuvB-based complexes is connected to progression through the cell cycle and explains the switch from repression to activation via the same DNA site in the target promoters, that is, the CHR element (Figure 1).

It has been discussed whether B-MYB and FOXM1 require additional direct DNA binding when they are in a complex with MuvB.[19,26,29,31,33–37] Generally, MYB consensus sites or forkhead binding sites are not observed close to the MuvB-binding CHR elements. For FOXM1 it was reported that it mostly binds to non-forkhead binding sites in the genome and that this nonspecific DNA binding may support association of MuvB with DNA.[35,36] Possibly, also B-MYB binds to sites far from CHR elements to augment MMB-LIN54 binding to DNA.

Recently, the importance of CHR sites in cancer signaling pathways yet again has been demonstrated when the computer software SWItchMiner (SWIM) was employed to search for crucial nodes in signaling networks – called switch genes – out of a large panel of cancer data sets from The Cancer Genome Atlas.[38] The analysis yielded 100 significant switch genes which are mostly upregulated in a panel of different tumor types. With this selection of genes a *de novo* motif search for promoter elements was carried out. Interestingly, the CHR element emerged as a crucial site central to the regulation of the switch genes from the cancer signaling nodes.[38]

In addition to binding to single E2F or CHR sites, DREAM binding can be supported by two other elements, CDE (cell cycle-dependent element) and CLE (CHR-like element) sites (Figure 2). CLE sites are weak CHR-like elements and augment binding of DREAM to E2F sites. In general, affinity of CLE sites toward MuvB-based complexes, also the activating complexes, is not sufficient for binding. CLE sites alone cannot bind DREAM and an E2F element is required in tandem. Also, promoters require a spacer of four nucleotides between E2F and CLE sites.[33] Similarly, CDE sites support binding of DREAM only when a CHR element is present in the promoter. Again, a spacer of four bases is found between CDE and CHR sites.[33] CHR and CLE sites are contacted by LIN54 of the MuvB core complex.[28,32] Thus, DREAM binds to promoter DNA by four different modes[33] (Figure 2).

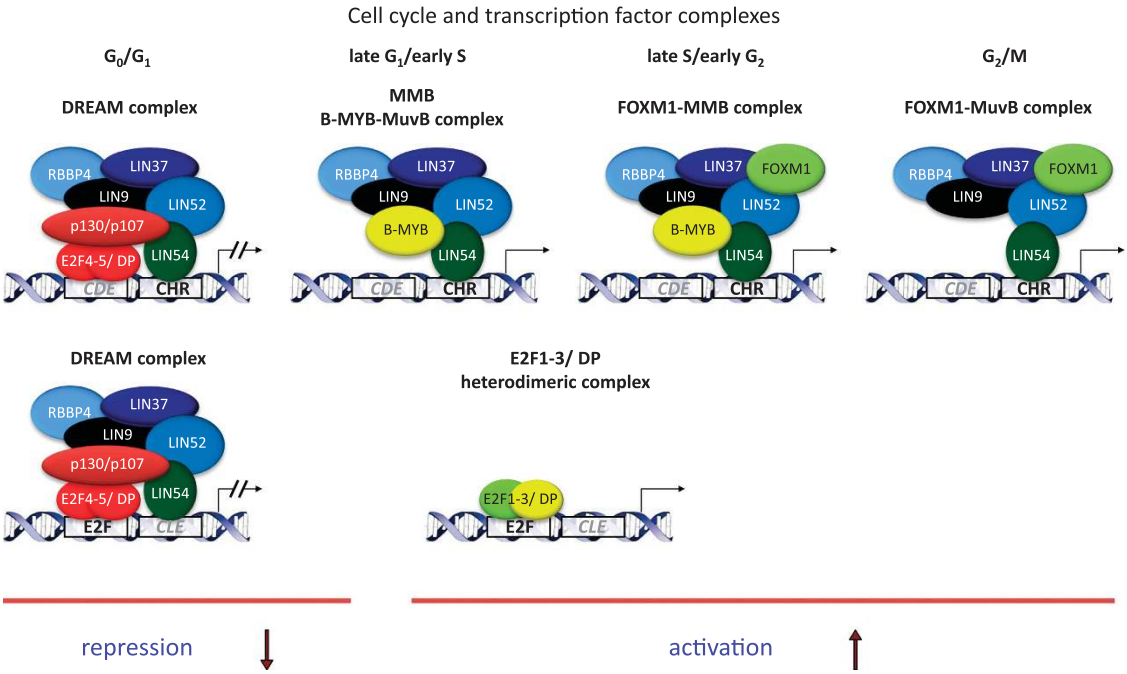


Figure 1 Cell cycle and transcription factor complexes**.** The protein complexes binding to DNA change during the cell cycle. Gene expression is repressed in the early phases of the cell cycle and becomes activated during the later phases. For this change, E2F and CHR (cell cycle genes homology region) promoter elements switch from repressor to activator sites. In G_0 and early G_1 phase the DREAM complex binds E2F, CHR, CDE (cell cycle-dependent element), and CLE (CHR-like element) sites to repress transcription. In G_2 phase and mitosis transcriptional repression is released and activation occurs via CHR sites. Only promoters with CHR sites can bind the MuvB-based complexes MMB (B-MYB-MuvB), FOXM1-MMB and FOXM1-MuvB. The MuvB core complex is composed of LIN9, LIN37, LIN52, LIN54 and RBBP4 proteins. LIN54 is the component which binds to CHR elements. For the switch from repressing to activating complexes, B-MYB and FOXM1 are recruited to the MuvB core when E2F4-5/DP and p107/p130 dissociate from the complex. B-MYB-MuvB (MMB), FOXM1-MMB and FOXM1-MuvB complexes serve as activators of late cell cycle genes which carry functional CHR elements. Early cell cycle genes with maximum expression in the S phase are activated by E2F1-3/DP heterodimers through E2F sites

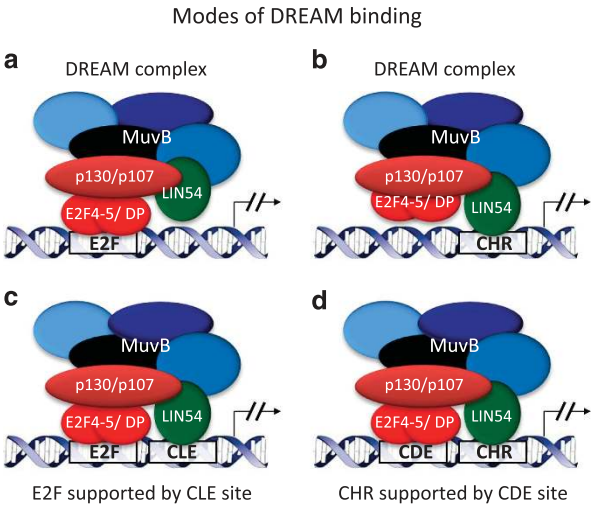


Figure 2 Modes of DREAM binding. DREAM can form two distinct contacts with DNA. It can bind to DNA via single E2F (**a**) or CHR (**b**) sites. E2F sites are contacted through E2F4-5/DP heterodimers. Distinct from this binding, contacts to CHR elements are made via the LIN54 protein. In the figure, the LIN54 component of the MuvB core complex is the only constituent that is labeled. Binding to E2F or CHR elements can be supported by CLE (**c**) or CDE (**d**) sites, respectively. CDE and CLE sites differ from E2F and CHR elements as CDE and CLE sites are unable to bind DREAM as single elements

The p53–p21–DREAM–E2F/CHR Pathway

After the discovery of DREAM binding to E2F and CHR elements, the pathway by which p53 downregulates many genes became evident.[39] In short, this pathway requires transcriptional upregulation of *p21/CDKN1A*. p21/CDKN1A inhibits cyclin-dependent kinases (CDKs) which phosphorylate the pRB-related proteins p107 and p130. Thus, p21/CDKN1A expression results in hypophosphorylation of p107 and p130. In this hypophosphorylated state, p107 and p130 can join other proteins to form the DREAM complex and thereby repress transcription through DREAM binding to E2F or CHR promoter sites (Figure 3).

The CDK inhibitor *p21/CDKN1A* (WAF1, CIP1) was the first transcriptional target identified for p53.[40,41] And with this target the more detailed description of the pathway starts. Upon p53 activation, *p21/CDKN1A* is transcriptionally upregulated through direct binding of p53 to sites in the *p21/CDKN1A* promoter (Figure 3).[39]

One question that still needs to be addressed systemically is how the p53-related p63 and p73 protein families influence transcription of *p21/CDKN1A*. Especially the TAp63/TAp73 variants have similar functions in regulating gene transcription as p53.[42,43] The DNA binding motifs for p63, p73 and p53 are apparently essentially identical,[44–47] suggesting that the transcriptionally active members of the p63 and p73 families may contribute to cell cycle arrest through activating *p21/CDKN1A*.[43,48,49] However, early experiments with overexpression of p63 and p73 variants indicated a reduced ability to induce *p21/CDKN1A* expression compared with p53 and showed only minor effects on genes which are downregulated by p53.[13,16,48,50,51]

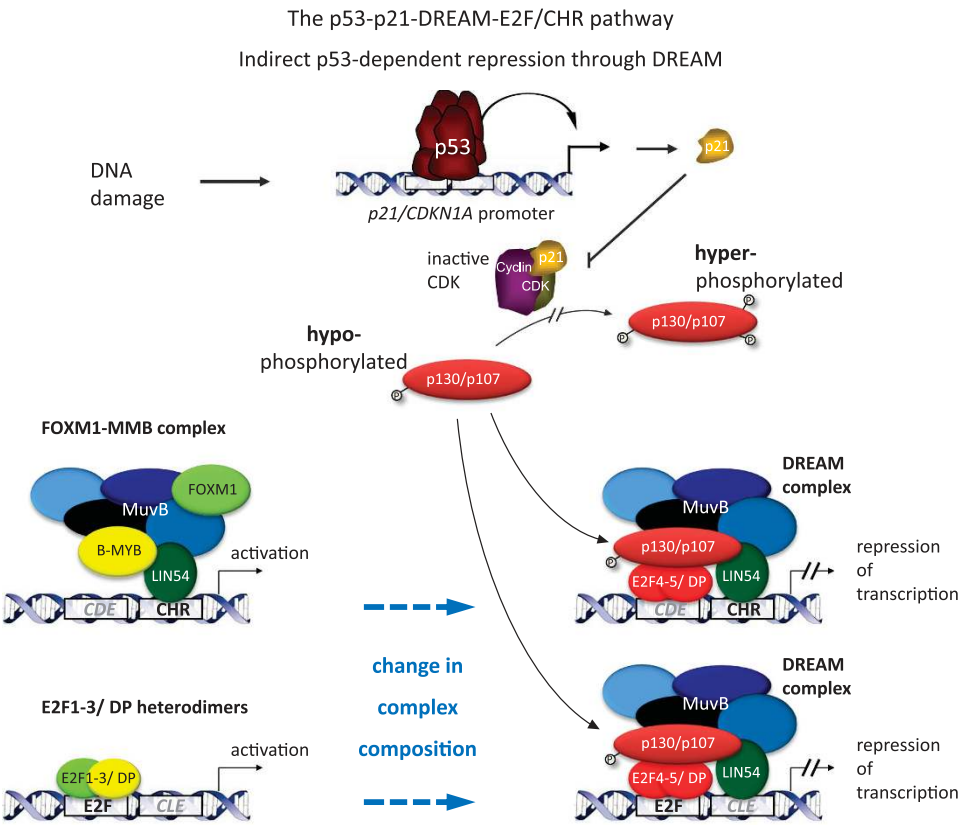


Figure 3 The p53–p21–DREAM–E2F/CHR pathway. Indirect p53-dependent repression through DREAM**.** Induction of p53 leads to downregulation of genes. This regulation is indirect as p53 does not bind to the regulated genes. Instead, induction of *p21/CDKN1A* expression by p53 causes hypophosphorylation of p107 and p130. Hypophosphorylation of these pRB-related pocket proteins facilitates DREAM formation. DREAM complexes then displace the activating complexes FOXM1–B-MYB-MuvB (FOXM1-MMB) and E2F1-3/DP on the target promoters. (In the figure, LIN54 is the only labeled MuvB component.) Overall, this switch causes previously activated genes to be indirectly downregulation by p53

Another challenge in delineating activation of *p21/CDKN1A* is the formation of hetero-tetramers between p53 isoforms and the various proteins of the p53/p63/p73 family.[52,53] In particular, tetramer formation including isoforms such as Δ40p53 and Δ133p53 may compromise activation of *p21/CDKN1A* by other p53 family members.[43] Which combination of p53 isoforms and other p53/p63/p73 family members compete for binding sites in the *p21/CDKN1A* promoter depends on cell type and developmental stage-specific expression of these factors.

As the next step in the p53–DREAM pathway, p21/CDKN1A inhibits cyclin-dependent kinase complexes such as cyclin E/A-CDK2 and cyclin D-CDK4/6.[54,55] In turn, these cyclin/CDK complexes are no longer able to phosphorylate p107 and p130.[56] The resulting hypophosphorylated p107 or p130 proteins attach to the MuvB core complex and shift the equilibrium from FOXM1-MMB to DREAM.[22,35,39] Concomitant to this shift in MuvB-derived complex composition, transcriptional activation through FOXM1-MMB switches to repression by DREAM. Thus, genes active before p53 activation become repressed following p53 induction (Figure 3). At this step, the DREAM pathway shows a parallel regulation to the control by pRB because hypophosphorylation of pRB leads to pRB/E2F complex formation.[57]

p21/CDKN1A is most likely not the only protein which can inhibit cyclin/CDK complexes that can phosphorylate p107 and p130, thereby promoting DREAM formation.[56] Other CDK inhibitor proteins can substitute for p21/CDKN1A to inhibit cyclin E/A-CDK2 and cyclin D-CDK4/6 combinations.

