Role of miRNAs and IncRNAs in hematopoietic stem cell differentiation

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ABSTRACT

Non-coding RNAs (ncRNAs) have diverse roles in the differentiation of hematopoietic cells. Among these transcripts, long ncRNAs (lncRNAs) and microRNAs (miRNAs) have especial contribution in this regard particularly by affecting levels of transcription factors that define differentiation of each lineage. miR-222, miR-10a, miR-126, miR-106, miR-10b, miR-17, miR-20, miR-146, miR-155, miR-223, miR-221, miR-92, miR-150, miR-126 and miR-142 are among miRNAs that partake in the differentiation of hematopoietic stem cells. Meanwhile, this process is controlled by a number of lncRNAs such as PU.1-AS, AlncRNA-EC7, EGO, HOTAIRM1, Fas-AS1, LincRNA-EPS and IncRNA-CSR. Manipulation of expression of these transcripts has functional significance in the treatment of cancers and in cell therapy. In this paper, we have provided a brief summary of the role of miRNAs and IncRNAs in the regulation of hematopoietic stem cells.

1. Introduction

Non-coding RNAs (ncRNAs) have diverse roles in the biologic processes. Compared with the mRNA-coding transcripts, ncRNA transcripts more abundant in the human genome [1]. Two groups of ncRNAs have attracted attention of researchers due to their regulatory roles on the expression of genes. These groups of transcripts are long ncRNAs (lncRNAs) and microRNAs (miRNAs) [1]. In addition to acting as enhancers of transcription, lncRNAs can function as signals, decoys, scaffold transcripts and guide transcripts to directly regulate gene expression or recruit other regulatory molecules to alter gene expression [2]. The regulatory role of miRNAs on gene expression is exerted via their incorporation into the RNA-induced silencing complex (RISC). Subsequently, they can decrease expression of their targets. Based on the extent of similarity between the miRNA and target sequences, they degrade mRNA or inhibit its translation [3]. Both lncRNAs and miRNAs can regulate differentiation of hematopoietic cells [4,5]. Fig. 1 represents a summary of ncRNAs with critical roles in the differentiation of hematopoietic cells.

In the present review, we have provided a brief record of the role of miRNAs and IncRNAs in the regulation of HSCs.

2. miRNAs role in differentiation of HSCs

After assessment of miRNA signature in normal human bone marrow, Georgantas et al. have described expression of more than 30 miRNAs in CD34+ hematopoietic stem-progenitor cells (HSPCs). Subsequently, they integrated miRNA signature with mRNA profile of these cells and predicted miRNA-mRNA interaction data. Among the identified miRNAs has been miR-155, a miRNA that can regulate myelopoiesis and erythropoiesis. miR-155 has been shown to decrease both myeloid and erythroid colony construction from HSPCs [9]. Another pioneer study in this field has shown the role of various miRNA families in controlling HSC self-renewal and differentiation with HSCs being described by a certain miRNA profile in each differentiation phase. For instance, expressions of miR-125a, miR-125b, miR-155, miR-99a, miR-126, miR-196b, miR-130a, miR-542-5p, miR-181c, miR-93b and let7e have been significantly increased in long term-HSCs (LT-HSCS) [10]. Over-expression of miR-125b-5p, miR-126–3p and miR-155 in bone marrow cells has led to a competitive engraft enhancement in the bone marrow in all downstream lineages, while miR-196b, miR-181c, let7e and miR-542-5p have conferred an opposite effect. These observations have suggested the functional effect of these miRNAs in the regulation of HSC homeostasis instead of a certain role in differentiation to some specific phenotypes [10].

Using a high throughput combinatorial technique, Petriv et al. have...
assessed miRNA signature in 27 different cell populations and categorized these cells based on miRNA profile into six chief groups namely stem cell populations and multipotent progenitor cells, lymphoid cells, and four diverse principal classes of myeloid cells. They have reported alterations in the expressions of numerous miRNAs at distinctive nodes. Notably, miR-125b, miR-196a/b, miR-130a, let-7d, miR-148b and miR-351 have been the utmost differentially expressed miRNAs between stem cell populations and progenitor cells compared with the more mature cells [11].

Chen et al. have reported specific expression of three miRNAs in the hematopoietic cells. They have also demonstrated dynamic regulation of their expression throughout early hematopoiesis and lineage definition. Among these small transcripts, miR-181 has been mostly expressed in the B-lymphoid cells, and its expression in HSPCs has resulted in the preferential expansion of B-lineage cells [12]. miR-23a cluster is also involved in the regulation of lymphopoiesis since deficiency of this cluster in mice has resulted in the enhancement of B lymphopoiesis at the cost of myelopoiesis. However, HSPCs have not been altered. Concomitant deletion of mirn23a and mirn23b in adult bone marrow has also twisted HSPC differentiation to B cells at the cost of myeloid cells. Notably, double-knockout of these miRNAs has reduced bone marrow cellularity and diminished HSC and HSPC populations, demonstrating the exacerbation of the phenotype detected in mirn23a deficient mice [13]. On the other hand, miR-29a has a prominent role in controlling differentiation of myeloid lineage. This miRNA is over-expressed in early progenitors contributing in preservation of the undifferentiated status, whereas its expression has been decreased in the course of differentiation [14]. Therefore, forced over-expression of miR-29a in mice HSCs has conferred self-renewal aptitudes of myeloid precursors, enhancing myelopoiesis [14]. Another study has demonstrated the impact of miR-125b over-expression in bone marrow in induction of a myeloproliferative condition that might lead to myeloid leukemia [10].

