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Review

Review

LncRNAs in DNA damage response and repair in cancer cells

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Abstract

In order to maintain integrity of the genome, eukaryotic cells develop a complex DNA damage/repair response network, which can induce cell cycle arrest, apoptosis, or DNA repair. Chemo- and radiation therapies, which act primarily through the induction of DNA damage, are the most commonly used therapies for cancer. Impairment in the DNA damage response and repair system that protect cells from persistent DNA damage can affect the therapeutic efficacy of cancer. To date, accumulating evidence has suggested that long non-coding RNAs (lncRNAs) are involved in the regulation of the DNA damage/repair network. LncRNAs have been demonstrated to be master regulators of the genome at the transcriptional and post-transcriptional levels and play a key role in many physiological and pathological processes of cells. In this review, we will discuss the function of lncRNAs in regulating the cellular response to DNA damage.

Key words: DNA damage response, apoptosis, cell cycle, cancer, lncRNA

Introduction

Genome integrity is essential to life, but DNA is constantly subject to damage caused by various endogenous and exogenous stresses, such as ionizing radiation, ultra violet, reactive oxygen species (ROS), and genotoxic drugs. To maintain the genome stability, eukaryotic cells evolve several systems to sense DNA damage, present damage signals, and mediate cellular responses to eliminate the damage. This process is so-called DNA damage response (DDR) [1–3]. Typical outcomes of the DDR include cell cycle arrest for DNA damage repair or apoptosis to remove the cell when the DNA damage is too severe to be repaired [4]. Failure to accurately repair of the damaged DNA in cells leads to serious clinical outcomes, including neurodegeneration, infertility, immune deficiencies, and cancer [5,6].

Cancer is a multi-step process characterized by a variety of genetic lesions. Cancer cells often show significant alterations in response to DNA damage and thus are resistant to DNA damage-inducing agents, reflected by resistance to this class of agents [7,8]. In the past decade, long non-coding RNAs (lncRNAs) have emerged as important new players in DDR, particularly in cancer cells [9,10]. This review updates the current understanding of lncRNAs in DDR and DNA damage repair.

DNA Damage Response

In response to DNA damage caused by a variety of intrinsic and extrinsic genotoxic factors, eukaryotic cells have evolved a stress response mechanism known as DDR [3,11]. The DDR involves a complex regulatory network connecting tumor suppressor genes to DNA repair, damage tolerance, cell cycle checkpoints, and apoptosis [2]. This regulatory network is predominantly initiated by phosphatidylinositol

3-kinase-like protein kinase (PIKK) family proteins, particularly ATM (ataxia-telangiectasia mutated), ATR (ATM and Rad3-related), and DNA-PKcs (DNA-dependent protein kinase catalytic subunit) triggering a series of downstream reactions [12]. ATM is generally activated in response to DNA double strand breaks (DSBs), the DNA lesions that are most lethal and difficult to be repaired [13], while ATR in particular responds to single strand DNA breaks (SSBs) [14,15].

These ATM and ATR protein kinases act as DNA damage sensors to detect the sites of damaged DNA [16,17]. Upon DNA damage, the ATM and ATR are activated by autophosphorylation and in turn phosphorylate and activate a large number of downstream effectors, coordinating the most appropriate cellular responses [18,19]. In the cell with mild DNA damage, the cell cycle checkpoint may be activated, cell cycle progression is arrest, and DNA repair process is initiated. However, in the cell with serious DNA damage that is not repairable, apoptosis may be triggered to remove the cell [1,20]. In the DDR, p53 is the most important intermediate regulator, involved in cell cycle arrest and/or apoptosis depending on the cellular context [2,21–24]. p53 is one of the most important tumor suppressor regulating expression of hundreds of genes; p53 gene mutations are described in almost all types of cancer and widely involved in tumor development and progression [25–27].

DNA damage is repaired through differential mechanisms upon the type of damage. The mismatch repair (MMR) machinery recognizes and repairs erroneous insertion, mis-incorporation, and deletion of bases during DNA synthesis or replication [28]. The nucleotide excision repair (NER) complex principally recognizes bulky DNA adducts and then replaces the abnormal bases with normal ones. The base excision repair (BER) complex removes single nucleotides. Error-prone non-homologous end joining (NHEJ) and error-free homologous recombination (HR) are distinct repair mechanisms for DSBs. Either NHEJ or HR is activated depending on the cell cycle stage. NHEJ is favored in G1 phase of the cell cycle whereas HR is favored in the S and G2 phases [29,30].

