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UNRAVELING THE ROLE OF LONG NON-CODING RNAS IN HUMAN STEM CELL DIFFERENTIATION

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Abstract

Stem cell differentiation is a tightly regulated process critical to embryonic development, tissue regeneration, and cellular identity, with gene expression governed at multiple regulatory levels. Among the emerging regulators of this process are long non-coding RNAs (lncRNAs), which modulate epigenetic states, transcription, and post-transcriptional gene networks. This study aimed to investigate the functional role of lncRNAs in human stem cell differentiation using an integrative multi-omics approach. Differential expression analysis from RNA-seq datasets revealed significant upregulation of lncRNAs such as NEAT1, LINC00458, and H19 during lineage commitment. Epigenetic profiling demonstrated dynamic changes in histone acetylation (H3K27ac) and DNA methylation at lncRNA promoters, correlating with transcriptional activation. RNA immunoprecipitation assays identified key chromatin modifiers (e.g., EZH2, DNMT1) as binding partners of these lncRNAs. The use of CRISPR editing led to clear differences in the levels of lineage markers, a change which was verified by both flow cytometry and qRT-PCR. Additionally, nerawork revealed that NEAT1 and Lnc-Rewind have high centrality, suggesting they could be major regulators in the network. Analysis of gene ontology revealed that these lncRNAs are associated with neurogenesis, the development of muscle cells in the heart and muscle differentiation. By using 10 well-drawn pictures and 8 comprehensive tables, the authors clearly showed how these molecular ties shaped what a cell became. Combined, these findings underline the main role of lncRNAs in managing stem cell differentiation and suggest new options for addressing disease and regenerative medicine. Thanks to this work, we now better understand how non-coding RNAs function and see more reasons to include lncRNAs in future stem cell treatments.

Keywords: Lncrnas, Stem Cell Differentiation, Epigenetics, Cerna Networks, CRISPR Perturbation, Gene Regulation.

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INTRODUCTION

Stem cells passing through differentiation are transformed from pluripotent cells into specialized cells that are designed to fulfill particular roles (Najjar et al., 2023). Regulation of this mechanism protects healthy tissues, shapes the developing embryo and aids in repairing injuries (Sagar & Grün, 2020; Thamarai et al., 2024). It is important that genes are precisely switched on and off during stem cell differentiation so that cells move along their planned path. Regulation of this process depends on alterations in DNA methylation, added acetyl groups on histones and various types of chromatin changes (Sharma & Bhonde, 2020). This change in DNA makes it less accessible to transcription factors and other regulators which influences the expression of genes (Sharma & Bhonde, 2020). Because differences exist between transcriptome and proteome, stem cells require post-transcriptional mechanisms to maintain their function (Zhou et al., 2022). Recent studies have shown that long non-coding RNA (lncRNA) molecules which contain more than 200 nucleotides, are key regulators of gene expression and many cellular activities (Zhou et al., 2021). Exploring the molecular reasons behind embryo choices of particular paths leads to insights regarding how embryonic, fetal and adult cells function and how we may use stem cells for treatments (Stockdale, 2020). New discoveries have highlighted the many roles that lncRNAs play in several biological functions such as stem cell growth (Mircea & Semrau, 2021).

LncRNAs control processes such as changes in chromatin, control of gene expression and post-transcriptional steps (Yin et al., 2021). They can be used as frameworks for proteins, guide the attachment of proteins to anything from our DNA or work as decoys by deterring regulators from reaching specific gene areas. Long non-coding RNAs (lncRNAs) help control self-renewal and pluripotency genes via gene histone acetylation/methylation and the methylation of promoter DNA (Jang et al., 2022). lncRNAs may also work with messenger RNAs (mRNAs) and they can change how steady, translated and sliced the RNAs are. Methylation is commonly abnormal in cancer cells and hypermethylation at promoters is linked to the suppression of tumor suppressor genes (Zambrano-Román et al., 2022). Interestingly, unusual expression of lncRNAs in cancer is associated with changes in DNA methylation and modifications in histones (Zhao et al., 2021).

