Long noncoding RNAs at the crossroads of cell cycle and genome integrity

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Abstract

The cell cycle is controlled by guardian proteins that coordinate the process of cell growth and cell division. Alterations in these processes lead to genome instability, which has a causal link to many human diseases. Beyond the well-characterized role of protein-coding genes, an increasing body of evidence has revealed that long noncoding RNAs (lncRNAs) actively participate in the regulation of cell cycle and safeguarding of genome integrity. LncRNAs are versatile molecules that act via a wide array of mechanisms. In this review, we discuss how lncRNAs are implicated in the control of cell cycle and maintenance of genome stability and how changes in lncRNA-regulatory networks lead to proliferative diseases such as cancer.

Keywords: long noncoding RNAs, cell cycle, cell division, genome stability, cancer.

Emerging roles for lncRNAs in cell cycle control and genome stability

Multiple protein networks are involved in regulation of the cell cycle (Box 1), which is crucial to avoid the transmission of any errors during DNA replication and mitosis to the progeny. Alterations in any of these processes can lead to **genome instability** (see Glossary) which underlies many human diseases. One of the surprising discoveries of the postgenomic era revealed that only 2% of the mammalian genome codes for protein-coding genes, with **long noncoding RNAs (lncRNAs)** representing a significant portion of the human genome [1-3]. Despite more than 50,000 lncRNAs being annotated to date [2, 3], functional characterization has been performed only for a subset. However, evidence is accumulating that many lncRNAs play important roles in the regulation of cell cycle and genome stability [4, 5]. Understanding the role of lncRNAs in this context will not only provide new insights into regulation of fundamental cellular processes but also reveal novel pathogenetic mechanisms that contribute to human diseases such as cancer.

LncRNAs are a heterogenous class of RNA molecules that are transcribed by RNA polymerase II (Pol II), are longer than 200 nucleotides and have low coding potential [6]. LncRNAs exhibit cell-type and tissue-specific expression, not only in healthy conditions, but also in pathological states, and are subjected to rapid turnover during evolution [5, 7]. LncRNAs can regulate numerous cellular processes including cell cycle, proliferation, apoptosis and **DNA damage response (DDR)**, all pathways whose dysregulation has been associated with cancer [4, 8, 9]. Mechanisms through which lncRNAs regulate these pathways include transcriptional and post-transcriptional gene regulation, chromatin organization, cell signalling and post-translational regulation of protein activity [5, 10]. LncRNAs are known to exhibit distinct subcellular localization [11], being found in the cytoplasm and/or nucleus where changes in lncRNA subcellular localization often have a profound effect on their function. Indeed, the biological significance of lncRNAs cellular distribution on the DDR is starting to emerge [12-16].

Expression of lncRNAs is deregulated in cancer and many cancer-associated lncRNAs are implicated in the cell cycle progression and maintenance of genome stability [2, 5, 17], whose misregulation is the hallmark of cancer [8]. In this review, we discuss recent findings that shed light on how lncRNAs control cell cycle and maintain genome stability. We highlight emerging lncRNA-mediated mechanisms in these processes (Fig. 1, Key Figure and Fig. 2) to better understand how alterations in lncRNA-regulatory networks contribute to human diseases such as cancer. For the purpose of this review we will categorize lncRNAs based on specific stages of the cell cycle where they have been implicated in, including quiescence (Box 2), DNA replication and cell division (Table 1), and those that directly or indirectly contribute to the DDR and maintenance of genome stability (Table 2).

***Box 1. An overview of the cell cycle regulation* (see Figure for Box 1)**

The cell cycle is a tightly controlled process of cell growth and cell division that is required for normal development and tissue homeostasis, a process usually altered in cancer [18]. The mammalian cell cycle is divided into four main stages: G1 (gap 1), S-phase (DNA synthesis), G2 (gap 2) and mitosis (M, cell and nuclear division). Quiescence (G0), the fifth stage of the cell cycle, is a reversible cell cycle arrested state where cells cannot proliferate but still maintain their ability to re-enter the cell cycle and resume proliferation. The main players of the cell cycle are four different classes of cyclins (the A-, B-, D- and E-type), CDKs, CDKi, retinoblastoma protein (Rb)- and p53-related pathways. Different CDKs have distinct roles during cell cycle progression and their activities are regulated not only by cyclins, but also by phosphorylation or dephosphorylation. For example, CDK4 and 6 are active during G1 phase, CDK2 functions during both G1 and S phase while CDK1 kinase is active during G2 and mitosis. In turn, INK4 ($p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$ and $p19^{INK4d}$) and/or Cip/Kip ($p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$) are families of CDKi, which can bind to cyclin-CDK complexes and inhibit their activities in specific stage of the cell cycle. While $p21^{Cip1}$, $p27^{Kip1}$ and $p57^{Kip2}$ inhibit a broader spectrum of cyclin-CDK complexes, $p15^{INK4b}$, $p16^{INK4a}$, $p18^{Ink4C}$ and $p19^{Ink4D}$ specifically inhibit CDK4/6 activity.

In early G1-phase D-type cyclins (cyclin D1, D2 and D3) bind to CDK4/CDK6, which is essential for CDK activation and for cells to enter the G1-phase of the cell cycle. The Rb tumor suppressor protein, which binds and inhibits the E2F transcription factors, is a target of cyclin D-CDK4/6 and cyclin E-CDK2 complexes. Phosphorylation of Rb leads to dissociation of Rb-E2F complex and activation of the E2F-dependent transcription of cell cycle genes. As the cell cycle progresses, CDK2 can now bind to cyclin E to control entry to S-phase or cyclin A during S-phase. In the G2-phase of the cell cycle, cyclin A binds to CDK1 and promotes cell cycle progression during the G2-phase. Finally, for cells to enter mitosis cyclin A is replaced by cyclin B and cyclin B-CDK1 complex is responsible for triggering mitosis where replicated chromosomes are equally distributed to daughter cells. To exit mitosis, cyclin B is degraded leading to inactivation of the cyclin B-CDK1 complex.

LncRNAs regulating G1-phase of the cell cycle

The first study that identified cell cycle-regulated lncRNAs examined by custom microarrays **noncoding RNAs (ncRNAs)** transcribed from 56 cell cycle-linked loci, and identified lncRNAs periodically expressed during the cell cycle in human cells [19]. The expression of some of these lncRNAs was found to be responsive to DNA damage and deregulated in human cancers. The cell cycle-dependent expression of lncRNAs was also confirmed using RNA sequencing (RNA-seq) in human cervical cancer cell line (HeLa) [20]. The **FANTOM** 6 project, which used antisense LNA-modified GapmeR **antisense oligonucleotide (ASOs)** to deplete 285 lncRNAs in human primary fibroblasts, identified several lncRNAs associated with cell cycle defects further supporting the role of lncRNAs in cell cycle progression [21]. By analyzing cell cycle-staged single-cell RNA-seq data from mouse embryonic stem cells (ESCs), which have a shorter G1-phase, lncRNAs were shown to regulate cell cycle and contribute to cell type-specific adaptations of ubiquitous processes [22]. Another study performed deep RNA-seq on synchronized human cancer cells and identified >2000 lncRNAs that had cell cycle phase-specific expression [23]. In particular, 42% of genes that had elevated expression in

specific stage of the cell cycle were ncRNAs with the majority being lncRNA genes. Interestingly, most of these lncRNAs had higher expression in the G1-phase. Although differential expression alone does not prove a role in the cell cycle, it is reasonable to hypothesize that some of these cell cycle-regulated lncRNAs might play a role in G1/S transition.