Tumor cells usually acquire the ability to escape from DDR and most cancer cells show multi-dysfunctions in DDR, including resistance to genotoxic drugs and ionizing radiations or abnormal cell cycle progression following DNA damage [10]. Recent evidence has shown that several lncRNAs regulate gene activity in response to DNA damage.

LncRNAs

LncRNAs are a novel group of non-coding RNA transcripts with a length longer than 200 nucleotides [31,32]. LncRNAs do not encode proteins and were long considered transcriptional noise [33]. Emerging evidence, however, has demonstrated that lncRNAs may serve as master gene regulators capable to control gene expression and protein synthesis [34,35]. LncRNAs are largely dysregulated in cancer, being novel biomarkers for diagnosis, treatment, and prognosis [36–38]. In the past decade, lncRNAs have been highlighted with their important functions in development, progression, and prognosis of human cancers [39–41]. They can regulate gene expression at transcriptional and/or translational levels, histone modifications and epigenetics, and RNA splicing [42,43].

LncRNAs in DNA Damage Response and Repair in Cancer Cells

A novel function of lncRNAs that recently emerges is that lncRNAs participate in the regulation of DDR through modulating multiple DDR signaling pathways, such as the key ATM and ATR pathways, and p53 pathway.

LncRNAs in ATM and ATR pathways

Wan *et al.* [44] conducted a genome-wide screening of lncRNA expression profiles in $Atm^{+/+}$ and $Atm^{-/-}$ mouse embryonic fibroblasts (MEFs) after treated with neocarzinostatin (NCS), a radiomimetic drug that generates DSBs. They found that DSBs induced widespread changes in the expression of lncRNAs, including marked increase of 100 ATM-dependent lncRNAs and noticeable decrease of 70 ATM-dependent lncRNAs. Particularly, they identified a novel lncRNA named lncRNA-JADE (JADE1 adjacent regulatory RNA). This lncRNA induces G1/S cell cycle arrest and inhibition of apoptosis in response to DNA damage. Inhibition of ATM suppresses DNA damage-induced JADE expression, suggesting JADE expression is ATM-dependent. JADE transcriptionally upregulates Jade1 (a PHD zinc finger protein) and thus increases Jade1-mediated histone H4 acetylation in response to DNA damage. H4 acetylation often results in chromatin remodeling and transcriptional activation [45,46]. JADE also positively regulates DNA damage repair by recruiting the DNA damage repair protein Mdc1.

Sharma *et al.* [47] performed a similar screening of genome-wide RNA transcripts in human skin fibroblasts exposed to DNA-damage agent neocarzinostatin, camptothecin, or etoposide. They identified a novel lncRNA named DDSR1 (DNA damage-sensitive RNA1). DDSR1 was upregulated in response to all three DNA-damage agents used. They further showed that DDSR1 was induced by NCS in PC3 (prostate), A549 (lung), U2OS (osteosarcoma), and HCT116 (colon) cells. Thus, DDSR1 responds to DNA damage without any cell type specificity. Similarly, DDSR1 expression is ATM-dependent and inhibition of ATM with a specific inhibitor KU55933 significantly suppressed DDSR1 induction by NCS. The authors further found that deficiency of DDSR1 impaired DDR signaling by downregulating several DDR signaling molecules, including γ-H2AX, phospho-RPA, and phospho-Chk1. γ-H2AX is a marker of DSBs that activates the ATM–Chk2 pathway [48]; RPA binds to ssDNA during the initial phase of HR [49–51]; and Chk1 is required for the initiation of DNA damage checkpoints [52]. Moreover, DDSR1 loss increased accumulation of HR repair factors BRCA1 and RAP80 to DSBs. RAP80 is a ubiquitin-binding protein and promotes recruitment of BRCA1 to DSBs [53]. Although BRCA1 recruitment at DSBs primarily promotes DNA repair by HR [54,55], aberrant activity of this BRCA1–RAP80 complex limits HR by restricting DSB end resection [56,57]. Thus, DDSR1 functions in DDR repair process.

