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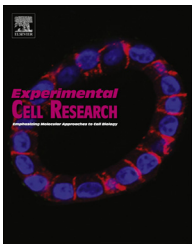

Review Article

microRNAs in hematopoiesis

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ABSTRACT

miRNAs have been implicated in all stages of hematopoiesis including maintenance of self-renewal of hematopoietic stem cells (HSCs) and differentiation into mature blood cells. Regulation by miRNAs is markedly intertwined with transcription factors. In this review, we highlight miRNAs shown to be important for HSC maintenance and lineage differentiation with focus on their interaction with transcription factors. We also pay attention to the diverse modes of miRNA regulation. Q2

Contents

Introduction

In hematopoiesis a limited number of multipotent hematopoietic stem cells differentiate into cells of all lineages that constitute the blood. This process of differentiation is well characterised and involves intermediate progenitors with decreasing self-renewal ability and increasing lineage commitment. Lineages are defined functionally and morphologically and lineage commitment is

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controlled by complex network of transcription factors that define specific gene expression patterns for every cell type. Hematopoiesis is extremely dynamic and responds to external stimuli, such as infection or injury, to favour differentiation or proliferation as necessary. Although multiple transcription factors have now been identified as important regulators of haematopoiesis, several microRNAs (miRNAs) have also been shown to be instrumental. In fact, the pathways of hematopoietic regulation involving miRNAs are often intertwined with transcription factor expression, both as targets and regulators.

Since their discovery in 1993, when miRNA Lin 4 repressing the Lin14 transcript was identified in *Caenorhabditis elegans* [1] more than 500 miRNAs have been identified, as listed in current databases, and the discovery of new miRNAs continues. miRNAs play an indispensable role in the formation and regeneration of multiple tissues including the hematopoietic system. Since the first reported study [2] progressively more information has accumulated on different aspects of miRNA dependent regulation of hematopoiesis, as a result, hundreds of putative miRNA targets have been identified, although for many their miRNA specific downregulation has not been experimentally confirmed. Evolutionarily, miRNA acquisition coincides with organismal complexity. It is hypothesised that the likelihood of novel miRNA formation is evolutionary easier than the emergence of novel protein coding genes, due to the ease at which RNAs form non-perfectly folded structures. Bioinformatic analyses reveal that ~80% of the affected transcripts share a short 6–8 nucleotides sequence in their 3′UTR which is complementary to the miRNA 'seed sequence' [3,4]. However, seed sequence-independent targets also exist, that can progressively better be predicted using improved algorithms.

Here, we provide a concise overview of miRNAs that have been documented to be relevant for the regulation of hematopoiesis. We first describe miRNAs involved in stem cell self-renewal and differentiation, and later focus on lineage specific miRNAs.

microRNAs that regulate self-renewal and differentiation in Hematopoietic Stem and Progenitor Cells

There are several miRNAs that appear to play a role in the most primitive hematopoietic compartments. The miR-125 family (consisting of three members, miR-125a, miR-125b1 and miR-125b2) is crucial for the maintenance of self-renewal and differentiation balance. As shown by several groups [5–7], members of the miR-125 family are highly expressed in Hematopoietic Stem and Progenitor Cells (HSPCs) and their expression decreases upon differentiation. Enforced expression of these miRNAs in HSPCs provides a proliferative advantage and skews differentiation towards the myeloid lineage [6,8]. Most recent data clearly show that all miR-125 family members promote increased stem cell self-renewal, but their exact targets are still unknown [8,9]. The phenotypes induced by miR-125s may be partially explained by the inhibition of apoptosis, as miR-125 targets several proapoptotic genes and genes involved in p53 pathway [10,11].

