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Review

Non-coding RNAs in Stem Cell

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ABSTRACT

Stem cells are cells that aren't specialized and have the potential to renew themselves and differentiate. Stem cells are critical for tissue regeneration, differentiation, and homeostasis. Recent studies have revealed that long non-coding RNAs and microRNAs, which are non-coding RNAs (ncRNAs) that play an important role in gene expression, development, and course of diseases, have important effects on the functions of stem cells. This chapter aimed to investigate the consequences of ncRNAs on stem cells in normal and diseased states, as well as their significance in differentiation.

Keywords: Adult stem cell, embryonic stem cells, lncRNA, microRNA, non-coding RNA, self-renewal, stem cell.

Stem cells are unspecialized cells that can differentiate into any cell of an organism and have the ability to self-renew. Stem cells are classified as embryonic stem cells (ESCs) and adult stem cells (ASCs) based on their location and totipotent, pluripotent, multipotent, oligopotent, and unipotent stem cells based on their differentiation ability.[1]

Regulatory mechanisms such as various cellular components, signal transduction pathways, epigenetic modifications, and molecules regulating gene expression are involved in the differentiation of stem cells.[2] Non-coding ribonucleic acids (ncRNAs), which are transcripts that do not produce protein, have an important role in stem cell regulation. Long non-coding RNAs (lncRNAs) and microRNAs (miRNAs) are two types of ncRNAs that have an effect on cell proliferation and differentiation.[3]

Long non-coding RNAs are 200 nucleotides long and have critical roles in biological processes such as transcription, translation, splicing, stem cell pluripotency, cell cycle, cellular structural integrity, apoptosis, and protein localization.[4]

Long intergenic ncRNAs (lincRNAs) account for the vast majority of long non-coding RNAs. The remainder is overlapping, antisense, or intronic for protein-coding genes.[5]

The lncRNAs, whose biogenesis varies according to cell type and stage, are transcribed by RNA polymerase II enzyme in different genomic regions such as enhancer, promoter, and intergenic regions and at lower levels in contrast to messenger RNA (mRNA) and comprise intron and exon structures. They lack open reading frames (ORFs), 3'UTRs, and termination regions and therefore have limited coding potential. Long non-coding RNAs are involved in biological processes in both the nucleus and the cytoplasm.[6,7] miRNAs, which are effective in many cellular processes such as stress tolerance, energy metabolism, self-renewal and differentiation of stem cells, cell division and proliferation, and initiation and development of cancer, are short non-coding RNAs of 19-25 nucleotides in length.[5,8]

Mature miRNAs bind to the 3'UTR, 5'UTR, ORF regions, or promoter regions of the target mRNA and cause negative gene expression through translation inhibition or through repressing or binding mRNA,[9,10] as shown in Figure 1.

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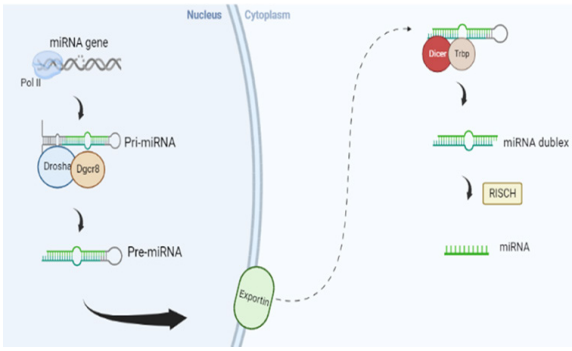

Figure 1. Biogenesis of miRNA. Pri-microRNA: primary microRNA, Drosha: RNAse III enzyme, DGCR8: DiGeorge critical syndrome region 8, pre-microRNA: Precursor-microRNA, RISC: RNA-induced silencing complex, Dicer: RNAse III enzyme, TRBP: HIV-1 TAR RNA- binding protein.

