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Multifactorial role of long non-coding RNAs (LncRNAs) in hematopoiesis

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1. ABSTRACT

Human genome project unveiled that only 1.5.-2.0.% of the genome is protein coding. ENCODE and related studies showed that most part of the genome transcribed into RNAs, and most of them do not code for a functional proteins, hence the name non-coding RNAs (ncRNAs). ncRNAs are small ncRNAs (less than 200 nucleotides) and long ncRNAs (longer than 200 nucleotides up to 10 kb). They act as a direct link between highly ordered chromosome structures, gene expression and serve as a bridge between genome and chromatin modification complexes as guides, scaffolds, and decoys. Highly regulated hematopoietic differentiation is required for formation of all types of blood cells. Among a variety of lncRNAs only few hematopoitic lncRNAs have been studied extensivelyand most of them are not functionally characterized. The role of these lncRNAs remains partially undetermined but their involvement in the regulation of various genes and protein synthesis has been proved even in hematopoiesis. So, the present review is a mere effort to highlight the role of lncRNAs involved in the development and regulation of hematopoiesis.

2. INTRODUCTION

Human genome project revealed the fact that human genome composed only of 1.5.–2.0.% protein-coding genes. Bulk of genome which was thought as junk is now believed to be transcribed actively. Collaborative effort like ENCODE project and other studies revealed that 76% to 90% of the genome is actively transcribed into RNAs (1–3). As most of these RNA transcripts astonishingly do not meant for the formation of a functional protein that's why these are generally designated as noncoding RNAs (ncRNAs) (4–6). During the past few years it has become evident that most of this DNA is not pervasive transcriptional noise. Recent advances in application of various new approaches like genome-wide gene expression screen, Transcription analysis, designed LncRNA array, transgenic expression, region-targeted association assay and conventional linkage screen, RIP-RNA sequencing, genomewide association studies, gene knockdown/ knockout and careful examination like advancement in sequencing technologies revealed that these are indeed functional molecules which play a major biological role in physiology, health and disease, predominantly in tissue carcinoma as well as in metastasis (7–9).

MicroRNAs (miRNAs), one of the most extensively studied class of noncoding RNAs (ncRNAs) for their oncogenic and tumor suppressive activity and are concerned with various cancer processes (10–14). Interestingly miRNAs represents a mere part among enormous variety of newly identified ncRNA species. Other important types of ncRNAs include small interfering RNA (siRNA), small nucleolar RNAs (snoRNAs), PIWI-interacting RNAs (piRNAs), large intergenic noncoding RNAs (lincRNAs), transcribed ultraconserved regions (t-UCRs), and some other species (7). ncRNAs are conventionally divided on the basis of their transcript size into two classes i.e. small ncRNAs and long ncRNAs (lncRNAs) (15;16). The ncRNAs less than 200 nucleotides in length are referred as Small ncRNAs which includes siRNAs, miRNAs, piRNAs, and transcription initiation RNAs (tiRNAs) which has recently been reported (17;18). snoRNAs are of intermediate size comprising from 60 to 300 bps. Except these mammalian also possess another type of ncRNAs (endogenous cellular RNAs) that are translationally mute and are longer than 200 nucleotides which are referred as lncRNAs and are