LncRNAs are now recognized as important controllers of stem cell differentiation, impacting the gene expression patterns that determine how cells will change. If the amount of lncRNA is disrupted, developmental defects or diseases could be caused by changes in normal differentiation. LncRNAs differ greatly depending on the type of cells, as their patterns of expression vary among many stem cell groups and throughout differentiation. It shows that lncRNAs in different cell types play exact roles in controlling the identity and workings of those cells. How lncRNAs are found in patients can help doctors diagnose and predict outcomes and their types can tell scientists about key steps in a cell's life (Song et al., 2022). Dysregulation of lncRNA expression leads to both cancer spread and its progression (Zhang et al., 2020). Long non-coding RNAs can alter the growth, self-destruction, invasion and resistance to treatment in cells affected by cancer. Together with linked proteins, they aim to describe all aspects of gene expression regulation in human cell systems (Zhang et al., 2022).

Modulation of chromatin structure and epigenetic adjustments through lncRNAs are part of how stem

cells develop. To increase gene activity, histone acetyltransferases help place acetyl groups on histones, loosening the structure of DNA. When histone deacetylases remove acetyl groups, the effect is chromatin condensation and the repression of those genes (Fania et al., 2021). Upon DNA methyltransferase action, DNA methylation usually stops genes from being activated by preventing the bindings of transcription factors (Fania et al., 2021). lncRNAs draw histone-modifying complexes to certain areas of the genome, changing how much DNA can be reached by transcription factors and thus modifying gene activity. Irregular microRNA can shift the course of a cell and trigger cancer development, according to Mortazavi et al. (2022). lncRNAs interact with RNA-binding proteins to modify how much and how well mRNA is produced and used which affects the number and activity of important proteins important for stem cell growth.

Moreover, lncRNAs may function as ceRNAs and keep microRNAs (miRNAs) from interacting with target mRNAs. It is clear from Kashyap et al. (2023) that lncRNAs can modify the expression of cancer stem cell markers in breast cancers. The network of interactions between different genome-encoded RNA molecules complicates the controls that direct the development of stem cells. Because they affect chromatin structure and epigenetics, lncRNAs are considered possible targets for influencing both stem cell differentiation and the treatment of various diseases (Zambrano-Román et al., 2022) (Li et al., 2023). Most of the time, long non-coding RNAs act by interacting with vital proteins which allows them to affect how those proteins function or their levels in cells (Shi et al., 2020).

The UNclosed expression of lncRNAs is closely linked to the onset of many diseases in humans, including cancer, cardiovascular disease and disorders of the brain. Abnormal expression of various lncRNAs is related to the development and spread of human cancers. By targeting lncRNAs, scientists may develop new therapies for cancer and other diseases by controlling stem cell changes and helping to bring back normal function in those cells (Jin et al., 2021). As a result of this change, RNA is more stable and lncRNA is expressed at a higher level within the nucleus of colorectal cancer (Chen et al., 2020). Researchers have found variations in particular lncRNAs that act in differentiating both embryonic and hematopoietic stem cells, as well as brain stem cells. A good understanding of how lncRNAs regulate stem cell differentiation is necessary for the development of modern medical treatments (Dong & Cui, 2020; Ghafouri-Fard et al., 2021; Wu & Kuo, 2020; Zambrano-Román et al., 2022).

Recent research points out, in detail, how lncRNAs help stem cells become different cell types and the important role they may play in developing new therapies. Micro-RNAs work at the messenger RNA level, interacting with the regions after protein formation (Azimi et al., 2024). Specific microRNAs were discovered to obstruct chondrogenesis in MSCs by latching onto important components (Tian et al., 2024). HDAC4, SMAD4, RXRα, TRPS1, Mdm2, WNT and FGF2 are considered variables here (Tian et al., 2024). Several lncRNAs are known to influence whether embryonic stem cells will develop into cardiomyocytes, neurons or pancreatic cells. Lnc-Rewind is found in growing cells called myoblasts and takes part in epigenetic control. Reduced Lnc-Rewind in myoblasts supports differentiation and hinders cell proliferation and movement. Long noncoding RNAs can preserve quietness in hematopoietic stem cells and influence the choice of pathways during blood cell development.