Felli et al. have shown the role of miR-221 and miR-222 in reduction of proliferation of CD34+ progenitors and enhancement of differentiation of erythropoietic cells. These effects have been complemented by a significant reduction of kit protein. Besides, miR-221 and miR-222 treated CD34+ cells had lower engraftment capability and impaired stem cell activity upon transplantation in NOD-SCID animals. Taken together, under-expression of miR-221 and miR-222 increases kit protein synthesis, therefore resulting in the development of early erythroblastic cells [15]. Garzon et al. A high throughput expression profiling of CD34+-derived megakaryocytes has shown under-expression of miR-10a, miR-126, miR-106, miR-10b, miR-17 and miR-20. miR-130a has been shown to alter expression of MAFB, a transcription factor which stimulates expression of platelet-related protein GPIIb. Besides, miR-10a reduces expression of HOXA1. Evaluation of miRNA signature in the megakaryoblastic leukemic cells and in vitro differentiated megakaryocytes has demonstrated over-expression of miR-101, miR-126, miR-99a, miR-135, and miR-20 in the former cells [16]. Fazi et al. have uncovered the role of miR-223, NFI-A and C/EBPα in the regulation of differentiation of human granulocytes. They have also demonstrated a competition between NFI-A and C/EBPα for binding with promoter of miR-223. While NFI-A retains miR-223 expression low, C/EBPα enhances miR-223 expression after induction of cell differentiation by retinoic acid. Therefore, miR-223 participates in the process of granulopoiesis. It also down-regulates NFI-A expression to further mediate gene reprogramming in the granulocyte lineage [17]. miR-150 is among miRNAs with specific expression in the hematopoietic cells. This miRNA has been shown to be predominantly expressed in the lymph nodes and spleen, being over-expressed in the course of development of mature T and B cells with a sharp up-regulation in the immature B cell phase. Forced up-regulation of miR-150 in HPSCs has impaired the development of mature B cells, with no significant effects.
The number of HSCs has been displayed governing numerous stages of lymphocyte expansion. miR-150 precisely [18]. miR-150 has been predicted to target c-Myb, a transcription factor scripts that have critical roles in development of pre- and pro-B cells lineage. Taken together, miR-150 possibly inhibits expression of tran

### Table 1

| lncRNA          | Cell lineage | Function                                      | Reference |
|-----------------|--------------|-----------------------------------------------|-----------|
| miR-181         | HSCs/HPCs & Pro-B lymphocyte | Attach to CXCR4 and induces B-lymphocyte differentiation | [9,12]    |
| miR-222         | HSCs/HPCs    | Attach to FOS, ELK1 and blocks erythropoiesis   | [9,15]    |
| miR-10a, 126, 106, 10b, 17, 20 | megakaryocyte | Regulate megakaryocyte differentiation         | [16]      |
| miR-146         | T helper lymphocyte | Block differentiation of T helper lymphocyte | [9]       |
| miR-155         | HSCs/HPCs    | Attaches to CREBBP, MEF1, PU1, LAGTR2 and FOS and blocks differentiation | [9]       |
| miR-223         | HSCs/HPCs & Pro-B cell | Attach to NFI-A and increase granulopoiesis and induces T-lymphocyte lineage | [9,12,17,21] |
| miR-221         | HSCs/HPCs    | Attaches to Fos and c-kit and blocks erythropoiesis | [9,15]    |
| miR-92          | HSCs/HPCs    | Attach to KLF | [9]       |
| miR-150         | B cell and T lymphocyte | Downregulates C-MYB and control proliferation and differentiation of B cell and T lymphocyte | [18,19]   |
| miR-126         | HSCs/HPCs    | Decrease self-renewal and enhance mobilization of HSCs | [22,23]   |
| miR-142         | Pro-B lymphocyte | Induces T lymphocyte lineage | [12]      |
| miR-125a        | HSCs/HPCs    | Was increased in HSC and decreases apoptosis by targeting the Bak1. | [24]      |
| miR-29a         | HSCs/HPCs    | Affects common myeloid progenitors and granulocyte macrophage progenitors; Induces myeloid biased differentiation | [25]      |
| miR-133         | MSC           | Blocks MSC differentiation | [26]      |
| miR-196b        | HSCs/HPCs    | Has a negative effect on the engrafment of bone marrow | [27]      |
| miR-29a         | HSCs/HPCs    | Downregulates actin-binding protein; regulate early HSCs; Was highly expressed in HSCs/ HPCs | [25,28]   |
| miR-130         | HSCs/HPCs    | Was enriched in long term HSC; increases self-renewal | [27]      |
| miR-34a         | Pro-B lymphocyte | Inhibition of Fosp1; regulation of pre-B to pre-B by miR-34a | [29]      |
| miR-299-5p      | Megakaryocyte | Modulates megakaryocyte differentiation | [30]      |
| miR-23a/b       | HSCs/HPCs    | Proper proliferation and differentiation of HSCs/HPCs | [31]      |
| miR-15/16       | HSCs/HPCs    | Erythroid differentiation | [32]      |
| miR-21          | HSCs/HPCs    | Myelopoiesis | [33]      |
| miR-22          | HSCs/HPCs    | HSC maintenance | [34]      |
| miR-145/146a    | HSCs/HPCs    | Involved in megakaryopoiesis | [35]      |
| miR-28          | HSCs/HPCs    | Prevents megakaryocyte differentiation | [36]      |
| miR-27a         | megakaryocyte | Attaches to RUNX1 and decreases its levels | [37]      |
| miR-144, 451    | HSCs/HPCs    | Erythroid homeostasis | [38,39]   |
| miR-451         | HSCs/HPCs    | Erythroid differentiation | [40]      |

