

Long Non-coding RNAs as Cellular Metabolism and Haematopoiesis Regulators

Anjali Sangeeth¹ Mahesh Malleswarapu¹, Amit Mishra² and Ravi Kumar Gutti^{1*}

¹ Department of Biochemistry, School of Life Sciences, University of Hyderabad, (PO)
Gachibowli, Hyderabad-500046 (TS), INDIA

²Department of Bioscience & Bioengineering, Cellular and Molecular Neurobiology Unit,
Indian Institute of Technology Jodhpur, Jodhpur-342037 (RJ), India.

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* Corresponding Author:
Ravi Kumar Gutti, Ph. D.
Department of Biochemistry
School of Life Sciences
University of Hyderabad,
Hyderabad- 500046 (TS) INDIA
Email guttiravi@gmail.com
Ph. +91-9052665597

Abbreviations.

ABCA1	ATP-binding cassette transporter 1
ACVR1B	Activin a receptor type 1B
alncRNA	Nuclear-localized antisense lncRNA
AMKL	Acute megakaryoblastic leukemia
AMPK	AMP-activated protein kinase
APL	Acute promyelocytic leukemia
ATRA	All-trans retinoic acid
CeRNA	Competing Endogenous RNA
DISC	Death-inducing signaling complex
EDN	Eosinophil derived neurotoxin
elncRNA	Enhancer-derived lncRNA
EZH	Enhancer of zeste
GAS5	Growth arrest-specific transcript 5
HAT	Histone acetyltransferase
HMGCR	3-Hydroxy-3-Methylglutaryl-CoA Reductase.
HNRNPU	Heterogeneous nuclear ribonucleoprotein U
HOTAIRM	HOX antisense intergenic RNA myeloid
Igf1r	Insulin-like growth factor1 receptor
ITPR1	Inositol triphosphate receptor type 1
KIF2A	Kinesin family member 2A
LDHA	Lactate dehydrogenase A
lincRNAs	Long intergenic non-coding RNAs
LncHSC	HSC specific lncRNA
ANRIL	Antisense noncoding RNA at the INK4 locus
CASC9	Cancer susceptibility 9
EGO	Eosinophil granule ontogeny
HISLA	HIF-1 α -stabilizing lncRNA
HOTTIP	HOXA transcript at the distal tip
HULC	Highly upregulated in liver cancer
PCGEM1	Prostate cancer gene expression marker 1

PVT1	Plasmacytoma variant translocation 1
RMST	Rhabdomyosarcoma 2-associated transcript
TUG1	Taurine-upregulated gene 1
Xist	X-inactive specific transcript
CRNDE	Colorectal Neoplasia Differentially Expressed
Dreh	Downregulated in hepatocellular carcinoma
GLCC1	Glycolysis-associated lncRNA of colorectal cancer
HSP90	Heat shock protein 90.
LGR	Liver GCK repressor
LUNAR1	Leukemia-induced noncoding activator RNA
MALAT1	Metastasis Associated Lung Adenocarcinoma Transcript 1
MAPK	Mitogen-activated protein kinase
MDS	Myelodysplastic syndromes
MEG3	Maternally expressed gene 3
MEP	Megakaryocyte-erythroid progenitor cell
MFAP4	Microfibril associated protein
Morrbid	Myeloid RNA regulator of Bim-induced death
mTOR	Mechanistic target of rapamycin
NATs	Natural antisense transcripts
NBR2	The neighbor of BRCA1 gene 2
NEAT1	Nuclear paraspeckle assembly transcript 1
NAFLD	Non-alcoholic fatty liver disease
PFKFB2	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 2
PIC	Pre-initiation complex
PKM2	Pyruvate Kinase M2
PPARs	Peroxisome proliferator-activated receptors
PRC2	Polycomb repressive complex 2
PTEN	Phosphatase and tensin homolog
RUNXOR	RUNX1 overlapping RNA
Set1A	SET Domain Containing 1A
SREBP1	Sterol regulatory element-binding protein 1
STAT3	Signal transducer and activator of transcription 3

T-ALL T-cell Acute Lymphoblastic Leukemia
T-UCRs Transcribed-Ultra Conserved Regions
UCA1 Urothelial carcinoma associated 1
 β linc1 β -cell long intergenic noncoding RNA 1

Abstract

Long non-coding RNAs (lncRNAs) are a category of non-coding RNAs (ncRNAs) which are more than 200 bases long and plays major regulatory roles in a wide range of biological processes including hematopoiesis and metabolism. Metabolism in cells is an immensely complex process that involves the interconnection and unification of numerous signalling pathways. A growing body of affirmation mark that lncRNAs do participate in the metabolism, both directly and indirectly, via metabolic regulation of enzymes and signalling pathway respectively. The complexities are disclosed by the latest studies demonstrating how lncRNAs could indeed alter tissue-specific metabolism? We have entered a new realm for discovery that is both intimidating and intriguing at the same time. Understanding the different functions of lncRNAs in various cellular pathways aids in the advancement of predictive and therapeutic capabilities for a wide variety of myelodysplastic and metabolic disorders. This review has tried to give an overview of the different ncRNAs and their effects on hematopoiesis and metabolism. We have focused on the pathway of action of several lncRNA, and has also delved into their prognostic value. Their use as biomarkers and possible therapeutic targets have also been discussed.

Significance statement

This review has tried to give an overview of the different ncRNAs and their effects on hematopoiesis and metabolism. The pathway of action of several lncRNA and their prognostic value was discussed. Their use as biomarkers and possible therapeutic targets have also been elaborated.

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1. Introduction

The long non-coding RNAs (lncRNAs) are classified into mutually non-exclusive sub-classes based on their genomic location from where they are transcribed. They can be stand-alone transcripts (also referred to as large intergenic or intervening non-coding RNAs) (Zhang et al., 2019) that typically rarely overlap protein-coding genes (Boland et al., 2017). LncRNAs can also be transcribed from enhancers, promoters or intronic regions of other genes (Losko et al., 2016). Bidirectional lncRNA transcripts from the same promoter of a protein-coding gene, but transcribed in the opposite direction (Ma et al., 2013). LncRNA transcripts from pseudogenes are natural antisense transcripts (NATs) which can be terminal, nested or divergent NATs or sense-overlapping lncRNAs that overlap with exon(s) and/or intron(s) of a protein-coding gene in the direction of the sense RNA strand ((Dahariya et al., 2019; Amin et al., 2019).

The classification of ncRNAs including lncRNAs are not well established because they have many challenges, such as nucleotide sequence composition and length of ncRNAs and their transcriptional and post-transcriptional behaviour are way too similar to protein-coding RNAs. Currently, there are no precise approaches and most of them rely on genome annotation for the species. Also, unguided transcripts assembly tools generate truncated partial-length protein-coding transcripts (Amin et al., 2019). Thus, they remain as a loosely classified group of RNA transcripts till the present day. But for study purposes, lncRNAs are simply classified in terms of structure (linear or circular), action, and location. Linear lncRNAs consist of long intergenic non-coding RNAs (lincRNAs), Transcribed-Ultra Conserved Regions (T-UCRs), Enhancer RNA (eRNA), NAT etc, whereas, circular include exonic circular RNA (*ecircRNA*) and Exon-Intron CircRNA (*ciRNA*). Based on the mode of action they could be classified as cis-acting RNA (cisRNA), Competing Endogenous RNA (CeRNA), Trans-acting RNA (TransRNA) and based on location, Intergenic, bidirectional, sense, antisense, intronic. (Bhat et al., 2020)

Like protein-coding mRNAs, lncRNAs transcription or biogenesis is also mediated by RNA polymerase II enzyme and many lncRNAs are structurally similar to mature mRNAs too with the absence of introns after splicing process and presence of post-transcriptional modifications such as 5'-end methyl-guanosine cap and 3' polyadenylated tail. But a set of novel non-polyadenylated lncRNA transcripts are also discovered recently in various species and biologists even classify the lncRNAs into polyadenylated or non-polyadenylated

transcripts (Liu et al., 2015). Yet differences and individuality dominate over similarities between mRNAs and lncRNAs, like the absence of long open reading frame (ORF) or having a small ORF in lncRNAs, mRNAs are longer than lncRNAs because they have more number of exons, also exons in lncRNAs are longer than mRNAs, lncRNAs are also transcribed by other polymerase enzymes like RNA polymerase III, IV or V besides RNA polymerase II. LncRNAs have lack of restraint over primary sequence conservation and they are expressed at relatively lower levels (exceptional high in lincRNAs). They exhibit more specific expression profiles than mRNAs but their stability is variable which is globally lower than mRNAs (Derrien et al., 2012). Splicing is less efficient in lncRNAs and some like macrolncRNA, vlincRNAs does not even undergo splicing process. Unlike mRNAs, the subcellular localization of lncRNAs is not restricted to nucleus, but also to cytosol and mitochondria. The functional differences between the mRNAs and lncRNAs are prominent enough to be noted (Jarroux et al., 2017).