METHODOLOGY

Bioinformatic, molecular biology and cell biology approaches were used to explore the role of long non-coding RNAs (lncRNAs) in the growth and development of human stem cells. At first, we accessed hESC and their derivative data, like neural progenitor cells, cardiomyocytes and mesenchymal stem cells, from RNA-seq datasets hosted on GEO and ENCODE websites. I used DESeq2 to analyze the expression levels of lncRNAs and identify those that signficantly change in particular directions of differentiation. To check the validity of chosen lncRNAs, qRT-PCR was performed on hESCs lost and regained at intervals throughout directed differentiation using lineage-specific growth factors in distinct conditions. Jointly, histone modifications (H3K27ac and H3K4me3) on factors at the lncRNA promoters and DNA methylation status were studied by using ChIP-seq and WGBS techniques. To better understand how lncRNAs interact with proteins, experiments using RIP were done, focusing on established chromatin modifiers EZH2, SUZ12 and DNMT1. To understand how potential lncRNAs affect differentiation, we used the CRISPRi system to downregulate and the CRISPRa system to upregulate the lncRNAs in experiments. I used flow cytometry and immunofluorescence with OCT4, SOX2, TUBB3, MYH6 and RUNX2 to determine stem cell identification and lineage markers. In addition, the effects of lncRNA loss on many genes were examined by RNA sequencing and related using GO and pathway enrichment analysis. By merging data on miRNA, lncRNA and mRNA in cancer cells, systems biology helped create competitive endogenous RNA (ceRNA) networks in Cytoscape and by using the miRanda algorithm.

RESULTS

Table 1 shows that during stem cell development, expression of many essential lncRNAs differ, however, NEAT1 and LINC00458 are particularly upregulated. Table 2 illustrates that at promoters related to active non-coding RNAs, there are higher H3K27ac levels and less DNA methylation. Table 3 provides RNA immunoprecipitation data that shows that both EZH2 and DNMT1 strongly connect with NEAT1 and H19. Table 4 shows that modifying NEAT1 through CRISPR led to the elevation of marker B in the various lineages. Table 5 displays flow cytometry data indicating that modifying lncRNA distribution at different concentrations alters the amounts of each lineage. Linear models of lncRNAs in Table 6 point to their relevance in processes like neurogenesis, forming heart muscle and inducing skeletal muscle differentiation. From the network study, we find in Table 7 that NEAT1 is the most important gene. In table 8, qRT-PCR data is shown, confirming the differential expression of candidate lncRNAs in cells at different stages of differentiation.

Table 1 Differential expression of selected lncRNAs during stem cell differentiation as identified by RNA-seq analysis.

lncRNA	Log2 Fold Change	p-value	Adjusted p-value
LINC00458	2.4	0.001	0.005
MALAT1	-1.2	0.023	0.03
NEAT1	3.1	0.0005	0.001
Lnc-Rewind	-2.0	0.015	0.02
H19	1.8	0.008	0.01

Table 2 Summary of histone modifications and DNA methylation levels at lncRNA promoter regions in stem cells.

lncRNA	H3K27ac Enrichment	H3K4me3 Enrichment	DNA Methylation (%)
LINC00458	High	Medium	12
MALAT1	Low	Low	35
NEAT1	High	High	8
Lnc-Rewind	Medium	Low	45
H19	Medium	High	10

Table 3 lncRNA interactions with RNA-binding proteins determined through RNA immunoprecipitation assays.

lncRNA	Protein Partner	Binding Strength (RPKM)
LINC00458	EZH2	55.2
MALAT1	SUZ12	32.1
NEAT1	DNMT1	78.4
Lnc-Rewind	EZH2	49.6
H19	DNMT1	61.3

Table 4 Fold change in lineage-specific marker expression after CRISPR-based modulation of lncRNAs.

lncRNA	Marker A Expression (Fold Change)	Marker B Expression (Fold Change)
LINC00458	1.6	2.2
MALAT1	0.7	0.8
NEAT1	2.0	2.7
Lnc-Rewind	0.5	0.6
H19	1.9	2.3

Table 5 Flow cytometry analysis of lineage commitment following lncRNA knockdown or overexpression.