These inhibitors include p27/Kip1/CDKN1B and p57/Kip2/CDKN1C, both members of the Cip/Kip family with broad complex formation capacity, as well as p16/INK4A/CDKN2A, p15/INK4B/CDKN2B, p18/INK4C/CDKN2C and p19/INK4D/CDKN2D of the INK4 family with narrow binding specificity towards cyclin D-CDK4/6 complexes.[58]

Although the function of p21/CDKN1A in cell cycle checkpoint control and thus a possible role in tumor suppression has been confirmed many times, one observation that may be related to this possible cdk inhibitor redundancy is the absence of p21/CDKN1A mutations in tumors and the lack of spontaneous tumorigenesis in *p21/Cdkn1a* (−/−) mice.[59,60] Consistently, recent results from several knockout models show that loss of p21/CDKN1A function alone is not sufficient for tumor development.[61,62]

Cyclin-dependent kinase regulation may even be more complex. Contrasting the canonical CDK inhibitor function, potential activation of cyclin/CDK complexes by p21/CDKN1A and p27/Kip1/CDKN1B has been discussed, with CDK

inhibitors functioning as cyclin/CDK assembly factors, mediating nuclear localization of D-type cyclins, and contributing to stability of cyclin D-CDK4 complexes.[58,63,64] Thus, it remains open whether additional signaling steps aside from the p53–p21/CDKN1A axis signal into the DREAM pathway.

Target gene selection by DREAM dictates the cellular response of indirect p53-mediated gene repression. Four types of binding represented by the two main classes of target genes with either E2F or CHR sites can be distinguished (Figure 2). Depending on the specific promoter of the gene, either E2F or CHR elements bind the complexes independently or with the support of CDE or CLE sites, respectively (Figures 2 and 3).

Before the p53-dependent switch to transcriptional repression, target genes are activated by two different mechanisms. E2F elements bind E2F1-3/DP proteins for activation, whereas promoters carrying CHR sites are activated by FOXM1-MMB. Both groups of promoter elements then switch to DREAM binding for repression (Figure 3).

Taken together, this sequence of reactions constitutes the p53–p21–DREAM–E2F/CHR or short the p53–DREAM pathway.[39]

Target Genes for Indirect p53-Dependent Repression

With the p53–DREAM pathway as a basis, criteria for identification of targets for indirect transcriptional downregulation by p53 are straightforward to define. Downregulation of target mRNA following p53 activation, DREAM binding to the target gene, and the presence of E2F or CHR sites in the proximal promoter are pivotal criteria for identification of target genes. There are many studies describing changes in mRNA levels employing a few different cell systems to compare expression with or without active p53.[17,65] Furthermore, the binding of DREAM components to these target genes can be assayed by ChIP. Subsequently, this information can be combined with the presence of E2F or CHR sites in the promoters. Of course, the quality of p53–DREAM target identification improves considerably the more results from independent studies are combined. We have employed bioinformatic tools to search for overlaps in a large number of reports on differential mRNA expression after p53 induction, on the binding of DREAM components by ChIP, and whether the potential target genes display E2F or CHR elements.[17,66] With a more recent analysis, the www.targetgenereg.org website was established. This site is updated with links to new data reports and allows retrieving results from genome-wide analyses easily.[65,67]

Here, a compilation of p53–DREAM target genes is provided (Table 1). In order to obtain a catalog of high-confidence targets, criteria for inclusion as targets were binding of p130, E2F4, LIN9, LIN54, and the lack of binding by p53 as assayed by ChIP in combination with downregulation of target gene mRNA after activation of p53. The data for individual genes were retrieved from www.targetgenereg.org and several meta-analyses.[17,29,31,65–67] Although most of the p53–DREAM target genes were identified merely by such meta-analyses, several genes such as *CCNB1, CDK1, CCNB2, KIF23, PLK4, BIRC5, CDC25C* and *PLK1* have already been found or confirmed in detailed experiments as targets of the p53–DREAM pathway.[19,22,39,68,69] Nevertheless, meta-analyses of genome-wide studies bypass such experimental efforts for individual genes and yield more than 250 high-confidence p53–DREAM targets (Table 1).

The compilation of p53–DREAM targets represents numerous cellular functions (Table 1 and Figure 4). The many protein classes found among the p53–DREAM targets are illustrated by examples such as kinases, protein chaperones, DNA helicases, ubiquitin ligases, phosphatases, methyltransferases, nucleases, ATPases and transcription factors (Table 1). Most gene products participate in cell cycle control. Examples for particular functions are DNA replication, nucleosome packaging, mitotic spindle assembly and chromosome segregation. Thus, it is becoming evident that the p53–DREAM pathway coordinately downregulates a plethora of genes which are categorized into functional groups (Figure 4).

Checkpoint Control from DNA Synthesis to Cytokinesis

p53 can induce cell cycle arrest at several stages, including G_1/S and G_2/M checkpoints.[1–4] For example, it has been shown that p53 can induce G_1 arrest via p21/CDKN1A-dependent inhibition of cyclin A/E-CDK2.[55] Also progression through G_2 phase and mitosis can be affected by p53, as several early studies showed that p53 is responsible for the downregulation of many genes important for checkpoint control from G_1 through cytokinesis.[70–73] However, at the time it was not evident that such checkpoint control by p53 is based on a common mechanism[17,39,66] (Figure 3). Now it is apparent that many proteins controlling cell cycle checkpoints are regulated by the p53–DREAM pathway and are clustered in functional groups (Table 1 and Figure 4).

Coordinated Transcriptional Repression by the p53–DREAM Pathway

A major feature of p53-dependent repression is that whole groups of functionally related genes are indirectly downregulated. Many such groups are defined by their function and timing of expression during the cell cycle. DREAM-dependent transcriptional repression employs binding to E2F or CHR sites as a determinant for early or late expression in the cell cycle, respectively.[31,33] Genes with maximum expression in the G_1 and S phases are controlled through E2F or E2F/CLE sites and can be activated by E2F1-3/DP complexes, whereas genes expressed in the G_2 phase and mitosis are upregulated by MMB and FOXM1-MuvB activator complexes through CHR or CDE/CHR elements (Figure 1).

G_1/S Checkpoint Genes are Repressed by DREAM Binding to E2F Sites

One group of DREAM target genes important for the G_1/S checkpoint is represented by *POLA1, MCM2* and *ORC1*[74,75] (Table 1). Furthermore, several DREAM targets, that is, *cyclin A, CDK2, CDC6* and *CDT1,* are active in a checkpoint preventing rereplication (Table 1).[73,76] Interestingly, many genes previously described as classical E2F targets and hallmark genes for S phase progression such as *TK1* and

Table 1 Genes regulated by the p53–DREAM pathway

Genes regulated by the p53–DREAM pathway				
Protein name	**Protein**	**Function, enzymatic activity**	**GO – Gene Ontology**	**Gene**
Adrenocortical dyspl. pr. hom., shelterin compl. sub. telom. recruit.	ACD	Complex form., DNA binding	Telomere maintenance	ACD
Anillin, actin-binding protein anillin	anillin	Actin binding	Mitosis	ANLN
Rho GTPase-activating protein 11A	ARHGAP11A	GTPase activator activity	Small GTPase-mediated signal transduction	ARHGAP11A
Rho GTPase-activating protein 11B	ARHGAP11B	Rho GTPase activation	Small GTPase-mediated signal transduction	ARHGAP11B
Rho guanine nucleotide exchange factor 39, C9orf100	ARHGEF39	Rho guanyl-nucleotide exch.	Cell migration, Rho protein signal transduction	ARHGEF39
ADP-ribosylation factor-like protein 13B	ARL13B	GTP binding	Cilium assmb., small GTPase signal transduction	ARL13B
ADP-ribosylation factor-like protein 6-interacting protein 1	ARL6IP1	Chromosomal pass. complex	Cotranslational protein targeting to membrane	ARL6IP1
Anti-silencing function 1B histone chaperone	ASF1B	Histone chaperone	Chromatin assembly, DNA replication	ASF1B
Abnormal spindle-like microcephaly-associated protein	ASPM	Complex formation	Spindle assembly, mitosis, neurogenesis	ASPM, MCPH5
ATPase family AAA domain-containing protein 2	ATAD2	ATPase	Transcriptional coactivator	ATAD2
Aurora kinase A	AURKA	Serine/threonine kinase	Spindle/microtubule formation, mitosis	AURKA
Aurora kinase B	AURKB	Serine/threonine kinase	Cytokinesis, histone modification, mitosis	AURKB
BLM, Bloom syndrome RecQ like helicase	BLM	DNA helicase	DNA replication and repair	BLM
MYB proto-oncogene like 2	B-MYB, MYBL2	Transcription factor	S phase, activator	MYBL2
Borealin, CDCA8	Borealin, CDCA8	Complex formation	Chromosomal passenger complex, spindle form.	CDCA8, Borealin
BRCA1, Breast cancer type 1 susceptibility protein	BRCA1	Ubiquitin ligase	DNA repair, transcription, ubiquitination	BRCA1, FANCS
BRCA2, Breast cancer type 2 susceptibility protein	BRCA2	Complex formation	DNA repair, transcription	BRCA2, FANCD1
BRIP1, BRCA1 interacting protein C-terminal helicase 1	BRIP1, BACH1	DNA helicase and ATPase	DNA replication and repair	BRIP1, FANCJ
BUB1, mitotic checkpoint serine/threonine kinase	BUB1	Serine/threonine kinase	Spindle formation, mitosis	BUB1
BUB3, mitotic checkpoint protein	BUB3	Protein binding, WD repeats	Spindle formation, mitosis	BUB3
BUB1, mitotic checkpoint serine/threonine kinase B	BUBR1, BUB1B	Serine/threonine kinase	Spindle formation, mitosis	BUB1B, BUBR1
Calcyclin-binding protein	CACYBP	Complex formation	Ubiquitin-mediated degradation of beta-catenin	CACYBP
Cancer susceptibility candidate 5, Kinetochore-null protein 1	CASC5, KNL1	Protein binding	Kinetochore, spindle formation, mitosis	KNL1, CASC5
Chromobox protein homolog 3, Heterochromatin prot. 1 hom. gam.	CBX3, HECH	Histone binding	Transcription, histone methyltransferase binding	CBX3
Coiled-coil domain-containing protein 150	CCDC150			CCDC150
Coiled-coil domain-containing protein 18, Sarco antig NY-SAR-24	CCDC18			CCDC18
Coiled-coil domain-containing protein 34, Ren carc ant NY-REN-41	CCDC34			CCDC34
CDC20, Cell division cycle protein 20	CDC20, p55CDC	Complex formation	mitotic spindle assembly checkpoint, mitosis	CDC20, p55CDC
CDC20, cell division cycle 25A, M-phase inducer phosphatase 1	CDC25A	Tyrosine phosphatase	G1/S and G2/M transition	CDC25A
CDC25B, Cell division cycle 25B, M-phase inducer phosphatase 2	CDC25B	Tyrosine phosphatase	G2/M phases and abscission during cytokinesis	CDC25B
CDC25C, cell division cycle 25C, M-phase inducer phosphatase 3	CDC25C	Tyrosine phosphatase	G2/M phases and abscission during cytokinesis	CDC25C
CDC6, cell division cycle 6	CDC6		G1/S transition, DNA replication	CDC6
CDC7, cell division cycle 7	CDC7	Protein kinase	G1/S transition	CDC7
CDCA2, cell division cycle-associated protein 2, Repo-Man	CDCA2	Complex formation	Chromosome segregation	CDCA2
Cell division cycle-assoc. prot. 3, trigger of mitotic entry protein 1	CDCA3, TOME-1	F-box-like protein	Protein ubiquitination	CDCA3, TOME-1
CDK1, cyclin-dependent kinase 1, cdc2	CDK1, CDC2	Serine/threonine kinase	G1/S and G2/M transition	CDK1, CDC2
CDK2, cyclin-dependent kinase 2	CDK2	Serine/threonine kinase	G1/S and G2/M transition	CDK2
CDKN2D, cyclin-dependent kinase 4 inhibitor D, p19-INK4d	CDKN2D, p19	CDK4/6 inhibitor	G1/S transition	CDKN2D

Table 1 (Continued)