Besides analyses of lncRNA expression during the cell cycle, the link between individual lncRNAs and G1/S transition has been specifically investigated. These G1-phase related lncRNAs control expression of cyclins, CDKs, CDKi and tumor suppressor genes by acting as protein scaffolds or as transcriptional, post-transcriptional or epigenetic regulators. For example, *ncRNA*$_{CCND1}$ (*ncRNA transcribed upstream of the CCND1 gene*) negatively regulates *CCND1* transcription in human cells through recruitment and activation of the **RNA binding protein (RBP)** TLS (Translocated in LipoSarcoma), leading to cell cycle arrest [24]. *NcRNA*$_{CCND1,}$ which is transcribed from the promoter region of *CCND1* is also the first example of lncRNA expressed upon DNA damage. LncRNA *LAST* (*LncRNA-Assisted Stabilization of Transcripts*), which cooperates with the single-stranded DNA/RNA-binding factor CNBP, also controls *CCND1* function in human cells by regulating its mRNA stability [25]. Furthermore, overexpression of tumor suppressive lncRNA *GAS5* (*Growth Arrest Specific 5*) leads to G1 cell cycle arrest and inhibition of cell proliferation in human cancer cells via negative and positive regulation of *CDK6* [26] and *P27*^{Kip1} levels [27], respectively. Additional examples of lncRNAs controlling G1-phase through post-transcriptional mechanisms are *Gadd7* (*growth-arrested DNA damage-inducible gene 7*) [28, 29], *CCAT1* (*colon cancer-associated transcript-1*) [30-32] and *MIR100HG* [33].

In addition to cyclins and CDKs, lncRNAs can also regulate CDKi levels. Together with *ARF* (*alternate reading frame*), *p16*^{INK4a} and *p15*^{INK4b} genes are located within the *INK4/ARF* locus, which is critical for cell cycle progression. Given the importance of the *INK4/ARF* locus in tumor suppression [34], its transcription must be tightly regulated. LncRNA *ANRIL* (*antisense non-coding RNA in the INK4 locus*, *p15AS* or *CDKN2B-AS1)* is involved in epigenetic repression of the *INK4/ARF locus,* and is also required for cell cycle progression in

human cells. Mechanistically, *ANRIL* recruits Polycomb Repressive Complex 1 and 2 (PRC1/PRC2) to the *INK4/ARF locus* resulting in a decrease of $p15^{INK4b}$ and $p16^{INK4a}$ levels [35, 36]. Another study showed that *KNCQ1OT1*, an **imprinted lncRNA**, regulates $p57^{Kip2}$ by binding to PRC2 and G9a chromatin regulators, which through epigenetic modifications repress $p57^{Kip}$ transcription [37, 38].

Rb-mediated E2F regulation has a key role in controlling G1-phase. Many lncRNAs act downstream of E2F1 and contribute to E2F1-regulatory networks such as *H19* [39], *ANRIL* [40], *MA-linc1* (*mitosis-Associated Long Intergenic Non-Coding RNA 1*) [41] and *ERIC* (*E2F1-Regulated Inhibitor of Cell death*) [42]. For example *H19* lncRNA, which acts as a primary miRNA precursor generating miRNA-675, downregulates Rb [43] and promotes breast cancer cell proliferation [39].

Some lncRNAs such as *MALAT1* (*Metastasis Associated Lung Adenocarcinoma Transcript 1*) [44] and *MA-linc1* [41] can affect more than one phase of the cell cycle. *MALAT1* is an abundant lncRNA that functions in G1/S transition and mitosis, and is deregulated in cancer [45-47]. p53 is a downstream mediator in *MALAT1* function and is required to induce G1- or S-phase arrest in *MALAT1*-depleted cells [44]. *MALAT1's* role in G1/S transition is independent of its function in mitosis, which is consistent with *MALAT1* expression being highest during the G1/S and M-phase. In addition to *MALAT1*, expression of *LAST* and *MIR100HG* is also peaking in the G1-phase indicating that expression of some lncRNAs is closely associated with its specific cell cycle stage function.

Since dysregulation of lncRNAs involved in G1/S transition have been observed in cancer, cardiovascular and overgrowth syndromes [26, 30-33, 38, 39, 41, 43, 45-48], these findings indicate that lncRNA-mediated cell cycle regulation has an important impact on physiological processes as well as pathogenesis of diseases.

LncRNAs regulating S-phase of the cell cycle

The role of lncRNAs in S-phase progression is less characterized compared to lncRNAs involved in G1-phase. An elegant study by *Marchese et al.* showed that *CONCR* (*COhesion regulator NonCoding RNA),* a lncRNA with peak expression in mid-late G1-phase, controls DNA replication and cell cycle progression [49]. *CONCR* interacts with and regulates the activity of a DNA helicase involved in DNA replication, and its depletion leads to sister chromatid cohesion and S-phase progression defects in human cells. Moreover, *CONCR* is activated by transcription factor MYC and its upregulation is observed in several cancers [49]. Similarly, *SUNO1* (*S-phase-upregulated Non-coding-1*) is a lncRNA whose levels are enriched during G1/S and early S-phase and *SUNO1*-depleted cells display S-phase progression defects in human cell lines [23]. Mechanistically, *SUNO1* promotes transcription of genes involved in cell proliferation by stabilizing the interaction between the RNA helicase DDX5 and Pol II on chromatin. In keeping with its role in promoting cell survival, increased levels of *SUNO1* have been associated with tumorigenicity in colorectal mucosa and poor colon cancer prognosis. Despite *SUNO1*-depleted cells being sensitive to **DNA damaging agents**, its function in the DDR remains to be identified. Since other lncRNAs were shown to bind DNA/RNA helicases [50, 51], it remains to be seen whether the interaction between lncRNAs and DNA/RNA helicases is a common mechanism for lncRNAs to regulate S-phase.

By using nascent RNA-seq in HeLa cells, *Ali et al.* identified S-phase specific lncRNAs with functions in cell cycle control and cancer [52]. LncRNA *SCAT7 (S-phase Cancer-Associated Transcript*) regulates the FGF/FGFR signalling and affects proliferation, invasion and migration. Depletion of *SCAT7* led to reduced FGF/FGFR signalling, which in turn affected expression of cell cycle genes such as *CCND1.* This work also represents a valuable resource of lncRNA-based oncogenic drivers with potential prognostic value. Subsequently, a similar study identified S-phase enriched lncRNAs in the non-transformed diploid cell line hTERT-RPE1, and showed diverse regulatory potential of *linc00704, MIAT* and *LUCAT1* lncRNAs in S-phase progression [53].

Taken together, these findings indicate that lncRNAs involved in S-phase progression act either as effectors of DNA/RNA helicases or as regulators of pivotal signaling pathways.