In a transcriptome analysis of lncRNAs in human fibroblast cells (GM0637) with DSBs induced by radiomimetic NCS, Wan *et al.* [58] identified another lncRNA named ANRIL (antisense noncoding RNA in the INK4 locus) that was markedly upregulated in response to DNA damage. They also found that the ANRIL was upregulated at the late stage of DDR in U2OS and HCT116 $p53^{+/+}$ cells. ATM silencing abolished the induction of ANRIL by NCS, suggesting that ANRIL is an ATM-dependent lncRNA in DDR. A putative E2F1-binding element is found in the ANRIL promoter and the ANRIL is induced by the transcription factor E2F1 during DDR. Upregulated ANRIL interacts with both PRC1 and PRC2 to form heterochromatin surrounding the INK4B–ARF–INK4A locus and repress its expression [59,60]. Knockdown of ANRIL induces expression of INK4B, ARF, and INK4A consistently in a high level throughout the DDR induced by NCS, while overexpression of

ANRIL reduces the levels of the three proteins. Since these proteins function as cyclin-dependent kinase inhibitors that contribute to cell cycle arrest in cell response to DNA damage [61], ANRIL contributes to mediate DNA repair efficiency.

LncRNA NEAT1 (nuclear enriched abundant transcript 1) is a non-coding RNA transcript functioning as a core structural component of the paraspeckle in the nucleus [62–64]. Aberrant NEAT1 expression has been reported in human cancers, including upregulation in laryngeal squamous cancer, pancreatic cancer, colorectal cancer, and pancreatic cancer and downregulation in esophageal carcinoma and hepatocellular carcinoma [65–68]. Recently, it is found that NEAT1 may be involved in carcinogenesis through regulation of DDR [69]. Silencing of NEAT1 sensitized preneoplastic cells to DNA damage-induced cell death with increase of the DNA damage marker γ-H2AX. In U2OS cells treated with hydroxyurea, NEAT1 knockdown decreased ATR-mediated phosphorylation of checkpoint kinase Chk1 and replication protein RPA32, indicating that NEAT1 promotes ATR signaling and checkpoint activation in response to replication stress.

LncRNAs in p53 regulatory network

Interaction network between p53 and lncRNAs is complex, but in general, these lncRNAs function as either p53 targets or p53 regulators. As p53 targets, lncRNAs may be involved in DDR through mediating p53-induced cell cycle progression and/or apoptosis. The regulator lncRNAs of p53 may participate in DDR by mediating p53 activity in response to DNA damage.

LncRNAs as targets of p53

To date, several lncRNAs have been characterized as direct targets of p53. They function in regulation of cell cycle progression and apoptosis in response to DNA damage. Hung *et al.* [36] identified five lncRNAs at the promoter of CDKN1A (a p53 target gene) in cells with DNA damage, and among them, lncRNA PANDA (p21 associated ncRNA DNA damage activated) is an antisense RNA of CDKN1A. PANDA is previously found to be significantly upregulated in osteosarcoma and intraductal papillary mucinous neoplasms [70,71]. However, it is found that PANDA acts as a tumor suppressor gene in diffuse large B-cell lymphoma [72]. It may be caused by limited samples or the different types of tumors. There is a p53-binding site between the CDKN1A locus and PANDA [73]. Knockdown of p53 significantly limits the induction of CDKN1A and PANDA following DNA damage [36]. PANDA mediates cell cycle arrest and survival by suppressing expression of pro-apoptotic genes, such as CCNB1, FAS, PUMA, and NOXA; silencing of PANDA sensitizes human fetal lung fibroblasts to DNA damage-induced apoptosis by doxorubicin. Thus, PANDAR promotes carcinogenesis through mediation of DNA damage-induced apoptosis.

LncRNA PINCR (p53-induced non-coding RNA) is a direct downstream target of p53 [74]. Doxorubicin-induced DNA damage activates p53 and upregulates PINCR in colorectal cancer cell lines, HCT116 and SW480 [75]. PINCR regulates cell cycle and has a pro-survival function in response to DNA damage, and silencing of PINCR enhances cell sensitivity to chemotherapeutics. PINCR can upregulate a subset of p53 targets following DNA damage, including BTG2, RRM2B, and GPX1. These proteins are involved in p53-mediated cell survival [76,77].

TP53TG1 (TP53 target gene 1) is a p53-induced lncRNA, identified as a tumor suppressor RNA [78]. Binding to the multifaceted DNA/RNA binding protein YBX1, TP53TG1 prevents YBX1 nuclear localization and thus suppresses YBX1-mediated activation of the PI3K/AKT signaling cascade [79–83]. Thus, targeted expression of TP53TG1 markedly increased the sensitivity of HCT116 cells to DNA damage agents (e.g. doxorubicin, carboplatin, and cisplatin). Oppositely, silencing or epigenetic loss of TP53TG1 in cancer cells activates the YBX1-mediated PI3K/AKT signaling and creates chemoresistance.