Genes regulated by the p53–DREAM pathway				
Protein name	**Protein**	**Function, enzymatic activity**	**GO – Gene Ontology**	**Gene**
CDKN3, cyclin-dependent kinase inhibitor 3, CDI1, CIP2, KAP	CDKN3, CIP2	CDK2 phosphatase	Regulation of cyclin-dependent kinase activity	CDKN3
Chromatin licensing and DNA replication factor 1	CDT1	Chromatin binding	DNA replication, mitosis	CDT1
CENP-A, Histone H3-like centromeric protein A	CENP-A	Chromatin binding	Nucleosome and kinetochore assembly	CENPA
CENP-C, centromere protein C	CENP-C	Kinetochore binding	Microtubule function, cytokinesis, mitosis	CENPC
CENP-E, centromere protein E	CENP-E	Kinetochore binding	Microtubule function, cytokinesis, mitosis	CENPE
CENP-F, centromere protein F, Mitosin	CENP-F, Mitosin	Kinetochore binding	Microtubule function, cytokinesis, mitosis	CENPF, CENF
CENP-L, centromere protein L	CENP-L, ICEN33	Chromatin binding	Nucleosome and kinetochore assembly	CENPL, ICEN33
CENP-N, centromere protein N	CENP-N, ICEN32	Chromatin binding	Nucleosome and kinetochore assembly	CENPN, ICEN32
CENP-O, centromere protein O	CENP-O	Complex formation	Nucleosome assembly, centromere, mitosis	CENPO
CENP-W, centromere protein W	CENP-W	Complex formation	Nucleosome assembly, centromere, mitosis	CENPW
CEP55, centrosomal protein of 55 kDa	CEP55	Complex formation	Mitotic exit, cell separation after cytokinesis	CEP55
CEP152, centrosomal protein of 152 kDa	CEP152	Protein kinase binding	Centriole and centrosome duplication	CEP152
CEP295, centrosomal protein 295, DD8	CEP295, DD8	Complex formation	centrosome, microtubules, cytoskeleton, cilium	CEP295, KIAA1731
CHAF1A, chromatin assembly factor 1 subunit A	CHAF1A	Histone binding	Histone octamer assembly, chromatin, replicat.	CHAF1A
CHEK1, checkpoint kinase 1	CHEK1	Serine/threonine kinase	DNA damage response, G2/M transition	CHEK1
CHEK2, checkpoint kinase 2	CHEK2	Serine/threonine kinase	DNA damage response, G2/M transition	CHEK2
CIP2A, cancerous inhibitor of protein phosphatase 2A	CIP2A	Phosphatase inhibitor	Oncoprotein, cell adhesion, transcription	KIAA1524, CIP2A
CIT, Citron Rho-interacting kinase	CIT, CRIK	Serine/threonine kinase	Cytokinesis, GTPase signal transduction	CIT, CRIK
Cytoskeleton-associated protein 2, tumor- and microtub.-assoc.	CKAP2, TMAP	Microtubule stabilizing	Apoptotic process, microtubule polymerization	CKAP2
CKAP2L, cytoskeleton-associated protein 2-like, Radmis	CKAP2L, Radmis	Complex formation	Microtubule bundles, centrioles during mitosis	CKAP2L
CKAP5, cytoskeleton-associated protein 5	CKAP5	Microtubule binding	Microtubule cytoskeleton polarity, spindle pole	CKAP5
Cyclin-dependent kinases regulatory subunit 1, CDC28 kin sub 1B	CKS-1, CKS-1B	Cyclin-dep. kinase binding	G1/S transition, CDK binding	CKS1B, CKS1
CKS-2, cyclin-dependent kinases regulatory subunit 2	CKS-2	Cyclin-dep. kinase binding	Meiosis I, CDK binding	CKS2
CMS1, ribosomal small subunit homolog	CMSS1, CMS1	Poly(A) RNA binding	Poly(A) RNA binding	CMSS1
CTD small phosphatase-like protein 2	CTDSPL2	Protein phosphatase	BMP signaling pathway, transport from nucleus	CTDSPL2
Cyclin A	Cyclin A, cyclin A2	Complex formation	Serine/threonine kinase activation, mitosis	CCNA, Ccna2
Cyclin B1	cyclin B1	Complex formation	Serine/threonine kinase activation, mitosis	CCNB1
Cyclin B2	Cyclin B2	Complex formation	Serine/threonine kinase activation, mitosis	CCNB2
DAP-5, Disks large-associated protein 5	DAP-5, DLGAP5		Metaphase/anaphase transition, ubiqutination	DLGAP5, DLG7
DARS2, Aspartate-tRNA ligase, mitochondrial	DARS2	Aspartate-tRNA ligase	Gene expression, aminoacylation for translation	DARS2
Protein DBF4 homolog B, activator of S phase kinase-like prot. 1	DBF4B, ASKL1	CDC7 kinase activation	DNA replication, G2/M transition	DBF4B, DRF1
DCAF16, DDB1- and CUL4-associated factor 16	DCAF16	Protein ubiquitination	Protein ubiquitination	DCAF16
DCK, deoxycytidine kinase	DCK	Nucleoside kinase	Nucleotide biosynthetic process	DCK
DCLRE1B, 5' exonuclease Apollo	DCLRE1B, APOLLO	5'–3' DNA exonuclease	Telomere maintenance, double-strand br. rep.	DCLRE1B
DCP2, m7GpppN-mRNA hydrolase	DCP2	mRNA-decapping enzyme	Regulation of mRNA stability, gene expression	DCP2
DNA damage-induced apoptosis suppressor, NO-inducible prot.	DDIAS, NOXIN		Apoptosis, DNA damage resp., cell cycle arrest	DDIAS, NOXIN
DDX10, ATP-dependent RNA helicase DDX10	DDX10	RNA helicase		DDX10

Table 1 (Continued)

Genes regulated by the p53–DREAM pathway				
Protein name	**Protein**	**Function, enzymatic activity**	**GO – Gene Ontology**	**Gene**
			RNA secondary structure unwinding	
DEK, proto-oncogene	DEK	Histone binding	Chromatin modification, mRNA processing	DEK
DEPDC1, DEP domain-containing protein 1A	DEPDC1	Transcriptional corepressor	GTPase activator activity, transcription	DEPDC1
DEPDC1B, DEP domain-containing protein 1B	DEPDC1B	GTPase activator activity	Cell migration, Wnt signaling pathway, GTPase	DEPDC1B, XTP1
Dihydrofolate reductase	DHFR	Oxidoreductase	DNA synthesis	DHFR
DLEU1, Leukemia-associated protein 1	DLEU1			DLEU1, XTP6
DNMt3B, DNA methyltransferase 3 beta	DNMT3B	Methyltransferase	Chromatin binding, transcriptional corepressor	DNMT3B
E2F1, E2F transcription factor 1	E2F1	Transcription factor	Cell cycle	E2F1
ECT2, epithelial cell transforming 2	ECT2	GTPase	Cytokinesis, spindle formation, mitosis	ECT2
establishment of sister chromatid cohesion *N*-acetyltransferase 2	ESCO2	Lysine N-acetyltransferase	Chromosome segregation	ESCO2
EXO1, Exonuclease 1	EXO1	DNA nuclease	DNA repair, recombination, replication	EXO1
EXOSC8, exosome component 8	EXOSC8	Exoribonuclease	RNA degradation	EXOSC8
EXOSC9, exosome component 9	EXOSC9	Complex formation	RNA degradation	EXOSC9
Exportin-2, CSE1 chromosome segregation 1-like	Exportin-2	Export receptor importin-a	Protein transport from/to nucleus	CSE1L
Histone-lysine N-methyltransferase, enhancer of zeste 2 polycomb	EZH2	Lysine *N*-methyltransferase	Histone modification, chromatin organization	EZH2
FAM64A, family with sequence similarity 64 member A	FAM64A	Complex formation	Mitosis	FAM64A
FAM83D, family with sequence similarity 83 member D	FAM83D	Complex formation	Mitosis	FAM83D
FANCA, Fanconi anemia complementation group A	FANCA	Complex formation	Fanconi anemia, DNA repair	FANCA
FANCB, Fanconi anemia complementation group B	FANCB	Complex formation	Fanconi anemia, DNA repair	FANCB
FANCC, Fanconi anemia complementation group C	FANCC	Complex formation	Fanconi anemia, DNA repair	FANCC
FANCD2, Fanconi anemia complementation group D2	FANCD2	Complex formation	Fanconi anemia, DNA repair	FANCD2
FANCE, Fanconi anemia complementation group E	FANCE	Complex formation	Fanconi anemia, DNA repair	FANCE
FANCG, Fanconi anemia complementation group G	FANCG	Complex formation	Fanconi anemia, DNA repair	FANCG
FANCI, Fanconi anemia complementation group I	FANCI	DNA binding, complex form.	Fanconi anemia, DNA repair	FANCI
FANCL, Fanconi anemia complementation group L	FANCL	Ubiquitin ligase	Fanconi anemia, DNA repair	FANCL
FANCM, Fanconi anemia complementation group M	FANCM	ATPase, DNA binding	Fanconi anemia, ubiquitination, DNA repair	FANCM
FBXO5, F-box protein 5, Early mitotic inhibitor 1, EMI1, FBX5	FBXO5	Complex formation	Mitosis	FBXO5
FEN1, flap structure-specific endonuclease 1	FEN1	DNA nuclease	DNA repair	FEN1, RAD2
FOXM1, forkhead box M1	FOXM1	Transcription factor	G2 phase, mitosis, activator	FOXM1
FZR1, fizzy/cell division cycle 20 related 1	FZR1	Activator of ubiquitination	Mitosis, anaphase promoting complex/cyclos.	FZR1
G2E3, G2/M-phase specific E3 ubiquitin protein ligaseprovided	G2E3	Ubiquitin ligase	G2 phase, mitosis	G2E3
GASL2L3, growth arrest specific 2 like 3	GAS2L3	Complex formation	Cytokinesis	GAS2L3
GPSM2, G-protein signaling modulator 2provided	GPSM2	GDP-dissociation inhibitor	G-protein coupled receptor sign., mitotic spindle	GPSM2
GTSE1, G2 and S-phase expressed 1	GTSE1	Complex formation	Microtubule organization	GTSE1
histone, H2A histone family member X	H2AFX, H2AX	Histone	Nucleosome formation, DNA repair	H2AFX
histone, H2A histone family member Z	H2AFZ, H2AZ	Histone	Nucleosome formation, embryonic development	H2AFZ
haspin, germ cell associated 2	haspin, GSG2	Serine/threonine kinase	Mitosis, microtubule organization	GSG2
HAUS augmin like complex subunit 6	HAUS6	Complex formation	Cytokinesis, spindle assembly	HAUS6
HAUS augmin like complex subunit 8	HAUS8, HICE1	Complex formation	Cytokinesis, spindle assembly	HAUS8
histone cluster 1 H2A family member e	HIST1H2AE, H2A.1	Histone	Nucleosome formation	HIST1H2AE
histone cluster 1 H2A family member m	HIST1H2AM	Histone	Nucleosome formation	HIST1H2AM
histone cluster 1 H2B family member f	HIST1H2BF	Histone	Nucleosome formation	HIST1H2BF
histone cluster 1 H2B family member h	HIST1H2BH	Histone	Nucleosome formation	HIST1H2BH
histone cluster 1 H2B family member i	HIST1H2BI	Histone	Nucleosome formation	HIST1H2BI
histone cluster 1 H2B family member m	HIST1H2BM	Histone	Nucleosome formation	HIST1H2BM
histone cluster 1 H3 family member c	HIST1H3C	Histone	Nucleosome formation	HIST1H3C
histone cluster 1 H3 family member d	HIST1H3D	Histone	Nucleosome formation	HIST1H3D

Table 1 (Continued)

Genes regulated by the p53–DREAM pathway				
Protein name	**Protein**	**Function, enzymatic activity**	**GO – Gene Ontology**	**Gene**
histone cluster 1 H4 family member c	HIST1H4C	Histone	Nucleosome formation	HIST1H4C
histone cluster 2 H2A family member b	HIST2H2AB	Histone	Nucleosome formation	HIST2H2AB
histone cluster 2 H2A family member c	HIST2H2AC	Histone	Nucleosome formation	HIST2H2AC
Holliday junction recognition protein	HJURP	DNA binding, chaperone	Centromere, nucleosome assembly	HJURP
HMGB2, High mobility group protein B2	HMGB2, HMG2	DNA binding	Chromatin, transcription, recombination	HMGB2
HMMR, Receptor for hyaluronan-med. motility, RHAMM, CD168	HMMR, RHAMM	Complex formation	Cell adhesion, mitosis, hyaluronic acid binding	HMMR, RHAMM
HNRNPA0, heterogeneous nuclear ribonucleoprotein A0	HNRNPA0	RNA binding	mRNA processing	HNRNPA0
HNRNPA2B1, heterogeneous nuclear ribonucleoprotein A2/B1	hnRNP A2/B1	RNA binding	RNA and single-stranded telomeric DNA binding	HNRNPA2B1
BORA, Aurora kinase A activator, protein aurora borealis	HsBora	Kinase binding	Spindle/microtubule formation, mitosis	BORA
IFT80, intraflagellar transport 80	IFT80	Complex formation	Cilia assembly	IFT80
INCENP, inner centromere protein	INCENP	Complex formation	Cytokinesis, centromere, microtubule binding	INCENP
ING1, inhibitor of growth family member 1	ING1	Complex formation	p53 interaction, tumor suppr., chromatin	ING1
Ki-67	Ki-67	Complex formation	Mitotic chromosome stabilization	MKI67
KIF11, kinesin family member 11	KIF11, EG5	Microtubule binding	Microtubule function, cytokinesis, mitosis	KIF11, EG5
KIF14, kinesin family member 14	KIF14	Microtubule binding	Microtubule function, cytokinesis, mitosis	KIF14
KIF15, kinesin family member 15	KIF15	Microtubule binding	Microtubule function, cytokinesis, mitosis	KIF15
KIF18A, kinesin family member 18A	KIF18A	Microtubule binding	Microtubule function, cytokinesis, mitosis	KIF18A
KIF20B, kinesin family member 20B, M-phase phosphoprotein-1	KIF20B, MPP1	Microtubule binding	Microtubule function, cytokinesis, mitosis	KIF20B, MPP1
KIF22, kinesin family member 22	KIF22, KID	Microtubule binding	Microtubule function, cytokinesis, mitosis	KIF22, KID
KIF23, kinesin family member 23, Mitotic kinesin-like protein 1	KIF23, MKLP1	Microtubule binding	Microtubule function, cytokinesis, mitosis	KIF23, MKLP1
KIF24, kinesin family member 24	KIF24	Microtubule binding	Microtubule function, cytokinesis, mitosis	KIF24
KIF2C, kinesin family member 2C, Mitotic centromere-ass. kinesin	KIF2C, MCAK	Microtubule binding	Microtubule function, cytokinesis, mitosis	KIF2C
KIF4A, kinesin family member 4A	KIF4A, KIF4	Microtubule binding	Microtubule function, cytokinesis, mitosis	KIF4A
KIFC1, kinesin family member C1	KIFC1	ATPase	Microtubule motor activity, spindle assembly	KIFC1
KPNA2, Importin subunit alpha-1, karyopherin subunit alpha 2	KPNA2	Protein transporter	Nuclear protein import, recombination	KPNA2
KPNB1, Importin subunit beta-1, karyopherin subunit beta 2	KPNB1	Protein transporter	Nuclear protein import	KPNB1
lamin B1	lamin B1	Lamin	Nuclear lamina	LMNB1
Acidic leucine-rich nuclear phosphoprotein 32 family member E	LANP-like protein	Histone chaperone	Histone exchange, chromatin modification	ANP32E
LIN-54 DREAM MuvB core complex component	LIN54	DNA binding	Transcription, activator, repessor, cell cycle	LIN54
LIN-9 DREAM MuvB core complex component	LIN9	complex, transcription	transcription, activator, repessor, cell cycle	LIN9
LSM5, U6 snRNA-associated Sm-like protein LSm5	LSM5	RNA binding	mRNA processing	LSM5
MAD2, Mitotic spindle assembly checkpoint protein MAD2A	MAD2	Complex formation	Mitotic spindle assembly checkpoint, mitosis	MAD2L1, MAD2
MAD3, Max dimerization protein 3	MAD3, MXD3	Transcription factor	MYC/MAX-related, repressor	MXD3
GREATWALL, microtubule associated serine/threonine kinase like	MASTL	Serine/threonine kinase	G2 phase, mitosis	MASTL
MCM2, minichromosome maintenance complex component 2	MCM2	Complex formation, ATPase	DNA helicase, replication	MCM2
MCM3, minichromosome maintenance complex component 3, HCC5	MCM3, HCC5	Complex formation, ATPase	DNA helicase, replication	MCM3
MCM4, minichromosome maintenance complex component 4	MCM4	Complex formation, ATPase	DNA helicase, replication	MCM4
MCM5, minichromosome maintenance complex comp. 5, CDC46	MCM5, CDC46	Complex formation, ATPase	DNA helicase, replication	MCM5
MCM6, minichromosome maintenance complex component 6, Mis5	MCM6, Mis5	Complex formation, ATPase	DNA helicase, replication	MCM6

