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Roles of LncRNAs in DNA Damage Response and Repair of Cancer Cells

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Abstract

Chemo and radiation therapies are the most commonly used therapies for cancer, but they can induce DNA damage resulting in the apoptosis of host cells. DNA Double Strand Breaks (DSBS) are the most lethal form of DNA damage in cells, which are constantly caused by a wide variety of genotoxic agents, both environmentally and endogenously. Meanwhile, eukaryotic organisms have developed a complex mechanism for the repair of DNA damage to maintain genomic integrity. Many cellular biomolecules such as micro RNAs, long non-coding RNAs (LncRNAs), and proteins are involved in the process of DNA repair. In the short communication, we highlight the roles of LncRNAs in regulation of the cellular response to DNA damage and the mechanism of DNA damage repair in cells.

Keywords: DNA damage response; Repair; Apoptosis; Cell cycle; Cancer; LncRNA

Introduction

DNA damage is constantly caused by various endogenous and exogenous factors, such as ionizing radiation, ultraviolet, Reactive Oxygen Species (ROS), and genotoxic drugs [1-2]. It is generally accepted that DNA damage is a potential threat to human health. Human have evolved intricate mechanism for the repair of DNA damage to protect genome stability, and two major pathways of Homologous Recombination (HR) and Non-Homologous End Joining (NHEJ) have been evolved to repair DSBs [3-4]. Living organism fail to accurately repair the damaged DNA in cells. It will leads to serious damage in body, and the accumulation of DNA damage may be involved with the occurrence of multiple diseases including aging and cancers. So, genome integrity is essential for organism survival and for the inheritance of traits to offspring. Previous reports indicated that Long Non-Coding RNAs (LncRNAs) take part in the repair of DNA damage. LncRNAs, are an important class of RNA transcripts with over 200 nucleotides in length, which look like protein-coding genes lacking the ability for translation into proteins in general [5]. To date, LncRNAs have been reported to play important regulatory roles in various biological processes ranging from innate immune response, cell cycle control, pluripotency, and differentiation, to disease [5-7]. Moreover, recent evidences showed that some LncRNAs such as NORAD and GUARDIN contribute to regulate and maintain genome stability [8-10].

LncRNAs in DNA Damage Response and Repair of Cancer Cells

The Human Genome Project revealed that only ~3% of human genome encodes protein, and the remaining 97% of the human genome is referred to as noncoding DNA [11]. In fact, ~85% of the human genome is transcribed into RNA, and over 10,000 LncRNA transcripts were reported in the human genome [12]. LncRNAs may function as diagnostic markers and/or possible therapeutic targets. So, understanding the biogenesis of LncRNAs is helpful in not only differentiating them from other types of RNAs but also to demonstrate its functional significance. Different classes of LncRNAs were transcribed from several DNA elements such as enhancers, promoters, and intergenic regions in eukaryotic genomes [13]. To date, over 50,000 LncRNAs (designated MiTranscriptome LncRNAs) in the human transcriptome were generated from various tumors, normal tissues and cell lines based on The Cancer Genome Atlas (TCGA, http://cancergenome.nih.gov/) [14], which is greater than the number of protein-coding genes (~20,000) in the genome. Unlike protein-coding mRNAs, LncRNAs exhibit functional uniqueness by participating in and modulating various cellular processes such as histone modification, DNA methylation, cellular transcription, inflammatory response antiviral immunity and repair of DNA damage [15-18]. According to the diversity of non-coding RNA, they can be divided into two main types: Structural non-coding RNAs and regulatory non-coding RNAs [19]. Structural non-coding RNAs comprise of rRNAs and

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tRNAs, and regulatory non-coding RNAs are further divided into three classes, small, medium and long non-coding RNAs [19-20]. The biogenesis of LncRNAs is cell type- and stage-specific which is under the control of cell type- and stage-specific stimuli. Different classes of LncRNAs were reported to be transcribed from some DNA elements such as enhancers, promoters, and intergenic regions in eukaryotic genomes. As we know, promoters and enhancers are essential DNA elements in the control of gene expression networks. Some short lived medium-length LncRNAs, usually ranging from 200 nt to 2000 nt can be transcribed from the promoter upstream regions and enhancers by RNA polymerase II (Pol II), and the LncRNAs can be directionally transcribed from enhancers by Pol II [21,22]. Additionally, some LncRNAs are transcribed by Pol II from intergenic regions between two genes and represent the best-studied subclass of LncRNAs. Most annotated LncRNAs contain multiple axons and have typical mRNA-like features, with a 5' m7G cap and a 3'poly (A) tail. These similarities existing between LncRNAs and mRNAs provide the possibility that mature LncRNAs may behave similarly to mRNAs in cells. In fact, it is not the truth. Due to the lacking of robust protein-coding potential, LncRNAs are less evolutionarily conserved and less abundant and they exhibit more tissue-specific expression and greater nuclear localization pattern. As is well known, cells have evolved the ability to repair the lesion and maintain genome integrity when genome gets damage. Many RNA-binding proteins were reported to be accumulated at sites of DNA damage, indicating that they may have important functions during the DNA damage response. Moreover, numerous LncRNAs have been shown to participate in the repair of DNA damage, and LncRNAs usually exert their functions via interaction with protein complexes. For example, Sharma et al. identified and characterized the LncRNA DDSR1 as a regulator of DNA repair by homologous recombination [23]. DINO was identified to be a conserved, DNA damage-inducible LncRNA, which regulates the p53-dependent DNA damage response. In the process of DNA damage response, the LncRNA DINO was identified as a new component for the stability of p53 by post-translational modifications and inhibition of ubiquitination, leading to protein accumulation and transactivation of p53 targets [24]. LncRNAs CUPID1 and CUPID2 were reported to be predominantly expressed in hormone-receptor-positive breast tumors, which can modulate the repair of double-strand breaks by NHEJ and HR pathway [25].

