MicroRNAs are shaping the hematopoietic landscape

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ABSTRACT

Hematopoiesis is regulated by microRNAs (miRNAs). These small regulatory RNAs are master regulators of developmental processes that modulate expression of several target genes post-transcriptionally. Various miRNAs are up-regulated at specific stages during hematopoietic development and the functional relevance of miRNAs has been proven at many different stages of lineage specification. Knockout of specific miRNAs can produce dramatic phenotypes leading to severe hematopoietic defects. Furthermore, several studies demonstrated that specific miRNAs are differentially expressed in hematopoietic stem cells. However, the emerging picture is extremely complex due to differences between species, cell type dependent variation in miRNA expression and differential expression of diverse target genes that are involved in various regulatory networks. There is also evidence that miRNAs play a role in cellular aging or in the inter-cellular crosstalk between hematopoietic cells and their microenvironment. The field is rapidly evolving due to new profiling tools and deep sequencing technology. The expression profiles of miRNAs are of diagnostic relevance for classification of different diseases. Recent reports on the generation of induced pluripotent stem cells with miRNAs have fuelled the hope that specific miRNAs and culture conditions facilitate directed differentiation or culture expansion of the hematopoietic stem cell pool. This review summarizes our current knowledge about miRNA expression in hematopoietic stem and progenitor cells, and their role in the hematopoietic stem cell niche.

Key words: hematopoiesis, microRNA, hematopoietic stem cell, mesenchymal stem cells, bone marrow microenvironment.

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miRNAs: master regulators of regulatory networks

MicroRNAs (miRNAs) are short non-coding RNAs of ~ 21 to 23 nucleotides in length that post-transcriptionally regulate mRNA expression. The first miRNAs were discovered in *Caenorhabditis elegans* in 1993[1,2] and only about ten years ago it was recognized that miRNAs represent a distinct class of biological regulators in many organisms including humans.[3,4] Since then the field has evolved rapidly. Currently, 1,424 different human miRNAs are listed in the miRBase registry (miRBase v17; http://www.mirbase.org/). Each miRNA has the potential to target hundreds of different mRNAs and, conversely, each mRNA can be targeted by multiple miRNAs.[5] It is estimated that more than 60% of the mammalian transcriptome is under miRNA control.[6] This demonstrates the central role of miRNAs within the complex regulatory networks of gene expression.

Biogenesis of miRNAs follows a unique and highly conserved evolutionary pattern.[7,8] Most miRNAs are encoded by intergenic chromosomal regions. Transcription of the primary transcript (pri-miRNA) is regulated by transcription factors and mediated by RNA polymerases in analogy to coding genes. The pri-miRNA contains a characteristic stem loop structure that is already cleaved in the nucleus by the Drosha microprocessor complex to generate a shorter pre-miRNA of about 70 nucleotides. The pre-miRNA is then exported to the cytoplasm where it is further processed by the endoribonuclease Dicer into mature double-stranded miRNAs, usually with a two-base overhang on the 3' end. Mature miRNAs are structurally similar to small interfering RNAs (siRNAs) which resemble exogenously produced dsRNAs that can be transfected into cells to specifically modulate target mRNAs. One strand of these double stranded RNAs is integrated into the RNA-induced silencing complex (RISC), a multiprotein compex that uses this template to target complementary mRNA sequences which are subsequently degraded.[9,10]

Despite evolutionary conservation, it is very likely that miRNAs are regulated differently and trigger different targets in different species, such as mice and men. A comparison of lymphocyte miRNA signatures in humans and mice revealed poor concordance.[11] Furthermore, it has been shown that miRNAs play distinct roles in different cellular, developmental and physiological processes.[12] Here, we will focus on their role in hematopoiesis.

miRNAs govern hematopoiesis

The biological role of miRNAs in hematopoiesis has been studied either by complete inactivation of miRNA formation or by selective targeting of specific miRNAs. The first approach is based on knockout of Dicer, the key enzyme for the processing of pre-miRNAs into mature miRNAs. As Dicer knockouts are