Table 1 (Continued)

Genes regulated by the p53–DREAM pathway				
Protein name	**Protein**	**Function, enzymatic activity**	**GO – Gene Ontology**	**Gene**
MCM7, minichromosome maintenance complex comp. 7, CDC47	MCM7, CDC47	Complex formation, ATPase	DNA helicase, replication	MCM7
MCM8, minichromosome mainten. 8 homolog. recomb. repair factor	MCM8	Complex formation, ATPase	Helicase, replication, homolog. recomb. repair	MCM8
MDC1, mediator of DNA damage checkpoint 1	MDC1	Complex formation	DNA repair, checkpoint control, S, G2, M phase	MDC1
MELK1, maternal embryonic leucine zipper kinase	MELK	Serine/threonine kinase	Apoptosis, G2/M transition	MELK
METTL4, methyltransferase like 4	METTL4	DNA Methyltransferase	DNA methylation, adenine-specific	METTL4
MIS18, kinetochore protein A	MIS18A	Complex formation	Centromere complexes, chromosome segregat.	MIS18A
MIS18BP1, MIS18 binding protein 1	MIS18BP1	Complex formation	Centromere complexes, chromosome segregat.	MIS18BP1
MND1, meiotic nuclear divisions 1	MND1	DNA binding	Meiosis, DNA recombination	MND1
MSH2, mutS homolog 2, Heredit. non-polyp. color. Canc. 1, HNPCC	MSH2	Complex formation, ATPase	DNA repair, mismatch repair	MSH2, HNPCC
MSH6, mutS homolog 6	MSH6	Complex formation, ATPase	DNA repair, mismatch repair	MSH6
metal response element bind. transcription fact. 2, polycomblike 2	MTF2, PCL2	DNA binding	Histone binding, transcription, repression	MTF2
MZT1, Mitotic-spindle organizing protein 1	MZT1, MOZART1	Complex formation	Tubulin binding, centrosome, spindle assembly	MZT1
NASP, nuclear autoantigenic sperm protein	NASP	Histone binding	DNA replication	NASP
NCAPD2, condensin, non-SMC condensin I complex subunit D2	NCAPD2	Complex formation	Chromosome condensation, mitosis	NCAPD2
NCAPD3, condensin, non-SMC condensin II complex subunit D3	NCAPD3	Complex formation	Chromosome condensation, mitosis	NCAPD3
NCAPG, condensin, non-SMC condensin I complex subunit G	NCAPG	Complex formation	Chromosome condensation, mitosis	NCAPG
NCAPG2, condensin, non-SMC condensin II complex subunit G2	NCAPG2	Complex formation	Chromosome condensation, mitosis	NCAPG2
NCAPH, condensin, non-SMC condensin I complex subunit H	NCAPH	Complex formation	Chromosome condensation, mitosis	NCAPH
NDC1, transmembrane nucleoporin	NDC1, TMEM48	Complex formation	Nuclear envelope assembly, nuclear transport	NDC1, TMEM48
NDC80, kinetochore complex component NDC80	NDC80	Complex formation	Chromosome segregation, microtubule binding	NDC80
NEIL3, nei like DNA glycosylase 3	NEIL3	DNA endonuclease	DNA repair	NEIL3
NEK2, NIMA related kinase 2	NEK2	Serine/threonine kinase	Chromosome condensation, spindle assembly	NEK2
NET1, neuroepithelial cell transforming 1	NET1	Rho guanyl-nucleotide exch.	Apoptosis, signal transduction	NET1
NOP58, ribonucleoprotein	NOP58	Complex formation	Ribosome biogenesis	NOP58
NOXIN, DNA damage-induced apoptosis suppressor	NOXIN, DDIAS		Apoptosis, response to DNA damage, mitosis	C11orf82, DDIAS
nuclear casein kinase and cyclin-dependent kinase substrate 1	NUCKS1, JC7	DNA binding	DNA damage response, homologous recomb.	NUCKS1
NUF2, NDC80 kinetochore complex component	NUF2, CDCA1	Complex formation	Chromosome segregation, microtubule binding	NUF2
NUP107, nucleoporin 107	NUP107	Complex formation	Nucleocytoplasmic transport	NUP107
NUP205, nucleoporin 205	NUP205	Complex formation	Nucleocytoplasmic transport	NUP205
NUP35, nucleoporin 35	NUP35, NUP53	Complex formation	Nucleocytoplasmic transport	NUP35
NUP85, nucleoporin 85, Pericentrin-1	NUP85	Complex formation	Nucleocytoplasmic transport	NUP85
NUSAP1, nucleolar and spindle associated protein 1	NUSAP1, SAPL	Complex formation	Mitotic spindle microtubules	NUSAP1
OCT1, POU class 2 homeobox 1, Octamer-binding protein 1	OCT1, POU2F1	Transcription factor	Proliferation, immune modulation	POU2F1
OIP5, Opa interacting protein 5	OIP5	Complex formation	Centromere binding, chromosome segregation	OIP5
ORC1, origin recognition complex subunit 1	ORC1	DNA binding	DNA replication	ORC1
PALB2, partner and localizer of BRCA2	PALB2, FANCN	Complex form., DNA bindg.	Fanconi anemia, DNA repair, replication	PALB2, FANCN
CENP-M, Centromere protein M	PANE1, CENP-M	Complex formation	Kinetochore formation, mitosis	CENPM
PARPBP, PARP1 binding protein	PARPBP	Complex formation	DNA repair, genomic stability	PARPBP
pericentrin	Pericentrin	Complex formation	Centrosome, microtubules, cilia assembly	PCNT
PHF19, PHD finger protein 19	PHF19	Complex formation		PHF19

Table 1 (Continued)

Genes regulated by the p53–DREAM pathway				
Protein name	**Protein**	**Function, enzymatic activity**	**GO – Gene Ontology**	**Gene**
			Histone binding, transcription, repression	
PICH, Plk1-interacting checkpoint helicase	PICH, ERCC6L	DNA helicase	DNA repair, spindle assembly, anaphase	ERCC6L
PIF1, 5'-to-3' DNA helicase	PIF1	ATPase, DNA helicase	DNA repair, telomere maintenance	PIF1
PLK1, Polo-like kinase 1	PLK1	Serine/threonine kinase	G2/M transition, mitosis	PLK1
PLK4, Polo-like kinase 4	PLK4	Serine/threonine kinase	G2/M transition, mitosis	PLK4, SAK
POC5, centriolar protein	POC5		Centriole elongation	POC5
POLA1, DNA polymerase alpha-1, catalytic subunit	POLA1	DNA polymerase	DNA replication	POLA1
POLD1, DNA polymerase delta 1, catalytic subunit	POLD1	DNA polymerase, exonucl.	DNA replication, DNA repair	POLD1
POLD3, DNA polymerase delta 3, accessory subunit	POLD3	DNA polymerase, exonucl.	DNA replication, DNA repair, mis-match repair	POLD3
POLE, DNA polymerase epsilon, catalytic subunit	POLE	DNA polymerase	DNA replication, DNA repair	POLE
POLQ, DNA polymerase theta	POLQ	DNA polymerase	DNA replication, DNA repair	POLQ
POP7 homolog, ribonuclease P/MRP subunit	POP7	Ribonuclease	tRNA processing	POP7
PPIH, peptidylprolyl isomerase H	PPIH	Peptidylprolyl isomerase	Protein folding, mRNA splicing	PPIH
PRC1, protein regulator of cytokinesis 1	PRC1	Complex formation	Cytokinesis, spindle formation, mitosis	PRC1
PRIM1, primase (DNA) subunit 1	PRIM1	DNA primase, RNA synthesis	DNA replication	PRIM1
PRIM2, primase (DNA) subunit 2	PRIM2	DNA primase	DNA replication, telomere maintenance	PRIM2
PRR11, proline rich 11	PRR11		Cell cycle regulation	PRR11
Partner of SLD Five 1, DNA replication complex GINS protein PSF1	PSF1, GINS1	DNA helicase	DNA helicase, replication	GINS1
Partner of SLD Five 2, DNA replication complex GINS protein PSF2	PSF2, GINS2	Complex formation	DNA helicase, replication	GINS2
PSRC1, proline and serine rich coiled-coil 1	PSRC1, DDA3	Complex formation	Microtubule polymerization, mitosis	PSRC1
Securin, PTTG1, pituitary tumor-transforming 1	PTTG1, securin	Complex formation	Mitotic spindle assembly check-point, mitosis	PTTG1
RACGAP1, Rac GTPase-activating protein 1	RACGAP1	Regulation of small GTPase	Cytokinesis, mitosis	RACGAP1
RAD18, E3 ubiquitin protein ligase	RAD18	Ubiquitin ligase	Detection of DNA damage, DNA repair	RAD18
RAD21, cohesin complex component	RAD21	Complex formation	Chromosome cohesion, DNA repair, apoptosis	RAD21
RAD51, recombinase	RAD51, FANCR	DNA-dependent ATPase	Fanconi anemia, DNA repair	RAD51, FANCR
RAD54-like	RAD54L	DNA helicase	DNA repair, mitotic recombination	RAD54L
RANGAP1, Ran GTPase-activating protein 1	RANGAP1	Ran GTPase activa-tor activity	Nuclear pore complex, kinetochore, mitosis	RANGAP1
RECQL4, RecQ like helicase 4	RECQL4	DNA helicase, ATPase	DNA repair, replication, recombination	RECQL4
REEP4, receptor accessory protein 4	REEP4	Complex formation	Microtubule bdg, nuclear envelope reassembly	REEP4
RHINO, RAD9-HUS1-RAD1 interacting nuclear orphan 1	RHINO	Complex formation	DNA repair, cellular response to DNA damage	RHNO1, C12orf32
RIF1, replication timing regulatory factor 1	RIF1	Complex formation	DNA repair, checkpoint control, telemore bindg.	RIF1
RNASEH2A, ribonuclease H2 subunit A	RNASEH2A	RNA endonuclease	DNA replication	RNASEH2A
RNF26, ring finger protein 26	RNF26	Ubiquitin ligase	Endosomal maturation and trafficking	RNF26
RPA2, replication protein A2	RPA2	Complex form., DNA bindg.	DNA repair, replication	RPA2
RTKN2, rhotekin 2	RTKN2	Rho GTPase effector	Cell cycle regulation, apoptosis	RTKN2
SAS-6 centriolar assembly protein, Spindle assem. abn. protein 6	SAS6, SASS6	Complex formation	Centrosome duplication, procen-triole formation	SASS6
SCLT1, sodium channel and clathrin linker 1	SCLT1	Complex formation	Clathrin binding, cilia assembly	SCLT1
Separase, extra spindle pole bodies like 1	Separase, ESPL1	Protease	Chromosome segregation	ESPL1
SETD8, lysine methyltransferase 5A	SETD8, KMT5A	Lysine *N*-methyltransferase	Protein methylation, transcriptional repression	KMT5A, SETD8
SGO1, shugoshin 1	SGO1, SGOL1	Complex formation	Chromosome segregation, centro-mere binding	SGOL1, SGO1
SGO2, shugoshin 2	SGO2, SGOL2	Complex formation		

Table 1 (Continued)