LncRNAs regulating G2/M transition of the cell cycle

Growing evidence suggests that RNA-based mechanisms contribute to the fidelity of cell division through the activity of RBPs and different ncRNAs present on the mitotic spindle, kinetochores and centrosomes, the major components of the mitotic apparatus [54]. Although centromeric lncRNAs have been linked to chromosome segregation and kinetochore formation in Drosophila [55], the majority of lncRNAs are not present on mitotic chromatin [11, 56]. A **Mitocheck consortium** used a genome-wide siRNA library targeting 21,000 protein-coding genes and identified new proteins in cell division [57]. Once **RNAi**, ASO and **CRISPR/Cas9**-based libraries became available for lncRNAs, similar approaches were employed to identify lncRNAs involved in different cellular processes including cell division (Box 3). By targeting 600 cancer-relevant lncRNAs and analyzing their impact on cell division in HeLa Kyoto cells, *linc00152* was identified as regulator of mitosis whose function was linked to the microtubule cytoskeleton and ubiquitin pathway [58]. However, no mitotic defects were observed in other human cell lines after *linc00152* depletion, possibly due to lncRNA cell type-specific functions [59, 60]. A second study performed a larger RNAi imaging screen by depleting 2231 lncRNAs in HeLa cells, and identified lncRNAs with key roles in mitotic progression, chromosome segregation and cytokinesis [56]. These include *linc00899* and *C1QTNF1-AS1* that regulate mitosis through diverse mechanisms and whose expression is also altered in cancer [61, 62]. For instance, nuclear *linc00899* was shown to regulate mitotic progression in multiple cell lines by binding and suppressing the transcription of *TPPP*, a microtubule-binding protein. By identifying lncRNAs with a role in mitosis and cytokinesis, these screens represent the basis for future studies aimed to understand how lncRNAs govern the fidelity of cell division.

Besides regulating the mitotic microtubule network certain lncRNAs control cell division by mediating interactions between proteins involved in mitosis. For example, lncRNA *GiniR (antisense transcripts Genomic Instability Inducing RNA*) [15] interacts with centrosomal protein Cep112 and BRCA1, a protein involved in DNA repair [63] and centrosome biogenesis

[64]. Overexpression of *GiniR* in mouse fibroblasts leads to mitotic defects and genome instability. Intriguingly, *Ginir* was found to be cytoplasmic in normal and nuclear in transformed cells indicating that nuclear localization of *Ginir* might contribute to its oncogenic nature [15].

In parallel, lncRNAs were shown to modulate activities of protein kinases by acting as chaperones, allosteric regulators or preventing their post-translational modifications [10]. Polo-Like Kinase 1 (PLK1) is a major regulator of mitosis, whose spatio-temporal activity is central to error-free chromosome segregation [65]. Several lncRNAs such as *lncRNA-RI* (*lncRNA Radiation Induced)* [66] and *APAL (Aurora A/Polo-like-kinase 1 [PLK1]–associated lncRNA*) [67] regulate PLK1 expression or activity. *OIP5-AS1* lncRNA was shown to regulate stability of cyclin G Associated Kinase (GAK), which is important for mitotic progression [68]. Depletion of *lncRNA-RI*, *APAL* and *OIP5-AS1* led to mitotic defects indicating that lncRNA-mediated regulation of mitotic kinases is essential for error-free cell division. By exploring the role of lncRNAs in skeletal myogenesis, lncRNA *SAM (Sugt1 associated muscle)* was shown to regulate proliferation of mouse muscle stem cells and myoblasts [69]. Since loss of *SAM* induced degradation of Sugt1, a protein involved in kinetochore assembly, these data suggest that *SAM*-Sugt1 interaction is required for fidelity of cell division.

In addition to G1/S transition roles described above, *MALAT1* [44] and *MA-linc1* [41] can also regulate mitosis. For example, *MALAT1* controls the expression of *B-MYB*, a transcription factor regulating expression of genes involved in mitosis. Notably *MALAT1*-depleted cells show mitotic defects and reduced levels of *B-MYB* due to its aberrant splicing. Differently from *MALAT1* and other lncRNAs involved in G1/S progression whose levels are cell cycle regulated [23, 25, 33, 44, 49, 52, 53], the expression of lncRNAs involved in G2/M phase does not seem to follow the same pattern. The reason for this could be either poor quantification of mitosis-specific levels of lncRNAs due to the shorter duration of mitosis or the lncRNA concentration is less crucial in mechanisms controlling the G2/M transition.

In summary, lncRNAs control cell division by regulating gene expression or modulating activities and stability of mitotic proteins. Their expression is often altered in cancer [41, 45, 47, 58, 61, 62, 67, 70] similarly to lncRNAs involved in other cell cycle stages.

Box 2. LncRNAs involved in cell cycle quiescence (G0)

Quiescence is a state of reversible proliferative arrest where cells are not dividing but still have the ability to re-enter the cell cycle upon receiving an appropriate stimulus [71]. Several lncRNAs have been showed to act in the G0 maintenance or in G0/G1 transition. LncRNA PAPAS (promoter and pre-rRNA antisense) was found to be upregulated in quiescent mouse embryonic fibroblasts (MEFs) and human cells [72]. By interacting with a histone lysine methyltransferase, PAPAS facilitates chromatin compaction in growth-arrested cells at specific genomic loci, contributing to the maintenance of a G0-specific transcriptional program. Another example is a PDCD4-AS1 lncRNA, which is expressed in human quiescent cells together with its sense counterpart, the tumor suppressor PDCD4. PDCD4-AS1 increases the stability of PDCD4, which by negatively regulating CCND1 expression, promotes the maintenance of G0-phase [73]. Similarly to PDCD4, expression of PDCD4-AS1 correlates with overall survival of triple negative breast cancer (TNBC) patients, indicating a tumor suppressive role also for PDCD4-AS1.

Quiescence has also been associated with cancer stemness, which protects cancer stem cells (CSCs) from antiproliferating anticancer drugs leading to CSC-mediated resistance to conventional therapies [74]. Several lncRNAs such as GAS5 have been identified as key players in maintaining the "stemness" state of tumors [75]. In addition, GAS5 was found to be highly expressed in a small fraction of human pancreatic cancer cells and its depletion released these cells from the cell cycle arrest [76]. Another study found lncRNA DANCR (Differentiation Antagonizing Non-Protein Coding RNA) to be upregulated in human leukemia stem cells (LSCs), which have abnormal self-renewal capacity and increased chemotherapy resistance [77]. Depletion of DANCR in LSCs led to decreased stem cell renewal and quiescence by downregulation of WNT pathway. Serum stimulation can also promote cell cycle re-entry and induce expression of lncRNAs regulating G0/G1 transition. For example, increased level of MIR222HG in serum-stimulated human fibroblasts dictates the cell cycle re-entry post quiescence by binding to ILF3/ILF2 RBPs and promoting stability of its interacting mRNAs [78].

Given the growing evidence of quiescence-specific lncRNAs and their link to cancer stemness, future studies will be required to address the mechanism how lncRNAs control the cell cycle re-entry and identify the upstream signalling networks that regulate lncRNA expression at the quiescence and proliferation crossroad.