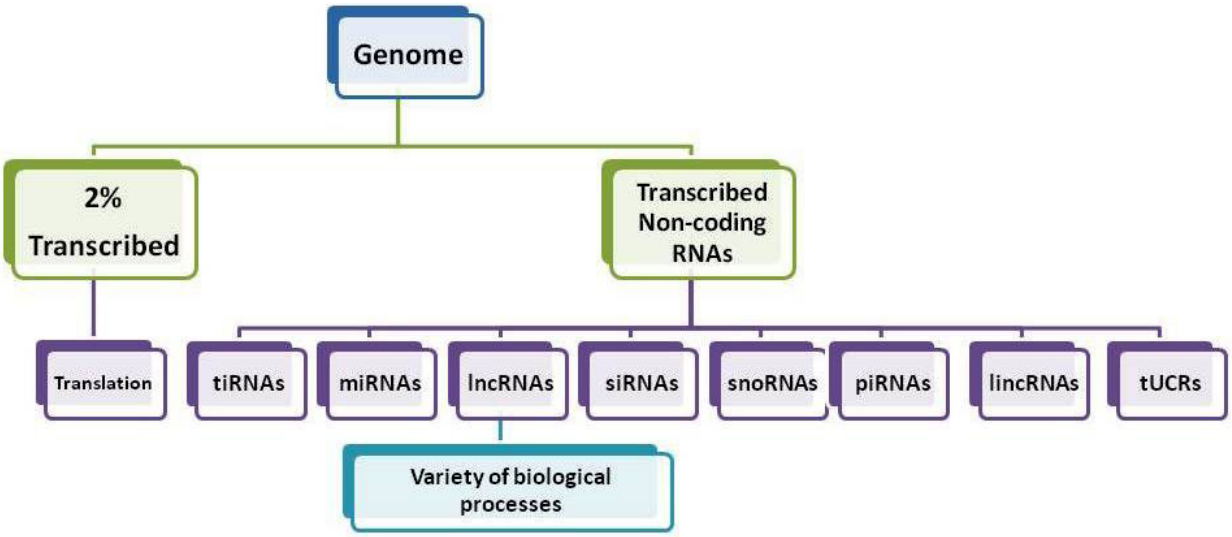

Figure 1. Non-coding RNAs and their classification. Different types of non-coding RNAs on the basis of their size and their mechanism of action.

very heterogeneous group of RNA molecules (19–23) (Figure 1).

Regulation of gene expression by lncRNAs through non-classical mechanisms is known for the last few decades i.e. the discovery of Xist (mediator of X-chromosome inactivation) in 1991 (24). The discovery of this lncRNA along with a few others was thought as sporadic until the large-scale transcriptome sequencing changed the whole scenario by identifying thousands more (25).

LncRNAs varies in their size range between 200 nucleotides and up to 10 kilobases which expressed at lower levels than the mRNAs meant for proteins, can be cytoplasmic or nuclear and which can be polyadenylated or not. Many of these lncRNA genes not only transcribed from conventional promoters and spliced as well as are associated with cell-type-specific nuclear factors just like protein-coding genes (26). While others appears to be arise from enhancers either these are polyadenylated or nonpolyadenylated (27). It is therefore, estimated that thousands of these lncRNAs are encoded and expressing exactly like tissue-specific patterns in human genome.

LncRNAs were found to play an integral role in regulation of expression of various genes at different levels i.e. transcription and post transcriptional processing as well as chromatin modification (7;28). A vast variety of these RNAs significantly expressed during various important cellular processes like pathogenesis or tumorigenesis, embryonic stem cell differentiation etc. (29) as well as regulate variety of biological processes, including cancer metastasis, developmental process, response to stress and cell cycle regulation (30;31) (Figure 2).

Recent studies have proved that lncRNAs are involved in the progression of various human diseases and also in the regulation of multiple developmental processes (31;32). These lncRNAs shows specific sequence information but have structural plasticity as well. They are specifically involved in the regulation of gene expression and function through variety of mechanisms because of their ability to interact directly to RNA and DNA via base pairing while to proteins by specific structural motifs. LncRNAs act as a direct link between highly ordered chromosome structures and gene expression and act as a bridge between genome and chromatin modification complexes acting like guides, scaffolds, and decoys (33). Variety of them alters the chromatin state and expression of genes by employing chromatin complexes specifically required for activation or repression of genome modification. Others performing post-transcriptional regulation and some other chromatin-templated processes remain in nuclear or cytoplasmic territories (34) (Figure 3).