Genes regulated by the p53–DREAM pathway				
Protein name	**Protein**	**Function, enzymatic activity**	**GO – Gene Ontology**	**Gene**
			Sister chromatid cohesion, meiosis, centromere	SGOL2, SGO2
SHCBP1, SHC binding and spindle associated 1	SHCBP1		Cell proliferation	SHCBP1
SKA1, Spindle and kinetochore-associated protein 1	SKA1	Complex formation	Kinetochore, microtubules, mitosis	SKA1
SKAP, kinetochore localized astrin/SPAG5 binding protein	SKAP, KNSTRN	Complex formation	Mitotic spindle, chromosome segregation	KNSTRN
SKP2, S-phase kinase associated protein 2	SKP2	F-box-like protein	Protein ubiquitination	SKP2
SLC25A40, solute carrier family 25 member 40	SLC25A40		Mitochondrial carrier	SLC25A40
SMC-2, structural maintenance of chromosomes 2	SMC-2	ATP binding	DNA condensation, mitosis	SMC2
SMC-4, structural maintenance of chromosomes 4	SMC-4	ATP binding	DNA condensation, mitosis	SMC4
structural maintenance of chromos. Flex. hinge domain contain. 1	SMCHD1	Complex formation	DNA methylation	SMCHD1
Sororin, CDCA5	Sororin, CDCA5	Chromatin binding	Mitotic sister chromatid cohesion	CDCA5, Sororin
Sp4, transcription factor	SP4	Transcription factor	Transcription	SP4
SPAG5, sperm associated antigen 5	SPAG5	Complex formation	Mitotic spindle, chromosome segregation	SPAG5
SPC25, NDC80 kinetochore complex component	SPC25	Complex formation	Chromosome segregation, microtubule binding	SPC25
Spindly, Coiled-coil domain-containing protein 99	SPDL1/ CCDC99	Kinetochore binding	Establishment of mitotic spindle orientation	SPDL1/ CCDC99
STIL, SCL/TAL1 interrupting locus	STIL		Embryonic development, cell proliferation	STIL
STK17B, serine/threonine kinase 17b (apoptosis-inducing)	STK17B, DRAK2	Serine/threonine kinase	Apoptosis	STK17B, DRAK2
Survivin, baculoviral IAP repeat containing 5	Survivin, BIRC5	Chromosomal pass. complex	Mitosis, cytokinesis, transcription	BIRC5
SUZ12, polycomb repressive complex 2 subunit	SUZ12	Complex formation	Transcriptional repession, histone methylation	SUZ12
TACC3, transforming acidic coiled-coil containing protein 3	TACC3, ERIC1	Complex formation	Spindle/microtubule formation, mitosis	TACC3
Tastin, Trophinin-assisting protein, TROAP	Tastin, TROAP	Complex formation	Cell adhesion	Tastin, TROAP
TCERG1, transcription elongation regulator 1	TCERG1, CA150	Transcription factor	Inhibition of transcript elongation	TCERG1
TIMELESS, timeless circadian clock	TIMELESS, TIM1	Complex formation	Circadian rhythm, DNA repair, replication	TIMELESS
Thymidine kinase 1	TK1	Kinase	DNA synthesis	TK1
Thymopoietin, Lamina-associated polypeptide 2, isoform alpha	TMPO, LAP2	Complex formation	Nuclear structure, post-mitotic nuclear assembly	TMPO, LAP2
TOP2A, topoisomerase (DNA) II alpha	TOP2A	DNA topoisomerase	Mitosis, meiosis, chromosome segregation	TOP2A
TPX2, microtubule nucleation factor	TPX2	Complex formation	Mitotic spindle assembly, apoptosis, G2/M trans	TPX2
TRAIP, TRAF interacting protein, TRIP	TRAIP, TRIP	Ubiquitin ligase	Signal transduction, apoptosis, spindle, mitosis	TRAIP, TRIP
Treslin, TOPBP1 interacting checkpoint and replication regulator	Treslin, SLD3	Complex formation	DNA replication, DNA repair, checkpoint control	TICRR, Treslin
TTK, Mitotic checkpoint kinase Mps1, TTK protein kinase	TTK, MPS1	Serine/threonine/tyr. kinase	Spindle formation, mitosis	TTK, MPS1
SNRPA, small nuclear ribonucleoprotein polypeptide A	U1A, SNRPA	Complex formation	U1 snRNA binding, splicing	SNRPA, U1A
UACA, Uveal autoantigen with coiled-coil domains and ankyrin repeats	UACA	Complex formation	Apoptosis	UACA
UBE2C, Ubiquitin-conjugating enzyme E2 C, UbcH10	UBE2C, UbcH10	Ubiquitin conjug. enzyme	Mitosis	UBE2C, UbcH10
UBE2S, Ubiquitin-conjugating enzyme E2 S	UBE2S	Ubiquitin conjug. enzyme	Exit from mitosis	UBE2S
UBE2T, Ubiquitin-conjugating enzyme E2 T	UBE2T, FANCT	Ubiquitin conjug. enzyme	Fanconi anemia, DNA repair, ubiquitination	UBE2T, FANCT
UDG, uracil DNA glycosylase	UDG, UNG	Uracil DNA *N*-glycosylase	DNA repair, base-excision repair	UNG
USP1, ubiquitin specific peptidase 1	USP1, UBP	Endopeptidase	De-ubiquitination, neg. regulation DNA repair	USP1
Wee1-like protein kinase	WEE1	Serine/threonine kinase	G2/M transition, mitosis	WEE1
WD repeat containing antisense to TP53, Telomerase Cajal body pr.	WRAP53, TCAB1	Telomerase component	Telomere maintenance, p53 antisense transcript	WRAP53

Table 1 (Continued)

Genes regulated by the p53–DREAM pathway				
Protein name	**Protein**	**Function, enzymatic activity**	**GO – Gene Ontology**	**Gene**
YEATS4, YEATS domain-containing 4	YEATS4, GAS41	Complex formation	Transcription, histone acetylation	YEATS4, GAS41
ZNF367, zinc-finger protein 367, CDC14B	ZNF367	DNA binding	Transcription	ZNF367
ZRANB3, zinc-finger, RAN-binding domain-containing 3	ZRANB3, AH2	Helicase and endonuclease	DNA repair, cellular response to DNA damage	ZRANB3, AH2

Genes listed bind DREAM components in their promoters and are downregulated following p53 activation. The list was compiled from meta-analyses reported in several studies.[17,29,31,66] Criteria for inclusion as genes regulated by the p53–p21–DREAM–E2F/CHR (p53–DREAM) pathway are binding of p130, E2F4, LIN9, LIN54, and the lack of binding by p53 as assayed by ChIP together with downregulation of target gene mRNA after activation of p53.[17,29,31,66] An updated compilation of data sets from several genome-wide studies has been published[65,67] and can be consulted to retrieve data on individual genes at www.targetgenereg.org.

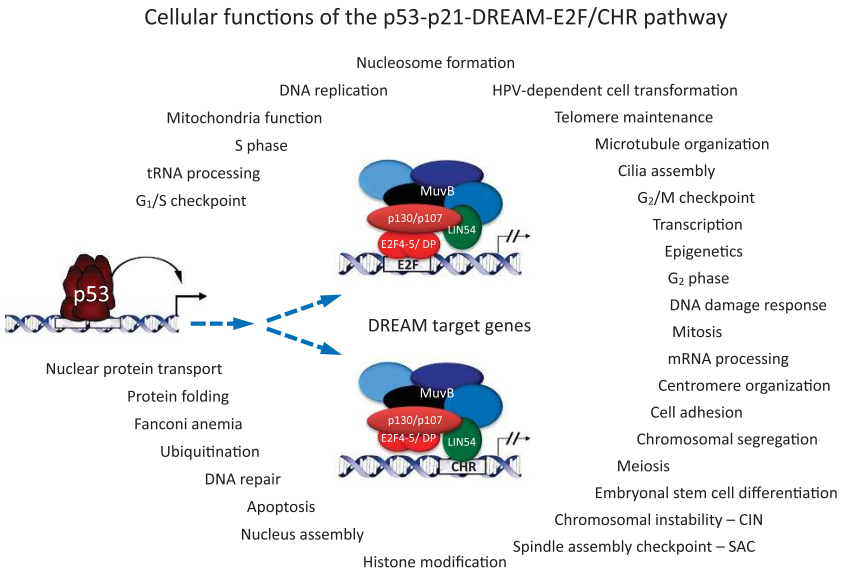


Figure 4 Cellular functions of the p53–p21–DREAM–E2F/CHR pathway. In order to summarize cellular functions regulated by the pathway, gene ontology terms for p53–p21–DREAM–E2F/CHR targets from Table 1 were compiled

DHFR are now considered p53–DREAM targets[77,78] (Table 1). The E2F or E2F/CLE sites in their promoters are bound by DREAM for repression in resting cells and the E2F elements may bind activating E2F complexes at later stages of the cell cycle[33] (Figure 1).

p53-Repressed Genes Required for the G_2 Phase and Mitosis are Controlled by CHR Elements

In addition to controlling the G_1/S checkpoint, p53 also has a role in regulating genes required for progression through G_2 phase and mitosis.[30,66,79] Cell cycle-dependent expression of these genes is controlled by CHR or CDE/CHR sites in their promoters[31,33] (Figure 1). Prominent examples for p53–DREAM-regulated genes involved in G_2/M checkpoint control and progression through mitosis are *CHEK2, CDK1, CCNB1, CCNB2* and *CDC25C*[10,14,31,39,66,80,81] (Table 1).

In addition to such central regulators, also genes coding for proteins required in the mechanical execution of mitosis are controlled by the p53–DREAM pathway, such as kinesins.[82] Of the many kinesins discovered in bioinformatic screens as p53–DREAM targets, *KIF2C, KIF23* and *KIF24* have been studied in detail and were validated to be controlled by DREAM[29,31,68,83] (Table 1).

The p53–DREAM Pathway and its Role in the Spindle Assembly Checkpoint, Chromosomal Instability, Aneuploidy in Cancer Cells and Mitotic Catastrophe

Several gene products mentioned above together with many additional cell cycle proteins are required for accurate segregation of chromosomes. Deregulation of their genes can perturb the spindle assembly checkpoint and lead to chromosomal instability (CIN).[84–87] CIN and resulting aneuploidy are considered hallmarks of cancer cells. Deregulated expression of mitosis genes has been shown in numerous studies to cause aneuploidy and tumor development.[88] Importantly, many genes involved in chromosome segregation are p53–DREAM targets (Table 1). Similarly, several genes important for mitosis which are downregulated by the p53–

DREAM pathway are part of the DNA damage response. Repression of these genes leads to perturbations in the mitotic machinery. As a consequence of depriving cells of these regulators, cells can arrest in mitosis and undergo the death program of mitotic catastrophe.[89]

As chromosomal missegregation causes elevated levels of p53 and p21/CDKN1A,[90] the p53–DREAM pathway becomes activated and many genes required for segregation of chromosomes are downregulated (Table 1). The lack of expression of segregation regulators results in cell cycle arrest. In cells that have lost p53 or p21/CDKN1A function, the ability to arrest the cell cycle is compromised causing CIN and aneuploidy.[90]

Numerous gene products involved in mitotic spindle formation, kinetochore function, microtubule binding, centromere organization and centrosome formation such as CENP-A/C/E/F/L/N/O/W, CAF1A, MCM2-8, INCENP and CEP152-/295 are implicated as p53–DREAM targets (Table 1). Furthermore, several genes involved in these processes – *BIRC5* (Survivin), *CEP55*, *PLK1, GAS2L3* and *PRC1* – have been established as DREAM targets in detailed experimental studies.[19,91–93]

As two examples, the histone H3-like CENP-A protein (CenH3) and its chaperone HJURP (Holliday junction recognition protein) have important functions in centromere formation. Their expression peaks in the G_2 phase. CENP-A is incorporated into centromeric chromatin between telophase and early G_1 to form centromere-specific nucleosomes and to facilitate kinetochore binding to the centromere.[94] *CENPA* and *HJURP* genes had been predicted as targets repressed by the p53–DREAM pathway.[66] Recently, it has been confirmed that these two factors are indeed downregulated indirectly by p53 requiring CDE/CHR sites in their promoters and a functional p21/CDKN1A CDK inhibitor.[95] Consistently, expression of *CENPA* and *HJURP* mRNA was found increased in several tumor types which lack functional p53 compared with samples with wild-type p53. Notably, the report suggests that overexpression of *CENPA* and *HJURP* is not simply a consequence but may be one of the causes of cell cycle deregulation after p53 inactivation and cellular transformation. This assumption stems from the observation that mRNA levels of the G_2/M genes *CENPA* and *HJURP* remain high even when a decreasing proportion of cells enters G_2/M and an increasing proportion of cells undergoes apoptosis.[95]

Also in the context of preventing supernumerary centrosomes, the formation of the PIDDosome from its components together with its regulatory effect on p53 displays a balancing network of feedback loops. The PIDDosome via Caspase-2 mediates MDM2 cleavage leading to p53 stabilization and p21/CDKN1A activation.[96] While expression of the PIDDosome constituent *PIDD1* is strongly induced, expression of another component, *CRADD* (*RAIDD*), is not significantly affected by p53.[17] In contrast, the *CASP2* (Caspase-2) component is clearly downregulated, possibly via p53–DREAM.[17]

Furthermore, it has been shown that loss of p53 causes centrosome amplification.[97] Particularly overexpression of cell cycle regulators such as PLK4, which is also downregulated by the p53–DREAM pathway, was reported to be central to the amplification of centrosomes.[69,98] More importantly, overexpression of these genes was implicated not as a consequence but rather as a cause contributing to the formation of tumors[92,98]

As a result, deregulation of p53 cell cycle targets leads to centrosome amplification which promotes aneuploidy and ultimately tumorigenesis.[98] In general, these observations suggest a tumor-suppressive function of the p53–DREAM pathway.