Box 3. High-throughput methods for functional profiling of lncRNAs

RNAi-, ASO- and CRISPR-based technologies have been used to perturb lncRNA expression and identified lncRNAs involved in pluripotency, differentiation, proliferation, growth, signaling, cell division and resistance to targeted therapeutics. One of the first loss-of function (LOF) approaches was a high-throughput shRNA screen targeting 226 lncRNAs in mouse ESC [79] indicating the importance of lncRNAs in maintenance of the pluripotency. Subsequently, other shRNA screens identified lncRNAs involved in pluripotency [80] and mouse fibroblast proliferation [81]. To identify lncRNAs involved in cell division, two RNAi-based screens were coupled with immunostaining [56] or live-cell imaging in human cancer cells [58].

CRISPR-Cas9 technology has been a break-through for manipulating lncRNA expression. The CRISPR-deletion screen targeted 700 cancer-associated lncRNAs and identified 51 candidates involved in cell proliferation of liver cancer cells [82]. An alternative CRISPR screen exploited sgRNA libraries targeting lncRNA splice sites and led to identification of lncRNA-mediated phenotypes in different cellular models [83]. A large ***CRISPR interference (CRISPRi)****-based screen targeted 16,041 lncRNAs in seven human cell lines and identified 499 lncRNAs affecting cell growth [59]. Interestingly, majority of lncRNAs had a phenotype only in one cell type indicating that lncRNAs can have cell-type specific functions regardless of their expression [59, 60]. A CRISPRi screen was also used to identify lncRNAs as new therapeutic targets in human glioblastoma [60]. Simultaneously, gain-of function (GOF) methods based on* ***CRISPR-activation (CRISPRa)*** *or* ***CRISPR/Cas9 synergistic activation mediator (SAM)*** *system have identified lncRNAs involved in AKT signaling [84] and drug resistance in melanoma [85] or acute myeloid leukemia (AML) [86]*

using human breast, melanoma and AML cell lines, respectively. Since majority of CRISPR screens have been performed in cancer cell lines, it is possible that cell-type specific function of lncRNAs could be due to higher mutational load of cancer cell lines and their ongoing instability [87, 88].

However, CRISPR-based approaches have some limitations. For instance, CRISPR-screens targeting lncRNA splice sites can result in false positives [89], while CRISPRi can inadvertently affect expression of neighboring genes [90] or lncRNAs close to other transcriptional units [91]. Instead, the FANTOM 6 project used ASOs to deplete lncRNAs in human primary fibroblasts and analyzed the effect of lncRNA depletion on cell growth and morphology [21]. They found a concordance between RNAi and ASO-mediated phenotype only for 3 out 9 lncRNAs. Since each LOF method can give rise to method-specific off-target effects [92], multiple LOF and GOF methods should be used when analyzing the function of individual lncRNAs [6].

LncRNAs that safeguard genome integrity

Maintenance of genome stability depends on DNA replication fidelity, DNA repair and accurate chromosome segregation throughout the cell cycle. Defects in any of these processes can lead to genome instability, a hallmark of cancer, aging and other diseases [8, 93]. Genome instability is known to activate the multifaceted DDR pathway, an integrated protein signaling network in charge of detecting DNA damage and triggering its repair (Box 4). Recent studies suggest that lncRNAs play an important role in this context by establishing multiple interactions with DNA, RNAs or proteins through which they can control different pathways impinging on genome stability [9].

Box 4. An overview of the multifaceted DNA damage response pathway (see Figure for Box 4)

DDR is a genome stability surveillance system consisting of DNA repair proteins, tumor suppressor genes, DNA damage-induced kinases, cell cycle checkpoints and apoptosis genes, which operate collectively to prevent the deleterious consequences of DNA damage [93]. DDR activation leads to cell cycle arrest to allow repair of the DNA damage or apoptosis to remove cells bearing severe levels of DNA damage. Deficiency in DDR is associated with increased mutational load, genome instability and a variety of human disease such as neurodegeneration, immunodeficiencies, cancer and aging. DDR pathway is often deregulated in cancer cells and leads to resistance to DNA damage inducing agents, presenting a hurdle to successful cancer treatment.

Treatment of cells with different DNA damaging agents such as ultraviolet (UV) and ionizing radiation (IR), topoisomerase poisons, alkylating and crosslinking agents activate specific DNA repair pathways to physically remove the damage. This includes ***base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), homologous recombination (HR) and non-homologous end joining (NHEJ)****. The main DNA damage sensors are ATM, ATR and DNA-PKcs kinases, which are activated by DNA damage and replication stress and initiate DNA damage signalling. A key factor in the DDR is also the tumor suppressor p53 whose function is conserved across all vertebrates [94]. p53 acts as a transcriptional regulator to control cell cycle arrest and apoptosis upon DNA damage.*

Most studies have focused on proteins involved in DDR pathway but recent evidence indicate unforeseen and important functions of RNA-based mechanisms in different stages of the DDR. In particular, lncRNAs have emerged as key players in DNA damage signalling and DNA repair, specifically in cancer cells [9]. Many of the lncRNAs involved in cell cycle control are also involved in DDR and are often deregulated in cancer. Indeed, many lncRNAs have cancer type-specific abberant expression and are involved in the onset and progression of cancer [17]. Expression of many lncRNAs is directly induced by DNA damage or alternatively damaging agents are used to activate p53, which then activates lncRNA expression. These

lncRNAs are involved in cell cycle arrest or apoptosis indicating their key roles in the DDR pathway. Understanding the varied mechanisms by which lncRNAs control cell cycle, DDR and DNA repair should provide new insights into the origins of cancer as well as the molecular basis for chemo- or radio-resistance, which in the future may open new RNA-based avenues for anti-cancer interventions.

Increasing evidence suggests that many lncRNAs have important roles in p53 signalling, where lncRNAs can control expression or activity of p53, or are regulated by p53 and mediate the p53 response [95]. The lncRNA *PANDA* (*p21 Associated NcRNA DNA damage Activated*) is transcribed antisense to $p21^{Cip1}$, a p53 target and a key regulator of G1/S progression, and its levels are induced upon DNA damage in a p53-dependent manner [19]. *PANDA* interacts with transcription factor NF-YA and inhibits apoptosis in human fibroblasts. *DINO* (*Damage Induced Noncoding*) is another lncRNA induced upon DNA damage in human fibroblasts and human cancer cells [96]. *DINO* is required for p53-dependent gene expression, cell cycle arrest and apoptosis and its depletion abrogates DNA damage signalling. Similar to *PANDA* [97], *DINO* can bind to and promote p53 protein stabilisation. Thus, by binding to transcription factors, lncRNAs contribute to DDR by creating a feedback loop to amplify cellular signalling networks.

LincRNA-p21 is another p53-regulated lncRNA, which triggers p53-dependent apoptosis upon DNA damage in human and mouse fibroblasts [98]. While nuclear *lincRNA-p21* regulates p53-dependent apoptosis and cell cycle arrest upon DNA damage by binding to RBP hnRNP-K [98, 99], cytoplasmic *lincRNA-p21* is involved in translation and hypoxia-enhanced glycolysis [100, 101]. *SNHG1* (*small nucleolar RNA host gene 1*) is another example how lncRNA subcellular distribution can affect p53 regulatory networks upon DNA damage. *SNHG1* is retained in the nucleus after DNA damage in human cancer cells to compete with p53 for binding to RBP hnRNPC [12] leading to higher p53 levels and apoptosis.