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embryonic lethal,[13] their *in vivo* role in adult hematopoiesis can only be studied by conditional knockouts. Likewise, embryonic stem cells deficient for DGCR8, a subunit of the microprocessor complex which mediates the biogenesis of microRNAs from the primary microRNA transcript, accumulate in the G1 phase of the cell cycle and exhibit defective differentiation.[14,15] However, when Dicer was deleted conditionally at an early stage of T-cell development using an Lck-Cre transgenic mouse, it was shown that Dicer does not seem to be essential for CD4/CD8 lineage commitment,[16] whereas it is involved in the development of regulatory T cells.[17] Furthermore, conditional inactivation of Ago2, a protein of the RISC complex, led to severe hematopoietic defects.[18]

Genetic inactivation of selective miRNAs can also produce dramatic phenotypes. Virtually every step in hematopoisis seems to be finely tuned by specific miRNAs, as reviewed by other authors[12,19] and summarized in Figure 1. For example, knockout of miR-155 affected T-cell differentiation, germinal center B-cell responses, and responses to bacterial and viral infection.[21,22] Ectopic expression of miR-181 in lineage negative (Lin-) hematopoietic progenitor cells from mouse bone marrow increased the fraction of B lineage cells ($CD19^+$) *in vitro* and *in vivo*.[23] Furthermore, it was demonstrated that miR-150 drives megakaryocyte-erythrocyte progenitor (MEP) differentiation towards megakaryocytes at the expense of erythroid cells.[24] Erythropoiesis was reported to be promoted by miR-451, miR-16 and miR-144, and negatively regulated by miR-150, miR-155, miR-221, miR-222 and miR-223.[25-28] The miRNA cluster miR-17-5p-92 controls monocytopoiesis[29] and miR-424 is up-regulated during monocyte/macrophage differentiation. Within the lymphoid lineage, the choice between T and B cells is regulated by miR-150.[30,31] miR-125b supports myelopoiesis but not G-CSF-induced granulocytic differentiation and it has been suggested that this involves targeting of the c-Jun and Jund pathways.[32] Overall, miRNA function is not only species and tissue dependent, but it also plays distinct roles in cells at different developmental stages.

miRNA expression in hematopoietic stem and progenitor cells

Most of the studies that have been performed so far on miRNA expression in hematopoietic stem and progenitor cells focus on hematopoietic lineage differentiation. The early steps of hematopoietic stem cell (HSC) differentiation, e.g. the role of miRNAs in self-renewal of long-term and short-term repopulating HSCs, is still little understood. miRNA expression profiling in HSC is hampered by the low number of available cells, the wide spectrum of surface marker combinations that are used to enrich for HSC, and the lack of human HSC marker for the isolation of a highly purified stem cell population. Expression of miRNAs has been analyzed in human primitive $Lin^-CD34^+CD38^-CD90^+CD45RA^-$ cells,[33,34] $CD34^+CD38^-$ cells,[35] $CD133^+$ cells[36,37] and murine HSCs.[33,38-40] Recently, Arnold *et al.*[41] identified miRNAs unique to various tissue-specific murine stem cells (including LT-HSCs, skeletal muscle stem cells and neural stem cells) and miRNAs shared by multiple tissue-specific stem cells. miRNA expression profiles are further available for $CD34^+$ progenitor cells from bone marrow, peripheral blood, mobilized peripheral blood and cord blood.[42-44] miR-125b was found to be highly expressed in HSCs ($Lin^-CD34^+CD38^-CD90^+CD45RA^-$) and MPPs ($Lin^-CD34^+CD38^-CD90^-CD45RA^-$) compared to more committed progenitor populations.[34] Recently, we presented the first relative and absolute miRNA copy number profile of $CD133^+$ bone marrow cells and directly compared donor-matched $CD133^+$ cells with the more differentiated $CD34^+CD133^-$ and $CD34^-CD133^-$ cells on miRNA and mRNA levels.[45,46] Eighteen miRNAs were significantly differentially expressed between $CD133^+$ and $CD34^+CD133^-$ cells. These differentially expressed miRNAs are involved in inhibition of differentiation, prevention of apoptosis, and cytoskeletal remodeling.