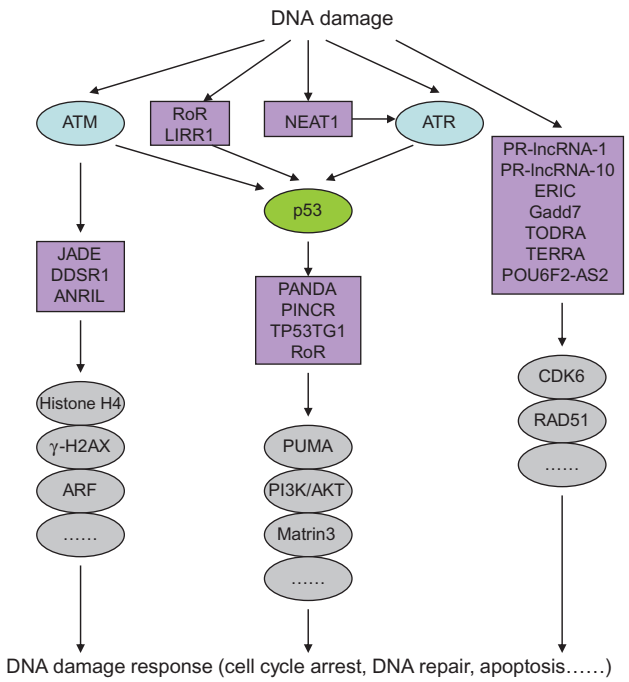

Figure 1. Scheme of lncRNAs involved DNA damage response

LncRNAs as regulators of p53

This group of lncRNAs modulates p53 activity through different mechanisms and thus is involved in DDR. For instance, lncRNA RoR reprograms differentiated cells into pluripotent stem cells [84]. RoR has been shown to be increased and promote tumor progression in pancreatic cancer, nasopharyngeal cancer, gallbladder cancer, and breast cancer [84–87]. Zhang *et al.* [88] revealed that RoR regulates p53 translation and thus controls the cellular p53 protein level. Targeted expression of RoR suppresses p53-mediated cell cycle arrest and apoptosis induced by doxorubicin. In the p53 regulatory function of RoR, heterogeneous nuclear ribonucleoprotein I (hnRNP I), an RNA binding protein may play a role through direct interaction of RAN–protein. Interestingly, increased p53 induces RoR forming a feedback loop between RoR and p53.

LncRNA LIRR1 regulates p53 activity through control of MDM2 expression, the main negative regulator of p53. Jiao *et al.* [89] reported that LIRR1 was induced by X-ray, an irradiation that induces DNA damage and stress signals. LIRR1 stimulates the formation of γ-H2AX and markedly radiosensitizes human bronchial epithelial BEAS-2B cells to X-ray radiation and arrests cells in G1 phase. Targeted expression of LIRR1 suppresses MDM2 expression, thus activating p53. LIRR1 also represses the expression of KU70 and KU80 (DSB sensors), RAD50 (a DNA damage repair protein) and CDK2 (a cell-cycle checkpoint), directly mediating DDR and DNA damage repair.

LncRNAs PR-lncRNA-1 and PR-lncRNA-10 were identified from HCT116 cells treated with 5-fluorouracil [90]. These two

Table 1. LncRNAs involved in DNA damage/repair

LncRNA	Regulator	Interaction with	Targets	Function	References
JADE	ATM		Histone H4	DDR and histone H4 acetylation	[44]
DDSR1	ATM		γ-H2AX and p-RPA	DSB repair	[47]
ANRIL	ATM and E2F1		INK4A and INK4B	Cell-cycle checkpoint	[48]
NEAT1			ATR, CHK1, and RPA32	DDR and cell-cycle checkpoint	[56]
PANDA	p53		CCNB1, FAS, PUMA, and NOXA	Cell cycle arrest and survival	[36]
PINCR	p53		Matrin 3	Cell cycle arrest and apoptosis	[74]
TP53TG1	p53	YBX1	PI3K/AKT	DDR	[78]
RoR	p53		p53	DDR	[84]
LIRRE			p53, MDM2, KU70, KU80, RAD50, and CDK2	DDR	[89]
PR-lncRNA-1/PR-lncRNA-10		p53	SERPINB5, CDKN1A, BCL2L1, and BBC3	Cell cycle arrest and/or apoptosis	[90]
ERIC	E2F1			Cell apoptosis	[91]
Gadd7		TDP-43	CDK6 and CDK	Cell cycle arrest	[93,94]
TODRA				DSB repair	[104]
TERRA				DDR and dysfunctioning telomeres	[105]
POU6F2-AS2		YBX1		DDR and cell survival	[106]