1.1. Hematopoiesis, Metabolism and LncRNAs

Hematopoiesis is a process of the formation, development, and differentiation of blood cellular components from hematopoietic stem cells (HSCs) (Bogdan et al., 2013). During the hematopoiesis, the self-renewing multipotent LT-HSCs first differentiate into ST-HSCs and then into lineage-restricted hematopoietic progenitor cells (HPCs) such as common myeloid progenitor (CMP) and common lymphoid progenitor (CLP), and finally, they give rise to all blood cell types. T lymphocytes, B lymphocytes, and natural killer cells arise from lymphoid lineage, while megakaryocytes, erythrocytes, granulocytes, mast cells, and macrophages arise from the myeloid lineage (Calvo et al., 2011, Kondo et al., 2010). Recent studies have revealed that abnormal hematopoiesis critically contributes to myelodysplastic syndromes (MDS) (Zhang et al., 2019). MDS is a category of clonal myeloid neoplasms marked by aberrant blood cell shape and risk of clonal development to acute myeloid leukemia. LncRNAs are known to be critical for sustaining the hematopoietic stem cell and its lineage diversification into the generation of various blood cells. There is currently limited research that focuses the role of lncRNAs in transcriptional and post-transcriptional modulation all through aberrant hematopoiesis.

The cell's metabolism refers to all of the biochemical processes that take place inside the cell. Hundreds of biochemical mechanisms occur regularly in cells to keep them alive and functioning. These processes are frequently connected in networks. Energy and dietary

transformations, biosynthesis, and breakdowns, and by-product expulsion are all metabolic processes that are entirely virtually catalysed by enzymes. As compared to normal cells cancer cells have unique metabolic properties that aid proliferation as well as their spread.

LncRNAs are now generally recognized for their vast regulatory impact on a number of metabolic processes in a variety of ways in both normal and malignant metabolism of cells. In this review, we put in a nutshell the advancing field of lncRNAs in hematopoiesis and metabolism and outline the interrelation between the dysregulation of lncRNAs and in myelodysplastic syndrome and tumor metabolism, with a distinct emphasis on particular functions of lncRNAs in glucose, glutamine and lipid metabolism.

2. LncRNAs reported in hematopoiesis

LncRNA may contain several domains that bind to proteins (transcription factors) or nucleic acid sequences of various genes. The functions of lncRNAs are still an ongoing research area and their significance is noticed in several biological processes of both vertebrates and invertebrates. Their role has also been investigated in the area of hematopoiesis (Dahariya et al., 2019). Recent studies suggest that lncRNAs are highly sophisticated regulators of the cell maintenance and differentiation of HSCs (satpathy and chang, 2015). Some of those lncRNAs are involved in hematopoiesis determined through loss-of-function studies are explained further in the upcoming sections (Table 1).

2.1. H19

H19 is the first eukaryotic lncRNA discovered. It is a spliced RNA polymerase II transcript with 5' and 3' ends, small ORF, and is about 2300 nucleotides long. It is highly expressed in LT-HSCs and its expression is gradually downregulated as LT-HSCs differentiate into ST-HSCs and HPCs (Venkataraman et al., 2013). H19 lncRNA is also termed as H19 imprinted maternally expressed transcript because its expression depends on the sex of the transmitting parent (maternal). While the neighboring IGF2 gene is expressed paternally. This reciprocal expression of H19 and IGF2 is determined by the differentially methylated region (H19-DMR) upstream to the H19 (Gabory et al., 2006). At the same time H19 exon 1 acts as the template for two microRNAs (miRNA), miR-675-5p and miR-675-3p, where miR-675 restricts the expression of IGF1 receptor (Keniry et al., 2012). The maternal-specific deletion of this control region resulted in activation of the IGF2-Igfr1 pathway and corresponding inactivation of Foxo3-mediated cell-cycle arrest, which leads to up-regulated activity and proliferation (Venkataraman et al., 2013). Thus, H19 actually promotes HSC quiescence by regulating the

Igf signaling pathway (A et al, 2013). Knockdown experiments revealed another HSC specific lncRNAs (LncHSC) that mediates the binding of transcription factors to active promoters of genes encoding hematopoiesis. Where, LncHSC-1 modulates myeloid differentiation while LncHSC-2 modulates in HSC self-renewal and lymphoid differentiation (Luo et al., 2015).

2.2. LincRNA-EPS

Certain other lncRNAs like lincRNA EC are highly tissue-specific and they are lost in between the developmental stages from fetus to adult. For example, lincRNAs EC-2, lincRNAs EC-4, and lincRNAs EC-9 are essentially required for fetal erythrocyte maturation, but are absent in the adult bone marrow (Juan et al., 2014). A group of lncRNAs such as lincRNA-EPS, elncRNA-EC3, shlncRNA-EC6, and alncRNA-EC7 is involved in megakaryocyte-erythroid progenitor cell (MEP) into erythrocytes and its subsequent maturation. LincRNA erythroid pro-survival (LincRNA-EPS), is a type of lncRNA that facilitates erythrocyte formation by repressing transcription of caspase-activating adaptor protein from a proapoptotic gene called PYCARD. This repression that protects erythroid progenitors from apoptosis is mediated by chromatin modifiers associated with LincRNA-EPS (Juan et al., 2011). From sequence analysis, this lncRNA is found to be a 2531 nucleotide long with 4 exons and 3 introns and 5'- 3' rapid amplification of cDNA. A study implied that this lncRNA is a RNA polymerase III transcript and is highly expressed during the terminal erythroid differentiation (Hu et al., 2011).

2.3. Bloodline

An enhancer-derived lncRNA named elncRNA-EC 3 was found to be cis-regulating the kinesin family member 2A (KIF2A) expressed during the erythrocyte formation. KIF2A is a plus end-directed kinesin motor required for assembling normal bipolar spindles, chromosomal movements, cytoskeletal reorganization and thus aids in mitosis progression during erythropoiesis (Juan et al., 2014).

Similarly, the nuclear-localized antisense lncRNA-EC7 (alncRNA-EC7) or Bloodline, is a lncRNA that is transcribed from a conserved super-enhancer and is about 3700 nucleotide long, capped and poly-adenylated lncRNA. It enhances the expression of neighboring BAND3 or anion exchanger 1 coding gene, which belongs to the Solute Carrier 4 family of bicarbonate transporters (SLC4A1). This primary anion exchanger was found to be a predominant glycoprotein of erythrocyte membranes and modulate erythroid maturation (Xu

et al., 2019). AlncRNA-EC7 accesses its target genes through chromatin interactions stabilized by a nuclear matrix protein called heterogeneous nuclear ribonucleoprotein U (HNRNPU) (Juan et al., 2017). Meanwhile, a knockdown study in mouse revealed that small RNA (sRNA) hosts lncRNA, shlncRNA-EC6 (also known as DLEU2), involved in downregulation of Rac1 and its downstream targets PIP5K and subsequently results in the activation of enucleation and maturation of erythrocytes (Wang et al., 2018).

2.4. Lnc-MC

High expression of hematopoiesis-specific transcription factor PU.1 in GMPs antagonizes the transcription factor C/EBP β function and favors monocyte development. In contrast, downregulation of PU.1 result in GMP's commitment to granulocyte differentiation. This transcription factor regulates the expression of long non-coding monocytic RNA (lnc-MC) and for the same reason, lnc-MC is up-regulated during monocytogenesis (Chen et al., 2015). PU.1 also blocks the silencing of the lncRNA by repressing the expression of miR-199a-5p. Coming to the role of the lnc-MC, it's up-regulation results in the expression of ACVR1B, and activin signaling is critical for differentiation of monocyte to macrophage, cytokine production and cell migration (Ahmed et al., 2020).

2.5. Fas-AS1

Fas-antisense 1 (Fas-AS1) is the first lncRNA to be induced and regulated by erythroid transcription factors during the maturation of erythrocytes. It is transcribed anti-sense to the intron 1 of the Fas gene. The expression of Fas-AS1 results in decreased expression of Fas on the surface and protects the maturing erythroblasts from Fas-mediated assembly of death-inducing signaling complex (DISC) and subsequent caspase activation and apoptosis. Fas-AS1 is highly expressed during erythroid differentiation by the activity of erythroid transcription factors, GATA-1 and KLF1, and in contrast, NF- κ B activity decreased the expression of the same (Villmizar et al., 2016).