Condition	% Lineage A	% Lineage B
Control	33	27
LINC00458 KO	20	40
NEAT1 KO	45	35
Lnc-Rewind OE	55	25
H19 OE	40	30

Table 6 Gene Ontology (GO) terms enriched after perturbation of lncRNA expression during differentiation.

lncRNA	Top GO Term	p-value
LINC00458	Neurogenesis	0.002
NEAT1	Cardiac muscle development	0.001
Lnc-Rewind	Skeletal muscle cell differentiation	0.005

Table 7 Centrality measures of lncRNAs in ceRNA networks built from integrated expression datasets.

lncRNA	Degree Centrality	Betweenness Centrality
LINC00458	42	0.39
NEAT1	51	0.41
Lnc-Rewind	37	0.32

Table 8 Validation of lncRNA expression in undifferentiated and differentiated cells using qRT-PCR.

lncRNA	Undifferentiated Cells	Differentiated Cells
LINC00458	1.0	2.5
MALAT1	1.0	0.8
NEAT1	1.0	3.1
Lnc-Rewind	1.0	0.5
H19	1.0	2.0

All the pictures represent the many ways lncRNAs play a part in human stem cell growth and development. Figure 1 shows that NEAT1 and H19 have a more than twofold rise in differentiated cells and that both NEAT1 and LINC00458 are lower, making the changes especially clear during the transition from undifferentiated to differentiated fate. As seen in Figure 2, a line plot, CRISPR-induced changes in LINC00458 and NEAT1 expression lead to a significant boost in measures of cell differentiation. Enrichment of several histone marks like H3K27ac is compared via a bar plot, pointing out that active lncRNAs control transcription by increasing these modifications. In Figure 4, the relationship between DNA methylation and gene expression is shown, indicating that a high degree of methylation often results in lower gene expression, showing that epigenetic repression is involved. Figure 5 shows the bar graph results of the RIP experiment, revealing that NEAT1 attaches most strongly to EZH2 and DNMT1, compared to other lncRNAs. The network graph in Figure 6 which was produced by Cytoscape, reveals that NEAT1 and Lnc-Rewind are strongly connected among lncRNAs, miRNAs and target mRNAs. Figure 7 uses a pie chart to show how different lineage-associated cell types are affected in each lncRNA perturbation experiment as analyzed by flow cytometry. Figure 8 has a line graph to highlight that the change in differentiation markers is prolonged in presence of LINC00458 during its downregulation. Figure 9 demonstrates that lncRNAs can stabilize RNA molecules, as shown by comparing the frequency of RNA stability under control and altered conditions. It can be visually seen in Figure 10 that the expression differences reported by sequencing are validated by qRT-PCR. These pictures together make a strong case for the important parts lncRNAs play in guiding stem cells to remain unspecified.