Many miRNAs reside at introns or within close proximity of protein coding genes and are often co-expressed with these genes [12,13]. A good example is the cluster of HOX genes, which encodes members of the miR-196 family. The HOX family of transcription factors is essential for the development and several HOX genes play an important role in hematopoiesis. In the mouse and human genomes miR-196b is positioned between HoxA9 and HoxA10 genes. Expression of miR-196b correlates with the expression pattern of HOXA9, and is highly expressed in HSPCs. MiR-196b regulates transcription of genes involved in cell survival and proliferation [13] but also maintains primitive cells at an undifferentiated state by repressing genes involved in differentiation [14]. The balanced expression of HOX genes is controlled by miR-196b which represses HOX genes that are normally upregulated during myeloid differentiation [14]. Other HOX genes involved in hematopoietic differentiation such as HOXA7 and HOXC8 were found to contain sequences complementary to the miR-196b seed sequence and have been confirmed as direct targets [14]. More evidence for miR-196b's role in suppressing differentiation comes from the observation that the transcriptional repressor Gfi1 required for myeloid differentiation downregulates miR-196b during myelopoiesis [15].

The miR-17–92 cluster is transcribed as a single non-coding RNA that is subsequently processed into seven mature miRNAs: miR-17-5p, miR-17-3p, miR-18a, miR-19a, miR-19b, miR-20a and miR-92a. Some miRNAs in the miR-17-92 cluster share expression patterns which is often the case for miRNA clusters as they are typically under control of the same promoter [16,17]. It has been shown that four of the eight miRNAs were higher expressed in hematopoietic stem cells compared to mature blood cells (miR-19a, miR-19b, miR-20a and miR-20b) [17] and overexpression of the entire cluster leads to stem cell expansion [18]. As expected, transcription factors targeted by miR-17-92 miRNAs are involved in differentiation and cell cycle regulation [19]. Yet overexpression of individual miRNAs induced various blood malignancies [18] highlighting the importance of the coordinated regulation of multiple targets involved in similar pathways for normal HSPC maintenance and self-renewal.

microRNAs involved in the regulation of erythropoiesis and megakaryopoiesis

Several miRNAs have been implicated in the regulation of erythropoiesis, among which are miR-15a, mir-24, miR-144 and miR-451 [20–22]. In order to enable erythroid differentiation, suppression of the self-renewal of HSPCs and a switch in gene expression to an erythroid signature pattern are imperative. Many of the miRNAs upregulated in erythroid cells target genes that normally promote myeloid lineage differentiation. These include GATA-1 and GATA-2, which are regulated by miRNA-24, miR-27a [21,23] and miR-451 [24]. Their interaction with PU.1 is a bifurcation point between myeloid and erythroid lineage commitment [25]. During erythropoiesis, GATA-1 progressively outcompetes GATA-2, and this particular GATA switch is mediated by miR-144 and miR-451 [20]. MiR-144 and miR-451 are both upregulated during erythroid differentiation and are transcribed as a single pri-miRNA transcript [20]. GATA-1 and GATA-2 are both able to bind upstream of miR-144/miR-451 but their ability to activate transcription differs: only GATA-1 activates transcription of miR-144/miR-451 pri-miRNA. In all reports GATA-1 is involved in a positive regulatory loop with the miRNAs that regulate the GATA-switch: GATA-1 activates transcription of miRNAs that repress GATA-2 and facilitate binding and transcriptional activation of erythroid genes by GATA-1. One of the suggested targets of miR-451 is c-Myc,

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a transcription factor and oncogene involved in HSC self-renewal. Consequently, its downregulation may allow for differentiation of progenitors into the erythroid lineage.

Interestingly, although initially believed to be primarily expressed in lymphocytes [26] miR-150 appears to also be important for megakaryopoiesis. One of its targets is c-myb that regulates transcription factors such as Kruppel Like Factor (Klf1) and Lmo2, which enhance erythropoiesis [27]. MiR-150 is upregulated during megakaryopoiesis but downregulated in erythropoiesis suggesting that its level of expression regulates cell lineage commitment towards differentiating megakaryocyte–erythrocyte progenitors.