Entire functional Groups of Genes are Downregulated by the p53–DREAM Pathway: DNA Repair, Telomere Maintenance and Fanconi Anemia

Bioinformatic analysis of mRNA expression, ChIP and promoter element conservation data pointed at several genes involved in DNA repair and telomere maintenance to be downregulated by the DREAM pathway.[17] Among the genes suggested to be regulated by DREAM were examples such as *FANCB*, *DCLRE1B* (*Apollo*), *RAD54L*, *RAD18* and *CHEK2*[17,31,66] (Table 1). Interestingly, some of the DREAM targets are genes of the Fanconi anemia complementation groups (Table 2).[17,99]

Fanconi anemia is the most common inherited bone marrow failure syndrome. It causes constitutive genomic instability and predisposes for myelodysplasia, myeloid leukemia and solid tumors such as squamous cell carcinomas.[100] Recently, expression of Fanconi anemia genes in the context of truncated vs full-length p53 was investigated in a mouse model. A truncated variant of p53 missing the C-terminal 31 amino acids was employed and its transcriptional program in comparison with full-length p53 was tested.[101] The p53Δ31 mutant lacks the C-terminal domain which interferes with DNA binding reducing p53 activity.[102] Thus, p53Δ31 displays elevated transcriptional activity compared with full-length p53 resulting in enhanced *p21/CDKN1A* activation and concomitant induction of the p53–DREAM pathway.[39,101] It was shown that several Fanconi anemia genes are repressed by p53, bind E2F4 after induction of p53 and contain candidate CDE/CHR sites in their promoters (Table 2). Detailed analyses were performed with *FANCD2, FANCI* and *RAD51 (FANCR)* by testing mutants of CDE/CHR sites in their promoters.[101] Consistently, all Fanconi anemia genes which were experimentally confirmed to be controlled through DREAM had also been predicted by bioinformatic analyses as DREAM targets[17,101] (Table 2). These data suggest that an entire group of functionally related genes is coordinately downregulated by the p53–DREAM pathway. The coordinate regulation of whole functional groups implies that the p53–DREAM pathway controls not just a partial aspect but an entire function of a cell (Figure 4).

Another group of genes associated with telomere maintenance partially overlaps with the Fanconi anemia gene family as some genes from both groups are involved in DNA repair.[101] The telomere-related *DKC1* (Dyskerin), *RTEL1* and *TINF2* genes are found mutated in *dyskeratosis congenita.* From the meta-analysis data it is unclear whether they are also DREAM targets[17,101] (Table 2). However, many genes with functions in telomere maintenance, length or replication as well as DNA repair – e.g. *DEK, FEN1, RECQL4, TIMELESS, BLM, RIF1, ACD, RPA2, WRAP53 (TCAB1)*, *TRAIP* and *PIF1*

Table 2 DREAM targets among Fanconi anemia, dyskeratosis congenita, and related DNA repair and telomere maintenance genes

Gene name	Fanconi	DREAM pathway	Repressed by p53
	Complementation Group or DC	Target Fischer *et al.*[17]	Jaber *et al.*[101]
BLM		✓	✓
BRCA1	FANCS	✓	✓
BRCA2	FANCD1	✓	✓
BRIP1 (BACH1)	FANCJ	✓	✓
DCLRE1B (Apollo)		✓	
DEK		✓	✓
DKC1 (Dyskerin)	Dyskeratosis Congen.	unclear	
ERCC4 (XPF, RAD1)	FANCQ	no	
FANCA	FANCA	✓	✓
FANCB	FANCB	✓	✓
FANCC	FANCC	✓	
FANCD2	FANCD2	✓	✓
FANCE	FANCE	✓	
FANCF	FANCF	no	
FANCG	FANCG	✓	
FANCI	FANCI	✓	✓
FANCL	FANCL	✓	
FANCM	FANCM	✓	✓
FEN1		✓	✓
GAR1		unclear	✓
PALB2	FANCN	✓	✓
RAD51	FANCR	✓	✓
RAD51C	FANCO	unclear	✓
RECQL4		✓	✓
RTEL1	Dyskeratosis Congen.	unclear	
SLX4 (BTBD12)	FANCP	no	
Timeless		✓	✓
TINF2 (TIN2)	Dyskeratosis Congen.	no	
UBE2T	FANCT	✓	✓
ACD		✓	
RIF1		✓	
PIF1 (RRM3)		✓	
RPA2		✓	
TRAIP		✓	
WRAP53 (TCAB1)		✓	

Abbreviation: DC, dyskeratosis congenita
To assess whether genes related to DNA repair, telomere maintenance[103,124] and Fanconi anemia[99,100,105] are DREAM targets, data on mRNA regulation after p53 activation and binding of DREAM components E2F4, p130, LIN9 and LIN54 were retrieved from a database by Fischer *et al.*[17] An updated data compilation can be accessed at www.targetgenereg.org.[65] Jaber *et al.*[101] have recently confirmed that p53 downregulates many of the Fanconi anemia genes by DREAM binding to CDE/CHR sites.

(RRM3) – are indirectly downregulated by p53. Correspondingly, binding of DREAM components to these genes was observed by genome-wide ChIP experiments, again indicating that a functionally related gene set is controlled by the p53–DREAM pathway[17,101,103,104] (Table 2).

Also breast and ovarian cancer susceptibility genes *BRCA1* and *BRCA2* are among the genes implied as DREAM targets by observations from several genome-wide screens.[17] *BRCA1* and *BRCA2* were originally described as Fanconi complementation groups FANCS and FANCD1, respectively.[100] This identity has been challenged recently.[105] Yet, downregulation of these genes by p53 and binding of DREAM components has been shown in a compilation of genome-wide expression and ChIP protein binding data.[17] Furthermore, before the discovery of mammalian DREAM, observations suggested that E2F4, p130 and p107 can bind at the *BRCA1* promoter after induction of hypoxia.[106] p53-dependent repression of *BRCA1* and binding of E2F4 to the gene was later confirmed.[107]

In general, these data suggest that gene groups representing pathways controlling important cell functions such as cell cycle checkpoint regulation, DNA repair, telomere maintenance and other functions are coordinately regulated by the p53–DREAM pathway (Figure 4). Again, this implies that p53 employs DREAM to exert its master regulator function by controlling entire sets of genes responsible for complete cell functions.

Cancer treatment: CDK Inhibitor Drugs and Rescue of the p53–DREAM Pathway

Cell cycle checkpoint control is in the focus of cancer treatment. Prominent examples for drugs targeting the cell cycle are Palbociclib (PD-0332991, tradename: Ibrance), Abemaciclib (LY2835219) and Ribociclib (LEE 011, Kisqali).[108] Palbociclib was the first of these small-molecule inhibitors to obtain FDA approval for the treatment of breast cancer. The drugs inhibit CDK4/6 cell cycle kinases and compensate for the loss of checkpoint control in cancerous cells. The CDK inhibitors were originally aimed at primarily decreasing pRB phosphorylation in order to promote formation pRB/E2F transcriptional repressor complexes. The

classical view is that hypophosphorylation of pRB is an important step in G_1/S checkpoint control.[58,108]

However, it has been established early – analogous to pRB itself – that the pRB-related proteins p107 and p130 are substrates for cyclin D/CDK4/6-dependent phosphorylation.[109,110] Thus, inhibition by drugs such as Palbociclib will lead to DREAM formation and cause down-regulation of its target genes. As DREAM controls genes which are required for G_1/S transition, the G_2/M checkpoint and for progression through mitosis (Table 1), CDK inhibitors such as Palbociclib will address several cell cycle checkpoints by causing DREAM formation. This suggests that the therapeutic effect of the CDK inhibitors may depend on DREAM.

Human Papilloma Virus HPV E7 – Destruction of DREAM Function

Human papilloma virus (HPV)-16 E7 has been shown to bind the retinoblastoma protein pRB and impair its tumor-suppressive function.[111] Consistently, also DREAM was reported to be disrupted by E7 binding to the pRB-related protein p130.[112] Moreover, it is established that HPV E6 targets p53 for ubiquitin-mediated destruction.[113] Also, the HPV E7 protein will compromise the function of p53 as a tumor suppressor through binding to the DREAM components p107 and p130. A genome-wide study listed the genes with their change in expression following HPV E7 protein expression.[114] In a report on *PLK4* transcription, we showed in regard to the mechanism that transcriptional deregulation by HPV E7 is mediated through the DREAM complex and CDE/CHR elements in the promoter of the gene.[69] In general, these results implied that all genes controlled by DREAM through E2F or CHR sites in their promoters are deregulated by HPV E7.[69] This notion emerged also from earlier data sets and a recent report on gene deregulation upon E7 expression in keratinocytes.[69,114,115] In a recent genome-wide meta-analysis we identified more than 90 genes, mostly coding for cell cycle regulators, which are upregulated following E7 expression.[116] Thus, these data suggest that deregulation of DREAM substantially contributes to HPV E7-mediated tumorigenesis.

DREAM and Epigenetics

DREAM also regulates genes involved in DNA methylation, nucleosome formation and histone modification, including *CHAF1A, EZH2, H2AFX, KMT5A, SMCHD1* and *SUZ12* (Table 1). Recently, it was shown that p53-dependent regulation of enzymes is required for DNA methylation homeostasis.[117] In p53-deficient cells, an imbalance in DNA methylation causes clonal heterogeneity in naïve embryonal stem cells and upon differentiation. The DNA methyltransferase gene *DNMT3B* contributes to DNA methylation homeostasis and appears to be – according to meta-analysis data – downregulated by the p53–DREAM pathway (Table 1). Thus, with their role in epigenetics, DREAM and the p53–DREAM pathway contribute to gene regulation on a global level.

Implications of the p53–p21–DREAM–E2F/CHR pathway

p53 is a key mediator of cell cycle arrest in response to cellular stress. With the plethora of genes downregulated by the p53–DREAM pathway, it has become likely that this signaling pathway is central to cell cycle arrest (Table 1). Considering that regulator functions of these genes span from the G_1 phase to the end of mitosis, it is evident that p53-dependent cell cycle arrest is not restricted to G_1/S transition but is also important for all checkpoints up to the completion of cell division (Figure 4).

An unresolved issue in cell cycle checkpoint control is how functions of pRB and DREAM differ or overlap. Both pRB/E2F complexes and DREAM bind DNA through E2F sites. However, DREAM also employs CHR elements without E2F sites. Thus, gene sets controlled by pRB/E2F or DREAM will overlap but a separate set will be controlled by DREAM and CHR sites (Figure 2). It has been shown that pRB and p21/CDKN1A have additive effects on G_1 phase regulation, which may suggest that pRB and DREAM are both required to control G_1/S transition.[118] Consistently, triple knockout cells for the pRB-related genes cannot undergo cell cycle arrest, in contrast to *Rb−/−* single or *p130−/−; p107−/−* double knockout cells which still arrest.[119] Genome-wide expression and protein/DNA binding studies will be instrumental in defining the distinct functions of pRB and p130/p107 – and thus DREAM.[65]

Another feature of the DREAM pathway may be quality of the induced cell cycle arrest. While transcriptional regulation of cell cycle proteins is slower than regulation via, for example, phosphorylation as employed by other pathways, the response to the p53–DREAM pathway may be more sustained, possibly leading to senescence as an irreversible cell cycle arrest or to induction of apoptosis.[2,6,74]

The function of many oncogenic factors is to stimulate cell division or, as seen from another perspective, to counteract cell cycle arrest. Consistently, p53 functions as a tumor suppressor through the p53–DREAM pathway by down-regulating many oncogenic proteins such as B-Myb, FOXM1, Cyclin B1/2 and CDK1/2 (Table 1). Thus, many of the genes repressed by p53 are found overexpressed in tumors once the p53–DREAM pathway is impaired. Expression signatures for many cancer types comprises genes downregulation by the p53–DREAM pathway.[120] In numerous studies on many cancer types, p53–DREAM targets head the list of signature genes whose aberrant expression is predictive for poor clinical outcome of cancer patients.[121–123] Considering that CDK inhibitors promote repression of these genes by DREAM, functional defects of p21/CDKN1A or upstream pathway elements can be attenuated by these drugs.

In summary, the p53–p21–DREAM–E2F/CHR pathway downregulates a plethora of cell cycle genes, contributes to cell cycle arrest and is a target for cancer therapy. Researchers working on p53 function, cell cycle regulation or cancer treatment may soon join in saluting: We have a DREAM!

Conflict of Interest

The author declares no conflict of interest.

Acknowledgements. I thank Drs Christine E Engeland and Gerd A Müller for their comments on the manuscript and for providing helpful suggestions.