2.6. LncEry

Recently, a deep sequencing study in murine hematopoietic cell populations revealed the presence of a novel lncRNA and its isoforms. Knockdown and knockout assays were used to confirm its importance in erythroid progenitor differentiation. Since it is highly expressed in erythrocytes and their progenitors it is named as lncEry. The downregulation of this lncRNA leads to impaired erythrocyte homeostasis or decreased erythroid differentiation-related

genes, including globin genes. LncEry interacts with WD Repeat Domain 82 (Wdr82), a component of the SET Domain Containing 1A, Histone Lysine Methyltransferase (Set1A) and Histone H3-Lys4 methyltransferase. It stabilizes the localization of Set1A/Wdr82 complex to facilitate the epigenetic modification of the promoter region of globin genes and thereby activating the expression of globin genes by regulating late-stage of erythropoiesis (Yang et al., 2020).

2.7. LncRNA EGO

During the development of eosinophil from CMP, besides the transcription of proinflammatory molecules, transcription factors (GATA-1, PU.1, , c/EBP α , and ϵ), the expression of lncRNA EGO (eosinophil granule ontogeny) was also detected. The isoforms of this RNA transcript have varying lengths, for example, EGO-A is about 1000 nucleotide long, whereas, EGO-B is 1700 nucleotides long. EGO is polyadenylated transcript nested within the conserved intron of ITPR1 gene (Aoki et al., 2010). EGO transiently increases interleukin-5 stimulation of high proliferative capacity CD34⁺ hematopoietic progenitors and facilitates corresponding differentiation into eosinophils. EGO also facilitates expression of an eosinophil granule protein called major basic protein (MBP) and an antimicrobial protein, known as eosinophil derived neurotoxin (EDN) (Wagner et al., 2007).

2.8. Lnc-DC

lncRNA DC is essential for dendritic cell (DC) differentiation from DC progenitors, where it activates the transcription factor STAT3 by sequestering it away from inhibitory phosphatase, namely SHP1. This favors STAT3 phosphorylation at tyr705 and thereby activating dendritic maturation genes. During the myeloid DC progenitor differentiation process, the transcription of lncRNA-DC was up-regulated by the ETS-domain transcription factor PU.1 (Wang et al., 2014).

2.9. Thy-ncR1

Expression profiling of ncRNAs in T-cell leukemia cell lines revealed the presence of thymus-specific HIT14168 ncRNA known as Thy-ncR1. This lncRNA is transcribed from human chromosome 1 within the olfactory receptor (OR) genes. Since the OR gene is expressed only in the olfactory bulb and Thy-ncR1 is expressed in organ specific manner. Thy-ncR1 may not regulate the OR genes expression. However, the expression of the CD1 gene cluster (classical cell surface marker antigen) of nearby locus is highly correlated with

Thy-ncR1 expression in the T-cell lineage. Even though CD1 cluster is expressed in both dendritic cell (DC) and T- cells, Thy-ncR1 does not regulate this gene cluster expression in the DC-cell lineage. Thy-ncR1 also reduces the mRNA MFAP4 level in T-cells thereby modulates the proliferation and differentiation of T-lymphocytes. Normally, MFAP4 produces a microfibril associated protein which involved in cell adhesion or intercellular interactions, but the physiological role of this mRNA in immature T cells remains unclear (Aoki et al., 2010).

2.10. Morrbid

The p50-Associated COX-2 Extragenic RNA (PACER) is a type of lncRNA that activates human COX-2 (cyclooxygenase 2) gene expression by sequestering repressive p50 subunit of NF- κ B1 away from the Cox2 promoter and recruiting histone acetyltransferase (HAT) and RNA polymerase II pre-initiation complex (PIC) to enhance histone acetylation (Krawczyk et al., 2014). A novel lncRNA termed Morrbid was recently identified that mediates the survival of human myeloid cells along with neutrophils, eosinophils and monocytes in response to cytokines by Polycomb repressive complex 2 (PRC2) dependent repression of the pro-apoptotic Bim transcription. Morrbid aids in promoting catalytic activity of PRC2 in methylation of histone H3 at Lys27 (H3K27me3) and thereby leaving the Bcl2L11 gene in poised state (Kotzin et al., 2016).

3. Differential expression of lncRNAs in Myelodysplastic Syndrome (MDS)

Recent advances in the field of lncRNA-chromatin interactions studies suggest that they might play a role in the regulation of not only in the normal hematopoiesis, but also in the neoplastic hematopoiesis (Dominguez et al., 2014). These lncRNA are differentially expressed in both normal and pathological conditions of hematopoiesis (Gao et al., 2020). Following are the lncRNAs that are known in blood cancers which are either tumor-suppressive or oncogenic (Table 2).

3.1. Xist

Xist, a lncRNA localized on one of the two female X chromosomes in mammals triggers X chromosome inactivation (XCI) in the early embryogenesis through transcriptional silencing of one X chromosome to balance gene expression between the sexes. This silencing takes place until embryonic days 4.5–5.5 and the inactive X chromosome enters into a "maintenance phase" where it propagates as inactive in subsequent cell divisions and Xist is

continuously expressed for the remainder of female life. X chromosome associated cancer in males is also seen but more frequent in trisomy (XXY). The deletion of the Xist gene in female mice revealed that the lncRNA transcript of this gene is essential for hematopoietic stem cell survival and function because heterozygous or homozygous mutants developed a group of blood cancers called myeloproliferative neoplasm (MPN) and myelodysplastic syndrome (MDS) due to progressive reactivation of inactive X chromosome (Yildirim et al., 2013).

3.2. HOTAIRM

HOTAIRM (HOX antisense intergenic RNA myeloid), a lncRNA or more specifically lincRNA having a genomic location in HOX gene cluster (HOXA, HOXB, HOXC, and HOXD), regulates the expression of several HOX genes (Beya et al., 2015). The target of these genes is transcription factors that aid in the transcriptional activation of genes involved in hematopoiesis (Bhatlekar et al., 2018). For example, HOXA9, -B4 and -B6 regulate HSCs self-renewal, HOX-A5 and -A9 involve in HSCs proliferation and differentiation to CMP and HOXA7 is involved in megakaryocyte differentiation. HOXA9 regulates HSC differentiation into CLP, HOXB3 regulates differentiation of pre-B lymphocytes into B lymphocytes, HOXA5, and -C8 differentiation of MEP into erythrocytes, whereas, HOXC3 and -C4 play an important role in the erythroid lineage differentiation and HOXC8 involved in GMP differentiation. HOTAIRM1 is an intergenic antisense lncRNA transcribed between the human HOXA1 and A2 genes specifically in the myeloid lineage and it is up-regulated during granulocyte differentiation. HOX lincRNAs are sometimes found to be over-expressed (from hundreds to nearly two thousand-fold) in patients with cancers or tumors (Bhatlekar et al., 2018, Hajjari et al., 2015). For example, overexpression of HOTAIRM1 results in an exaggerated expression of HOXA4 gene and defective differentiation of myeloid progenitor cells. At the same time, the downregulation of HOTAIRM1 in NB4 cell line resulted in decreased granulocytic maturation (Bhat et al., 2020).

3.3. LUNAR1

The dysregulation of LUNAR1 (leukemia-induced noncoding activator RNA) expression promotes T-cell Acute Lymphoblastic Leukemia (T-ALL) in humans. The LUNAR1 gene is located in closely to IGF1R gene. Upon activation, NOTCH-regulated oncogenic ceRNA the transcription coactivators called mediator complex are recruited on the IGF1R promoter,

which interacts with transcription factors and RNA polymerase II, thereby promoting IGF1R expression and IGF1R signaling to induce T-ALL cell proliferation (Trimachi et al., 2014).

3.4. LncRNA-CRNDE

Studies in U937 cells and normal mononuclear cells revealed the presence of highly expressed oncogenic lncRNA Colorectal Neoplasia Differentially Expressed (lncRNA-CRNDE) in the bone marrow tissues of acute myeloid leukemia (AML) patients (Wang et al., 2018). LncRNA-CRNDE promoted the proliferation and inhibit apoptosis in the abnormal myeloid cell line by targeting various miRNAs, genes and cell signaling pathways. For example, Wnt/ β -catenin, PI3K/AKT/mTOR, NF- κ B/AKT, MAPK and Notch1 pathway and numerous microRNAs including miR-181a-5p, 136-5p, 217, 384, 203, 186, 205, 145 and 451 (Lu et al., 2020).