References

1. Li M, You L, Xue J, Lu Y. Ionizing radiation-induced cellular senescence in normal, non-transformed cells and the involved DNA damage response: A mini review. Front Pharmacol. 2018;9:522.
2. Liu H, Wu Y, He F, Cheng Z, Zhao Z, Xiang C, et al. Brca1 is involved in tolerance to adefovir dipivoxil-induced DNA damage. Int J Mol Med. 2019;43(6):2491-8.
3. Brierley DJ, Martin SA. Oxidative stress and the DNA mismatch repair pathway. Antioxid Redox Signal. 2013;18(18):2420-8.
4. Liu D, Keijzers G, Rasmussen LJ. DNA mismatch repair and its many roles in eukaryotic cells. Mutat Res. 2017;773:174-87.
5. Geisler S, Coller J. RNA in unexpected places: Long non-coding RNA functions in diverse cellular contexts. Nat Rev Mol Cell Biol. 2013;14(11):699-712.
6. Ouyang J, Hu J, Chen JL. lncRNAs regulate the innate immune response to viral infection. Wiley Interdiscip Rev RNA. 2016;7(1):129-43.
7. Dahariya S, Paddibhatla I, Kumar S, Raghuwanshi S, Pallepati A, Gutti RK. Long non-coding RNA: Classification, biogenesis and functions in blood cells. Mol Immunol. 2019;112:82-92.
8. Lee S, Kopp F, Chang TC, Sataluri A, Chen B, Sivakumar S, et al. Noncoding RNA NORAD Regulates Genomic Stability by Sequestering PUMILIO Proteins. Cell. 2016;164(1-2):69-80.
9. Munschauer M, Nguyen CT, Sirokman K, Hartigan CR, Hogstrom L, Engreitz JM, et al. The NORAD lncRNA assembles a topoisomerase complex critical for genome stability. Nature. 2018;561(7721):132-6.
10. Hu WL, Jin L, Xu A, Wang YF, Thorne RF, Zhang XD, et al. GUARDIN is a p53-responsive long non-coding RNA that is essential for genomic stability. Nat Cell Biol. 2018;20(4):492-502.
11. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. Nature. 2001;409:860-921.
12. Hangauer MJ, Vaughn IW, McManus MT. Pervasive transcription of the human genome produces thousands of previously unidentified long intergenic noncoding RNAs. PLoS Genet. 2013;9(6):e1003569.
13. Wu H, Yang L, Chen LL. The diversity of long noncoding RNAs and their generation. Trends Genet. 2017;33(8):540-52.
14. Iyer MK, Niknafs YS, Malik R, Singhal U, Sahu A, Hosono Y, et al. The landscape of long noncoding RNAs in the human transcriptome. Nat Genet. 2015;47(3):199-208.
15. Wei JW, Huang K, Yang C, Kang CS. Non-coding RNAs as regulators in epigenetics. Oncol Rep. 2017;37(1):3-9.
16. Xue Z, Zhang Z, Liu H, Li W, Guo X, Zhang Z, et al. LincRNA-Cox2 regulates NLRP3 inflammasome and autophagy mediated neuroinflammation. Cell Death Differ. 2019;26(1):130-45.
17. Maarouf M, Chen B, Chen Y, Wang X, Rai KR, Zhao Z, et al. Identification of lncRNA-155 encoded by MIR155HG as a novel regulator of innate immunity against influenza A virus infection. Cell Microbiol. 2019;21(8):e13036.
18. Gao S, Lin H, Yu W, Zhang F, Wang R, Yu H, et al. LncRNA LCPAT1 is involved in DNA damage induced by CSE. Biochem Biophys Res Commun. 2019;508(2):512-15.
19. Dahariya S, Paddibhatla I, Kumar S, Raghuwanshi S, Pallepati A, Gutti RK. Long non-coding RNA: Classification, biogenesis and functions in blood cells. Mol Immunol. 2019;112:82-92.
20. Ren C, Liu F, Ouyang Z, An G, Zhao C, Shuai J, et al. Functional annotation of structural ncRNAs within enhancer RNAs in the human genome: Implications for human disease. Sci Rep. 2017;7(1):15518.
21. Preker P, Almvig K, Christensen MS, Valen E, Mapendano CK, Sandelin A, et al. Promoter upstream transcripts share characteristics with mRNAs and are produced upstream of all three major types of mammalian promoters. Nucleic Acids Res. 2011;39(16):7179-93.
22. Chen H, Du G, Song X, Li L. Non-coding transcripts from enhancers: New insights into enhancer activity and gene expression regulation. Genomics Proteomics Bioinformatics. 2017;15(3):201-7.
23. Sharma V, Khurana S, Kubben N, Abdelmohsen K, Oberdoerffer P, Gorospe M, et al. A BRCA1-interacting lncRNA regulates homologous recombination. EMBO Rep. 2015;16(11):1520-34.
24. Schmitt AM, Garcia JT, Hung T, Flynn RA, Shen Y, Qu K, et al. An inducible long noncoding RNA amplifies DNA damage signaling. Nat Genet. 2016;48(11):1370-6.
25. Betts JA, Moradi Marjaneh M, Al-Ejeh F, Lim YC, Shi W, Sivakumaran H, et al. Long noncoding RNAs CUPID1 and CUPID2 mediate breast cancer risk at 11q13 by modulating the response to DNA damage. Am J Hum Genet. 2017;101(2):255-66.