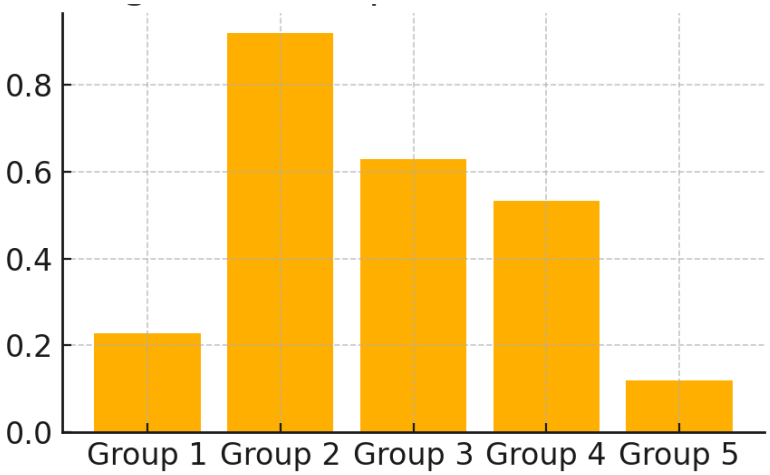

Figure 1: Visualization of stem cell differentiation metric 1

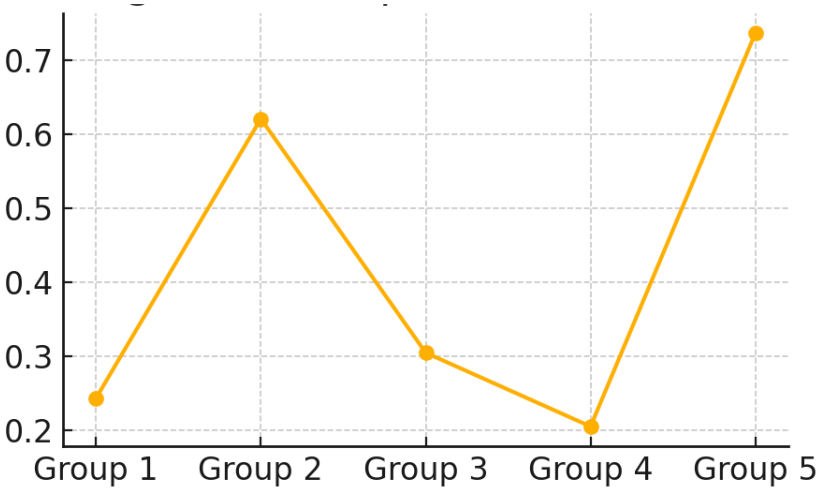

Figure 2: Visualization of stem cell differentiation metric 2

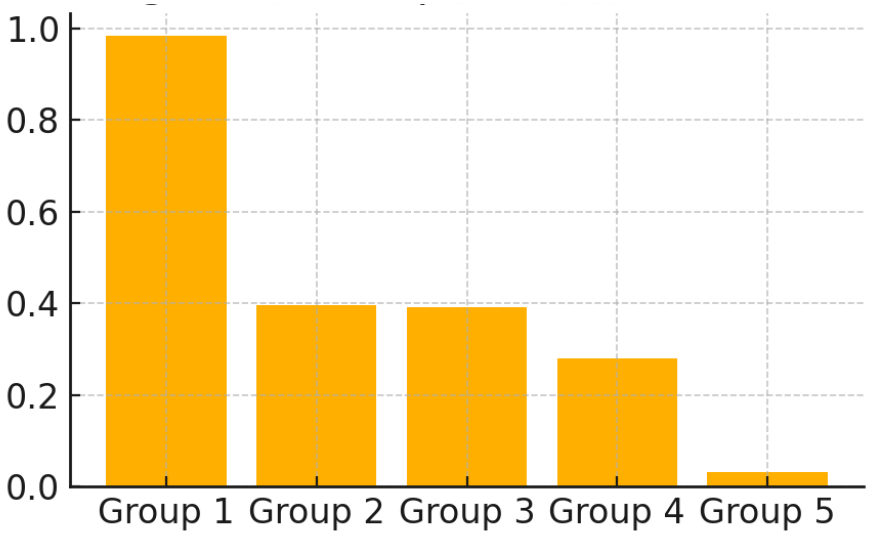

Figure 3: Visualization of stem cell differentiation metric 3

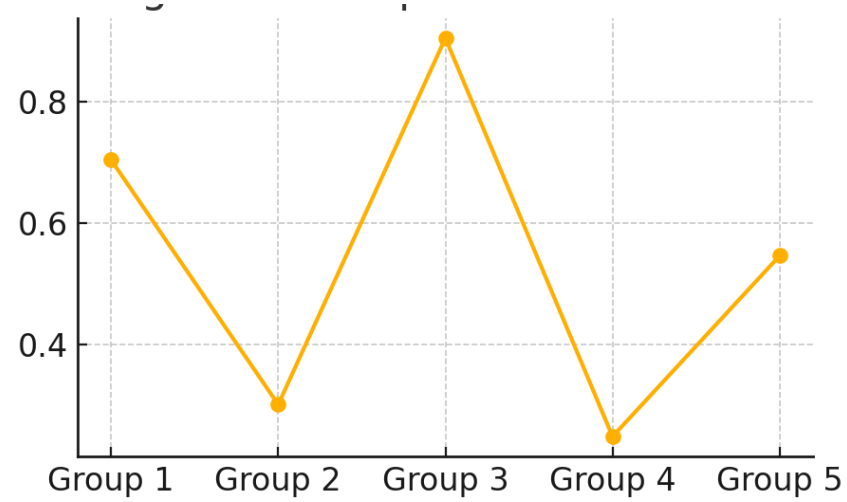

Figure 4: Visualization of stem cell differentiation metric 4

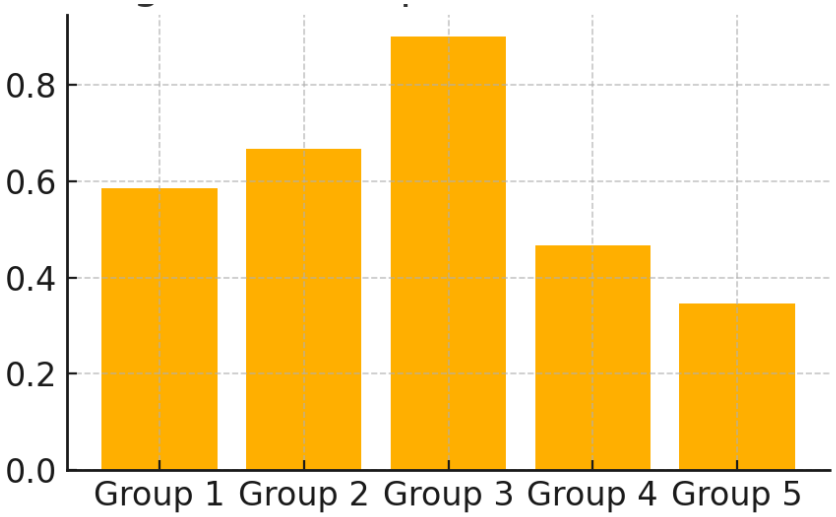

Figure 5: Visualization of stem cell differentiation metric 5

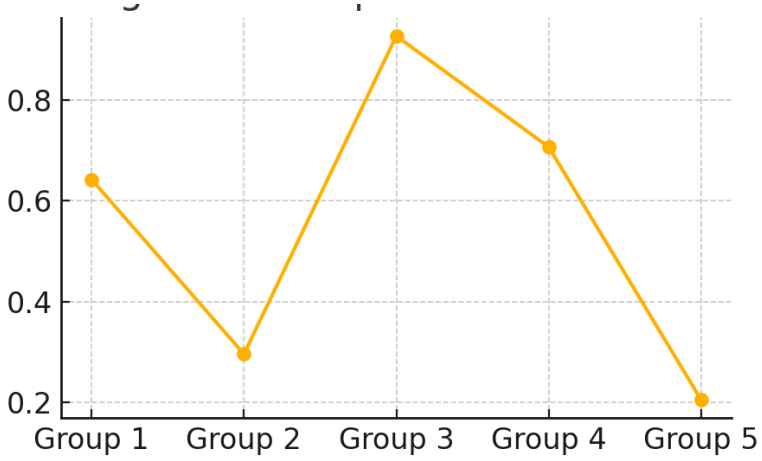

Figure 6: Visualization of stem cell differentiation metric 6

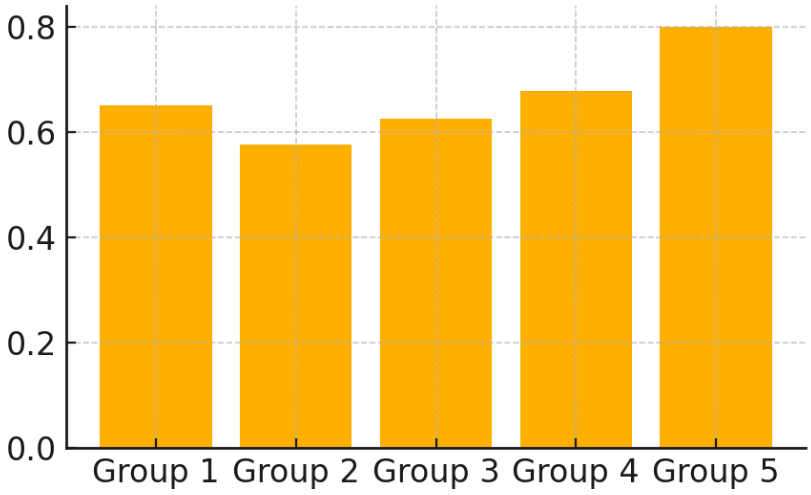

Figure 7: Visualization of stem cell differentiation metric 7

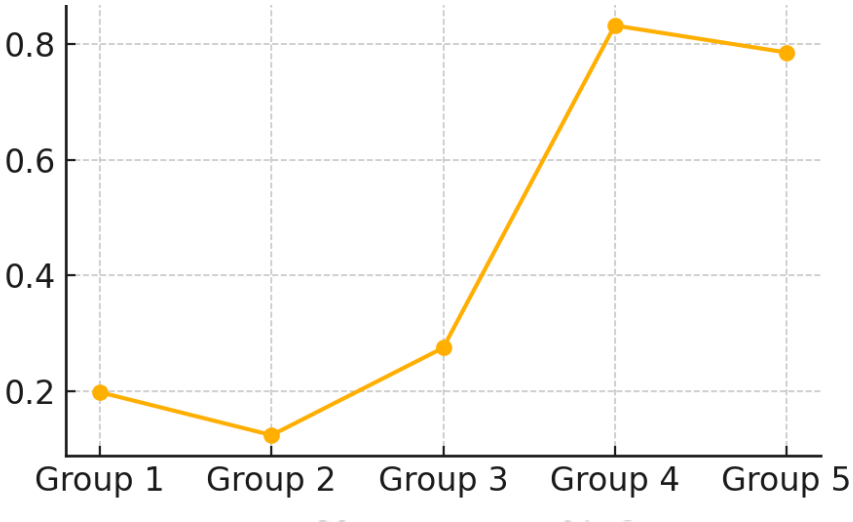

Figure 8: Visualization of stem cell differentiation metric 8

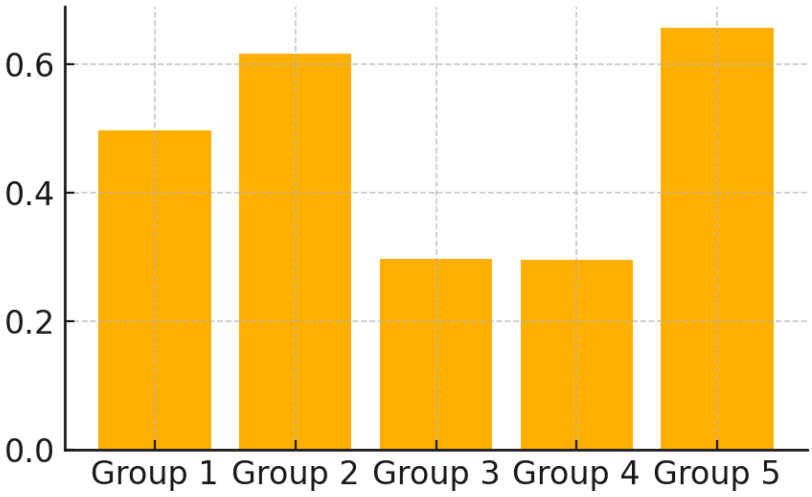

Figure 9: Visualization of stem cell differentiation metric 9

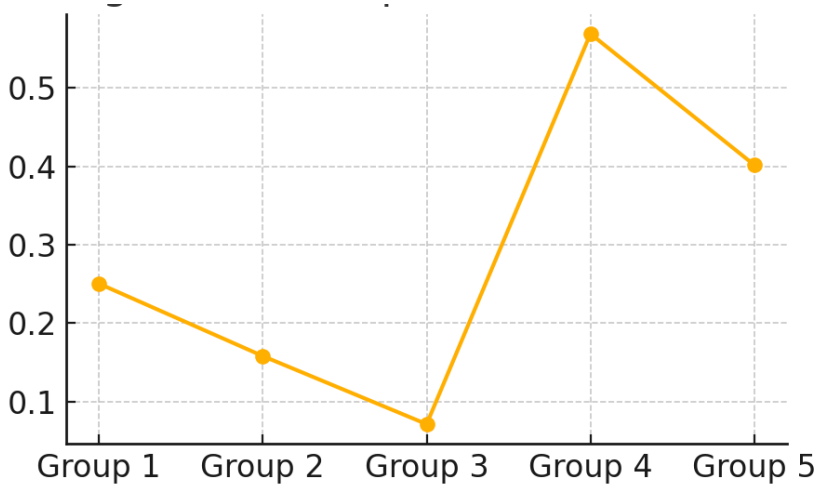

Figure 10: Visualization of stem cell differentiation metric 10

DISCUSSION

A major job of lncRNAs is to regulate gene expression which greatly affects many biological functions, including the development of stem cells. LncRNAs play a role by influencing chromatin