3.5. RUNXOR

RUNX1 or AML1, a hematopoietic master regulator that transcribes a Runt-related transcription factor plays an important role in hematopoiesis. It is considered to be one of the most mutated genes in AML patients. RUNX1 is required for the production of HSCs, self-renewal or maintenance of HSCs and the differentiation of diverse hematopoietic cell lineages. RNA-guided chromatin conformation capture study revealed the presence of a novel lncRNA transcribed upstream of exon 1 and overlapping to the protein-coding region of this gene referred to as RUNX1 overlapping RNA (RUNXOR). This intragenic lncRNA is about 2160 nucleotide long and it directly binds to promoter and enhancer elements of RUNX1 gene. It recruits H3-K27 methylase EZH2, a component of PRC2 to RUNX1 and thereby epigenetically regulates the RUNX1 gene to impair the hematopoiesis (Wang et al., 2014).

3.6. MIR99AHG and MIR100HG

LincRNAs, MIR99AHG (also known as MONC) and MIR100HG, are predominantly expressed in normal HSPCs and erythroid cells or megakaryocytic cells. Enforced MIR99AHG expression in normal HSPCs leads to interference in erythroid lineage commitment and development of immature erythroid progenitor cells. MONC and MIR100HG with their respective miRNA polycistrons are highly expressed in acute megakaryoblastic leukemia (AMKL) blasts. The knockdown of MIR100HG resulted in a change in lineage surface marker expression, impaired cell viability and replicating-

efficiency of AMKL cells. While, knockdown of MIR99AHG impaired cell proliferation in AMKL cells (Emmrich et al., 2014).

3.7. NEAT1

Nuclear paraspeckle assembly transcript 1 (NEAT1) with two isoforms (NEAT1-1 and NEAT1-2) were recently identified as a crucial component of paraspeckle, a ribonucleoprotein body within the mammalian nuclei. This subnuclear structure with the nuclear-restricted lncRNA regulates the expression of certain genes by nuclear retention of mRNA. Experimental studies revealed the significant downregulation of these NEAT1 isoforms in peripheral blood mononuclear cells of the acute promyelocytic leukemia (APL) patient due to the expression of PML-RAR α fusion gene. PML-RAR α oncoprotein is an initiation factor for APL (a subtype of AML) that represses retinoic acid as well as non-retinoic acid target genes transcription and subsequent blockade in promyelocyte (immature white blood cells) differentiation and promotes immature cells' survival. The repression of NEAT1 induced by PML-RAR α fusion protein could be reversed by the treatment of ATRA. The increased NEAT1 expression and subsequent decrease in the concentration of leukemic blast cells after ATRA treatment, suggests the involvement of NEAT1 lncRNA in cell differentiation and leukemogenesis. But the underlying molecular mechanisms are still unknown (Zeng et al., 2014).

Besides the above-mentioned lncRNAs, many more are discovered or suspected to be functional in hematopoiesis in different organisms. But still not all lncRNAs functions, mode of action and characterization remain fully understood and they are yet to be clinically studied.

4. LncRNA in normal and malignant metabolism

Cross-talk between lncRNAs and cellular metabolism has been implicated in both normal cells and tumor cells. Cancer cells have unique metabolic properties that aids their development and progression, when equated to the normal cells. These reprogrammed functions, regarded as hallmarks of cancer are triggered by remarkable alterations in the expression of associated lncRNAs in the specific pathways activated by tumor cells. To showcase the possibilities for targeted therapies in specific cancers, a proposed framework is required to understand the correlation between metabolic reprogramming and lncRNA

dysregulation, with a focus on the assigned roles of lncRNAs in carbohydrate, aminoacid, and lipid metabolism in both normal as well as tumour cells (Tan et al., 2020).

4.1. LncRNA and glucose metabolism

Glucose is the most common final source that reaches tissue and converts to ATP at the cellular level through metabolic transformation. Glucose is essential for energy metabolism. Carbohydrates, lipids and proteins are all metabolized into glucose or its byproducts in the end. It also stands as an important substrate for various carbohydrates such as glycolipids, glycoproteins, ribose and deoxyribose. LncRNA mediate precise aspects of glucose metabolism varying from regulation of insulin biogenesis in pancreas, synthesis and breakdown of glycogen as well as glucose in liver to maintain homeostasis in various tissues (Shankaraiah et al., 2018).

A lncRNA produced by the β linc1 locus has been reported to affect the genesis and activity of islet β cells (Singh et al., 2020). Linc1 deletion in mice resulted in glucose intolerance due to abnormal β -cell maturation and secretions. Let-7 together with Akt pathway modulation by lncRNA H19 was found to control pancreatic β -cell growth. In infants, H19 silencing reduced β -cell growth, but re-expression enhanced β -cell expansion in adolescents (Tan et al., 2020).

In pancreatic cells, lncRNA MEG3 has been said to epigenetically control β -cells by regulating the expression of transcription factors such as Rad21, Smc3 and Sin3 via EZH2-mediated methylation (Wang et al., 2018). MEG3 also affects insulin secretion by lowering Pdx-1 and MafA levels (Zhu et al., 2016). Hepatocytes in the liver are accountable in regulation of major glucose metabolism such as glycogen production, glycogen breakdown, glucose release into the bloodstream via glycogenolysis and gluconeogenesis. Many of these processes are under the regulation of various lncRNAs (Zhang et al., 2020). LncRNA-LGR triggered by fasting resembles fasting repressed GCK expression. When lncRNA-LGR was over-expressed, lowered hepatic glycogen level in mice through interaction with nuclear ribonucleoprotein L, a silencer of GCK. LncRNAs have recently been shown to affect glucose metabolism in skeletal muscles. In C2C12 skeletal cells, knocking down the lncRNA-Dreh lowered glucose production and elevated glucose transporter expression (Takashi et al., 2020).

Metabolic reprogramming of glucose is common in a variety of clinical conditions, especially in cancer. Warburg effect, for instance, is the preferentially important example among them. LncRNAs have a myriad of repercussions in glucose metabolism in pathological conditions.

They are a part of the development of biological processes in cancer, mediated through the regulation of various receptors, enzymes, transcriptional factors and signaling molecules. The silencing of lncRNA-ANRIL reduced glucose absorption and hindered acute myeloid leukemia development by targeting adiponectin receptors at the cellular level (Fan et al., 2017).

4.1.1. LncRNA mediated regulation of metabolic enzymes and transcriptional factors

LncRNAs control energy metabolism substantially by modifying metabolic enzymes and transcription factors involved in metabolism after they have been translated (Fig.1). The link between lncRNAs and metabolic enzymes is very intricate due to their significant effect on each other. LncRNA-mediated post-translational changes adversely impact metabolic enzymes such as HK (Hexokinase) and PK (Pyruvate Kinase) to alter glucose metabolism in different malignancies such as cancers (Sun et al., 2018). The initial and irreversible stage of glycolysis is catalyzed by HK. In osteosarcoma, upregulation of the lncRNA PVT1 amplified glucose metabolism via modulating the miR-497/HK2 axis (Song et al., 2017). The rate-limiting enzyme in glycolysis is pyruvate kinase (PK), whose mode of action is influenced through both allosteric and covalent changes. Pyruvate Kinase M2 (PKM2) produces ATP by catalyzing the conversion of phosphoenolpyruvate to pyruvate. By inhibiting aerobic glycolysis by means of the AKT/mTOR signaling pathway, the lncRNA LINC01554 facilitated ubiquitin-mediated degradation of PKM2 in hepatocellular carcinoma (Zheng et al., 2021). Additionally, the lncRNA HULC boosted phosphorylation of Lactate dehydrogenase A (LDHA) and PKM2, which improved glycolysis and promoted the proliferation of liver cancer cells (iong et al., 2021). LncRNA AGPG influences the expression of PFKFB2, which is important in glucose metabolism through its phosphorylation activity (Liu et al., 2020). Others on the list include lncRNAs such as LINC00092, XIST and UCA1 which have been discovered to affect glucose metabolism through altering the same enzyme (Sun et al., 2018).

Since lncRNA alters the control of transcription factors on their targets they can amend energy metabolism via modulating metabolism-associated transcription factors. LncRNAs control the function of these polypeptides by different post-translational modifications including phosphorylation and ubiquitination of the target transcription factors, boosting the expression of enzymes involved in metabolism.

LncRNA RMST is needed for neuronal development because it promotes SOX2 binding to nearly 50 percent of its binding sites. LncRNAs appear to have an essential role in controlling HIF-1 activity. In several metabolic disorders, lncRNA (HISLA) suppressed HIF-1 hydroxylation and breakdown, while favoring aerobic glycolysis by preventing the connection between PHD2 and HIF-1. Another LncRNA CASC9 interacts with HIF-1, leading to induction of HIF-1 thereby stimulating glycolytic metabolism in reprogrammed cells (Sun et al., 2018). Knocking down the lncRNA UCA1 increased the cytotoxic potential of adriamycin and impeded HIF- α -dependent glycolysis, which has been shown to help patients with acute myeloid leukemia to overcome chemoresistance (Zhang et al., 2020).