Since the majority of human cancers acquire mutations that abrogate p53 function, it is not surprising that expression of p53-regulated lncRNAs is also altered in cancer [102-105].

For example, lncRNA *LINC-PINT,* which is induced upon DNA damage [106] is downregulated in multiple types of cancer [107]. Furthermore, *LINC-PINT* has tumor suppressive function by inhibiting invasion and migration of human colon and lung cancer cells [107]. *NEAT1*, a nuclear lncRNA acting as an integral part of **paraspeckles**, is another p53-regulated lncRNA involved in a negative feedback loop that attenuates oncogene-dependent activation of p53 [108]. Depletion of *NEAT1* leads to **replication stress** and its targeting can increase the sensitivity of human breast cancer cells to genotoxic chemotherapeutics. Similarly, mouse *Neat1* was also shown to be a p53 target by suppressing transformation and cancer initiation [109]. In addition*, NEAT1* was also shown to be deregulated in various cancers and its dysregulation is linked to tumor progression [110, 111].

Several lncRNAs such as *lincRNA-RoR* (*Regulator of Reprogramming*) and *MEG3 (human maternally expressed gene 3),* act upstream of p53 to fine-tune p53 levels following DNA damage. *LincRNA-RoR* negatively regulates p53-mediated apoptosis in human induced pluripotent stem cells [112], and suppresses p53 mRNA translation in human cancer cells [113]. High expression of *LincRNA-RoR* has been observed in human breast cancer where it correlates with worse survival, suggesting an oncogenic function for *lincRNA-RoR* [114]. On the other hand, the imprinted lncRNA *MEG3* binds and activates p53 targets to induce cell cycle arrest and apoptosis in human cancer cells [115, 116]. However, in cardiac fibroblasts *MEG3* does not affect the p53 response indicating that *MEG3* regulates p53 in a cell type-specific manner [117]. *MEG3* can also protect endothelial function by regulating DDR [118], and is downregulated in multiple cancers where *MEG3's* tumor suppressive role was linked to its tertiary structural elements [119].

Several other lncRNAs can contribute to DDR independently of p53. One such lncRNA is *DDSR1* (*DNA damage-sensitive RNA1*), which is induced by DNA damage in an ATM-dependent manner [120]. *DDSR1* binds to BRCA1 and hnRNPUL1, a RBP involved in DNA repair [121] (Fig. 2a). Depletion of *DDSR1* impairs DDR by increasing the accumulation of BRCA1 at the laser-induced double-strand breaks (DSBs). Induction of *ANRIL* upon DNA damage in human fibroblasts and cancer cells is also ATM dependent and increased levels of

ANRIL were shown to suppress the expression of *INK4B–ARF–INK4A*, forming a negative feedback loop to the DDR [40]. Recently *HITT* (*HIF-1α inhibitor at translation level*) was identified as the first lncRNA that binds and inhibits ATM activation in human cancer cells [122]. *HITT* is downregulated in many cancers and can restrain HR activity, which might have a role in sensitising cancer cells to genotoxic treatments. The expression of some lncRNAs such as estrogen-regulated *CUPID1* and *CUPID2* (*CCND1-upstream intergenic DNA repair 1 and 2*) can be affected by **single-nucleotide polymorphisms** (SNPs) that contribute to the risk of developing breast cancer by modulating pathway choice of DSB repair [123].

In addition to *DDSR1* and *HITT*, other lncRNAs can also serve as a platform for DDR proteins and thus directly contribute to DNA repair. For instance, lncRNA *PRLH1* (*p53-regulated lncRNA for HR repair 1*) regulates HR-mediated DSB repair in human liver cancer cells through binding and stabilization of RNF169, an E3 ubiquitin ligase which acts as a negative regulator of the ubiquitin-dependent signaling at sites of DNA damage [124]. *MALAT1* was shown to bind PARP1 and Ligase III [47], key proteins in **alternative NHEJ** (alt-NHEJ) [125], and its depletion inhibits alt-NHEJ activity. Another example is *LINP1* (*lncRNA in nonhomologous end joining (NHEJ) pathway 1*) that can enhance DSB repair in human breast cancer cells by acting as a scaffold for DNA-PKcs and Ku70/80, major players of the NHEJ [126] (Fig. 2b). Indeed, *LINP1* depletion leads to reduced level of DNA-PKcs after DNA damage and increased the sensitivity of human breast cancer cells to radiation treatment, indicating that *LINP1* is a functional lncRNA regulating DDR in TNBC. Furthermore, *LINP1* is overexpressed not only in TNBC but also other cancers [16, 127] suggesting that *LINP1*-dependent repair mechanism is a broad mechanism present in multiple cancers. Interestingly, *LINP1* is another lncRNA whose cellular distribution changes upon DNA damage, with *LINP1* translocating from the cytosol to the nucleus upon IR treatment of HeLa cells [16]. Recently, *LINP1* was shown to be a flexible RNA molecule that can self-assemble into phase-separated condensates through RNA-RNA interactions and interact with Ku70/80 [128]. Furthermore, *LINP1* can substitute PAXX, a protein involved in NHEJ that binds Ku70/80 and is recruited to DNA damage sites [129]. This work [128] together with structural studies on *MEG3* [119]

represents the starting platform for future studies to unravel how lncRNA structure-to-function relationships impact lncRNA function in the cell cycle and in genome stability.

Some lncRNAs can also be recruited to the site of DNA damage or are directly formed at the DNA lesion sites to contribute to the DDR. Within 5 minutes after generation of DSBs, *BGL3* lncRNA localizes to the chromatin and accumulates at the site of DNA damage in human cancer cells [14] (Fig. 2c). *BGL3* binds to PARP1 and BARD1, key regulators of DDR [130]. Accordingly, *BGL3* depletion causes genome instability and also sensitises cells to DNA damaging agents. Thus, *BGL3* is required for HR and acts as RNA scaffold to enhance interaction between BRCA1/BARD1 complex and other DDR proteins. *GiniR* is another lncRNA that binds BRCA1 and its high levels can impair the interaction between BRCA1 and Cep112 leading to mitotic defects and genome instability [15]. Intriguingly, these studies indicate that the BRCA1/BARD1 complex is a very common interactor of lncRNAs, which is consistent with the findings that many DNA repair proteins have RNA-binding capacities [131]. DSBs can also serve as a promoter for Pol II and induce the synthesis of damage-induced lncRNAs (dilncRNAs) in mouse and human cells [132], which contribute to efficient DNA repair indicating the importance of site-specific ncRNAs in DDR (Fig. 2d).