Table 1 sums up the results of investigations that appraised the role of miRNAs in HSC differentiation.

### 3. LncRNAs role in differentiation of HSCs

The function of LncRNAs in the differentiation of HSPCs has been investigated in numerous studies. LncRNAs can regulate expression of transcription factors which regulate hematopoiesis. Luo et al. have assessed LncRNA profile of HSCs by high throughput sequencing and recognized more than 300 unannotated LncRNAs. Comparison of expression of these LncRNAs in differentiated lineages has led to identification of 159 HSC-enriched LncRNAs (LncHSCs). Silencing of two LncHSCs has conferred specific impact on HSC self-renewal and lineage commitment possibly through modulation of principal hematopoietic transcription factor, namely E2A [41]. Expression of the transcription factor PU.1 has been controlled by an antisense LncRNA which is transcribed from the same locus namely PU.1-AS. This LncRNA has been shown to suppress PU.1 expression through regulating its translation [42]. Notably, others have described that high level of PU.1 is required for the development of macrophage compared with neutrophils [43]. Therefore, fine-tuning of PU.1 expression by its antisense transcript might define the lineage development. Paralark et al. have identified more than 1000 polyadenylated LncRNAs expressed in erythroblastic cells, megakaryocytes, and megakaryocyte-erythroid precursor cells of mouse, and about 600 LncRNAs in human erythroblasts. The majority of these LncRNAs have been shown to be controlled by chief transcription factors including GATA1 and TAL1 [44]. Wagner et al. have reported over-expression of EGO in human bone marrow and in mature eosinophilic cells. This LncRNA has been shown to be transcribed from an intronic region of the Ifpr1 gene. Stimulation of CD34+ hematopoietic progenitors with IL-5 has enhanced expression of EGO. EGO knock down has reduced expression of MBP and EDN in developing CD34+ hematopoietic progenitors [45]. HOTAIR1M1 is another antisense transcript originating from the same CpG island that is around the initiation site of HOX1 gene. HOTAIR1M1 is the most noticeable intergenic RNA which is over-expressed in the course of induced granulocytic differentiation of hematopoietic cells. This LncRNA contributes to the myelo-poiesis cia regulation of HOXA cluster [46]. Expression of Fas-AS1 has also been induced in the course of erythropoiesis via the activity of important erythroid transcription factors GATA-1 and KLF1. This LncRNA is inhibited by NF-κB. Besides, up-regulation of Fas-AS1 in HSPCs-originated erythroblasts has decreased surface levels of Fas and induced defense against Fas-mediated apoptosis [47]. LincRNA-EPS has a role in the erythroid differentiation as its suppression has blocked erythroid differentiation and enhanced apoptosis. This LncRNA has been shown to suppress expression of the pro-apoptotic gene Pycard [48]. Linc-MAF-4 is a chromatin-related LncRNA with specific expression in T helper 1 cells. Its expression has been inversely correlated with expression of the T helper 2-associated transcription factor MAF. Linc-MAF-4 silencing has twisted T cell differentiation to the T helper 2 route [49]. H19 is another LncRNA with critical role in the emergence of HSCs. Absence of H19 in the early developmental stages has suppressed endothelial-to-hematopoietic transition. Besides, H19 deficiency in pre-HSCs has resulted in promoter hypermethylation and simultaneous down-regulation of numerous important hematopoietic transcription factors, such as Runx1 and Spp1. The detected defects in the hematopoietic system following H19 deficiency has been attributed to the enhanced function of S-adenosylhomocysteine hydrolase, a controller of DNA methylation [50]. An animal study has indicated the role of Xist RNA in the suppression of hematologic cancer as deletion of this lncRNA in the blood of mice has resulted in initiation of an extremely aggressive myeloproliferative condition being described by a number of characteristics including myelofibrosis and leukemia. Deficiency of this
Table 2
Influence of lncRNAs in hematopoietic stem cell differentiation.