Furthermore, the post-translational alteration of c-Myc by lncRNAs has been linked to the jurisdiction of cancer energy metabolism. The lncRNA-GLCC1 safeguards c-Myc against ubiquitination by associating specifically with the heat shock protein 90(HSP90) (Xu et al., 2021). Interestingly, the transcriptional profile change of c-Myc target genes like LDHA lead to reprogramming glycolytic metabolism for CRC cell growth. Additionally, in multiple myeloma, the lncRNA PD1A3P associates with c-Myc to improve its transactivation and boosts pentose phosphate pathway by interacting with the promoter of glucose 6-phosphate dehydrogenase (Zhang et al., 2020). Increased ubiquitination of c-Myc and its target genes implicated in the glycolytic process, such as LDHA and HK2, have been linked to lncRNA MEG3 over-expression (Xu et al., 2021). Several lncRNAs have indeed been correlated to transcription factors in the NF- κ B cascade in a variety of ways.

Disruptions in metabolism-related proteins are characterized by significant changes in metabolic signaling networks. The AMPK, AKT, mTOR and p53 are particularly prominent among the main effector molecules which play a central role in these regulations ([Fig.2](#)).

4.1.2. lncRNA and Central players of metabolism

Many studies in recent years have observed alteration of various signaling pathways in relation to lncRNA expression patterns. Nevertheless, just a limited amount of studies explain the regulatory mechanism. Due to their capability to influence multiple factors of signaling cascades such as AKT, mTOR, P53 and AMPK, lncRNAs have surfaced as potentially therapeutic and their deregulation plays a significant role in pathology of many human malignancies.

Akt

The serine/threonine kinase Akt, (protein kinase B), is a crucial regulator of cell signaling. Stimulation by growth factors leads to activation of Akt resulting in phosphorylation and inhibition of multiple elements of the apoptotic pathway, preventing cell death. Akt genes have distinct functions in normal cell physiology and cancer pathogenesis and are expressed both at the mRNA and protein levels. Apoptosis-related kinases and GLUTs are two metabolic variables linked to Akt (RB et al., 2006). Akt activation can boost both ATP synthesis and oxygen uptake in cells. Akt controls glycolysis through a variety of ways, including raising GLUT expression and increasing the production of glycolytic enzymes such as HK2, PKM2 and suppressing mitochondrial respiration (Koelwyn et al., 2001).

In many metabolic pathways, Akt is a main server among several signaling cascades, and it is quite often altered by different lncRNAs. MALAT1, LINK-A, LINC00470 and AK023391 are examples of lncRNAs that enhance the activation of the Akt signaling pathway through a variety of methods (El et al., 2002). LINC00470 glues to the FUS protein, trapping Akt in the cytoplasm and boosting its activity. In xenograft malignant cells, the lncRNA AK023391 modulates the expression of Ki-67, p-FOXO3a, p-PI3K, p-AKT and p-NFkB. Recently FAL1, an lncRNA that suppresses p21 by deregulating its transcription and stimulates cell proliferation, has been discovered. The lncRNA FER1L4, on the other hand, promotes cell cycle arrest through regulating the Akt signaling pathway. LncRNA H19 works as a molecular sieve to block the action of miRNA let-7. The phosphorylation of the miRNA processing factor k5RP by the PI3K/Akt/ pathway lowers H19 expression. H19 inhibition raises let-7 levels, hindering the insulin/PI3K/Akt pathway and resulting in decreased glucose absorption. The Akt signaling pathway is also inactivated by lncRNAs. For example, LncHD1 regulates the SREBP-1c protein level, which is a major regulator of lipid metabolism in many malignancies, via modulating the phosphorylation of the PDK1/Akt/FOXO cascade (Krycer et al., 2010).

mTOR

mTOR (mechanistic target of rapamycin) is a significant signaling center that regulates necessary cellular responses and metabolism. mTOR is a PI3K-related serine/threonine-protein kinase that is a catalytic member of two different protein complexes called mTORC1 and mTORC2, which differ in their mode of action as well as in their structure. Gene transcription, translation, endocytosis and other growth-related activities are all regulated by mTORC1, while the function of mTORC2 is unknown. However, it is assumed to enhance

cell survival and actin cytoskeleton structure. Although several regulators participate in regulation of mTOR activity, new research has revealed lncRNAs as putative mTOR controllers.

According to recent reports, UCA1 activates mTOR by over-expressing HK2 and promotes glycolysis by activating STAT3 and blocking miR-143. In bladder cancer cells, this revealed a new cascade of regulation on the metabolism of glucose in UCA1-mTOR-STAT3/miR-143/HK2 axis. LncRNA ANRIL has been shown to aid neural progenitor cells (NPCs) development by up-regulation of GLUT1 and LDHA. The mechanism of action likely entails ANRIL-induced Akt phosphorylation, resulting in stimulating the mTOR pathway, which in turn potentiates GLUT1 and LDHA levels leading to increased NPC development (ZW et al., 2016). MetaLnc9, also known as LINC00963 interacts with the phosphoglycerate kinase 1 (PGK1) protein and is found on chromosome 9 (AN et al., 2013). This connection stops PGK1 from being ubiquitinated, resulting in accumulation of PGK1 and mTOR activation. Many lncRNAs in the Dlk1-Gtl2 locus gives birth to numerous miRNAs that aim for mTOR components. Dlk1-Gtl2 expression is essential for the maintenance HSCs in the mouse fetal liver and ablation of imprinting at the loci results in a large decrease of HSCs owing to AKT-mTOR over-expression and metabolic problems (JE et al., 2006).

AMPK

AMP-activated protein kinase (AMPK) is a crucial energy monitor in cells. When AMPK is active, the TSC2 complex is triggered, which leads to the deactivation of the mTOR-stimulated GTP-binding protein RHEB (Hardie et al., 2007). Impaired AMPK signaling, a crucial metabolic gatekeeper, contributes to high cell division and diminished autophagy in energy-stressed cells. Once intracellular ATP levels have dropped, the tumor suppressor LKB1 acts as an upstream regulator of kinases, phosphorylating and stimulating AMPK. As a result, when AMP is present, ATP-depleting processes are significantly suppressed and ATP generation is accelerated in the body (Shackelford et al., 2009). LncRNA LINC00473, as well as NBR2, are found to be associated with LKB1 dysregulation. LKB1 inactivation prompted LINC00473, while the LKB1-AMPK signaling pathway promoted lncRNA NBR2. By regulating the levels of AMPK kinase, NBR2 can operate as a tumor suppressor (Liu et al., 2016). AMPK slows ATP-drained anabolism and promotes ATP-induced catabolism via promoting a variety of downstream effectors. The NBR2, linc00473, and LKB1/AMPK

pathway could therefore play a big part in cancer cells through modulating pathways involved in many cellular metabolisms (Chen et al., 2016).

P53

Most human cancers effectively inhibit the transcription factor p53, which acts as a tumor suppressor. The lack of p53 in a cell can result in mitochondrial respiratory impairment as well as an upsurge in glycolysis (Bensaad and Vousden, 2007). P53 suppresses the activity of GLUT1 and GLUT4 while boosting HK, SCO2 and PTEN. Several p53-related lncRNAs have been implicated in metabolic diseases (Kim et al., 2016). MALAT1 was discovered to modulate p53 levels and MALAT1 knockout fibroblasts accelerated DNA damage repair, resulting in p53 activation and consequent target gene expression (Chen et al., 2012). In nasopharyngeal cancer, the HULC lncRNA HULC has been seen to suppress the function of p53 and p21 to encourage cell proliferation. (Matoba et al., 2006).

4.2. LncRNA and lipid metabolism

Lipids are fundamental components of membranes, energy stores and signal molecules which are essential for cell survival. The liver and adipose tissue are the key systems for generation of energy as well as storage. Lipid metabolism is a complicated process since it involves many distinct molecular networks and transcriptional factors, some of which have been studied so far. Many disorders of considerable relevance to human health, such as non-alcoholic fatty liver disease (NAFLD) and cardiovascular diseases are caused by the dysregulation of lipid homeostasis mechanisms. Noncoding RNAs have surfaced as essential integrators of lipid metabolism in both the cell and the body. The link between different lncRNAs associated with lipid metabolism and their modes of action have been demonstrated. Majority of the associated molecular mechanisms are based on lncRNA-RNA or lncRNA-Protein inter-connections, where they function either as transcription regulators that function at the DNA level or post-transcription and translation controllers that operate at the RNA level and lastly as post-translation regulators that works at the protein level.