1. Schwartz D, Rotter V. p53-dependent cell cycle control: response to genotoxic stress. *Semin Cancer Biol* 1998; **8**: 325–336.
2. Vousden KH, Prives C. Blinded by the light: the growing complexity of p53. *Cell* 2009; **137**: 413–431.
3. Levine AJ, Oren M. The first 30 years of p53: growing ever more complex. *Nat Rev Cancer* 2009; **9**: 749–758.
4. Böhlig L, Rother K. One function–multiple mechanisms: the manifold activities of p53 as a transcriptional repressor. *J Biomed Biotechnol* 2011; **2011**: 464916.
5. Bunz F, Dutriaux A, Lengauer C, Waldman T, Zhou S, Brown JP *et al.* Requirement for p53 and p21 to sustain G2 arrest after DNA damage. *Science* 1998; **282**: 1497–1501.
6. Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. *Nature* 2000; **408**: 307–310.
7. Jackson MW, Agarwal MK, Yang J, Bruss P, Uchiumi T, Agarwal ML *et al.* p130/p107/p105Rb-dependent transcriptional repression during DNA-damage-induced cell-cycle exit at G2. *J Cell Sci* 2005; **118**: 1821–1832.
8. Innocente SA, Abrahamson JL, Cogswell JP, Lee JM. p53 regulates a G2 checkpoint through cyclin B1. *Proc Natl Acad Sci USA* 1999; **96**: 2147–2152.
9. Taylor WR, DePrimo SE, Agarwal A, Agarwal ML, Schonthal AH, Katula KS *et al.* Mechanisms of G2 arrest in response to overexpression of p53. *Mol Biol Cell* 1999; **10**: 3607–3622.
10. Krause K, Wasner M, Reinhard W, Haugwitz U, Lange-zu Dohna C, Mössner J *et al.* The tumour suppressor protein p53 can repress transcription of cyclin B. *Nucleic Acids Res* 2000; **28**: 4410–4418.
11. Taylor WR, Schonthal AH, Galante J, Stark GR. p130/E2F4 binds to and represses the cdc2 promoter in response to p53. *J Biol Chem* 2001; **276**: 1998–2006.
12. Haugwitz U, Tschöp K, Engeland K. SIRF—a novel regulator element controlling transcription from the p55Cdc/Fizzy promoter during the cell cycle. *Biochem Biophys Res Commun* 2004; **320**: 951–960.
13. Rother K, Kirschner R, Sänger K, Böhlig L, Mössner J, Engeland K. p53 downregulates expression of the G(1)/S cell cycle phosphatase Cdc25A. *Oncogene* 2007; **26**: 1949–1953.
14. Haugwitz U, Wasner M, Wiedmann M, Spiesbach K, Rother K, Mössner J *et al.* A single cell cycle genes homology region (CHR) controls cell cycle-dependent transcription of the cdc25C phosphatase gene and is able to cooperate with E2F or Sp1/3 sites. *Nucleic Acids Res* 2002; **30**: 1967–1976.
15. Agarwal MK, Ruhul Amin AR, Agarwal ML. DNA replication licensing factor minichromosome maintenance deficient 5 rescues p53-mediated growth arrest. *Cancer Res* 2007; **67**: 116–121.
16. Rother K, Li YY, Tschöp K, Kirschner R, Müller GA, Mössner J *et al.* Expression of cyclin-dependent kinase subunit 1 (Cks1) is regulated during the cell cycle by a CDE/CHR tandem element and is downregulated by p53 but not by p63 or p73. *Cell Cycle* 2007; **6**: 853–862.
17. Fischer M, Steiner L, Engeland K. The transcription factor p53: not a repressor, solely an activator. *Cell Cycle* 2014; **13**: 3037–3058.
18. Ho J, Benchimol S. Transcriptional repression mediated by the p53 tumour suppressor. *Cell Death Differ* 2003; **10**: 404–408.
19. Fischer M, Quaas M, Nickel A, Engeland K. Indirect p53-dependent transcriptional repression of Survivin, CDC25C, and PLK1 genes requires the cyclin-dependent kinase inhibitor p21/CDKN1A and CDE/CHR promoter sites binding the DREAM complex. *Oncotarget* 2015; **6**: 41402–41417.
20. Litovchick L, Sadasivam S, Florens L, Zhu X, Swanson SK, Velmurugan S *et al.* Evolutionarily conserved multisubunit RBL2/p130 and E2F4 protein complex represses human cell cycle-dependent genes in quiescence. *Mol Cell* 2007; **26**: 539–551.
21. Schmit F, Korenjak M, Mannefeld M, Schmitt K, Franke C, von Eyss B *et al.* LINC, a human complex that is related to pRB-containing complexes in invertebrates regulates the expression of G2/M genes. *Cell Cycle* 2007; **6**: 1903–1913.
22. Mannefeld M, Klassen E, Gaubatz S. B-MYB is required for recovery from the DNA damage-induced G2 checkpoint in p53 mutant cells. *Cancer Res* 2009; **69**: 4073–4080.
23. van den Heuvel S, Dyson NJ. Conserved functions of the pRB and E2F families. *Nat Rev Mol Cell Biol* 2008; **9**: 713–724.
24. Sadasivam S, DeCaprio JA. The DREAM complex: master coordinator of cell cycle-dependent gene expression. *Nat Rev Cancer* 2013; **13**: 585–595.
25. Osterloh L, von Eyss B, Schmit F, Rein L, Hubner D, Samans B *et al.* The human synMuv-like protein LIN-9 is required for transcription of G2/M genes and for entry into mitosis. *EMBO J* 2007; **26**: 144–157.
26. Sadasivam S, Duan S, DeCaprio JA. The MuvB complex sequentially recruits B-Myb and FoxM1 to promote mitotic gene expression. *Genes Dev* 2012; **26**: 474–489.
27. Musa J, Aynaud MM, Mirabeau O, Delattre O, Grunewald TG. MYBL2 (B-Myb): a central regulator of cell proliferation, cell survival and differentiation involved in tumorigenesis. *Cell Death Dis* 2017; **8**: e2895.
28. Schmit F, Cremer S, Gaubatz S. LIN54 is an essential core subunit of the DREAM/LINC complex that binds to the cdc2 promoter in a sequence-specific manner. *FEBS J* 2009; **276**: 5703–5716.
29. Müller GA, Quaas M, Schümann M, Krause E, Padi M, Fischer M *et al.* The CHR promoter element controls cell cycle-dependent gene transcription and binds the DREAM and MMB complexes. *Nucleic Acids Res* 2012; **40**: 1561–1578.
30. Müller GA, Engeland K. The central role of CDE/CHR promoter elements in the regulation of cell cycle-dependent gene transcription. *FEBS J* 2010; **277**: 877–893.
31. Müller GA, Wintsche A, Stangner K, Prohaska SJ, Stadler PF, Engeland K. The CHR site: definition and genome-wide identification of a cell cycle transcriptional element. *Nucleic Acids Res* 2014; **42**: 10331–10350.
32. Marceau AH, Felthousen JG, Goetsch PD, Iness AN, Lee HW, Tripathi SM *et al.* Structural basis for LIN54 recognition of CHR elements in cell cycle-regulated promoters. *Nat Commun* 2016; **7**: 12301.
33. Müller GA, Stangner K, Schmitt T, Wintsche A, Engeland K. Timing of transcription during the cell cycle: protein complexes binding to E2F, E2F/CLE, CDE/CHR, or CHR promoter elements define early and late cell cycle gene expression. *Oncotarget* 2017 (doi:10.18632/oncotarget.10888).
34. Down CF, Millour J, Lam EW, Watson RJ. Binding of FoxM1 to G2/M gene promoters is dependent upon B-Myb. *Biochim Biophys Acta* 2012; **1819**: 855–862.
35. Chen X, Müller GA, Quaas M, Fischer M, Han N, Stutchbury B *et al.* The forkhead transcription factor FOXM1 controls cell cycle-dependent gene expression through an atypical chromatin binding mechanism. *Mol Cell Biol* 2013; **33**: 227–236.
36. Sanders DA, Gormally MV, Marsico G, Beraldi D, Tannahill D, Balasubramanian S. FOXM1 binds directly to non-consensus sequences in the human genome. *Genome Biol* 2015; **16**: 130.
37. Zhao B, Barrera LA, Ersing I, Willox B, Schmidt SC, Greenfeld H *et al.* The NF-kappaB genomic landscape in lymphoblastoid B cells. *Cell Rep* 2014; **8**: 1595–1606.
38. Paci P, Colombo T, Fiscon G, Gurtner A, Pavesi G, Farina L. SWIM: a computational tool to unveiling crucial nodes in complex biological networks. *Sci Rep* 2017; **7**: 44797.
39. Quaas M, Müller GA, Engeland K. p53 can repress transcription of cell cycle genes through a p21(WAF1/CIP1)-dependent switch from MMB to DREAM protein complex binding at CHR promoter elements. *Cell Cycle* 2012; **11**: 4661–4672.
40. el-Deiry WS, Tokino T, Velculescu VE, Levy DB, Parsons R, Trent JM *et al.* WAF1, a potential mediator of p53 tumor suppression. *Cell* 1993; **75**: 817–825.
41. Abbas T, Dutta A. p21 in cancer: intricate networks and multiple activities. *Nat Rev Cancer* 2009; **9**: 400–414.
42. Melino G. p63 is a suppressor of tumorigenesis and metastasis interacting with mutant p53. *Cell Death Differ* 2011; **18**: 1487–1499.
43. Marcel V, Dichtel-Danjoy ML, Sagne C, Hafsi H, Ma D, Ortiz-Cuaran S *et al.* Biological functions of p53 isoforms through evolution: lessons from animal and cellular models. *Cell Death Differ* 2011; **18**: 1815–1824.
44. el-Deiry WS, Kern SE, Pietenpol JA, Kinzler KW, Vogelstein B. Definition of a consensus binding site for p53. *Nat Genet* 1992; **1**: 45–49.
45. Yang A, Zhu Z, Kettenbach A, Kapranov P, McKeon F, Gingeras TR *et al.* Genome-wide mapping indicates that p73 and p63 co-occupy target sites and have similar dna-binding profiles in vivo. *PLoS ONE* 2010; **5**: e11572.
46. Marshall CB, Mays DJ, Beeler JS, Rosenbluth JM, Boyd KL, Santos Guasch GL *et al.* p73 is required for multiciliogenesis and regulates the Foxj1-associated gene network. *Cell Rep* 2016; **14**: 2289–2300.
47. Pellacani D, Bilenky M, Kannan N, Heravi-Moussavi A, Knapp DJ, Gakkhar S *et al.* Analysis of normal human mammary epigenomes reveals cell-specific active enhancer states and associated transcription factor networks. *Cell Rep* 2016; **17**: 2060–2074.
48. Dietz S, Rother K, Bamberger C, Schmale H, Mössner J, Engeland K. Differential regulation of transcription and induction of programmed cell death by human p53-family members p63 and p73. *FEBS Lett* 2002; **525**: 93–99.
49. Candi E, Agostini M, Melino G, Bernassola F. How the TP53 family proteins TP63 and TP73 contribute to tumorigenesis: regulators and effectors. *Hum Mutat* 2014; **35**: 702–714.
50. Rother K, Dengl M, Lorenz J, Tschöp K, Kirschner R, Mössner J *et al.* Gene expression of cyclin-dependent kinase subunit Cks2 is repressed by the tumor suppressor p53 but not by the related proteins p63 or p73. *FEBS Lett* 2007; **581**: 1166–1172.
51. Sohr S, Engeland K. RHAMM is differentially expressed in the cell cycle and downregulated by the tumor suppressor p53. *Cell Cycle* 2008; **7**: 3448–3460.
52. Gebel J, Luh LM, Coutandin D, Osterburg C, Lohr F, Schafer B *et al.* Mechanism of TAp73 inhibition by DeltaNp63 and structural basis of p63/p73 hetero-tetramerization. *Cell Death Differ* 2016; **23**: 1930–1940.
53. Billant O, Leon A, Le GS, Friocourt G, Blondel M, Voisset C. The dominant-negative interplay between p53, p63 and p73: A family affair. *Oncotarget* 2016; **7**: 69549–69564.
54. Harper JW, Elledge SJ, Keyomarsi K, Dynlacht B, Tsai LH, Zhang P *et al.* Inhibition of cyclin-dependent kinases by p21. *Mol Biol Cell* 1995; **6**: 387–400.
55. Dulic V, Kaufmann WK, Wilson SJ, Tlsty TD, Lees E, Harper JW *et al.* p53-dependent inhibition of cyclin-dependent kinase activities in human fibroblasts during radiation-induced G1 arrest. *Cell* 1994; **76**: 1013–1023.
56. Farkas T, Hansen K, Holm K, Lukas J, Bartek J. Distinct phosphorylation events regulate p130- and p107-mediated repression of E2F-4. *J Biol Chem* 2002; **277**: 26741–26752.
57. Dyson NJ. RB1: a prototype tumor suppressor and an enigma. *Genes Dev* 2016; **30**: 1492–1502.
58. Sherr CJ, Roberts JM. CDK inhibitors: positive and negative regulators of G1-phase progression. *Genes Dev* 1999; **13**: 1501–1512.
59. Shiohara M, el-Deiry WS, Wada M, Nakamaki T, Takeuchi S, Yang R *et al.* Absence of WAF1 mutations in a variety of human malignancies. *Blood* 1994; **84**: 3781–3784.