EFFECT OF MIRNAS ON NORMAL DIFFERENTIATION OF STEM CELLS

Role of miRNAs in Embryonic Stem Cells

Embryonic stem cells have the potential to become all types of cells as they are pluripotent, which is why they can form the three germ layers (endoderm, mesoderm, and ectoderm).

It is a known fact that miRNAs play a critical role in the regulation of stem cell self-renewal and differentiation.[11]

There are specific miRNA transcripts specific to ESCs. These are clusters of miR-290-295, miR-302, miR-17-92, miR-106b-25 and miR-106a-363.[12]

Embryonic stem cells' miRNAs facilitate G1/S transition by suppressing the expression of RNA binding proteins.[12,13]

Nanog regulates the differentiation of miR-296, miR-470 and miR-134 ESC by affecting the coding regions of Oct4 and Sox2.[14] Co-transfection of miRNAs in lateral and paraxial mesodermal cells transiently increases the differentiation potential of both lateral and paraxial mesodermal cells.[15]

In a study, it was observed that knockout of the Dicer1 enzyme involved in RNA interference increased the level of apoptosis and human embryonic stem cells (hESCs) could not renew themselves. It was also observed that mir-302-367 and mir-371-373 clusters containing the AAGUGC seed sequence can reverse apoptosis.[16]

Wu et al.[17] showed that the mir-290 cluster contributes to the regulation of alternative splicing and gene expression programs for ESC fate determination and that mir-290 enhances the regulation of alternative splicing factors in ESCs by targeting the negative regulator of Mbnl1/2.

Meta-analysis of microRNA-seq, RNA-seq, and metabolomics datasets were taken from humans and mice uncovered 115 miRNAs with a distinctive expression profile as the transition from pure to prime occurred. [18]

Role of miRNAs in Adult Stem Cells

miRNAs are known to have a major impact on ASC proliferation and differentiation. It's been observed that there are varying miRNA expressions between myeloid and lymphoid lineages, indicating that miRNAs are involved in the differentiation of some hematopoietic lineages.[11,19]

In these stem cells, miRNAs are expressed differently in long-term hematopoietic stem cells (LT-HSCs) compared to short-term HSCs and are characterized by cell surface markers such as c-Kit+/Sca-1+/Lin- (KSL).[20]

miRNA-320a obstructs the differentiation of adipocytes from bone marrow MSCs (BMSCs), as well as the development of osteoblasts, by targeting RUNX2. miRNA-320a-5p contributes to osteogenesis and adipogenesis homeostasis in bone marrow mesenchymal stem cells (MSCs).[21] microRNA-7-5p promotes osteogenic differentiation in human MSCs (hMSC) by targeting CMKLR1.[22]

In a study, miR-540 was found to be a negative regulator during the differentiation of adipose tissue-derived stromal cells (ADSCs).[23]

EFFECT OF LNCRNAS ON NORMAL DIFFERENTIATION OF STEM CELLS

Effect of lncRNAs in Embryonic Stem Cells

Non-coding RNAs regulate pluripotency and differentiation in ESCs.

There was a study that demonstrated long non-coding RNAs have a crucial role in ploripotency, and that the lncRNA genes of the transcription factor Oct4 and Nanog binding sites, which are necessary for the self-renewal of undifferentiated ESCs, are in close proximity.[24]

In a study investigating lincRNAs in mouse ESCs, they found that lincRNAs affect gene expression

in ESCs. They showed that long intergenic ncRNAs are effective in preventing ESC differentiation in the maintenance of pluripotency by affecting the expression levels of Nanog, a transcription factor, and identified lincRNAs involved in the formation of three germ sheets. They also showed that lincRNA transcripts bind with multiple chromatin remodeling proteins.[25]

In a study investigating the effect of lncRNAs on pluripotency and neuronal differentiation in hESCs, hESCs were differentiated into neurons and the expression of thousands of lncRNAs was profiled by microarray. In this study, lncRNAs required for neurogenesis were determined and it was emphasized that lncRNAs have an important role in brain development.[26]

Li YP et al.[27] showed that the knockout of TRIM71-interacting long non-coding RNA 1 (Trincr1) and up-regulation of phosphorylated ERK and ERK pathway target genes caused a decrease in ESC self-renewal.