| lncRNA        | Full name                                  | Cell lineage          | Function                                                                 |
|--------------|--------------------------------------------|-----------------------|--------------------------------------------------------------------------|
| PU.1-AS      | *                                          | Monocytes; macrophages| Regulates translation of PU.1 in HSCs differentiation                    |
| AlncRNA-EC7  | *                                          | erythrocyte           | Downregulates expression of BAND3 and inhibit maturation of erythrocyte  |
| AlncRNA-EC3  | *                                          | erythrocyte           | Modulate red blood cell (RBC) formation                                  |
| ShlncRNA-EC6 | *                                          | erythrocyte           | Promotes red blood cell maturation                                       |
| EGO          | Eosinophil granule ontogeny                | Leukocyte            | Modulates MBP in the development of HSCs CD34+                         |
| HOTAIR1M1    | HOX antisense intergenic RNA myeloid 1    | Myeloid progenitors   | Modulation of granulocytic differentiation genes and the neighboring 3' |
| HotaiRM1     | HOX antisense intergenic RNA myeloid 1    | Leukocyte            | HOXA genes in HSCs                                                      |
| Fas-AS1 (or SaF) | Eosinophil granule ontogeny               | erythrocyte           | During erythropoiesis some erythroid transcription factors such as       |
| LincRNA-EPS  | LincRNA erythroid prosurvival             | erythrocyte           | Downregulates expression of PyCARD and enhance erythropoiesis          |
| 8mp          | *                                          | Th17 CD4+ T           | Change the expression of RORgt transcription factor in the Th17         |
| IncRNA-CSR   | LncRNA-class switch DNA recombination      | B lymphocyte         | Regulates function of lymphocyte B and antibody secretion               |
| NeST (Tmevpg1 or IFNG-AS1) | Eosinophil granule ontogeny                | Th1 CD4+ T           | In Th1 lymphocyte, NeST binds to WDR5 and changes histone 3 methyl        |
| Linc-MAF-4   | *                                          | Th1 CD4+ T           | Changes T- lymphocyte differentiation toward Th2 by the change in      |
| Linc-Ccr2-5′AS | Eosinophil granule ontogeny                | Th2 CD4+ T           | Changes the expression of specific genes that modulate the migration of |
| GATA3-AS1    | GATA3-Antisense1                           | Th2 CD4+ T           | Regulate secretion of IFN-γ and TNF-a and modify function of lymphocytes |
| Th2-LCR      | TH2-locus control region                   | CD8+ T               | Changes the secretion of cytokines in Th2- lymphocyte                  |
| LncRNA-CD244 | *                                          | CD8+ T               | Changes expression of IFN-γ and TNF-a and modify function of lymphocytes |
| NRON         | noncoding (RNA) repressor of NFAT          | T lymphocyte         | Regulator of NFAT1 transcription factor                                 |
| BIC          | B-lymphocyte integration cluster          | B lymphocyte         | Regulator of B- lymphocyte differentiation                              |
| Hicr         | Foxp3 long intergenic non-coding RNA       | Treg                 | Modulates Treg functions, strength antiviral responses                   |
| Lnc-EGFR     | Lnc-epidermal growth factor receptor;      | Treg                 | Changes the differentiation of Treg and induced immunosuppression        |
| IncRNA-Cox2  | *                                          | B lymphocyte         | Regulate secretion of IFNs                                              |
| GRNDE        | Colorectal neoplasia differentially expressed | B lymphocyte         | Regulates function of primarily pre-B1, pre-B2, and centroblasts         |
| NeST         | *                                          | T lymphocyte         | Regulates immune function of T lymphocyte                              |
| LinR-Ccr2-5′AS | Eosinophil granule ontogeny                | T lymphocyte         | Regulation of Ccr1, Ccr2, Ccr3, and Ccr5 genes                          |
| Thy-nrct1    | *                                          | Thymic T             | Destruction of MAFAP4 and modulate proliferation and differentiation of |
| TMEVPG1      | *                                          | T lymphocyte         | Changes the expression of IFN-γ gene and modify proliferation and       |
|              |                                             |                      | differentiation of Th- lymphocyte                                      |
| H19          | *                                          | HSC                  | Preserves long-term HSC quiescence and self-renewal                     |
| EGO          | Eosinophil granule ontogeny                | Eosinophils          | Regulates eosinophils differentiation and maturation of eosinophils      |
| HotaiRM1     | Myeloid progenitors                         | Eosinophils          | Suppression of HoxA1 and HoxA4 genes in myeloid progenitors             |
| LincRNA-EPS  | Erythrocyte                                 | Erythrocyte          | Elevates apoptosis                                                      |
| DLEU2; elncRNAEC1,3; lincRNAC2,4,5,6,9; alncRNAEC1,2,3,7 | Erythrocyte          | Regulates erythrocyte maturation                                       |
| DBK1-Gt2 Locus-derived lncRNAs | *                                          | HSC                  | lncRNAs inhibit PI3K-mTOR signaling, resulted in maintain HSC self-    |
| IncRNA Evx1  | *                                          | Pluripotent cells     | Binds to chromatin and increases EVX1 transcription; regulate gene expression, proliferation, and differentiation. |
| IncRNA H19   | *                                          | Embryonic HSC         | Participates in endothelial-to-HSC transition by regulation of           |
| IncHSC-1/2   | Hematopoietic stem cell                    | HSC                  | Controls long-term HSC quiescence and self-renewal                      |
| IncRNA Xist  | *                                          | HSC                  | Regulates HSC quiescence and self-renewal                               |
| IncRNA DC    | Dendritic cells                            | DC                   | Regulates DC differentiation by increasing phosphorylation and nuclear   |
| IncRNA Letha | *                                          | Macrophage/DC         | Partakes in innate immune response; regulate and limit inflammation     |
| IncRNA-Cox2  | *                                          | Macrophage/DC         | Regulates homeostasis and activation of inflammatory reaction;         |
| IncRNA-THRIL | TNF- and hnRNPL-related immunoregulatory | Macrophage/DC         | necessary for expression of inflammatory cytokines                      |
| IncRNA PACER | p50-associated COX-2 extragenic RNA         | Macrophage/DC         | Has an important role in decay molecule in the NF-kB signaling pathway. |
| IncRNA-NKILA | NF-kB-interacting lncRNA                   | Macrophage/DC         |                                                                           |