60. Deng C, Zhang P, Harper JW, Elledge SJ, Leder P. Mice lacking p21CIP1/WAF1 undergo normal development, but are defective in G1 checkpoint control. *Cell* 1995; **82**: 675–684.
61. Valente LJ, Grabow S, Vandenberg CJ, Strasser A, Janic A. Combined loss of PUMA and p21 accelerates c-MYC-driven lymphoma development considerably less than loss of one allele of p53. *Oncogene* 2016; **35**: 3866–3871.
62. Valente LJ, Aubrey BJ, Herold MJ, Kelly GL, Happo L, Scott CL *et al.* Therapeutic response to non-genotoxic activation of p53 by Nutlin3a is driven by PUMA-mediated apoptosis in lymphoma cells. *Cell Rep* 2016; **14**: 1858–1866.
63. Cheng M, Olivier P, Diehl JA, Fero M, Roussel MF, Roberts JM *et al.* The p21(Cip1) and p27(Kip1) CDK 'inhibitors' are essential activators of cyclin D-dependent kinases in murine fibroblasts. *EMBO J* 1999; **18**: 1571–1583.
64. Cerqueira A, Martin A, Symonds CE, Odajima J, Dubus P, Barbacid M *et al.* Genetic characterization of the role of the Cip/Kip family of proteins as cyclin-dependent kinase inhibitors and assembly factors. *Mol Cell Biol* 2014; **34**: 1452–1459.
65. Fischer M, Grossmann P, Padi M, DeCaprio JA. Integration of TP53, DREAM, MMB-FOXM1 and RB-E2F target gene analyses identifies cell cycle gene regulatory networks. *Nucleic Acids Res* 2016; **44**: 6070–6086.
66. Fischer M, Quaas M, Steiner L, Engeland K. The p53-p21-DREAM-CDE/CHR pathway regulates G2/M cell cycle genes. *Nucleic Acids Res* 2016; **44**: 164–174.
67. Fischer M. Census and evaluation of p53 target genes. *Oncogene* 2017; **36**: 3943–3956.
68. Fischer M, Grundke I, Sohr S, Quaas M, Hoffmann S, Knörck A *et al.* p53 and cell cycle dependent transcription of kinesin family member 23 (KIF23) is controlled via a CHR promoter element bound by DREAM and MMB complexes. *PLoS One* 2013; **8**: e63187.
69. Fischer M, Quaas M, Wintsche A, Müller GA, Engeland K. Polo-like kinase 4 transcription is activated via CRE and NRF1 elements, repressed by DREAM through CDE/CHR sites and deregulated by HPV E7 protein. *Nucleic Acids Res* 2014; **42**: 163–180.
70. de Toledo SM, Azzam EI, Keng P, Laffrenier S, Little JB. Regulation by ionizing radiation of CDC2, cyclin A, cyclin B, thymidine kinase, topoisomerase IIalpha, and RAD51 expression in normal human diploid fibroblasts is dependent on p53/p21Waf1. *Cell Growth Differ* 1998; **9**: 887–896.
71. Gottifredi V, Karni-Schmidt O, Shieh SS, Prives C. p53 down-regulates CHK1 through p21 and the retinoblastoma protein. *Mol Cell Biol* 2001; **21**: 1066–1076.
72. Spurgers KB, Gold DL, Coombes KR, Bohnenstiehl NL, Mullins B, Meyn RE *et al.* Identification of cell cycle regulatory genes as principal targets of p53-mediated transcriptional repression. *J Biol Chem* 2006; **281**: 25134–25142.
73. Vaziri C, Saxena S, Jeon Y, Lee C, Murata K, Machida Y *et al.* A p53-dependent checkpoint pathway prevents rereplication. *Mol Cell* 2003; **11**: 997–1008.
74. Bartek J, Lukas J. Pathways governing G1/S transition and their response to DNA damage. *FEBS Lett* 2001; **490**: 117–122.
75. Prioleau MN, MacAlpine DM. DNA replication origins-where do we begin? *Genes Dev* 2016; **30**: 1683–1697.
76. Yan Z, DeGregori J, Shohet R, Leone G, Stillman B, Nevins JR *et al.* Cdc6 is regulated by E2F and is essential for DNA replication in mammalian cells. *Proc Natl Acad Sci USA* 1998; **95**: 3603–3608.
77. Dou QP, Zhao S, Levin AH, Wang J, Helin K, Pardee AB. G1/S-regulated E2F-containing protein complexes bind to the mouse thymidine kinase gene promoter. *J Biol Chem* 1994; **269**: 1306–1313.
78. Blake MC, Azizkhan JC. Transcription factor E2F is required for efficient expression of the hamster dihydrofolate reductase gene in vitro and in vivo. *Mol Cell Biol* 1989; **9**: 4994–5002.
79. Taylor WR, Stark GR. Regulation of the G2/M transition by p53. *Oncogene* 2001; **20**: 1803–1815.
80. Krause K, Haugwitz U, Wasner M, Wiedmann M, Mössner J, Engeland K. Expression of the cell cycle phosphatase cdc25C is down-regulated by the tumour suppressor protein p53 but not by p73. *Biochem Biophys Res Commun* 2001; **284**: 743–750.
81. Wasner M, Tschöp K, Spiesbach K, Haugwitz U, Johne C, Mössner J *et al.* Cyclin B1 transcription is enhanced by the p300 coactivator and regulated during the cell cycle by a CHR-dependent repression mechanism. *FEBS Lett* 2003; **536**: 66–70.
82. Cross RA, McAinsh A. Prime movers: the mechanochemistry of mitotic kinesins. *Nat Rev Mol Cell Biol* 2014; **15**: 257–271.
83. Iltzsche F, Simon K, Stopp S, Pattschull G, Francke S, Wolter P *et al.* An important role for Myb-MuvB and its target gene KIF23 in a mouse model of lung adenocarcinoma. *Oncogene* 2017; **36**: 110–121.
84. Musacchio A, Salmon ED. The spindle-assembly checkpoint in space and time. *Nat Rev Mol Cell Biol* 2007; **8**: 379–393.
85. Rao CV, Yamada HY, Yao Y, Dai W. Enhanced genomic instabilities caused by deregulated microtubule dynamics and chromosome segregation: a perspective from genetic studies in mice. *Carcinogenesis* 2009; **30**: 1469–1474.
86. Nam HJ, Naylor RM, van Deursen JM. Centrosome dynamics as a source of chromosomal instability. *Trends Cell Biol* 2015; **25**: 65–73.
87. Funk LC, Zasadil LM, Weaver BA. Living in CIN: mitotic infidelity and its consequences for tumor promotion and suppression. *Dev Cell* 2016; **39**: 638–652.
88. Nath S, Ghatak D, Das P, Roychoudhury S. Transcriptional control of mitosis: deregulation and cancer. *Front Endocrinol (Lausanne)* 2015; **6**: 60.
89. Vitale I, Galluzzi L, Castedo M, Kroemer G. Mitotic catastrophe: a mechanism for avoiding genomic instability. *Nat Rev Mol Cell Biol* 2011; **12**: 385–392.
90. Thompson SL, Compton DA. Proliferation of aneuploid human cells is limited by a p53-dependent mechanism. *J Cell Biol* 2010; **188**: 369–381.
91. Wolter P, Hanselmann S, Pattschull G, Schruf E, Gaubatz S. Central spindle proteins and mitotic kinesins are direct transcriptional targets of MuvB, B-MYB and FOXM1 in breast cancer cell lines and are potential targets for therapy. *Oncotarget* 2017; **8**: 11160–11172.
92. Wolter P, Schmitt K, Fackler M, Kremling H, Probst L, Hauser S *et al.* GAS2L3, a target gene of the DREAM complex, is required for proper cytokinesis and genomic stability. *J Cell Sci* 2012; **125**: 2393–2406.
93. Li C, Lin M, Liu J. Identification of PRC1 as the p53 target gene uncovers a novel function of p53 in the regulation of cytokinesis. *Oncogene* 2004; **23**: 9336–9347.
94. Muller S, Almouzni G. Chromatin dynamics during the cell cycle at centromeres. *Nat Rev Genet* 2017; **18**: 192–208.
95. Filipescu D, Naughtin M, Podsypanina K, Lejour V, Wilson L, Gurard-Levin ZA *et al.* Essential role for centromeric factors following p53 loss and oncogenic transformation. *Genes Dev* 2017; **31**: 463–480.
96. Fava LL, Schuler F, Sladky V, Haschka MD, Soratroi C, Eiterer L *et al.* The PIDDosome activates p53 in response to supernumerary centrosomes. *Genes Dev* 2017; **31**: 34–45.
97. Fukasawa K, Choi T, Kuriyama R, Rulong S, Vande Woude GF. Abnormal centrosome amplification in the absence of p53. *Science* 1996; **271**: 1744–1747.
98. Levine MS, Bakker B, Boeckx B, Moyett J, Lu J, Vitre B *et al.* Centrosome amplification is sufficient to promote spontaneous tumorigenesis in mammals. *Dev Cell* 2017; **40**: 313–322.
99. Wang AT, Smogorzewska A. SnapShot: Fanconi anemia and associated proteins. *Cell* 2015; **160**: 354.
100. Ceccaldi R, Sarangi P, D'Andrea AD. The Fanconi anaemia pathway: new players and new functions. *Nat Rev Mol Cell Biol* 2016; **17**: 337–349.
101. Jaber S, Toufektchan E, Lejour V, Bardot B, Toledo F. p53 downregulates the Fanconi anaemia DNA repair pathway. *Nat Commun* 2016; **7**: 11091.
102. Hupp TR, Meek DW, Midgley CA, Lane DP. Regulation of the specific Dna-binding function of P53. *Cell* 1992; **71**: 875–886.
103. Greider CW. Regulating telomere length from the inside out: the replication fork model. *Genes Dev* 2016; **30**: 1483–1491.
104. Hoffmann S, Smedegaard S, Nakamura K, Mortuza GB, Raschle M, Ibanez de OA *et al.* TRAIP is a PCNA-binding ubiquitin ligase that protects genome stability after replication stress. *J Cell Biol* 2016; **212**: 63–75.
105. Michl J, Zimmer J, Tarsounas M. Interplay between Fanconi anemia and homologous recombination pathways in genome integrity. *EMBO J* 2016; **35**: 909–923.
106. Bindra RS, Gibson SL, Meng A, Westermark U, Jasin M, Pierce AJ *et al.* Hypoxia-induced down-regulation of BRCA1 expression by E2Fs. *Cancer Res* 2005; **65**: 11597–11604.
107. Valenti F, Ganci F, Fontemaggi G, Sacconi A, Strano S, Blandino G *et al.* Gain of function mutant p53 proteins cooperate with E2F4 to transcriptionally downregulate RAD17 and BRCA1 gene expression. *Oncotarget* 2015; **6**: 5547–5566.
108. O'Leary B, Finn RS, Turner NC. Treating cancer with selective CDK4/6 inhibitors. *Nat Rev Clin Oncol* 2016; **13**: 417–430.
109. Beijersbergen RL, Carlee L, Kerkhoven RM, Bernards R. Regulation of the retinoblastoma protein-related p107 by G1 cyclin complexes. *Genes Dev* 1995; **9**: 1340–1353.
110. Bruce JL, Hurford RK Jr., Classon M, Koh J, Dyson N. Requirements for cell cycle arrest by p16INK4a. *Mol Cell* 2000; **6**: 737–742.
111. Dyson N, Howley PM, Munger K, Harlow E. The human papilloma virus-16 E7 oncoprotein is able to bind to the retinoblastoma gene product. *Science* 1989; **243**: 934–937.
112. Nor Rashid N, Yusof R, Watson RJ. Disruption of repressive p130-DREAM complexes by human papillomavirus 16 E6/E7 oncoproteins is required for cell-cycle progression in cervical cancer cells. *J Gen Virol* 2011; **92**: 2620–2627.
113. Scheffner M, Werness BA, Huibregtse JM, Levine AJ, Howley PM. The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell* 1990; **63**: 1129–1136.
114. Rozenblatt-Rosen O, Deo RC, Padi M, Adelmant G, Calderwood MA, Rolland T *et al.* Interpreting cancer genomes using systematic host network perturbations by tumour virus proteins. *Nature* 2012; **487**: 491–495.
115. Zhou Y, Zhang Q, Gao G, Zhang X, Liu Y, Yuan S *et al.* Role of WDHD1 in human papillomavirus-mediated oncogenesis identified by transcriptional profiling of E7-expressing cells. *J Virol* 2016; **90**: 6071–6084.
116. Fischer M, Uxa S, Stanko C, Magin TM, Engeland K. Human papilloma virus E7 oncoprotein abrogates the p53-p21-DREAM pathway. *Sci Rep* 2017; **7**: 2603.
117. Tovy A, Spiro A, McCarthy R, Shipony Z, Aylon Y, Allton K *et al.* p53 is essential for DNA methylation homeostasis in naive embryonic stem cells, and its loss promotes clonal heterogeneity. *Genes Dev* 2017; **31**: 959–972.
118. Brugarolas J, Bronson RT, Jacks T. p21 is a critical CDK2 regulator essential for proliferation control in Rb-deficient cells. *J Cell Biol* 1998; **141**: 503–514.
119. Sage J, Mulligan GJ, Attardi LD, Miller A, Chen S, Williams B *et al.* Targeted disruption of the three Rb-related genes leads to loss of G(1) control and immortalization. *Genes Dev* 2000; **14**: 3037–3050.

120. Cheng WY, Ou Yang TH, Anastassiou D. Biomolecular events in cancer revealed by attractor metagenes. *PLoS Comput Biol* 2013; **9**: e1002920.
121. van 't Veer LJ, Dai H, van de Vijver MJ, He YD, Hart AA, Mao M *et al.* Gene expression profiling predicts clinical outcome of breast cancer. *Nature* 2002; **415**: 530–536.
122. Carter SL, Eklund AC, Kohane IS, Harris LN, Szallasi Z. A signature of chromosomal instability inferred from gene expression profiles predicts clinical outcome in multiple human cancers. *Nat Genet* 2006; **38**: 1043–1048.
123. Chibon F, Lagarde P, Salas S, Perot G, Brouste V, Tirode F *et al.* Validated prediction of clinical outcome in sarcomas and multiple types of cancer on the basis of a gene expression signature related to genome complexity. *Nat Med* 2010; **16**: 781–787.
124. Holohan B, Wright WE, Shay JW. Cell biology of disease: telomeropathies: an emerging spectrum disorder. *J Cell Biol* 2014; **205**: 289–299.