A comparison of the available miRNA profiles of primitive human hematopoietic cell populations is shown in Table 1. miR-142-3p and miR-142-5p expression was lower in the stem cell fraction in all three data sets. miR-10 and miR-146a were more highly expressed in $CD133^+$ cells in the data of Jin *et al.*[37] and Bissels *et al.*[45] Liao *et al.*[35] described 22 miRNAs as down-regulated in $CD34^+CD38^-$ cells and 9 as over-expressed. Notably, none of the more highly expressed miRNAs was significantly differentially expressed in the data set of Jin *et al.*[37] and Bissels *et al.*[45] Some of this discrepancy might be due to the different stem cell sources. A comparison between $CD34^+$ cells from CB and BM carried out by Merkerova *et al.*[44] revealed 13 differentially expressed miRNAs. This included, for example, miR-

Table 1. Comparison of different miRNA profiling studies in HSC.

	Jin *et al.*[37]	Liao *et al.*[35]	Bissels *et al.*[45]	
Source	mPB	CB	BM	BM
Stem cell fraction	$CD133^+$	$CD34^+CD38^-$	$CD133^+$	$CD133^+$
Control fraction	PB	$CD34^+$	$CD34^+CD133^-$	$CD133^-CD34^-$
miR-10a	1	n.a.	1	1
miR-146a	1	n.a.	1	1
miR-142-3p	-1	-1	-1	-1
miR-142-5p	-1	-1	-1	-1
miR-130a	1	-1	0	1
miR-181a	n.a.	-1	0	1
miR-30b	-1	n.a.	0	1
miR-19b	1	-1	0	1
miR-20a	n.a.	-1	0	1
miR-221	1	n.a.	0	1
miR-126-3p	1	n.a.	0	1
miR-26a	1	n.a.	0	1
miR-144	n.a.	-1	0	-1
miR-15a	n.a.	-1	0	-1
LET-7i	-1	n.a.	0	-1
miR-18a	n.a.	-1	0	-1
miR-191	-1	n.a.	0	-1
miR-16	-1	-1	0	0
miR-17	1	-1	0	0
miR-21	-1	-1	0	0
miR-93	1	-1	0	0
miR-19a	1	-1	0	0
miR-20b	1	-1	0	0
miR-29b	-1	n.a.	1	0
miR-29a	-1	n.a.	1	0

miRNAs differentially expressed by at least two of the three datasets are listed. 1: miRNAs higher expressed in the stem cell fraction; -1: miRNA lower expressed in the stem cell fraction; 0: no differential expression; n.a.: not analyzed.

520h, one of the HSC enriched miRNAs found by Liao *et al.*[35] that was only detected in CD34$^+$ cells from CB. miR-29a and miR-29b expression was lower in the CD34$^+$CD38$^-$ cells analyzed by Liao *et al.*[35] but more highly expressed in CD34$^+$CD38$^-$ analyzed by Han *et al.*[33] and in the CD133$^+$ cells analyzed by Bissels *et al.*[45] Taken together, there is considerable variation in miRNA expression profiles of HSC in different studies that can be attributed to the different stem cell fractions used for comparison. Improved methods to separate specific cell populations will increase our knowledge about miRNA expression in HSCs. The revolution in deep sequencing technologies facilitates the discovery of new miRNAs in highly purified cell populations, further evaluation of already annotated miRNAs, and the analysis of miRNA variants such as editing events.[43,47] This technology, in combination with improved cell separation methods, may identify a common miRNA signature of HSC; if it exists at all. Either way, the situation becomes even more complex with the different signal cascades and pathways which are activated in different cell types and which are potentially regulated by specific miRNAs.

The role of specific miRNAs in HSCs

For each miRNA, a fairly large number of potential mRNA targets can be predicted by bioinformatic algorithms based on sequence homology comparisons. However, such target genes have to be functionally validated; if possible by using the same primary cells. Despite limitations in the material available, several target genes could be validated in HSCs, especially in CD34$^+$ cells (Table 2). This supports the notion that expression of key regulatory genes in hematopoiesis is influenced by specific miRNAs, and most likely their action is at the same time interwoven into various other pathways.