(continued on next page)
incRNA in HSCs has resulted in abnormal maturation and age-dependent defects [51]. Dlk1-Gtl2 is another ncRNA with an important impact in inhibition of LT-HSCs. This locus contains a miRNA mega-cluster locus that inhibits the whole PI3K-mTOR pathway, suppressing mitochondrial synthetic processes and metabolic function and protecting LT-HSCs from reactive oxygen species (ROS) [52]. Table 2 reviews the investigations that assessed the role of IncRNAs in HSC differentiation.

### 4. Discussion

NcRNAs have critical regulatory functions in cell proliferation, programmed cell death, organ development, and differentiation. Both miRNAs and IncRNAs are important elements of the molecular pathways that regulate hematopoiesis. A number of these transcripts influence the expression of transcription factors that regulate differentiation of certain lines of hematopoietic cells. Few antisense transcripts have been identified that modulate expression of transcription factors in cfs. Identification of other overlapping complementary transcripts with regulatory roles on the expression of transcription factors would facilitate clarification of molecular mechanisms of HSPCs differentiation. The majority of IncRNAs in the hematopoietic cells which have been identified through high throughput methods are unannotated, highlighting the prospect for novel discovery via investigating specialized cell kinds [44]. Several of IncRNAs which are extensively expressed during erythropoiesis have been shown to be controlled by critical erythroid transcription factors such as GATA1, TAL1, or KLF1 [53], revealing the mutual interactions between transcription factors and IncRNAs.

Notably, a vast body of literature about the contribution of ncRNAs in the differentiation of hematopoietic cells has come from the animal studies. Although these studies have provided invaluable clues about this subject, verification of their results in the human cells is a necessary step for implementations of these results in the clinical settings. Few comparative studies have demonstrated lack of conservation of hematopoietic cell-associated IncRNAs between mammalian species [44], signifying the importance of assessment of expression of these transcripts in each species.

Notably, exosomes originated from HSPCs have been shown to encompass ncRNAs, therefore transferring these transcripts to the recipient cells to modulate their function [23]. Exosome-mediated transfer of ncRNAs represents an important way of modulation of bone marrow microenvironment.

High throughput sequencing methods have shown significant differences in the miRNA profile between hematopoietic and non-hematopoietic cells. In addition, miRNA signature is slightly different in hematopoietic cells. Few antisense transcripts have been shown to be specifically expressed in mature hematopoietic cells, but not their progenitors [19], thus regulating certain stages of development of hematopoietic cells. It is possible that miRNAs regulate the expression of only limited numbers of crucial target proteins in specific cellular settings [19]. Besides, miRNAs have a cell-stage-specific regulatory role in HSCs through which they control the stem cell bulk [20].

Manipulation of expression of these transcripts has functional significance in the treatment of cancers and in cell therapy. In vitro studies have shown the effects of silencing or over-expression of a number of ncRNAs in changing the differentiation process of hematopoietic cells, suggesting these methods as putative enrichment strategies before bone marrow transplantation.

### Declaration of competing interest

The authors declare they have no conflict of interest.