Compelling evidence of how lncRNAs contribute to DDR comes from a study on lncRNA *NORAD (noncoding RNA activated by DNA damage*), which act as a decoy for RBPs to maintain genome stability. Inactivation of *NORAD* leads to increased rate of chromosome segregation errors resulting in aneuploidy and chromosomal instability (CIN) in human normal and cancer cells [133, 134] (Fig. 2e). *NORAD* is a conserved cytoplasmic lncRNA that maintains genome stability by sequestrating PUMILIO proteins, RBPs that repress expression of genes involved in mitosis, DNA replication and repair [133-135]. Interestingly, deletion of *Norad* in mice leads to premature aging, aneuploidy, and mitochondrial defects [136]. Since genome instability is a hallmark of cancer and aging, the *Norad-Pumilio* regulatory axis could have an important role in the maintenance of genome stability for normal physiology and aging. Other *NORAD*-mediated mechanisms in genome stability have also been described. These include the formation of the high-order ribonucleoprotein complex with *NORAD* binding

to proteins involved in DNA replication and repair [13]. Although the origin of chromosome segregation errors in *NORAD*-depleted cells has not been determined, cells without *NORAD* exhibit reduced replication speed suggesting that these errors could be a consequence of DNA replication defects [13]. Notably, *NORAD* can change its localization to the nucleus upon DNA damage in human colon cancer cells [13], although another study did not observe a similar re-distribution [135]. In addition to *NORAD*, *CCAT2* (*Colon cancer associated transcript 2*) is another lncRNA that contributes to CIN in human colon cancer cells [137, 138] and promotes colon cancer progression [32].

Some lncRNAs can have pleiotropic roles in genome stability, as observed with some lncRNAs involved in cell cycle regulation [41, 44]. One of them is lncRNA *GUARDIN* that regulates genome stability through two mechanisms [139] (Fig. 2f). Cytoplasmic *GUARDIN* acts as a miRNA sponge and indirectly contribute to DNA repair by stabilizing the expression of TRF2, an essential factor for telomerase protection. Simultaneously, *GUARDIN* promotes DNA repair by promoting the formation of the BRCA1/BARD1 complex, which regulates HR [63]. Accordingly, *GUARDIN* depletion leads to enhanced cytotoxicity to genotoxic drugs suggesting that *GUARDIN* may represent a new target for cancer treatment.

In summary, lncRNAs have a multi-faceted role in the DDR by regulating p53 signalling, directly binding DNA repair proteins at the site of DNA lesions or acting indirectly in transcriptional and translational regulation of genes involved in genome stability and DNA repair. Most studies on lncRNAs involved in the DDR employed DNA damaging agents that induce DSBs, which might have introduced a publication bias towards these agents. This could also explain why lncRNAs were frequently observed to bind to proteins involved in HR and NHEJ. By using various damaging agents to trigger other repair pathways, further work will reveal if lncRNAs can also bind other DNA repair proteins in order to maintain genome integrity.

Concluding Remarks

The main challenges in deciphering the mechanisms whereby lncRNAs regulate cell cycle progression and safeguard genome integrity relate to the diversity of the lncRNA *modus operandi*. Since lncRNA genes can function through their RNA transcripts, by the action of their transcription or via regulatory DNA elements, multiple LOF and GOF methods are required to establish whether the function of lncRNAs in cell cycle progression and genome stability is RNA-dependent.

The cell cycle and DDR are evolutionary conserved processes but the mechanisms contributing to their control might not be similarly conserved. In this context, lncRNAs contribute to diversity and precise control of the cell cycle progression and represent an additional regulatory layer in the maintenance of genome stability in conjunction with the well-characterized protein-based mechanisms. We noted that the majority of lncRNAs with a function in the cell cycle act during the G1-phase, which correlates with their higher expression in the G1/S phase and the larger number of core protein-coding genes controlling G1-phase compared to other cell cycle stages [23]. Although we categorize lncRNAs according to their roles in the cell cycle, future studies should dissect lncRNA-mediated mechanisms affecting cell proliferation without directly interfering with the cell-cycle control machinery. Further, lncRNA structure-to-function and sequence-to-function studies will be crucial to determine their role in cell cycle and genome stability. Since **CRISPR-Cas13** system has been used to detect lncRNAs in live cell, the field could exploit this powerful system to investigate lncRNAs dynamics during the cell cycle and after DNA damage [140].

Continued efforts of the scientific community and constant technological improvement will help provide further insight into the RNA-based regulatory networks and uncover new mechanisms of how lncRNAs control cell cycle to safeguard genome integrity (see Outstanding Questions).

Glossary

- **Genome instability**: chromosomal, microsatellite and nucleotide-associated instability are three types of genome instability occurring from defects in cell division, replication stress, defects in DDR and telomere maintenance.
- **Long noncoding RNAs (lncRNAs)**: heterogeneous class of ncRNAs that are longer than 200 nucleotides.
- **DNA damage response (DDR)**: a network of multiple DNA repair pathways, damage tolerance processes and cell-cycle checkpoints that sense, detect and repair DNA lesions.
- **Noncoding RNAs (ncRNAs)**: RNA molecules transcribed from mammalian genome but are not translated into proteins.
- **Functional ANnoTation Of the Mammalian genome (FANTOM)**: international research consortium focused on functional annotation of the mammalian genome and characterization of transcriptional regulatory networks.
- **Antisense oligonucleotide (ASO)**: single stranded DNA or RNA molecule that targets RNAs to induce its silencing or degradation via the RNase H endonuclease.
- **RNA binding proteins (RBPs)**: proteins that directly bind to single or double stranded RNA molecules through RNA binding domains.
- **Imprinted lncRNA**: lncRNA transcribed from a gene that is regulated in a parent-of-origin specific manner.
- **DNA damaging agents**: reactive molecules that damage DNA and are widely used to treat cancer.
- **Mitocheck consortium:** a study providing in depth analysis of cell division phenotypes after RNAi-mediated depletion of ~21,000 proteins (https://www.mitocheck.org/).
- **RNA interference (RNAi)**: process of post-transcriptional gene silencing involving RNA-dependent cleavage of RNA molecules.

- **CRISPR/Cas9**: genome editing method involving the RNA-guided Cas9 nuclease which introduces DNA double strand breaks at specific genomic loci.
- **CRISPR interference (CRISPRi)**: genome editing method involving Cas9 protein without its endonuclease activity (dCas9) fused to a Krüppel-associated box (KRAB) repression domain that can be directed to a specific genomic locus to prevent transcription.
- **CRISPR activation (CRISPRa)**: genome editing method involving dCas9 fused to active domains such as VP64 to enhance gene expression.
- **CRISPR/Cas9 synergistic activation mediator (CRISPR SAM)**: engineered protein complex activating gene expression composed of dCas9 fused to an active VP64 domain.
- **Base excision repair (BER):** DNA repair pathway that deals with single-base modifications where the damaged base is recognized and removed.
- **Nucleotide excision repair (NER):** DNA repair pathway that corrects bulkier and/or helix distorted lesions often induced by UV irradiation.
- **Mismatch repair (MMR):** DNA repair pathway that deals with base-base mismatches and insertion/deletions mispairs generated during DNA replication and recombination.
- **Homologous recombination (HR):** DNA repair pathway repairing DSBs. The HR process requires a homologous template to direct DNA repair and is generally recognised as a high-fidelity pathway. HR functions on stalled or collapsed replication forks in S phase and also contributes to DSB repair during G2 phase.
- **Nonhomologous end joining (NHEJ):** second major pathway to correct DSBs, operating predominately during G1 phase.
- **Paraspeckles**: nuclear membranelles bodies that regulate gene expression through the retention of RNAs and proteins.
- **Replication stress**: a major source of genome instability arising from the impairment of DNA replication.