The functional sequel of miRNAs in hematopoisis can also be assessed by lineage specific colony forming unit (CFU) assays. Georgantas and co-workers[42] showed that miR-155 transduced CD34$^+$ cells generated fewer myeloid and erythroid colonies. Labbaye *et al.*[52] demonstrated that miR-146 transduced CD34$^+$ cells generated fewer megakaryocytic colonies. Bissels and co-workers[45] provided the first evidence for a direct regulation of CD133 by miR-142-3p that has a lower expression in CD133$^+$ cells as compared to CD34$^+$CD133$^-$ cells. Overexpression of miRNAs in CD133$^+$ cells demonstrated that miR-142-3p has a negative influence on the overall colony forming ability in HSC-CFU assays. miR-520h was found to be over-expressed in CD34$^+$CD38$^-$ stem cells and it was suggested that miR-520h promotes differentiation into progenitor cells by inhibiting ABCG2 expression.[35] Han *et al.*[33] were able to show that miR-29a induces aberrant self-renewal capacity in CMPs and GMPs. These results support the notion that specific miRNAs play a fundamental role in the regulation of hematopoiesis, whereas their role in the regulation of self-renewal and differentiation in primitive HSCs has not yet been clearly understood.

miRNAs in the hematopoietic stem cell niche

It is commonly accepted that HSC function is tightly controlled by their cellular microenvionment, i.e. the hematopoietic stem cell niche.[57,58] Hence, the cellular composition in the bone marrow has a direct impact on hematopoiesis. Mesenchymal stromal cells (MSC) are precursors for osteoblasts, adipocytes and chondrocytes[59] and there is sound evidence that interaction of HSC and MSC is involved in maintenance and regulation of stem cell function.[60-63]

MicroRNAs regulate proliferation and differentiation of MSC;[64] miR-125b, miR-146a and miR-196a affect osteogenic differentiation and cell proliferation.[65-67] Adipogenic differentiation is stimulated by miR-143[68] and miR-204[69] whereas miR- 21 and miR-27 have been shown to down-regulate adipogenesis by directly targeting the adipogenic transcription factor PPARG.[70,71] Recently, Bork and co-workers[72] have for the first time identified miR-369-5p and miR-371 as two additional adipogenic regulators. Adipogenic differentiation was significantly impaired by miR-369-5p, whereas it was enhanced by miR-371. However, it has to be stated that MSC are very heterogeneous and that the function of specific miRNAs might vary between different cell preparations or even between different subpopulations within MSC.[73]

The stromal function of MSC changes in the course of cellular aging.[74] Early passages have been shown to maintain a primitive CD34$^+$CD133$^+$ immunophenotype upon culture expansion, whereas later passages stimulate proliferation and differentiation.[75] These functional changes are accompanied by continuous changes in their gene expression profile[76] and DNA-methylation pattern.[77] Furthermore, miRNA expression profiles vary in the course of culture expansion[78,79] and these may contribute to the supportive hematopoiesis function of MSC. Interestingly, secretion of the chemo-attractant stromal derived factor 1 (SDF1 or CXCL12) is also influenced by miRNAs: miR-886-3p specifically targets the 3´untranslated region of SDF1 mRNA thereby modulating the expression of this chemokine which plays a critical role in hematopoietic regulation.[80] Thus, miRNAs do not only regulate the cellular constituents of HSC and their niche, they are also involved in their crosstalk.

Intercellular communication via miRNA containing vesicles

Extracellular vesicles, including exosomes, microvesicles and apoptotic bodies, are emerging as important mediators of intercellular communication.[81] Microvesicles derived from embryonic stem cells have been reported to reprogram hematopoietic progenitors and to enhance their proliferation through the delivery of mRNA.[82] Besides mRNA and proteins, the embryonic stem cell microvesicles have often been reported to transfer miRNAs.[74] Exosomes may also contain AGO2 and GW182, two main components of the RISC complex.[84,85] Recent reports indicate that exosomal miRNAs can be transferred to other hematopoietic cells and modulate their function. Mittelbrunn *et al.*[86] demonstrated the existence of antigen-driven unidirectional transfer of miRNA-loaded exosomes from T cells to antigen-presenting cells. A miRNA transfer between T and B cells was shown by Rechavi *et al.*[87] The transfer of miR-126a via apoptotic bodies derived from endothelial cells induces production of the chemokine CXCL12 leading to progenitor mobilization from bone marrow.[88] Data obtained by Chen *et al.*[89] showed that MSCs secrete microvesicles enriched in pre-miRNAs and suggested that MSCs can exert miRNA-mediated biological effects on other cells through the pre-miRNA containing microvesicles. A specific pattern of miRNAs seems to be involved in this shuttling via microvesicles.[90] On the other hand, HSCs also release small membrane vesicles containing CD133 during differentiation. It is still not clear whether the CD133 containing vesi-