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### References

1. M.A. Diamantopoulos, P. Tsialakakis, A. Scorilas, Non-coding RNAs: the riddle of the transcriptome and their perspectives in cancer, Ann. Transl. Med. 6 (12) (2018) 241.
2. Y. Fang, M.J. Fullwood, Roles, functions, and mechanisms of long non-coding RNAs in cancer, Dev. Reprod. Biol. 14 (1) (2016) 42–54.
3. L.-A. Macfarlane, P.R. Murphy, MicroRNA: biogenesis, function and role in cancer, Curr. Genom. 11 (7) (2010) 537–561.
4. W. Li, Y. Ren, Y. Si, F. Wang, J. Yu, Long non-coding RNAs in hematopoietic regulation, Cell Regen. 7 (2) (2018) 27–32.
5. U. Bissels, A. Boxio, W. Wagner, MicroRNAs are shaping the hematopoietic landscape, Haematologica 97 (2) (2012) 160–167.
6. M. Luo, M. Jeong, D. Sui, H.J. Park, B.A. Rodriguez, Z. Xiu, et al., Long non-coding RNAs control hematopoietic stem cell function, Cell stem cell 16 (4) (2015) 426–438.
7. X. Tian, J. Tian, X. Tang, J. Ma, S. Wang, Long non-coding RNAs in the regulation of myeloid cells, J. Hematol. Oncol. 9 (1) (2016) 99.
8. H. Mayani, The regulation of hematopoietic stem cell populations, F1000Research 5 (2016).
9. R.W. Georgetrant, R. Hildreth, S. Morisot, J. Alder, C.g Liu, S. Heimfeld, et al., CD34+ hematopoietic stem progenitor cell microRNA expression and function: a circuit diagram of differentiation control, Proc. Natl. Acad. Sci. Unit. States Am. 104 (8) (2007) 2750–2755.
10. R.M. O’Connell, A.A. Chaudhuri, D.S. Rao, W.S. Gibson, A.B. Balanz, D. Baltimore, MicroRNAs enriched in hematopoietic stem cells differentially regulate long-term hematopoietic output, Proc. Natl. Acad. Sci. U. S. A. 107 (32) (2010) 14235–14240.
11. G.O. Cremel, F. Kuchenbauer, A.D. Delaney, V. Lecault, A. White, D. Kent, et al., Comprehensive microRNA expression profiling of the hematopoietic hierarchy, Proc. Natl. Acad. Sci. U. S. A. 107 (35) (2010) 15443–15448.
12. C.-Z. Chen, L. Li, H.F. Lodish, D.P. Bartel, MicroRNAs modulate hematopoietic lineage differentiation, science 303 (2004) 83–86, 5654.
13. J.J. Karkewich, A. Boucher, N. Kleinfeldstein, R. Basker, R. Kapur, R. Dahl, The mirn23a and mirn23b microRNA clusters are necessary for proper hematopoietic progenitor cell production and differentiation, Exp. Hematol. 59 (2018) 14–29.
14. Y.C. Han, C.Y. Park, G. Bhagat, J. Zhang, Y. Wang, J.B. Fan, et al., microRNA-29a induces aberrant self-renewal capacity in hematopoietic progenitors, biased
myeloid development, and acute myeloid leukemia, J. Exp. Med. 207 (3) (2010) 475–489.

[15] N. Kanai, L. Fontana, E. Pelosi, R. Botti, D. Bonci, F. Facchiano, et al., MicroRNAs 221 and 222 inhibit normal erythropoiesis and erythroleukemic cell growth via a kit receptor down-modulation, Proc. Natl. Acad. Sci. Unit. States Am. 102 (50) (2005) 18081–18086.

[16] R. Garzon, P. Picciotti, T. Palumbo, R. Iuliano, A. Ciriminno, R. Apollani, et al., MicroRNA fingerprints during human megakaryocytosis, Proc. Natl. Acad. Sci. Unit. States Am. 103 (13) (2006) 5078–5083.

[17] F. Fazi, A. Rosa, A. Fatica, V. Gelmetti, M. Marchis, C. Nervi, et al., A minicircuitry comprised of microRNA-221 and transcription factors NFI-A and C/EBP alpha regulates human granulopoiesis, Cell 123 (5) (2005) 819–831.

[18] B. Zhou, S. Wang, C. Mayr, D.P. Bartel, H.F. Lodish, miR-150, a microRNA that regulates kit receptor down-modulation, Proc. Natl. Acad. Sci. Unit. States Am. 102 (50) (2005) 18081–18086.

[19] V. Niazi, B. Parseh, M. Ahani, F. Karami, S. Gilanchi, K. Atarodi, et al., The interplay between miR-27a and Runx1 during megakaryopoiesis, Proc. Natl. Acad. Sci. Unit. States Am. 104 (17) (2007) 7080–7085.

[20] S. Guo, J. Lu, R. Schlangner, H. Zhang, J.Y. Wang, M.C. Fox, et al., MicroRNA miR-221 and 222 inhibit normal erythropoiesis and erythroleukemic cell growth via a kit receptor down-modulation, Proc. Natl. Acad. Sci. Unit. States Am. 103 (13) (2006) 5078–5083.

[21] S. Ghafouri-Fard, V. Niazi, M. Taheri, Role of miRNAs in conveying message of the forkhead box transcription factor Foxp1, Immunity 33 (1) (2010) 48–58.

[22] O. Salvucci, K. Jiang, P. Gasperini, D. Maric, J. Zhu, S. Sakakibara, et al., Fas-antisense long noncoding RNA is differentially expressed during maturation of human erythrocytes and confers resistance to Fas-mediated cell death, Blood Cell Mol. Dis. 58 (2016) 57–66.

[23] W. Hu, B. Yuan, J. Figgay, H.F. Lodish, Long noncoding RNA-mediated anti-apoptotic activity in human erythroid terminal differentiation, Genes Dev. 25 (2011) 2573–2578.

[24] O. Pianzani, G. Rossetti, I. Panzeri, A. Aringoni, R.J. Bonnal, S. Curti, et al., The long intergenic noncoding RNA landscape of human lymphocytes highlights the role of T cell differentiation by line-MAF-4, Nat. Immunol. 16 (3) (2015) 318.

[25] J. Zhou, J. Xu, L. Zhang, S. Liu, Y. Ma, X. Wen, et al., Combined single-cell profiling of IncRNAs and functional screening reveals that H19 is pivotal for embryonic hematopoietic stem cell development, Cell Stem Cell 24 (2) (2019) 285–298 e5.