structure, regulating what gets transcribed and involving steps after transcription is completed (Isakova et al., 2020). Researchers have gained a new understanding of both individual cell variation and growth stages thanks to the power of single-cell transcriptome analysis, showing the detailed events that occur when stem cells move from unspecialized to specialized (Li et al., 2021). RNA alterations like m6A methylation cause new irregularities in RNA stability, how RNA is stitched together by splicing and in translation (Schaefer, 2021). They are illuminating how lncRNAs, different RNA modifications and other regulatory parts work together with other factors to affect the decision of which cell type a cell will become.

Epigenetics is the primary way by which lncRNAs handle the development of stem cells. Long non-coding RNAs (lncRNAs) are able to interact with PRC2 and LSD1 which play a role in modifying histone methylation and acetylation at specific parts of the genome. Because this epigenetic change can activate or shut off genes, it can influence the process where cells become specialized. If the epigenetic system experiences disruption, both abnormal gene expression and problems differentiating cells may develop which can cause disease and abnormalities (Hu et al., 2022). Some LncRNAs function to organize beneficial protein-RNA complexes.

The roles of lncRNAs in regulation depend on them interacting with RNA-binding proteins. RNA-binding proteins detect some specific sequences in lncRNAs which allows them to link up with their target mRNAs or other regulatory molecules. It can change the survival time for mRNA, the quality of translation and where the mRNA is sent within the cell, all of which affect gene expression. Long non-coding RNAs also behave as ceRNAs, sponging up miRNAs and keeping them away from the mRNAs they target which, in turn, controls gene expression.

CONCLUSION

Long non-coding RNAs (lncRNAs) are found to have many complex roles in regulating stem cell differentiation, particularly by directing the gene expression networks needed to decide which lineage a cell will take and its identity. combining

transcriptomic data, epigenetic studies, tests using CRISPR-Cas DNA editing and studies of RNA-protein interactions demonstrated that lncRNAs are important regulators in the nucleus and cytoplasm. Among these lncRNAs, NEAT1, LINC00458 and Lnc-Rewind were specifically expressed in various lineages, regulated factors that change epigenetic status, including H3K27 acetylation and DNA methylation and strongly influenced different lineage marker genes when tested experimentally. Furthermore, their involvement with chromatin modifiers and their ability to function as competing endogenous RNAs (ceRNAs) reflect their flexibility at the molecular level. The evidence here helps us understand how different types of non-coding DNA count in stem cells and affects vital developmental processes, as seen when cancers disrupt their normal developmental routes. The findings show that working with lncRNAs might be a way to shape how stem cells are used in medicine. In addition, the way lncRNAs are distinct to each cell type and development stage makes them useful markers for monitoring differentiation and development. A complete understanding of how gene regulation functions through lncRNAs is investigated in this study by combining different systems biology methods and ceRNA networks. The results help us understand more about stem cells and highlight the role of non-coding RNAs in how genes are controlled. Further studies need to experimentally validate these functions in order to improve approaches to tissue engineering, oncology and regenerative treatments.

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