In another study investigating the role of long non-coding RNAs in the regulation of ESC self-renewal and early embryogenesis, they showed that lncKdm2b, a lncRNA, is conserved among five mammalian species and is highly expressed in ESCs and early embryos. It was also shown that knocked-out LncKdm2b impairs ESC self-renewal and causes early embryonic death, and in addition, LncKdm2b activates the transcription of TF Zbtb3, which in turn contributes to ESC self-renewal.[28]

Impact of lncRNAs in Adult Stem Cells

HOTTIP, a lncRNA, accelerates osteogenic differentiation and accelerates osteogenic differentiation and angiogenesis by interacting with TATA box-binding protein-associated factor 15 (TAF15).[29]

In a study investigating the effects of lncRNA SNHG1 on the osteogenic differentiation of BMSCs, inhibition of lncRNA SNHG1 was found to inhibit the osteogenic differentiation of BMSCs.[30]

The lncRNA NEAT1, which is important in the osteogenic differentiation of human bone marrow-derived MSCs (hBMSCs), regulates miR-29b-3p/BMP1 interaction and affects the osteogenic differentiation of hBMSCs.[31]

In the osteogenic differentiation of periodontal ligament stem cells (PDLSCs) under mechanical force, lncRNAs promoted osteogenic differentiation of PDLSCs by reducing the expression of small nucleolar RNA host gene 8 (SNHG8).[32]

The interaction of lncRNA and miRNA is effective in the osteogenesis of MSCs which are effective in bone development and molecular mechanism.[33,34]

AK141205, a lncRNA induced by osteogenic growth peptide (OGP) in mouse MSCs, is effective in osteogenic differentiation by increasing CXCL13 regulation.[35]

Another lncRNA involved in the osteogenic differentiation of human tooth follicle stem cells is maternally expressed MEG3 (maternally expressed 3). Down-regulation of MEG3, which is effective in reducing gene expression, is involved in the osteogenic differentiation of human dental follicle stem cells.[36]

H19 is another lncRNA that is effective in the development of cancer cell proliferation. Knockdown of H19 suppresses angiogenesis in human amniotic MSCs (HAMSC).[37]

The lncRNA taurine up-regulated gene 1 (TUG1) is involved in the endothelial differentiation of adipose-derived stem cells (ADSCs).[38]

lncRNAs are non-coding RNAs involved in the regulation of hematopoiesis and the development of hematopoietic stem cells. They are effective in the regulation of gene expression during the stages of red blood cell development and differentiation.

There are specific transcripts involved in the expression of transcription factors involved in the differentiation of hematopoietic cell lines.[39]

The Effect of Non-Coding RNAs on Cancer Stem Cells

It is known that non-coding RNAs have an impact on both the normal stem cells and cancer stem cells' functioning. Cancer stem cells possess the same ability as ordinary stem cells, which is the potential to self-renew and differentiate into various cell types. In contrast to regular stem cells, these are malignant as they advance tumor development and metastasis. Therefore, non-coding RNAs have a crucial role in cancer stem cells.[40]

Cancer cell research demonstrated that transmembrane 4 sub-L family member 1 (TM4SF1), which is usually highly expressed in esophageal cancer cells, is elevated but miR-141 is reduced and TM4SF1 is a direct target of miR-141 and could be a feasible option for the development of new treatments and effective drugs.[41]

It was discovered that miR-34a, which is known to have a negative effect on the growth, movement, and invasion of osteosarcoma cells, can suppress Sox-2 by increasing its expression and has a potential antitumorigenic effect in tumors.[42]

A different study showed that an overabundance of miR-145 in cervical cancer stem cells lessened tumor invasion and colony formation by reducing the expression of important stem cell transcription factors like Sox2, Nanog, and Oct4.[43]

