Long Non-coding RNAs

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Long noncoding RNAs (lncRNAs) constitute important group of RNA molecules with various biological activities. Despite significant progress in the understanding of lncRNAs, pivotal functions of this class of molecules are emerging. Among these, role in DNA damage response (DDR) seems to be fundamental. Various lncRNAs were found to modulate DNA repair on different levels: through TP53 activity modulation at transcriptional and translational level, through recruitment of chromatin remodelers that modulate the access of DNA repair proteins to the site of damage, and by working as scaffolds and mediators for DNA repair proteins, and acting as sponges for various DNA-damage-associated miRNAs. Considering that, lncRNAs involvement in DDR constitute interesting field of research with numerous future applications, such as development of new targeted anticancer therapies.

Keywords: DNA repair ; long-noncoding RNA ; DNA damage response

1. Introduction

Long noncoding RNAs (lncRNAs) comprise an abundant group of diverse RNA molecules with length exceeding 200 nucleotides [1]. These non-coding RNAs perform different biological functions, including transcription regulation, modulation of chromatin structure through DNA methylation, histone modification and chromatin remodeling, posttranscriptional regulation, modulation of protein activity, and others extensively reviewed elsewhere [2][3]. The function of lncRNAs is highly dependent on their subcellular localization. There are three different fractions of lncRNAs reckoning their place of action: cis nuclear lncRNAs that are localised close to their sites of transcription, lncRNAs that perform functions in the nucleus but regulate expression of genes distant from their own sites of transcription (in a trans-dependent manner) and lncRNAs that need to be exported (transported) to cytoplasm to perform their regulatory functions [1]. Furthermore, based on their immediacy to protein coding genes, lncRNAs have been classified into several groups: sense, antisense, intronic, intergenic transcripts and pseudogenes.

Significant scientific progress has been made regarding the role of lncRNAs in DNA repair. LncRNAs are considered to play a prominent role in DSB repair. They have been shown to alter DSB repair through several mechanisms: (a) through TP53 activity modulation at transcriptional and translational level, (b) through recruitment of chromatin remodelers that modulate the access of DNA repair proteins to the site of damage, (c) by working as scaffolds and mediators for DNA repair proteins, and (d), last but not least, acting as sponges for various DNA-damage-associated miRNAs [4].

2. Long Non-coding RNAs in DNA Damage Response

Double strand breaks (DSBs) occurrence lead to recruitment of DNA damage sensors, such as MRN complexes and Ku proteins, at the site of DNA damage. This is followed by firing of signaling cascades and downstream protein activation [5]. The key component activated upon DSB is ATM protein kinase. ATM phosphorylates H2AX histones at the site of damage, leading to γH2AX foci formation at break sites [6]. Moreover, ATM activation leads to CHK1- and CHK2-dependent TP53 phosphorylation [7]. TP53, often perceived as a “guardian of the genome”, is one of the best-studied tumor suppressor proteins. It has been estimated that almost half of human tumors carry a mutation in the *TP53* gene. Activation of TP53 upon DNA damage leads to either cell cycle arrest or apoptosis depending on the nature and severity of the damage. TP53 acts as a key transcriptional regulator of different proteins inside the cell [8]. Moreover, CHK1/2 activation leads to inhibition of cyclin-dependent kinase activity that slows down or arrests the cell cycle in G1-S or G2-M phase [9]. The expression of lncRNAs can be induced following DNA damage. This may occur in a TP53-dependent manner. Additionally, some lncRNAs may regulate expression of TP53 downstream targets, further complicating the interactions.