Table 2. miRNAs in human HSCs and their targets.

miRNA	Function	Cell type expressing miRNA	Target Genes	Reference
miR-10a	Down-regulated during megakaryocytopoiesis	$CD34^+$ cells	HOXA1	[48]
miR-15a	Overexpression of miR-15a blocked erythroid and myeloid colony formation	$CD34^+$ cells	MYB	[49]
miR-24	Inhibits erythropoiesis	$CD34^+$ cells	ALK4	[50]
miR-29a	Promotes progenitor proliferation	$Lin^-CD34^+CD38^-CD90^+CD45RA^-$ cells	HBP1	[33]
		$CD133^+$ cells	FZD5, TPM1	[36]
miR-34a	Up-regulated during megakaryocyte differentiation, involved in regulation of dendritic cell differentiation	$CD34^+$ cells	CDK4, CDK6, MYB	[51]
miR-125b	Expansion of HSCs	$Lin^-CD34^+CD38^-CD90^+CD45RA^-$ cells	BMF, KLF13	[34]
miR-130a	Down-regulated during megakaryocytopoiesis	$CD34^+$ cells	MAFB	[48]
miR-142-3p	Negative influence on the proliferation of $CD133^+$cells	$CD133^+$ cells	PROM1	[36]
miR-146	Down-regulation during megakaryopoises	$CD34^+$ cells	CXCR4	[52]
miR-150	Drives differentiation towards megakaryocytes	MEP ($CD34^+CD38^+IL\text{-}3R\alpha^-CD45RA^-$)	MYB	[24]
miR-155	Inhibition of myeloid and erythroid colony generation by $CD34^+$ cells	$CD34^+$ cells	Ets-1, MEIS1	[42, 53]
miR-221	Inhibits erythropoiesis	$CD34^+$ cells	KIT	[25, 27]
miR-222	Inhibits erythropoiesis	$CD34^+$ cells	KIT	[25, 27]
miR-223	Inhibits granulocyte and erythroid differentiation	$CD34^+$ cells	LMO2, NFI-A	[54, 55]
miR-424	Up-regulated during monocyte/macrophage differentiation	$CD34^+$ cells	NFI-A	[56]
miR-451	Promotes erythroid differentiation	$CD34^+$ cells	n.a.	[25, 26, 28]
miR-520h	Promotes differentiation of HSCs into progenitor cells	$CD34^+CD38^-$ cells	ABCG2	[35]
miR-17-92 cluster	Controls monocytic differentiation	$CD34^+$ cells	AML1, M-CSFR	[29]

cles carry miRNAs. Such vesicles might be internalized by MSC feeder cells and miRNAs might thereby be further implicated in the crosstalk of stem cells with their niche.[91] There is also evidence that a significant fraction of extracellular miRNAs resides outside of vesicles[92] and that Ago2 complexes carry the extracellular circulating miRNAs independent of vesicles in human plasma.[93,94] However, whether these complexes are released on purpose with the aim of targeting specific cell surface receptors needs to be further investigated. Taken together, intercellular communication via miRNA containing vesicles is an exciting new research field but cell type specificity and functional relevance need to be further validated.