- **Single-nucleotide polymorphisms (SNPs)**: a genetic variation of a single base pair present in a large fraction of the population.
- **Alternative-NHEJ**: a highly error prone DNA repair pathway that repair DSBs in less -efficient backup reactions.
- **CRISPR-Cas13**: CRISPR-Cas system involving Cas13 ribonuclease for targeted RNA knockdown.

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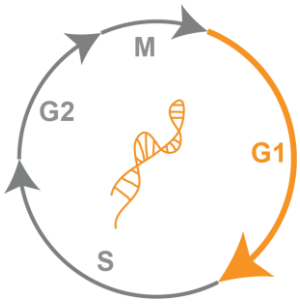
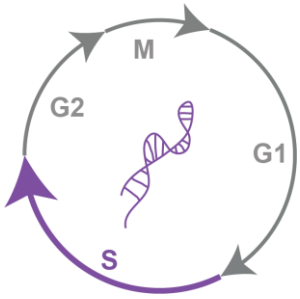
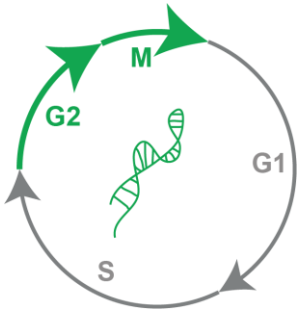
Declaration of Interests

The authors declare no competing interests.

5 **Table 1. LncRNAs involved in cell cycle regulation**

Cell cycle phase	LncRNA	Mechanism	Regulation	Link to disease	Ref.
	*ncRNA*$_{CCND1}$	Suppression of *CCND1* transcription by binding to TLS	Induced upon IR	Unknown	[24]
	LAST	Stabilization of *CCND1* mRNA by binding to CNBP	c-MYC regulated; elevated levels during G1-phase	Potential oncogene	[25]
	GAS5	Negative regulation of *CDK6* mRNA. Enhancement of E2F1 binding to the p27^{Kip1} promoter increasing p27^{Kip1} levels.	Unknown	Downregulated in multiple cancers	[26, 27]
	Gadd7	Negative regulation of *CDK6* mRNA by binding to TDP43	Induced upon UV, cisplatin, alkylating agents and growth arrest signals	Unknown	[28, 29]
	CCAT1	Downregulation of *CCND1* and *CDK4*	c-MYC regulated	Upregulated in multiple cancers	[30-32]

		by binding to miRNAs			
	MIR100HG	Binding to HuR to promote its association with target mRNAs	c-MYC regulated; elevated levels during G1-phase	Upregulated in multiple cancers	[33]
	ANRIL	Epigenetic silencing of the INK4/ARF locus by binding to PRC1/PRC2	ATM/E2F1-regulated	Deregulated in multiple cancers and cardiovascular diseases	[35, 36, 40, 48]
	KNCQ1OT1	Suppression of $p57^{kip2}$ transcription through recruitment of PRC2 and G9a	Paternal expression	Involved in overgrowth disease and cancer	[37, 38]
	H19	Downregulation of *Rb* mRNA through miRNA-675	E2F1- and cell cycle regulated	Deregulated in multiple cancers	[39, 43]
	MA-linc1	Unknown	E2F1-regulated	High levels of *MA-linc1* correlate with reduced survival of breast and lung cancer patients	[41]
	ERIC	Inhibition of E2F1-induced apoptosis	E2F1-regulated; induced upon etoposide	Unknown	[42]

	MALAT1	Positive regulation of genes involved in G1/S transition	Elevated levels during G1/S-phase	Deregulated in multiple cancers	[44-46]
	*CONCR*	Binding to DDX11 helicase and modulation of its activity	Mid/late G1-phase expression; induced upon 5-FU and doxorubucin	Upregulated in multiple cancers	[49]
	SUNO1	Interaction with DDX5 to promote transcription of genes involved in proliferation	S-phase specific expression	High expression of *SUNO1* correlates with poor prognosis of colon cancer patients	[23]
	SCAT7	Regulation of FGF/FGFR, PI3K/AKT and MAPK signalling	S-phase specific expression	Upregulated in multiple cancers	[52]
	Linc00704 *MIAT* *LUCAT1*	Regulation of gene expression to promote S-phase progression	S-phase specific expression	Upregulated in different types of cancer	[53]
	*Linc00152*	Unknown	Unknown	Upregulated in multiple cancers	[58]
	Linc00899	Repression of *TPPP* transcription	Not cell cycle-regulated	Downregulated in breast cancer	[56, 62]
	C1QTNF1-AS1	Unknown	Not cell cycle-regulated	Downregulated in	[56, 61]

				hepatocellular carcinoma	
	GiniR	High expression of *GiniR* perturbs the Cep112/BRCA1 interaction leading to mitotic defects	Developmental regulation	*Ginir* overexpression induces oncogenic transformation	[15]
	LincRNA-RI	Binding to miRNA-210-3p and regulation of *PLK1* mRNA stability	Induced by IR	Unknown	[66]
	APAL	Binding to PLK1 and Aurora A to promote PLK1 activity	Unknown	Deregulated in multiple cancers	[67]
	OIP5-AS1	Binding to *GAK* mRNA leading to decreased GAK levels	Unknown	Deregulated in multiple cancers	[68, 70]
	SAM	Interaction with Sugt1 to regulate kinetochore assembly	Highly expressed in mouse myoblasts and satellite cells	Loss of *SAM* impairs muscle regeneration after injuries	[69]
	MALAT1	Positive regulation of *B-MYB* expression	Elevated levels during mitosis	Deregulated in multiple cancers	[44-46]
	MA-linc1	Repression of *Pur*α expression	E2F1-regulated	High levels of *MA-linc1*	[41]

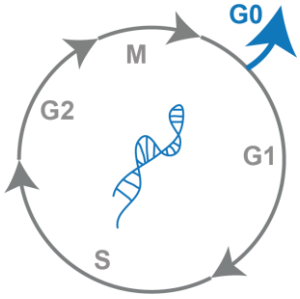
				correlate with reduced survival of breast and lung cancer patients	
	*PAPAS*	Chromatin compaction by interacting with Suv4-20h2	Upregulated in G0	Unknown	[72]
	PDCD4-AS1	Stabilization of *PDCD4* mRNA by forming RNA duplexes	Upregulated in G0	Downregulated during breast cancer progression	[73]
	GAS5	Negative regulation of glucocorticoid receptor transcriptional activity	Sox2-regulated during G0 phase	Involved in cancer stemness	[75, 76]
	DANCR	Post-transcriptional regulation of *β-catenin*	Unknown	Involved in cancer stemness	[77]
	MIR222HG	Interaction with ILF2/3 to positively regulate the stability of *DNM3OS* lncRNA	Induced upon serum stimulation	Upregulated in prostate cancer	[78, 141]

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Table 2. LncRNAs involved in the maintenance of genome stability