Research revealed that silencing miR-21, which is known to control LATS1 expression in kidney cancer cells, decreased proliferation, invasion, and phenotype of cancer stem cells in an investigation of its effect on kidney cancer cell function and LATS1 expression.[44]

A study of breast cancer highlighted the importance of miR-155, an oncogenic miRNA that is overexpressed in many cancers, as a potential therapeutic target. It was found that when miR-155 was inhibited, breast cancer stem cell formation decreased, and sensitivity to doxorubicin, a chemotherapy drug, increased.[45]

In another study on breast cancer, they showed that miR-29a has a significant effect on EMT (epithelial to mesenchyme transition in cancer) and metastasis of breast cancer cells by targeting SUV420H2 and will lead to new therapeutic approaches.[46]

The researchers found that HAND2-AS1, a lncRNA that is abundant in hepatocellular carcinoma, the most common liver cancer type with high recurrence and heterogeneity, encourages the self-renewal of liver cancer stem cells and may be used as a potential biomarker for liver cancer diagnosis.[47]

In a study conducted to elucidate the molecular mechanisms underlying the self-renewal and chemoresistance of bladder cancer stem cells (BCSCs), it was shown that lncRNA termed low expressed in bladder cancer stem cells (lnc-LBCS) plays an important tumor suppressor role in the self-renewal and chemoresistance of BCSCs, contributes to differentiated tumor formation and enhanced chemosensitivity, and may represent a therapeutic target for clinical intervention.[48]

H19, a potential oncogenic factor, is upregulated in breast cancer tissues and negatively correlates with miR-138 expression. It contributes to the arrest and apoptosis of the breast cancer cell cycle, according to a study investigating its regulatory function.[49]

In a study investigating the role of H19 in *Helicobacter pylori*-infected gastric cancer tissues and cells, it was found that overexpression of H19 promoted cell proliferation, migration, and invasion by activating the Nuclear factor kappa B (NF-κB) signaling pathway.[50]

In a study investigating the function of lncRNA KLK8 in colon cancer stem cells, KLK8 was shown to be up-regulated in colon cancer tissues and may be a potential biomarker candidate for colon cancer patients. KLK8's expression is linked to tumor size and metastasis and is positively correlated with genes associated with cancer stem cells in colon cancer tissues.[51]

An investigation was conducted to explain the mechanism behind the self-renewal of cancer stem cells and it was highlighted that HotairM1, a lncRNA, is only faintly present in human colorectal carcinoma and uveal melanoma and affects the development of cancer stem cells through the HOXA1-nanog signaling cycle.[52]

An examination into the role of lncRNA CASC11, an oncogenic lncRNA in colorectal cancer, in small cell lung cancer, revealed that lncRNA CASC11 and transforming growth factor beta (TGF-β1) was increased in small cell lung cancer and demonstrated that lncRNA CASC11 can upregulate TGF-β1 to augment the stemness of small cell lung cancer cells.[53]

In their research on the function of ADAMTS9-AS1, a lncRNA, when it comes to the stemness of lung adenocarcinoma cancer cells, they showed that it can counter the advancement of the cancer cell stemness by modulating the miR-5009-3p/NPNT axis.[54]

Research into breast cancer revealed that lncRNA SNHG1, a lncRNA, was able to control tumor growth and angiogenesis by stimulating the M2-like polarisation of macrophages.[55]

A study on the part of lncRNA H19 in the development of osteosarcoma and its connection to the NF-κB signaling pathway found that when H19 was silenced, the nuclear factor-κB pathway was also suppressed, leading to a decrease in the migration and invasion of osteosarcoma cells.[56]

In conclusion, this chapter summarises the current data on the effects of lncRNAs in stem cell proliferation and differentiation. The knowledge of how lncRNAs collaborate in stem cells on a molecular level will be beneficial in medical applications down the line.

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