Application potential of miRNAs in hematopoiesis

There is evidence that specific miRNAs harbor prognostic significance to predict response to therapy or to provide indicators of clinical outcome.[95] Several studies indicate that expression profiling of miRNAs is a suitable method for cancer subtype classification with prognostic value.[96,97] miRNAs can be detected in body fluids including serum and, therefore, are promising novel non-invasive biomarkers for diagnosis. A few studies have described the miRNA expression profiles of plasma[98] and serum,[99] and provide a basis for further analysis. In addition, a number of studies analyzed miRNA levels in the circulation and correlated them to physiological conditions. A summary of these studies has been provided by Schöler *et al.*[100]

Apart from such biomarker approaches, miRNAs can also be used to generate induced pluripotent stem cells (iPS). In 2006, it was discovered that somatic cells could be reprogrammed into iPS cells by ectopic expression of Oct4, Soc2, Klf4 and Myc.[101] Several studies have analyzed the roles of miRNAs in reprogramming, as summarized by Mallanna and Rizzino.[102] Oct4 and Sox2 bind to a conserved promoter region of miR-302 cluster and are required for the transcriptional regulation of miR-302a.[103] It has been demonstrated that miR-302 and miR-372 promote reprogramming of human fibroblasts to iPS by accelerating mesenchymal-epithelial transition.[104,105] Furthermore, introduction of miRNAs specific to embryonic stem cells, such as subsets of the miR-290 cluster, increases the generation of mouse iPS cells in combination with Sox2, Oct4 and Klf4.[106] Recently, it has even been shown that expression of the miR302/367 cluster can directly reprogram mouse and human somatic cells to a pluripotent stem cell state in the absence of the commonly used transcription factors.[107] It has also been shown that the miRNA-based reprogramming approach is two orders of magnitude more efficient than standard methods. Reprogramming of murine and human cells is even feasible by direct transfection of mature miRNAs with a non-viral approach.[108] Other authors demonstrated that ectopic expression of Oct4, together with treatment by specific transcription factors can directly mediate conversion of human fibroblasts to multipotent hematopoietic progenitor cells.[109] It is, therefore, conceivable that miRNAs may also be used for direct conversion into hematopoietic cell types.

Another possible application for miRNAs is the *in vitro* expansion of HSCs. Generation of higher cell numbers may enhance engraftment and reconstitution upon hematopoietic stem cell transplantation, especially with small volume transplants, e.g. those derived from cord blood: despite the progress achieved over the last decades, there are still no validated and clinically approved protocols available for HSC expansion. Overexpression of miR125