microRNAs important for granulopoiesis

As discussed above, miRNAs can act in positive regulatory loops but additionally, miRNAs are also able to act in negative feedback regulatory pathways and this characteristic aids in the regulation of lineage commitment. An exemplary case is provided by miR-223 [28]. During granulopoiesis miR-223 acts in a negative cascade pathway to both repress the erythroid transcription factor NFI-A at the RNA level [29] while at the same time associating with Ying Yang 1 (YY1, a member of Polycomb Repressive Complex 1 (PRC1). This is quite an atypical association for miRNAs, as they rarely associate with proteins outside of the RISC complex. This provides a good example of how miRNA regulation can occur through binding with other proteins, to form complexes able to repress gene transcription. All of the above proteins bind in proximity of the NFI-A locus to repress its transcription [30] and collectively lead to enhanced granulopoiesis induced by C/EBP/α [28]. While miR-223 transcription is activated by the binding of either NFI-A or C/EBP/α to its promoter, C/EBP/α is the more potent activator. Both transcription factors compete for binding at the miR-223 promoter but they differ in their degree of transcriptional activation. During granulopoiesis, however, NFI-A is unable to compete with C/EBP/α resulting in increasing miR-223 transcription and sustained NFI-A repression [28].

microRNA expression in B and T lymphocytes

Regulation of hematopoiesis by miRNAs is spatio-temporally controlled, and the effect of a particular miRNA at different times or lineages may change. MiR-150, for example, is expressed in both mature B and T cells but enforced expression at the HSPCs level results in a block in B cell differentiation at the pro-B cell stage [31]. MiR-150 expression may enhance T cell development in the thymus not only through enhancing genes and pathways critical for T cell development (like the Notch Pathway [32]) but by suppressing alternative lineage differentiation, such as B cell differentiation, in progenitor cells.

OncomiRs in blood malignancies regulate HSC self-renewal

microRNAs overexpressed in hematopoietic malignancies are often associated with maintenance and self-renewal. Due to the tendency of these miRNAs to be involved in malignant transformations, they are termed oncomiRs. Several oncomiRs have already been identified including miR-22 [33], miR-221 [34], miR-155 [35] and miRNAs previously mentioned in this review such as miR-29a [36], miR-125 [10,37] and miR-126 [38] family members.

OncomiRs miR-29a, miR-125 and miR-126 family members are all regulators of hematopoietic stem cell self-renewal and their overexpression has been reported in patients with Acute Myeloid Leukaemias (AML) [36,37,39]. The acquisition of self-renewal by leukaemic stem cells is a typical component for the malignant properties of leukaemias. miR-29a enhances self-renewal through the repression of HBP1, an inhibitor of G1 to G2 cell cycle progression [36]. The miR-126 target PLK2 is also a cell cycle regulator involved in G2 checkpoint activation [40]. Moreover the antiapoptotic effect of miR-125b1 is associated with acute B-lymphoblastic leukaemia [41]. These miRNAs qualify as oncomiRs, they are involved in the cell cycle regulation through G1/G2 checkpoint activation [36,40] and repression of apoptotic genes like Bak-1, PLK3, or TP53INP1 [10].

The acquisition of self-renewal alone cannot account for the large variation in blood malignancies that develops upon dysregulation of miRNA expression. Rather, miRNAs also contribute to the development of blood malignancies through aberrant regulation of lineage-specific transcription factors. Specifically, C/EBP/α is able to activate PU.1 expression and both have been shown to be required for granulopoiesis and macrophage activation [42,43]. Downregulation of C/EBP/α by miR-155 is reported in AML cases [35]. In hematopoiesis, miR-155 is normally upregulated during inflammation, and its expression can be stimulated by LPS, resulting in expansion of the granulocyte and macrophage pool [35,44–46]. The requirement for immune stimulation for miR-155 upregulation appears to be lost in AML and the increased level of miR-155 is independent of antigen stimulus [35]. This leads to the downregulation of the transcription factors C/EBP/α and PU.1 allowing for uncontrolled expansion of immature myeloid cells [35].