The examples of *TP53*-linked lncRNAs are *lincRNA-p21* [10] and *PANDA* [11], both located upstream of *CDKN1A (p21)* gene. P21 is a protein that binds to certain CDKs, forming inactive complexes that compromise cell cycle arrest and apoptosis. *lincRNA-p21* was shown to repress transcription induced by TP53 through interaction with heterogeneous

nuclear ribonucleoprotein-K (hnRNP-K), which constitutes an important component of repressor complexes. These complexes are recruited to the promoters of downstream *TP53* transcriptional targets and prevent effective *TP53*-mediated transcription [10]. In contrast, *CDKN1A* upstream lncRNA, *DINO*, was shown to stabilize TP53 protein and stimulate its transactivatory activity [12]. Other lncRNAs, like *WRAP3α* lncRNA directly bind to *TP53* mRNA after DNA damage to stabilize the protein, and thus affect its level inside the cell [13]. *LINP1*, on the other hand, works as a scaffold for NHEJ proteins (Ku70–Ku80 and DNA-PKcs) during DNA repair, where it promotes the religation of broken DNA strand ends [14]. Another lncRNA worth mentioning, *MALAT1*, constitutes a link between sirtuins and *TP53*. *MALAT1* sequesters DBC1, a negative regulator of SIRT1, and thus promotes SITR1-mediated deacetylation of TP53. This results in altered expression of TP53 target genes and *TP53*-linked lncRNAs [15][16][17]. Misteli et al. demonstrated that intergenic lncRNA *DDSR1* expression could be elevated in response to DNA-damaging drugs. *DDSR1* induction is greatly dependent on ATM and NF-Kb activation but TP53 is not necessary for its induction—nevertheless, it still may regulate its expression. Interestingly, *DDSR1* can regulate TP53-target gene expression. Moreover, *DDSR1* knockdown leads to impaired homologous recombination (HR) and upregulation of TP53-dependent gene expression, especially of those genes that contribute to cell proliferation [18][19]. The choice between HR and NHEJ repair pathways is further attributed to two noncoding RNAs—*CUPID1* and *CUPID2*—located in the enhancer region of the *CCND1* gene, coding for cyclin D1 [20]. The lncRNA *GUARDIN* plays an important role in genome stability maintenance. Sequestering of miRNA-23a by *GUARDIN* leads to sustained expression of telomeric repeat factor 2 (TRF-2), which prevents chromosome end fusion. Furthermore, *GUARDIN* regulates the stability of BRCA1 and promotes its association with BRCA1-associated RING domain protein (BARD1) for effective HR [21]. *TODRA*, an antisense lncRNA transcribed upstream of the RAD51 recombinase gene, has also been shown to be implicated in HR, where it regulates RAD51 expression and protein activity [22]. Numerous lncRNAs have been confirmed to play a role in DDR. These include the following lncRNAs: *ANRIL* [2], *BARD1 9´L* [23], *Gadd7* [24][25], *HOTAIR* [26][27], *JADE* [28], *LincROR* [29], *LIRRE* [30], *MDC1-AS* [31], *NEAT1* [32], *PCAT-1* [33][34][35], *PINCR* [36], *PINT* [37][38], *PURPL* [39], *PR-lncRNA-1*, *PR-lncRNA-10* [40], *TERRA* [41][42].

The importance of lncRNAs in cellular physiology is certainly unquestionable. LncRNAs play a significant role in DNA repair through various cis and trans mechanisms. Besides the influence of lncRNAs in gene expression, they can act as scaffolds for DNA repair proteins or work as miRNA scavengers, affecting both the activity and abundance of DDR components. It remains unclear how the primary and secondary structure of lncRNAs molecules affects DDR protein activity. The growth and progress of advanced RNA-directed technologies allow researchers to explore functions of genome “dark matter”. The greatest burden, however, is the tremendous and ambiguous amount of data generated during RNA-seq, which requires further interpretation. Moreover, lncRNA action is highly context-dependent, and the subcellular localization of RNA molecules seems to be fundamental. The dynamics of how the compartmentalization is achieved constitute another question. Plenty of studies have been carried out to clarify the role of lncRNAs in cancer. These require a more comprehensive approach encompassing the complex signaling networks related to lncRNAs. Determination of possible tumor-inducing and tissue-specific lncRNAs raise hopes for development of new targeted antineoplastic agents [43].

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