[26] R. Dahl, J.C. Walsh, D. Lancki, P. Laslo, S.R. Iyer, H. Singh, et al., Regulation of the forkhead box transcription factor Foxp1 during lymphocyte development, Cell 152 (4) (2013) 743–755.

[27] A.K. Ebralidze, F.C. Guibal, U. Steidl, P. Zhang, S. Lee, B. Bartholdy, et al., Ego, a novel, noncoding RNA gene, regulates eosinophil granulocyte protein transcript expression, Blood 109 (12) (2007) 5191–5198.

[28] X. Zhang, Z. Lian, C. Padbin, M.B. Gerstein, J. Rozovskiy, M. Snyder, et al., A myeloid-associated regulatory intergenic noncoding RNA transcript within the human HOXA cluster, Blood, The Journal of the American Society of Hematology 113 (11) (2009) 2526–2534.

[29] X. Jiang, C. Hu, S. Arnovitz, J. Bugno, M. Yu, Z. Zuo, et al., miR-22 has a potent effect on erythropoiesis and erythroleukemia, Leuk. Lymphoma 51 (4) (2010) 694–698.

[30] X. Zhang, S.M. Weissman, P.E. Newburger, Long intergenic non-coding RNA landscape of human lymphocytes highlights the role of T cell differentiation by line-MAF-4, Nat. Immunol. 16 (3) (2015) 318.

[31] X. Zhang, Z. Lian, C. Padbin, M.B. Gerstein, J. Rozovskiy, M. Snyder, et al., A myeloid-associated regulatory intergenic noncoding RNA transcript within the human HOXA cluster, Blood, The Journal of the American Society of Hematology 113 (11) (2009) 2526–2534.

[32] R. Dahl, J.C. Walsh, D. Lancki, P. Laslo, S.R. Iyer, H. Singh, et al., Regulation of the forkhead box transcription factor Foxp1 during lymphocyte development, Cell 152 (4) (2013) 743–755.

[33] A.K. Ebralidze, F.C. Guibal, U. Steidl, P. Zhang, S. Lee, B. Bartholdy, et al., Ego, a novel, noncoding RNA gene, regulates eosinophil granulocyte protein transcript expression, Blood 109 (12) (2007) 5191–5198.

[34] X. Zhang, Z. Lian, C. Padbin, M.B. Gerstein, J. Rozovskiy, M. Snyder, et al., A myeloid-associated regulatory intergenic noncoding RNA transcript within the human HOXA cluster, Blood, The Journal of the American Society of Hematology 113 (11) (2009) 2526–2534.
[66] H. Zhang, C.E. Nestor, S. Zhao, A. Lentini, B. Bohle, M. Benson, et al., Profiling of human CD4+ T-cell subsets identifies the TH2-specific noncoding RNA GATA3-AS1. J. Allergy Clin. Immunol. 132 (4) (2013) 1095–1100.

[67] C.F. Spurlock, J.T. Tonberg, J.Y. Guo, S.P. Collier, P.S. Crooke, T.M. Aune, Expression and functions of long noncoding RNAs during human T helper cell differentiation, Nat. Commun. 6 (1) (2015) 1–12.

[68] V. Schlaphoff, S. Lunemann, P.V. Suneetha, J. Jaroszewicz, J. Grabowski, J. Dietz, et al., Dual function of the NK cell receptor 2B4 (CD244) in the regulation of HCV-specific CD8+ T cells, Proc. Natl. Acad. Sci. Unit. States Am. 112 (29) (2015) E3883–E3892.

[69] S. Sharma, G.M. Findlay, H.S. Bandukwala, S. Oberdoerffer, B. Baust, Z. Li, et al., Regulation of the MIR155 host gene in mature human dendritic cells, Sci. Signal. 3 (2010) ra8.

[70] S. Ghafouri-Fard et al., A candidate gene for \( T \)-mevpg1, Proc. Natl. Acad. Sci. Unit. States Am. 105 (2008) 10053–10058.

[71] P.S. Eis, W. Tam, L. Sun, A. Chadburn, Z. Li, M.F. Gomez, et al., Accumulation of long noncoding RNA derived from CD244 signaling epigenetically controls CD8+ T-cell immune responses in tuberculosis infection, Proc. Natl. Acad. Sci. Unit. States Am. 112 (2015) 1–12.

[72] Y. Wang, H. Zhong, X. Xie, C.Y. Chen, X. Xie, D. Huang, L. Shen, et al., A long noncoding RNA mediates both activation and repression of immune response genes, Science 341 (2013) 789–792.

[73] T.S. Elton, H. Selemon, S.M. Elton, N.L. Parinandi, Regulation of the MIR155 host gene in physiological and pathological processes, Gene 532 (1) (2013) 1–12.

[74] G.A. Calin, C-g Liu, M. Ferracin, T. Hyslop, R. Spizzo, C. Sevignani, et al., Ultraconserved regions encoding ncRNAs are altered in human leukemias and carcinomas, Cancer Cell 12 (3) (2007) 215–229.