3. LncRNAs IN HEMATOPOIESIS

A very carefully and tightly regulated hematopoietic differentiation is necessary to form all types of blood cells *viz,* RBCs, WBCs as well as thromobocytes throughout the life. Hematopoiesis at the time of embryonic development initiates in yolk sac followed by development in placenta and afterwards in some major arteries of body, fetal liver and finally in the bone marrow (35;36). Although a variety of lncRNAs have been discovered which were found to be involved in various biological activities but only some of hematopoietic lncRNAs have been studied extensively. During terminal erythropoiesis, the expression of a mouse

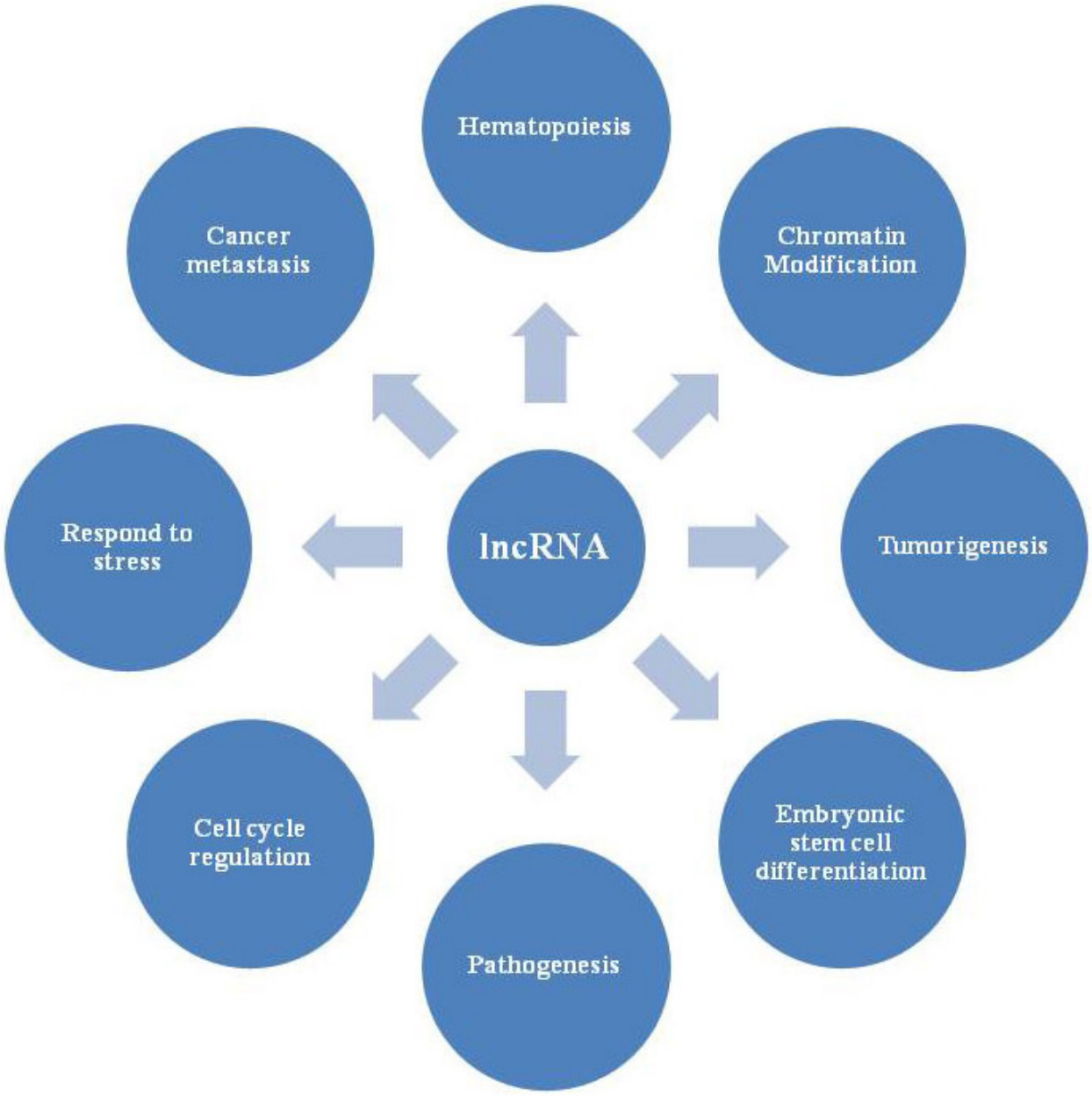

Figure 2. Variety of biological activities regulated by lncRNAs. LncRNAs regulate various biological processes i.e. embryonic stem cell differentiation, pathogenesis, cell cycle regulation, cancer metastasis *etc*.

nuclear lncRNA, LincRNA-EPS is upregulated while the expression of a pro-apoptotic gene, Pycard is repressed. Similarly, in erythroblasts RNAi knockdown of LincRNA-EPS leads to de-repression of Pycard that in turn results in apoptosis. In contrast to it, LincRNA-EPS protects the erythroblasts from apoptosis if over-expressed *in vitro*, during erythropoietin deprivation (37). A hematopoietic lncRNA EGO was identified to be involved in the regulation of eosinophil granule protein expression, and expression of another lncRNA named as HOTAIRM1 (HOXA cluster), was reported to be upregulated during myeloid development as well as involved in stimulation of various HOXA and myeloid differentiation genes (38). A number of abstracts presented in Annual Meeting of American Society of Hematology held in 2012 reported the identification and categorization of lncRNAs in various cells i.e. erythroblasts, hematopoietic stem cells, megakaryocytes and myeloid cells. So, it can be speculated that in the next coming few years various important biological functions will be emerged from some of these lncRNAs.

A large number of lncRNAs have been identified which are involved in the development of blood