LncRNA	DNA damaging agents	DNA lesions	Mechanism	Regulation	Link to disease	R
SUNO1	Doxorubucin, Etoposide, HU	DNA breaks	Unknown	FOS, JUND and EGR1-regulated	High *SUNO1* expression correlates with poor prognosis of colon cancer patients	[
PANDA	Doxorubicin, Etoposide	DNA breaks	Inhibition of apoptotic gene expression by sequestering NF-YA	p53-regulated	Deregulated in multiple cancers	[19 1 1
DINO	Doxorubicin, Etoposide	DNA breaks	Binding and stabilization of p53; inducing p53 target genes	p53-regulated	Unknown	[
lincRNA-p21	Doxorubicin	DNA breaks	Repression of $p21^{Cip1}$ transcription by recruiting hnRNPK	p53-regulated	Downregulated in leukemia and colon cancer	[98 1 1 1
SNHG1	Doxorubicin	DNA breaks	Stabilization of p53 by disruption of p53-hnRNPC interaction	Nuclear retention upon doxorubicin	Upregulated in various cancers and associated with poor prognosis	[1

LINC-PINT	Doxorubicin	DNA breaks	Silencing of genes involved in cell growth and proliferation by binding to PRC2	p53-regulated	Downregulated in multiple cancers	[1 1
NEAT1	Doxorubicin, UV, ROS	DNA breaks, DNA adducts, SSBs, oxidized bases	Modulation of ATR signalling and attenuation of oncogene-dependent activation of p53	p53-regulated	Deregulated in in multiple cancers	[1 1
LincRNA-RoR	Doxorubicin, UV	DNA breaks, DNA adducts	Suppression of p53 translation through binding to hnRNP-I	p53-regulated	Overexpressed in breast cancer; high expression of *lincRNA-ROR* associates with poor prognosis	[11 114
MEG3	Doxorubicin	DNA breaks	Binding to p53 and activation of p53 target genes	Maternal expression	Downregulated in multiple cancers and during cardiac remodeling	[1 1
DDSR1	Campothecin, Etoposide, Neocarzinostatin, Bleomycin	DNA breaks	Binds to BRCA1 and regulates BRCA1/RAP80 recruitment to laser-induced DSBs to promote HR; controls expression of DDR genes	ATM-NF-κB mediated upregulation upon DNA damage	Unknown	[12

MALAT1	PARP inhibitor, bortezomib	Site-specific induction of DSBs	Binding to PARP1 and Ligase III to regulate alt-NHEJ	*MALAT1* inhibition induces DNA damage	Overexpressed in multiple myeloma	[
ANRIL	Neocarzinostatin, Etoposide, Bleomycin	DNA breaks	Suppression of INK4/ARF locus; regulation of cell cycle, apoptosis and HR	ATM-E2F1 regulated	Deregulated in multiple cancers and cardiovascular diseases	[40
CUPID1 *CUPID2*	IR	DNA breaks	Regulation of RAD51 recruitment at DSBs to promote HR and control end resection	Estrogen-regulated	Genomic locus affected by the breast cancer risk variant at 11q13	[1
HITT	Doxorubicin, Etoposide, Bleomycin	DNA breaks	Binding and inhibition of ATM activity to restrain HR	EGR1-regulated	Downregulated in colon cancer	[1
PRLH1/ linc01419	Adriamycin	DNA breaks	Binding and stabilization of RNF169 to promote HR	p53-regulated	Upregulated in hepatocellular carcinoma	[1
LINP1	Doxorubicin, IR	DNA breaks	Recruitment of Ku70/80 and DNA-PKcs at DSBs to promote NHEJ; replacement of PAXX function	EGF-regulated	Overexpressed in multiple cancers	[1 1

BGL3	Camptothecin, Etoposide, IR, HU	DNA breaks	Regulation of BRCA1/BARD1 complex at DSBs to promote HR and control end resection	Recruited to DNA damage site after laser-induced DSBs	Negative correlation of *BGL3* expression with survival rate of breast cancer patients	[
GiniR	None	Unknown	Perturbation of Cep112/Brca1 interaction	Developmental regulation	*Ginir* overexpression induces oncogenic transformation	[
dilncRNAs	None	Site-specific induction of DSBs	Precursors for small ncRNAs to promote DDR	Expressed upon DSBs	Unknown	[1
NORAD	Doxorubicin, Camptothecin, UV	DNA breaks, DNA adducts	Decoy for PUMILIO; *NORAD* forms also a ribonucleoprotein complex	Induced by DNA damage and indirectly regulated by p53	Loss of *NORAD* is associated with premature aging	[1 1
CCAT2	Bleomycin, 5-FU, Oxaliplatin	DNA breaks	Binding to and stabilization of BOP1	WNT-regulated	Upregulated in colon cancer	[1 1
GUARDIN	Doxorubicin, IR	DNA breaks	Sponging with miR-23a to regulate TRF2; RNA scaffold for BRCA1/BARD1 complex to promote HR and NHEJ	p53-regulated	Downregulated in colon cancer with p53 mutation	[1

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HU, Hydroxyurea; UV, Ultraviolet radiation; Reactive oxygen species, ROS; Double strand breaks, DSBs; Single strand breaks, SSBs; IR, Ionizing radiation; 5-Flurouracil, 5-FU.

Figure legends:

Box 1. An overview of the mammalian cell cycle progression. The cell cycle is regulated by different cyclin/CDK complexes and CDK inhibitors throughout the different stages of the cell cycle.

Box 4. The components of the DNA damage response pathway.

Figure 1, Key Figure. LncRNA-mediated control of the cell cycle progression and genome stability.

Figure 2. Emerging mechanisms how lncRNAs mediate DDR to maintain genome stability.

(A) *DDSR1* modulates HR by interacting with hnRNPUL1 and BRCA1. Loss of *DDSR1* or hnRNPUL1 leads to aberrant recruitment of BRCA1 and its recruitment factor RAP80 at laser-induced DSBs.

(B) In response to DSBs, Ku70/80 recruits DNA-PKcs to the damage site. Depletion of *LINP1* leads to reduction in chromatin-associated DNA-PKcs. *LINP1* promotes NHEJ repair by acting as a scaffold for DNA-PKcs and Ku70/Ku80.

(C) At early time points after DNA damage, *BGL3* is recruited to damaged sites by interacting with PARP1. Later on, *BGL3* binds BARD1 to control HR. Depletion of *BGL3* leads to compromised recruitment of BRCA1/BARD1 and its downstream factors (Rad51, RPA70) at DSBs.

(D) DSBs can induce synthesis of dilncRNAs that act as precursors for small ncRNAs. Both classes of ncRNAs contribute to DNA damage signalling and repair by forming a scaffold for their recruitment to DNA damage site.

(E) Upon DNA damage, *NORAD* localizes more to the nucleus (i) or in the cytoplasm (ii). *NORAD* can form a higher-order ribonucleoprotein complex by binding to proteins involved in DNA replication and repair (i,[13]), or can sequester PUMILIO proteins, which repress genes necessary for genome integrity (ii, [133-135]. Inactivation of *NORAD* leads to chromosome segregation errors and aneuploidy-induced genome instability.

(F) Cytoplasmic *GUARDIN* can sequester miR-23a to stabilise TRF2 expression and prevents chromosome end-to-end fusion. Simultaneously, *GUARDIN* acts as a scaffold for BRCA/BARD1 complex and regulates HR and NHEJ. It is not clear whether *GUARDIN* is involved in the formation of BRCA/BARD1 complex in the nucleus to regulate DNA repair.

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