4.2.1. Role of LncRNA in lipoprotein and triglyceride metabolism

Adipocyte maturation and triacylglycerol synthesis are both influenced by lncRNA Blnc1 via LXR stimulation, overexpression of Blnc1 greatly boosted SREBP1c expression, thereby elevating gene expression involved in the synthesis of triacylglycerol and hepatic steatosis in primary hepatocytes (Zhang et al., 2021). When liver X receptors (LXRs) were

mechanistically activated through drugs, the expression of lncRNA LeXis elevated in the liver, acting as a moderator of genes implicated in cholesterol homeostasis (Li et al., 2017). In mice, triggered LeXis lowered cholesterol biosynthetic pathway gene expression levels, particularly SREBF2 and HMGCR, as well as, systemic and hepatocyte total cholesterol. In mouse hepatic cells, palmitate-stimulated enhancement of MALAT1 expression was accompanied by a rise in SREBP1c level in primary murine hepatocytes via its ubiquitination and thereby stabilization of SREBP-1c in the nucleus. Knockdown of MALAT1 reduced MALAT1 to SREBP-1c interaction resulting in the accumulation of lipid in hepatocytes (Li et al., 2017). *In vivo* studies of lncRNA, lncARSR has shown that over-expression of the lncRNA has boosted liver cholesterol biogenesis by up-regulating the rate-limiting enzyme, HMGCR, in the biogenesis of cholesterol. lncARSR, leads to the activation of SREBP-2, a key transcription factor of the rate-limiting enzyme through PI3K/Akt pathway. Also, H19 levels in hepatocytes were found to become higher by diet-induced fatty liver, resulting in increased triacylglycerol buildup (Schmidt et al., 2018). The activity of apolipoproteins that serve as a source for plasma lipoproteins production has been found to be regulated by two AS lncRNAs, APOA1-AS and APOA4-AS. But the mechanism of action needs to be studied (Qin et al., 2016). lncRNA BM450697 regulates low-density lipoprotein (LDL) receptors, important for swallowing and eliminating LDL particles from circulation. LDLRs are activated by BM450697 silencing. The inhibition of interactions with RNA pol II and perhaps SREBP1a at the LDLR promoter by BM450697 resulted in a reduction in LDLR mRNA levels. New data suggests that lncRNAs have a role in adipogenesis, promoting lipid storage and disposal. The lncRNA SRA1, for instance, has been shown to induce preadipocyte development in part through linking to PPAR γ by acting as a ceRNA for miR-31 to target C/EBP- α in adipose tissue-derived mesenchymal stem cells (Li et al., 2019; Nuermairaiti et al., 2018).

Lipid metabolism may also undergo adaptations in the metabolic reprogramming of tumor cells, which require a high quantity of lipid to create organelles and key signaling components throughout aggressive proliferation, have their lipid biosynthesis altered to a substantial extent. In these cells, lncRNAs may have a role in the control of various fat metabolism-associated genes. For example in cervical cancer, lncRNA-LNMICC, by modulating a facilitator of fatty acid absorption and trafficking, fatty acid-binding protein 5, enables reprogramming to improve lymph node invasion. FASN is a crucial rate-limiting enzyme of fatty acid synthesis. lncRNA HOTAIR expression is favorably linked with FASN

expression in human nasopharyngeal cancer. Knocking down HOTAIR diminished free fatty acid and FASN levels at the genomic level. Other lncRNAs such as NEAT1 promotes uptake of lipid in macrophages through miR-342-3p-CD36 axis (Wang et al., 2014). NEAT 1 also has shown to modulate ATGL expression and impact the aberrant lipidosis of hepatocellular carcinoma cells (Wang et al., 2019). Two lncRNAs, GAS5 and RP5-833A20.1 has been found to reduce the efflux of cholesterol in macrophage derived cells. GAS5 regulates cholesterol levels through suppression of ABCA1 transcription, while RP5-833A20.1 exert their regulation through miR-382-5p-NFIA axis. (Meng et al., 2016; Hu et al., 2009)

Research has shown that lncRNAs operate on the promoters of the gene associated with lipid metabolism. When mice primary hepatocytes were treated with GW3965, an agonist to the liver X receptor (LXR), which governs cellular cholesterol homeostasis and suppresses cholesterol production, the lncRNA LeXis was found to be the most up-regulated one among the other lncRNAs. The presence of an LXR response element in the LeXis promoter was later demonstrated utilizing a luciferase reporter experiment (Zhang et al., 2021).

The dysregulation of the lncRNA HULC has been linked to a variety of cellular processes, including hepatoma cell proliferation and infiltration. In hepatoma cells, cholesterol drives HULC production through the retinoic receptor RXRA, which enhances lipogenesis by inhibiting miR-9 target, peroxisome proliferator-activated receptors (PPARs). HULC suppresses miR-9 expression by methylating the CpG islands, which epigenetically silences the miR-9 promoter (Cui et al., 2015). This will lead to higher PPAR expression of the fatty acid synthase and acyl-CoA synthetase. This suggests that it is unreasonable to disregard the importance of lncRNA-mediated metabolic reprogramming in tumor development. They could be used in conjunction with other cancer treatments.

4.3. LncRNA and amino acid metabolism

Amino acids are the building blocks of proteins, a vital macromolecule that is further modified into various essential cellular effectors and regulator components such as enzymes, hormones and neurotransmitters. A succession of enzymatic and transcriptional events completes the intracellular metabolism of amino acids (Heiden V, 2011). LncRNA has been discovered to be engaged in the mechanism of amino acid metabolism by regulating these molecules in addition to being implicated in the control of glycolysis and lipid metabolism (Fig.3). Many of them have found different functions such as modulating enzyme, glutaminase alternative splicing pathway, as a competing endogenous RNA which

coordinates with glutamine metabolism-associated miRNA (Tennant et al., 2010; Le., 2012). In addition to that certain amino acid transporters have been identified to be regulated by lncRNAs and many controls the protective effects against antioxidants in cells. But more confirmative studies are needed to be performed for identifying their exact mode of action.

A growing body of data suggests that cancer cell growth is aided by a relatively high requirement for amino acids. A range of amino acids serves an increasingly important role in tumor metabolism (Sivanand et al., 2020). Prior investigations have revealed information about the involvement of glutamine in cancer. Cancer cells rely on an external glutamine supply for amino acid metabolism. Glutamine is a key reservoir of reduced nitrogen for various metabolic pathways, as well as a supplier of carbon to refill the tricarboxylic acid (TCA) cycle. UDP-N-acetylglucosamine is a component in protein folding and trafficking and glutamine aids in its production. Protein folding will be defective and the ER-related stress response will be triggered in absence of glutamine in the cells. Knowledge of how lncRNAs are related to amino acid metabolism especially glutamine metabolism in malignant cells is still at the preliminary stage. The hepatocellular carcinoma-associated lncRNA HOTTIP which is an oncogene too is implicated in GLS1-associated metabolism of glutamine and overexpression of HOTTIP is expected to promote GLS1 expression and hence glutamine metabolism (Ge.,2015). By sponging miR-145, lncRNA TUG1 has been shown to increase glutamine metabolism in intrahepatic cholangiocarcinoma. Sirt3, a direct target of miR-145, has been shown to favorably regulate GDH production by deacetylating GDH in the mitochondrial matrix (Zeng et al., 2017). Another lncRNA PCGEM1 has been shown to affect prostate cancer metabolism, especially TCA and glutamine metabolism, by activating c-Myc, which recruits PCGEM1 to the promoters among its gene of interest, resulting in increased transactivation activity. lncRNA HOTAIR expression is discovered to be aberrantly elevated in glioma cells. It was found since the lncRNA HOTAIR, acts as a sponge for miR-126-5p and increases glutamine metabolism (Schlicker et al., 2008). Polypeptides synthesized from lncRNA have been proven to prevent cancer in amino acid metabolism in recent data. lncRNA HOXB-AS3, for example, slows down colon metastasis through a conserved peptide comprising 53 residues that suppresses amino acid metabolism (Tennant et al., 2010). The influence of lncRNAs on glutamine metabolism and other aspects of amino acid metabolism in tumor cells have to be investigated further since it might lead to effective therapeutic intervention.

4.4. Therapeutic potential of lncRNA

LncRNAs are involved in almost every biological activity and have been related to a number of diseases. The mechanisms through which lncRNAs regulate gene expression are poorly understood. RNA-based therapeutic methods have made substantial progress in recent years. The results of the research have been recognized several advantages of using lncRNA as therapeutic targets. LncRNAs have grown to attention as a promising new class of molecules with the potential to alter diagnosis and treatment (Kim., 2020).