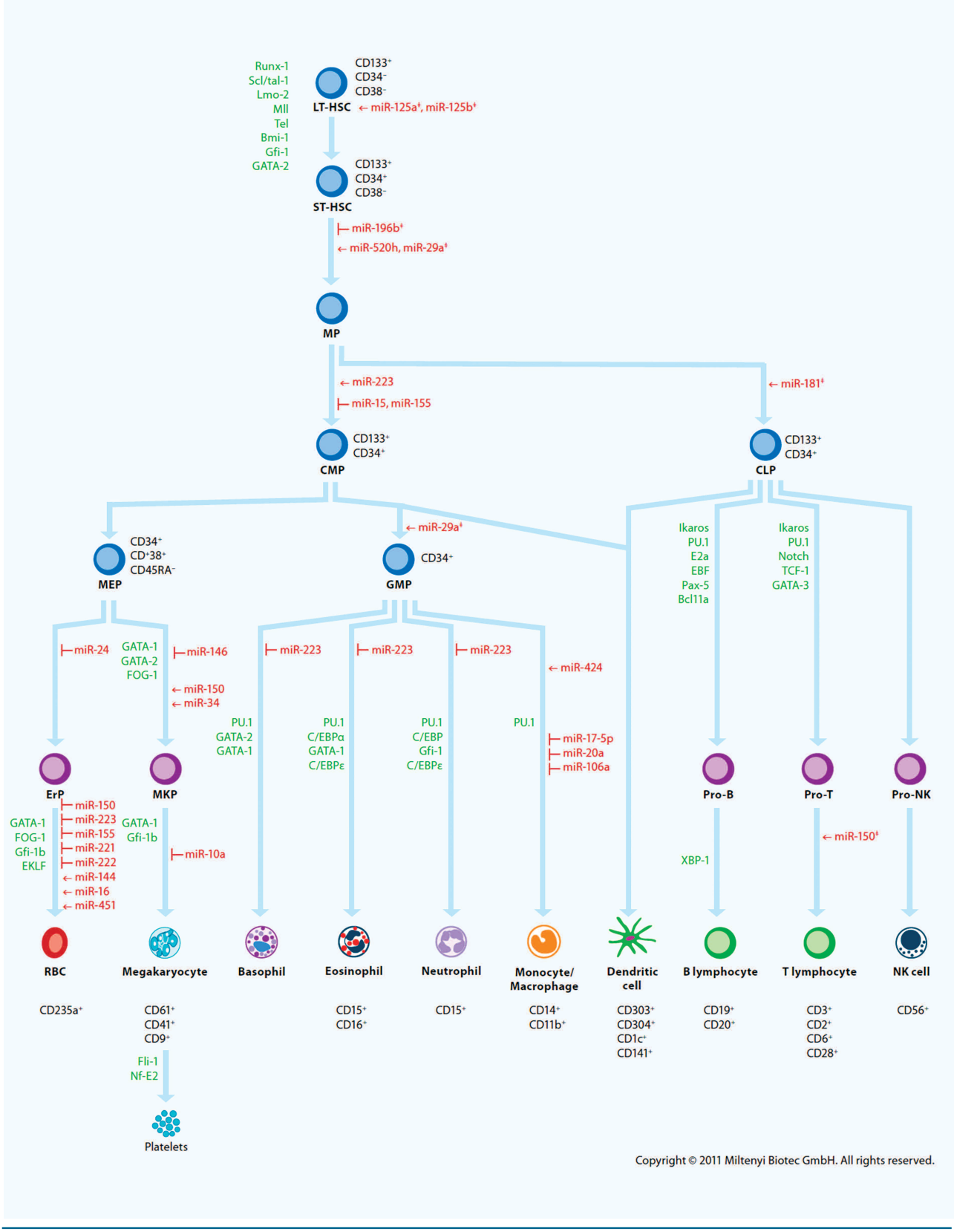

Figure 1. The role of miRNAs in hematopoietic development. miRNAs that regulate different steps of hematopoiesis are indicated in red. These miRNAs were mainly identified using *in vitro* assays with human cells - only those miRNAs labeled with ‡ were identified in the murine system. Some transcription factors are demonstrated in green according to Orkin and Zon.[20] LT-HSC: long-term hematopoietic stem cell; ST-HSC: short-term hematopoietic stem cell; MP: multipotent progenitors; CMP: common myeloid progenitor; CLP: common lymphoid progenitor; MEP: megakaryocyte-erythroid progenitor; GMP: granulocyte-macrophage progenitor; ErP: erythroid progenitor; MkP: megakaryocyte progenitor; RBC: red blood cells; NK: natural killer.

has been suggested to increase HSC numbers *in vivo* by more than 8-fold, potentially through targeting of multiple proapoptotic genes.[38] Starczynowski *et al.*[110] have overexpressed miR-146a in murine HSC. As mentioned above, this miRNA was up-regulated in HSC-fractions of various different studies. Overexpression of miR-146a in HSC, followed by bone marrow transplantation, resulted in a transient myeloid expansion, decreased erythropoiesis, impaired bone marrow reconstitution in recipient mice, and reduced survival of HSC.[110] So far, miRNAs have not enhanced the stem cell pool and it is conceivable that they have to be applied in combinations or in a time dependent manner. The complex mechanism of miRNAs acting in a cell type dependent manner in an orchestra of target genes and pathways make miRNAs a challenging tool for culture expansion. However, the recently achieved breakthroughs in the generation of iPS cells by using miRNAs raises hopes for successful *in vitro* expansion of HSCs with miRNAs.

Conclusion

miRNAs are master regulators of hematopoiesis with a high potential for use in regenerative medicine. Many miRNAs have been implicated in lineage choices of hematopoietic development. They can act through numerous pathways that synergize to regulate and enforce cell fate decisions, if the corresponding target mRNAs are transcribed and accessible at the time. There is also growing evidence that miRNAs resemble targets as well as effectors in epigenetic changes such as DNA methylation.[72,111,112] Thus, a mono-causal relation between a miRNA targeting a specific gene and thereby developing a specific function is unlikely. Quantitative miRNA data derived from highly purified cell populations, together with sophisticated bioinformatic analysis and systems biology, appear to be necessary to understand how miRNA shape the hematopoietic landscape.

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