lncRNAs do not affect the p53 protein expression or phosphorylated activation, but affect the binding of p53 to its transcriptional targets, such as SERPINB5, CDKN1A, BCL2L1, and BBC3 genes, thus regulating their expression in response to DNA damage. Silencing of PR-lncRNA-1 or PR-lncRNA-10 markedly increases cell number in S-phase and inhibits apoptosis when cells are exposed to doxorubicin to induce DNA damage. Therefore, PR-lncRNA-1 and PR-lncRNA-10 regulate p53-mediated cell cycle arrest and apoptosis in response to DNA damage.

LncRNAs in other pathways

There are also some lncRNAs that are not effectors in the ATM/ATR pathways and p53 network, but participate in the regulation of cell cycle and apoptosis after DNA damage. For instance, lncRNA ERIC (E2F1-regulated inhibitor of cell death) is upregulated by etoposide, a chemotherapeutic drug which can induce DNA damage and apoptotic cell death [91]. E2F1 is a transcription factor that regulates gene expression required for cell cycle progression [92]. Inhibition of ERIC expression increases cell apoptosis induced by etoposide. This is a p53-independent manner as p53 deletion does not affect the activation of E2F1-inducted ERIC expression.

LncRNA Gadd7 (growth-arrested DNA damage-inducible gene 7) is upregulated by UV irradiation, cisplatin and DNA alkylating agents (e.g. methyl methanesulfonate, *N*-methyl-N4-nitro-*N*-nitrosoguanidine, and mechlorethamine), and oxidizing hydrogen peroxide [93,94]. This lncRNA functions through specifically binding to TDP-43 through UG/GU repeats. The TDP-43 associates with Cdk6 mRNA, blocking its degradation [95]. By binding to TDP-43, Gadd7 interrupts the TDP-43/Cdk6 mRNA association, leading to Cdk6 mRNA degradation and CDK6 protein decrease. CDK6 associates with Cyclin D and regulate G1/S transition in cell cycle [96]. UV irradiation stimulates the interaction of Gadd7 with TDP-43, and thus leads to cell accumulation at G1 phase. The Gadd7 functions in DDR through regulation of G1/S checkpoint.

LncRNA HOTAIR (HOX antisense intergenic RNA) is an oncogenic RNA transcript upregulated in different human cancers [97,98]. HOTAIR epigenetically regulates gene expression and functions in multiple cellular pathways [99–101]. Recently, Ozes *et al.* [102] revealed that HOTAIR is involved in platinum resistance in ovarian cancer cell lines and patient. HOTAIR is induced in response to platinum-induced DNA damage and in turn enhances phosphorylation activation of Chk1 and thus suppresses apoptosis. Thus, HOTAIR is a new lncRNA player in DDR.

RAD51 plays a crucial role in HR and DSB repair; dysregulation of RAD51 leads to genome instability and cancer development [103]. LncRNA TODRA (transcribed in the opposite direction of RAD51) is transcribed upstream of RAD51 in the opposite direction [104]. TODRA downregulates RAD51 and affects RAD51-dependent DSB repair. The lncRNA TERRA (telomeric repeat-containing RNA) is involved in the DDR triggered by dysfunctioning telomeres [105]. In addition, lncRNA POU6F2-AS2 is involved in DDR and regulates cells survival in response to ionizing radiation [106]. Knockdown of POU6F2-AS2 expression abrogated the YBX1's localization to DNA damage sites. YBX1 is a chromatin-bound and DNA repair related protein that binds to ssDNA and regulates cell survival following DNA damage [107]. Thus, POU6F2-AS2 participates in DDR through targeting the YBX1 protein (**Fig. 1** and **Table 1**).

Conclusion

The rapid development of genome-wide transcriptome analysis has led to the identification of numerous lncRNAs. LncRNAs have been demonstrated to play a critical role in various biological and pathological processes. Although significant progresses have been made in the understanding of lncRNAs in the past years, the function and regulation network of lncRNA is not fully understood. Herein, we summarize the most recent advances in lncRNA regulation and function in response to DNA damage. The increased understanding of lncRNAs in DDR will expand our knowledge of lncRNAs in DNA damage repair, cancer progression, and chemo- and radioresistance, which may eventually improve the management of cancer.

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