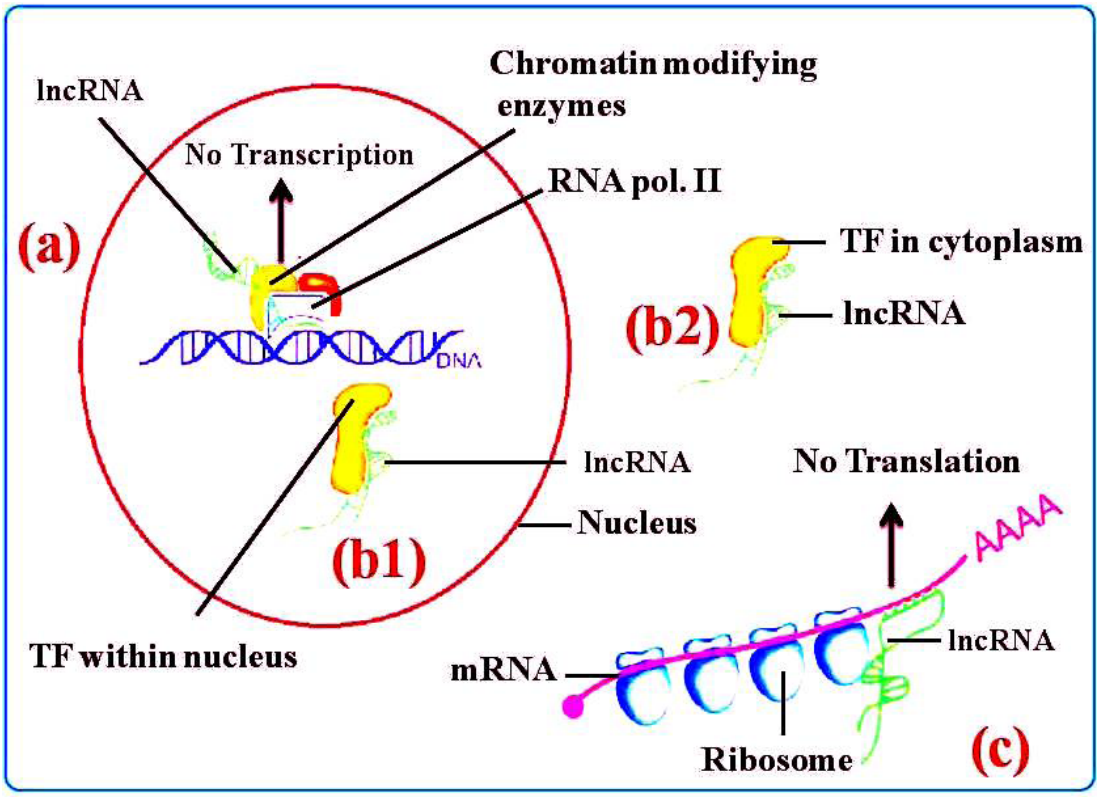

Figure 3. Mechanism of gene regulation by lncRNAs. (a) lncRNAs leads to downregulation of gene expression by guiding chromatin modifying enzymes to promoter of genes. (b1) lncRNAs may bind to transcription factors in nucleus to repress transcription. (b2) lncRNAs may bind to the transcription factors present in cytoplasm. (c) lncRNAs may directly approach mRNA in cytoplasm to prevent translation resulting in gene repression.

cells, however most of them are still not characterized functionally. One of the earliest lncRNAs was the Eosinophil Granule Ontogeny lncRNA EGO (39). EGO was first time identified from CD34 hematopoietic progenitor cells differentiating into eosinophils, where they regulate eosinophil granule protein expression to not only stimulate the differentiation as well as maturation of cell function at transcription level however, its exact method of action is not fully understood and described yet (39). Later on it leads to the discovery of an "antisense to PU.1"; a lncRNA, which was found antisense and to negatively regulating the expression of master hematopoietic transcriptional factor PU.1 as well (40). Normal expression of PU.1 is necessary for normal hematopoietic development and inhibition of uncontrolled division of WBCs (leukemia). It was speculated by the author of this model that this lncRNA "antisense to PU.1," would negatively regulate PU.1 mRNA translation by checking the PU.1 expression levels from being very high. In fact, this model provides the first insight of how antisense lncRNA acts in the inhibition of translation in cytoplasm even though the exact mechanism not characterized and understood fully.