There is a well-established relationship between lncRNA and disorders, notably malignancies. Several non-coding RNAs have been found as diagnostic and prognostic indicators as a result of the discovery of their functions in cancer (Wang et al., 2020; Mishra et al., 2019). Recent findings have shown the significance of lncRNAs in a wide variety of clinical conditions other than cancer, such as metabolic disorders (Masayuki et al., 2017). Because of their significant functions in different aspects of cellular metabolism, they are important. It's a new field with a lot of potential for future lncRNA-mediated therapies focused against various metabolic disorders.

Moreover, diseases, such as immunological dysfunction, have been linked to lncRNAs in research. According to mounting data, long noncoding RNAs (lncRNAs) are critical regulators of viral diseases and host immune responses, covering mechanisms involved in the control of COVID-19 and consequent clinical conditions (Wu et al., 2021; Henzinger H et al., 2020). Cellular lncRNAs govern genetic material and influence viral replication and pathogenesis during viral infections by influencing the host transcriptome via virus-mediated changes. Certain lncRNAs have important regulatory functions in the viral course of infection in SARS-CoV-2 patients (Yu B et al., 2021). MALAT1 and NEAT1 lncRNAs do seem to be strongly linked to immunological responses and may play a role in the inflammatory course of SARS-CoV-2 infected cells according to the latest reports (Agwa SHA et al., 2021; Henzinger H et al., 2020). Elevated levels of LINC02207 and LINC01127 were known to be correlated to severe COVID-19, whilst LINC02084, LINC02446, LINC00861, LINC01871, and ANKRD44-AS1 were discovered to be correlated to mild COVID-19 (Saha C et al., 2021). When comparing severe COVID-19 patients to mild COVID-19 patients, PVT1 was also found to be downregulated (Yang Q et al., 2021). In the clinical treatment of COVID-19, medications such as remdesivir, baricitinib, dexamethasone, and tocilizumab are already being used (Wu et al., 2021; Cheng J et al., 2021). Focused studies might lead to the development of lncRNA-based techniques and therapeutics by determining the prevalence and role of lncRNAs during SARS-CoV-2 infection. More research is needed due to the numbers of

lncRNA coded by the human genome and the lack of coherence on the altered lncRNA in SARS-CoV-2 infection.

5. Conclusion

The heterogeneity of responses seen in various tissues and disorders exemplifies the varied roles of lncRNAs in the cell. A deeper knowledge of the functions of lncRNAs in various phases of hematopoiesis and metabolism, as well as their altered regulation in hematopoietic and metabolic diseases, would benefit to improve disease prediction and would lead to innovative treatment techniques that target regulatory molecules. The studies reviewed here have provided enough evidence that lncRNAs play vital roles in regulating various stages of hematopoiesis. Involvement of more functional studies are required to look at the role of lncRNAs in transcriptional and post-transcriptional modulation throughout hematopoiesis and how its aberrant expression results in the dynamic progression of myelodysplastic syndrome. As previously mentioned, the interaction of lncRNAs with key transcription factors or metabolic enzymes efficiently impacts glucose, lipid and amino acid metabolism while also promoting tumor growth. Pathways such as PI3K/AKT/mTOR, p53 and AMPK which are integral for the regulation of glucose metabolism, especially in cancer are under the regulation of different lncRNAs. They also shown to have an impact on lipid metabolism such as apolipoproteins, cholesterol and triglyceride metabolism via interacting with SREBP transcription factors. Furthermore, lncRNA has been found to play functions in amino acid metabolism altering amino acid transporters and controlling glutamine metabolism specifically in cancer. Despite the fact that numerous essential biological roles of lncRNAs have been found in the last years, the vast majority of lncRNAs remain uncharacterized, and there is a good distance to cover before we can define, describe, and interpret the real functions of lncRNAs. As a result, a thorough analysis of the importance of lncRNA in regulating different targets and even the strategies by which it achieves it, would therefore aid in the development of new tools to manage myelodysplastic and metabolic syndrome, as well as the development of improved treatment interventions.

Author contributions statement

Sangeeth A, Mahesh M, Mishra A and Gutti R. wrote or contributed to the writing of the manuscript.

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The name and full address and e-mail address of person to receive reprint requests.

Prof. Ravi Kumar Gutti

Department of Biochemistry, School of Life Sciences, University of Hyderabad, (PO)
Gachibowli, Hyderabad-500046 (TS), INDIA

Email: guttiravi@gmail.com

Authors' names and listed in order of appearance.

Anjali Sangeeth¹

Mahesh Malleswarapu¹

Amit Mishra²

Ravi Kumar Gutti²

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Table 1: LncRNAs reported in normal hematopoiesis.

	LncNA	Stage associated	Mechanism	References
1	H19	HSC quiescence	Regulating the Igf2-Igfr1 signalling pathway	Luo et al., 2015
2	LncHSC-1 LncHSC-2	myeloid differentiation HSC self-renewal and lymphoid differentiation	Mediates transcription factors binding to promoters of genes of hematopoiesis	Hu et al., 2011
3	elncRNA-EC 3	Erythropoiesis	cis-regulating of 2A (KIF2A) expression	Juan et al., 2014
4	Bloodlinc	Erythroid maturation	Enhances BAND3 of Solute Carrier 4 family of bicarbonate transporters (SLC4A1).	Wang et al., 2018
5	lnc-MC	Monocytopoiesis	Regulated by the expression of PU.1 in GMPs	Ahmed et al., 2020
6	Fas-AS1	Erythrocyte maturation	Regulated by erythroid transcription factors	Villmizar et al., 2016
7	lncEry	Erythroid differentiation	Interact with WD Repeat Domain 82 to facilitate the epigenetic modification of the promoter region of globin genes	Yang et al., 2020
8	lncRNA EGO	CD34+differentiation into esnophils.	Transiently increase cytokine, interleukin-5 stimulation of high proliferative capacity CD34+ hematopoietic progenitors	Wagner et al., 2007
9	lnc-DC	Dendritic cell (DC) differentiation	Activates the transcription factor STAT3.	Wang et al., 2014
10	Thy-ncR1	Proliferation and Differentiation of T lymphocytes	Reduce the mRNA MFAP4 level in T-cell	Aoki et al., 2010
11	Morrbid	Myeloid cells survival	Mediates response to pro-survival cytokines	Kotzin et al., 2016

Table 2: LncRNAs reported in Myelodysplastic Syndrome.

	LncRNA	Stage associated	Mechanism	Associated MDS	References
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1	Xist	Early embryogenesis	Trigger X chromosome inactivation	Myeloproliferative neoplasm	Yildirim et al.,2013
2	HOTAIRM	Various stages of hematopoiesis	Transcriptional activation of genes involved in different lineages of hematopoiesis	Promyelocytic leukemia	Bhat et al., 2020
3	LUNAR1	T-ALL cell proliferation	Promotes IGF1R expression and IGF1R signalling	T-cell Acute Lymphoblastic Leukemia	Trimachi et al., 2014.
4	lncRNA-CRNDE	Myeloid Proliferation	Inhibition of apoptosis by targeting miRNAs and cell signalling pathways	Acute myeloid leukemia	Lu et al., 2020
5	RUNX1	HSC self-renewal and differentiation haematopoietic cell lineages	epigenetically regulates the RUNX1 via H3-K27 methylase Enhancer of zeste	Acute myeloid leukemia	Wang et al., 2014
6	MIR99AHG MIR100HG	Lineage commitment Erythroid progenitor cells	Regulation of lineage commitment of MEP cells	megakaryoblastic leukemia	Emmrich et al., 2014
7	NEAT1	Mononuclear cells differentiation	Induces PML-RAR α fusion protein.	Acute promyelocytic leukemia	Zeng et al., 2014.