[75] H. Swallwell, J. Latimer, R.M. Haywood, M.A. Birch-Machin, Investigating the role of melanin in UVA-UVB-and hydrogen peroxide-induced cellular and mitochondrial ROS production and mitochondrial DNA damage in human melanoma cells, Free Radic. Biol. Med. 52 (3) (2012) 626–634.

[76] R. Ji, J. Tang, Y. Chen, L. Deng, J. Ji, Y. Xie, et al., The long noncoding RNA Inc-EGFR stimulates T-regulatory cells differentiation thus promoting hepatocellular carcinoma immune evasion, Nat. Commun. 8 (1) (2017) 1–15.

[77] S. Vigneau, P.-S. Rohrlich, M. Brahic, J.-F. Bureau, Tmevpg1, a candidate gene for \( T \)-mevpg1, PLoS Pathog. 7 (5) (2011), e1002045.

[78] T. Kino, D.E. Hurt, T. Ichijo, N. Nader, G.P. Chrousos, Noncoding RNA gas5 is a growth arrest and starvation-associated repressor of the glucocorticoid receptor, Sci. Signal. 3 (2010) ra8.

[79] M. Winkle, J. Kluiver, A. Diepstra, A. van den Berg, Emerging roles for long noncoding RNA Inc-BC controls human dendritic cell differentiation, Science 344 (2014) 310–313.

[80] S. Carpenter, D. Aiello, M.K. Atianand, E.P. Ricci, P. Gandhi, L.L. Hall, et al., A cytoplasmic NF-κB interacting long noncoding RNA blocks \( \alpha \)κB phosphorylation and suppresses breast cancer metastasis, Cancer Cell 23 (3) (2013) 370–381.

[81] S. Sun, B.C. Del Rosario, A. Szanto, Y. Ogawa, Y. Jeon, J.T. Lee, Jpx acts as Xist by evicting CTCF, Cell 153 (7) (2013) 1537–1551.

[82] C. Arriaga-Canon, Y. Fonseca-Guzmán, C. Valdes-Quezada, A. Arzate-Mejía, G. Guerrero, F. Recillas-Targa, A long non-coding RNA promotes full activation of adult gene expression in the chicken α-globin domain, Epigenetics 9 (1) (2014) 173–181.

[83] L. Sehgal, R. Mathur, F.K. Braun, J.F. Wise, Z. Berkova, S. Neelapu, et al., FAS-ligand (Fasl) is required for long-term survival and function of long noncoding RNA RNAs, Proc. Natl. Acad. Sci. Unit. States Am. 108 (2011) 11381–11386.

[84] A. Venkatraman, X.C. He, J.L. Thorvaldsen, R. Sugimura, J.M. Perry, F. Tao, et al., A long noncoding RNA promotes full activation of adult gene expression and lineage differentiation in pluripotent cells, Cell Stem Cell 18 (4) (2016) 637–642.

[85] J. Zhou, J. Xu, L. Zhang, S. Li, X. Wen, et al., Combined single-cell profiling of IncRNAs and functional screening reveals that H19 is pivotal for embryonic hematopoietic stem cell development, Cell Stem Cell 24 (2) (2019) 285–298.

[86] S. Sharma, G.M. Findlay, H.S. Bandukwala, S. Oberdoerffer, B. Baust, Z. Li, et al., Dephosphorylation of the nuclear factor of activated T cells (NFAT) transcription factor is regulated by an RNA-protein scaffold complex, Proc. Natl. Acad. Sci. Unit. States Am. 108 (28) (2011) 11381–11386.

[87] P.S. Eis, W. Tam, L. Sun, A. Chadburn, Z. Li, M.F. Gomez, et al., Accumulation of mir-155 and BIC RNA in human B cell lymphomas, Proc. Natl. Acad. Sci. Unit. States Am. 102 (10) (2005) 3627–3632.

[88] W. Tam, Identification and characterization of human BIC, a gene on chromosome 21 that encodes a noncoding RNA, Gene 274 (1–2) (2001) 157–167.

[89] T.S. Elton, H. Selemon, S.M. Elton, N.L. Parinandi, Regulation of the MIR155 host gene in physiological and pathological processes, Gene 532 (1) (2013) 1–12.

[90] G.A. Calin, C-g Liu, M. Ferracin, T. Hyslop, R. Spizzo, C. Sevignani, et al., Ultraconserved regions encoding ncRNAs are altered in human leukemias and carcinomas, Cancer Cell 12 (3) (2007) 215–229.

[91] H. Swallwell, J. Latimer, R.M. Haywood, M.A. Birch-Machin, Investigating the role of melanin in UVA-UVB-and hydrogen peroxide-induced cellular and mitochondrial ROS production and mitochondrial DNA damage in human melanoma cells, Free Radic. Biol. Med. 52 (3) (2012) 626–634.

[92] R. Ji, J. Tang, Y. Chen, L. Deng, J. Ji, Y. Xie, et al., The long noncoding RNA Inc-EGFR stimulates T-regulatory cells differentiation thus promoting hepatocellular carcinoma immune evasion, Nat. Commun. 8 (1) (2017) 1–15.

[93] S. Vigneau, P.-S. Rohrlich, M. Brahic, J.-F. Bureau, Tmevpg1, a candidate gene for \( T \)-mevpg1, PLoS Pathog. 7 (5) (2011), e1002045.