FANTOM and ENCODE, international research consortia, when reported the first lncRNA, and later on various high-throughput technologies utilized to measure lncRNAs expression gave a boom to the identification of lncRNAs from different cell types i.e. blood cells. Microarray analysis identified one of these lncRNAs, HOTAIRM1, during granulocytic differentiation of APL cell lines mediated by all-trans retinoid acid (ATRA) (41). This important lncRNA is transcribed from the HOXA cluster whose knockdown results in altered expression of various HOXA genes (key regulators of both normal and malfunctioned hematopoiesis. This lncRNA not only modulates the expression of granulocytic differentiation genes (41;42) as well as its knockdown leads to delayed ATRA-induced granulocytic differentiation but its exact molecular mechanism is still unknown (42). Hu *et al.,* (2011) identify "Erythroid ProSurvival lincRNA" (lincRNA-EPS) among 400 different lncRNAs involved in mouse erythroid differentiation using RNA-sequencing (37). This transcript is of worth consideration because of its involvement in the repression of Picard (pro-apoptotic gene) resulting in the inhibition of mature erythrocytes apoptosis as well as in terminal differentiation of erythrocytes, but the exact mechanism is still unknown (37). Similarly, 132 novel lncRNAs were identified with restricted erythroid expression by RNA-seq in murine erythropoiesis in a second high-throughput study, and most of these are regulated by key erythroid transcription factors (43). Erythroid maturation was severely impaired upon the knockdown of only 12 of these lncRNAs, this