Conclusion

In the last decade, after the first study on miRNA in hematopoiesis [2], a widespread role of miRNA-mediated regulation of all stages of hematopoiesis has been revealed. So far, dozens of different miRNAs have been reported in the literature as regulating either maintenance of HSCs or directing their differentiation into specific lineages (Table 1). These miRNAs comprise only a small part of all known miRNAs. It has become clear that many miRNAs are similar and are likely to exert redundant functions and display tissue specificity (especially members of the same miRNA family). The exact mode of action of each particular miRNA remains to be unravelled, but it has become evident that this is highly variable. The miRNAs covered in this review illustrate the diversity of regulatory pathways which involve miRNAs as crucial components, including the control of positive and negative regulatory feedback loops and, the regulation of transcription itself by associating with transcriptional repressors or activators.

While current research efforts have primarily focused on targets of miRNAs using computational prediction tools, many of these have yet to be experimentally validated. A sizeable proportion of the miRNA-mediated regulation of targets is not a complete repression of translation, but rather a fine-tuning of expression. It is possible, or even likely that the level of downregulation of many targets may not be detectable by current experimental tools. The overall picture is

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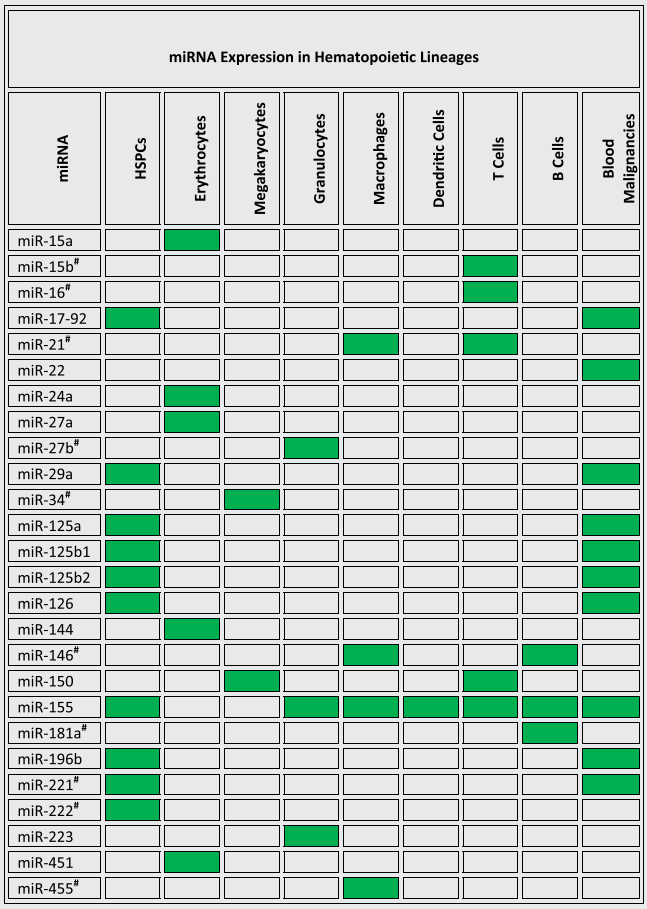
Table 1 – miRNA expression in hematopoietic lineages. Green boxes indicate lineage specific expression of miRNAs. # denotes miRNAs not covered in this review.



undoubtedly highly complex as many more targets may be affected by a single miRNA and many miRNAs may have overlapping or even opposing functions in different stages of lineage commitment (a good example is miR-150).

While most studies have focused on miRNA target identification, only few have investigated the regulators of miRNAs themselves. Further research on this is needed to improve our understanding of the regulatory network between miRNAs, transcription factors and miRNA expression regulators. More effort is required to build an integral view of the coordinated regulation of hematopoiesis by networks of transcription factors, microRNAs, epigenetic modifiers, signalling pathways, and how all these components mutually interplay. Progress in this field will also require improving the genomic tool box and computational algorithms to achieve the next level of understanding of the molecular basis of maintenance and differentiation of hematopoietic cells.

Authorship

Contribution: S.S.L., E.E.W., L.V.B., G.d.H.

Conflict-of-interest disclosure

The authors declare no competing financial interests.

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