Figure Legends

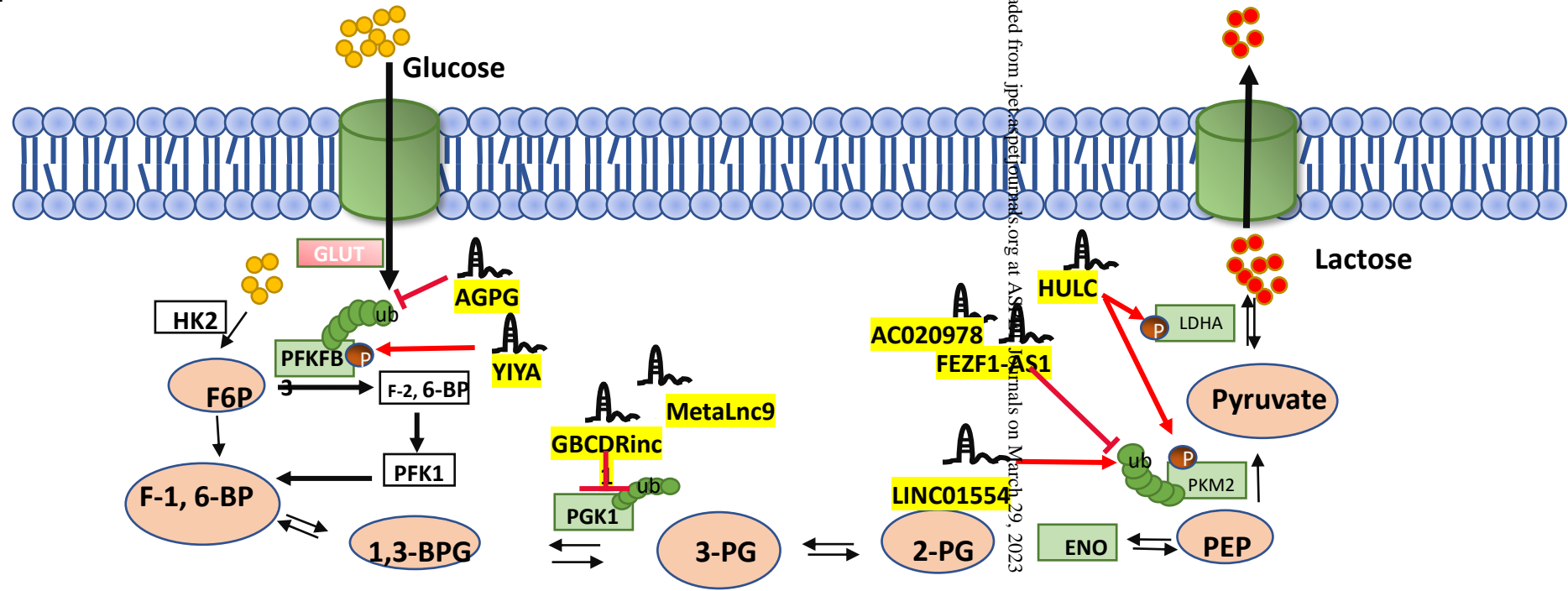
Figure 1: Alteration of of Glucose metabolism by LncRNAs via: A) Enzymes; Different LncRNAs mediate phosphorylation and ubiquitination of critical metabolic enzymes associated with the metabolism of glucose. **B) Transcription Factors:** Aerobic glycolysis is under regulation of different LncRNAs through ubiquitination, hydroxylation and phosphorylation of associated transcriptional factors.

Figure 2: LncRNA mediated alteration of metabolism related signaling pathways. LncRNAs mediate modification of components of various signalling pathways; AMPK and PI3K/ AKT pathway through phosphorylation of various factors in the cascade. P53 and mTOR pathway through phosphorylation, acetylation and ubiquitination of different components leading to the metabolic regulation.

Figure 3: Overall illustration of lncRNA mediated regulation of metabolism. Schematic representation of various lncRNAs involved in regulation of carbohydrate, lipids and amino acid metabolism.

Figure 1

A



B

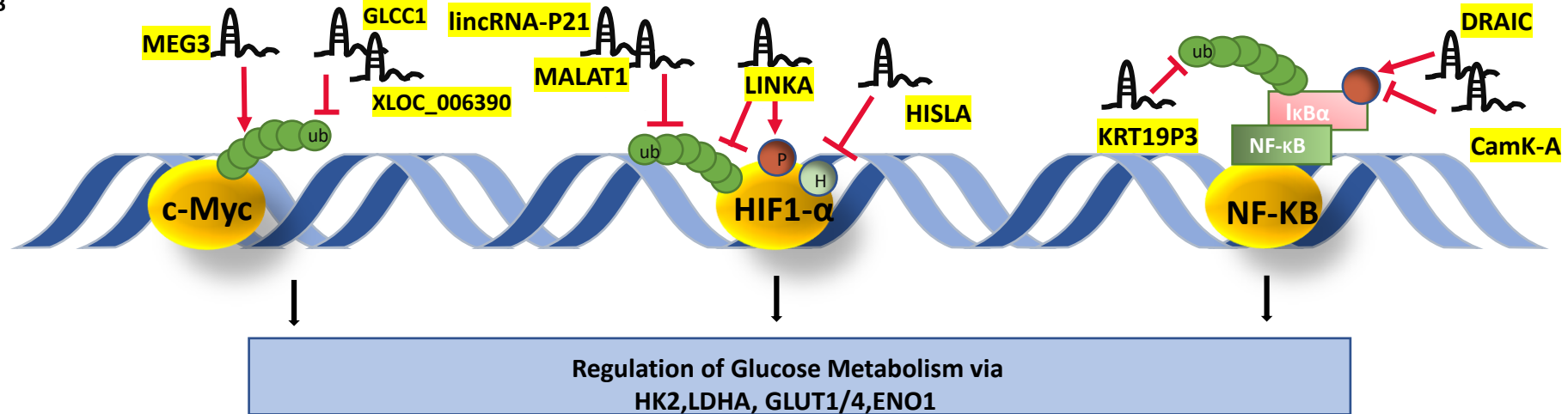


Figure 2

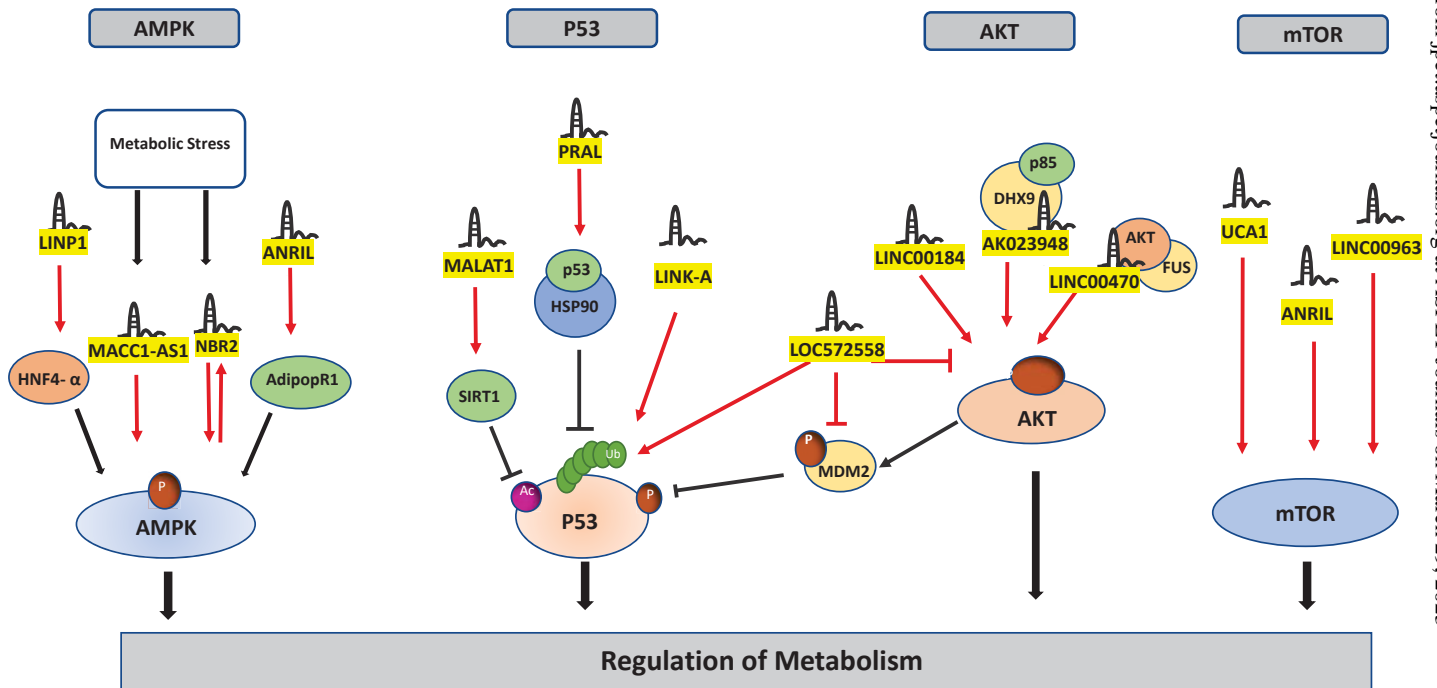


Figure 3