model was a clear reflective of important regulatory functions of these lncRNAs during erythropoiesis. One of them was found to act as an enhancer RNA (eRNA) that is necessary for major anion transporter across erythrocyte membrane and is necessary for transcriptional activation is transcribed from an enhancer region of the BAND3 gene (43). Paralkar VR *et al.*, (2014) conducted a similar study involving megakaryocytes, erythroblasts, megakaryocyte-erythroid precursors as well as human erythroblasts (44). This study reported the identification of a number of cell specific lncRNAs, many of which were found to be regulated by GATA1 and TAL1 (key hematopoietic transcription factors). They reported by knock down of murine lncRNAs, 21 of which were most abundant, the involvement of 7 out of 21 of these were absolutely required for erythroid terminal differentiation despite the lack of conservation.

Moreover, in an independent study Alvarez-Dominguez *et al.,* reported four of the functional lncRNAs. Astonishingly, most of these lncRNAs were not found conserved in human RBCs. Their decreased conservation may be explained by considering the fact that the tertiary structure of these lncRNAs is much more important than their primary sequence as compared to protein-coding RNAs. In fact, most of these lncRNAs provides a platform where various macromolecular complexes are assembled (45;46). Lnc-DC was identified during the profiling of lncRNA expression involved in the process of differentiation of monocytes into dendritic cells (DCs) (47). This Lnc-DC (a cytoplasmic lncRNA) plays an important role in the DCs differentiation because it activates transcription factor STAT3 involved in the differentiation of DCs. Lnc-DC specifically maintains active phosphorylated form of STAT3 and prevents its dephosphorylation, by binding directly to it, carried out by Src homology region 2 domain-containing phosphatase-1 (SHP-1). Significant contributions and involvement of lncRNAs in the development as well as function of adaptive immune cells have been reported in recent data. 29 different lymphocytes specific lncRNAs were identified through Microarray analysis of purified CD8+ T-cells from human and mouse. Interestingly, expression of 81 lncRNAs was modulated during lymphocyte activation, while 21 out of them in memory T-cell differentiation and 4 during both transitions. A more comprehensive study was carried out on lncRNAs expression at various developmental and differentiation stages utilizing 42 different types of T-cell using RNA-seq (48). 1,524 different genomic regions were highlighted during this ample study that were involved in lncRNAs and were reported much more specific for developmental stage and lineage compared to protein coding RNAs. A variety of transcription factors of T-cells i.e. STAT4, STAT6, T-bet and GATA-3 are reported to regulate the specific expression of a variety of these identified lincRNAs from different T-cells lineages. Indeed, many of these lncRNAs are found in adjoining regions to the genes specifically involved T-cell function by encoding proteins. One of these is LincR-Ccr2–5'AS which was found specifically involved in the migration of T-cells through a mechanism still not known, by controlling the expression of a variety of chemokine receptors.

Recently, another comprehensive study has been performed by RNA-seq on human T- and B-lymphocytes at different stages of differentiation for lncRNA profiling that leads to the identification of more than 500 previously unknown lncRNAs (49). One out of these lncRNAs, linc-MAF4, is involved in regulation of the expression of MAF through recruitment of chromatin modifiers because it is a key transcription factor for T-cell function. Involvement of lncRNAs in regulation of inflammatory and innate immune responses has been previously described in detail (50). So, it is clear from the above given account that lncRNAs play key role in the development and differentiation of various cell lineages.

4. SUMMARY AND PRESPECTIVES

A new level of regulation has been added recently with the discovery of a novel class of regulatory non-coding RNAs. There is no doubt in the fact that the role of these lncRNAs remains partially undetermined but their involvement in the regulation of various genes and protein synthesis has been proved even in hematopoiesis. But still there is a need of further studies to reveal their specific roles to use them as therapeutics in near future.

5. ACKNOWLEDGEMENTS

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