MicroRNAs in platelet production and activation

Running title: miRNAs in megakaryocytes and platelets

Leonard C. Edelstein and Paul F. Bray

1Thomas Jefferson University, The Cardeza Foundation for Hematologic Research and the Department of Medicine, Jefferson Medical College, Philadelphia

Corresponding author: Paul F. Bray, MD, Thomas Jefferson University, The Cardeza Foundation for Hematologic Research and the Department of Medicine, Jefferson Medical College, Curtis Bldg, Room 324, 1015 Walnut St., Philadelphia, Pennsylvania 19107. Telephone: (215) 955-8544; Fax: (215) 955-9170; E-mail: paul.bray@jefferson.edu
Abstract

MicroRNAs are small RNA molecules that modulate protein expression by degrading mRNA or repressing translation. They have been shown to play important roles in hematopoiesis including embryonic stem cell differentiation, erythropoiesis, granulocytopoiesis/monocytopenes, lymphopoiesis, and megakaryocytopoiesis. miR-150 and miR-155 play divergent roles in megakaryocytopoiesis with the former promoting development of megakaryocytes at the expense of erythrocytes and the latter causing a reduction in megakaryocyte colony formation. Platelets also contain fully functional miRNA machinery and certain miRNA levels in platelets have been found to coordinate with reactivity to specific agonists and to pathological states. This review will cover the current state of knowledge of miRNAs in megakaryocytes and platelets and the exciting possibilities for future research.
Introduction

The linear string of nucleotides that forms a genome has a simplicity that is incongruous with the sometimes overwhelming complexity of organism anatomy and physiology. Some order is achieved by considering messenger RNA (mRNA), linking the proteins responsible for organism intricacy with specific genomic locations. But this “coding gene centric” point of view does not easily explain the large amount of non-coding DNA sequence, representing ~70% of the genome.\(^1\) Although protein coding genes may substantively contribute to the increased complexity of *C. elegans* compared to *E. coli* (a 439% increase in gene number), differences in protein coding genes do not seem to sufficiently explain the greater complexity between *H. sapiens* and *C. elegans* (an increase of only 21%). On the other hand, unlike *C. elegans*, humans have 21-fold more transcribed, non-coding sequence than transcribed, coding sequence, while *C. elegans* has only 1.25-fold.\(^2\) This intriguing association between organism complexity and transcribed, non-coding sequence suggests a role for noncoding RNA, and the last decade has clearly established an important role for non-coding RNA in biology. Non-coding RNAs are classified as large (greater than 200 bp) or small (less than 200 bp). Small regulatory RNAs include microRNAs (miRNAs), endogenous small interfering RNAs, piwi-interacting RNAs, small nucleolar RNAs and others (reviewed in reference 3 and 4). The best studied non-coding RNA are miRNAs. MiRNAs were discovered in *C. Elegans* in 1993\(^5\,^6\) and have been shown to play important roles in developmental biology, cellular stress, circadian rhythm and immunology, as well as numerous disease states, including Alzheimer’s disease, cancer and heart failure. Abundant evidence demonstrates a critical role for miRNAs in normal human hematopoiesis, and dysregulated miRNA biology has been associated with and shown to cause numerous hematologic diseases (Table 1). This review will focus on the role of miRNAs in megakaryocytopenesis and platelet biology.
MiRNA biogenesis and function

MiRNAs are 21-23 nucleotide regulatory RNAs expressed in multicellular organisms, from viruses to plants to humans. There are at least 400 human miRNAs, although some predictions estimate >1,000. MiRNAs regulate most (>60%) mammalian protein coding genes primarily by repressing gene expression. Some miRNAs are expressed ubiquitously, but many are tissue and/or developmental stage specific. Cell miRNA content is highly variable from 1 copy to 10,000 copies.

About 30% of miRNA genes are located in intergenic regions and ~70% are located within introns or exons of protein coding genes. Figure 1A illustrates the canonical understanding of intergenic miRNA biogenesis, although exceptions have been described to some of these steps. MiRNAs located within introns are transcribed as part of the surrounding coding gene’s mRNA, while miRNAs located intergenically utilize an independent transcriptional apparatus. RNA polymerase II is responsible for most miRNA transcription, although RNA polymerase III has been identified transcribing miRNAs located within repetitive elements. A several kilobase primary transcript (pri-miRNA) is then capped and polyadenylated, and forms a hairpin structure. The pri-miRNA is cleaved into a ~60-70 bp pre-miRNA by Drosha, an RNase type III endonuclease, which is complexed with DiGeorge syndrome critical region 8 (DGCR8). The pre-miRNA is transported out of the nucleus via exportin 5. In the cytoplasm, the 3’ overhang of the pre-miRNA is recognized by the Dicer-TAR RNA-binding protein 2 (TRBP2) complex. Dicer is another RNase type III endonuclease, which generates the miRNA duplex for many miRNAs. The strands separate and the mature miRNA associates with a macromolecular complex called the RNA-induced silencing complex (RISC), which guides the miRNA to its mRNA target. The process of miRNA generation is regulated at both transcriptional and post-transcriptional levels, occasionally comprising positive feed-forward, or negative feed-back circuitry, in which the
miRNA targets a transcriptional activator or repressor of itself. The defining RISC protein is Argonaute 2 (Ago2), which catalyzes mRNA cleavage. Notably, Ago2-dependent, dicer-independent miRNA processing pathways have been identified.\textsuperscript{16,17}

A fundamental aspect of miRNA function relates to mRNA targeting: most miRNAs are predicted to target multiple mRNAs, and most mRNAs have predicted targets for many miRNAs. Different algorithms are publicly available that predict miRNA binding sites, including Miranda, TargetScan, PicTar and MiRBase. The miRNA associates with mRNA by complementary Watson-Crick base pairing (Figure 1B), with sequences usually – but not always \textsuperscript{18} – in the 3’UTR of mRNA. The seed region of nucleotides 2-8 at the 5’ end of the miRNA has perfect complementarity, and this sequence defines families of miRNAs. The miRNA sequence 3’ to the seed sequence has variable degrees of complementarity with the mRNA. The traditional view of miRNA-mediated translation repression posits that lower complementarity induces translation inhibition. But recent work by Guo et al. indicates that miRNA knock-down of protein expression is primarily via mRNA degradation, with translation inhibition representing only a minor mechanism.\textsuperscript{19} MiRNAs have been aptly referred to as "rheostats" because their regulatory impact is generally to fine-tune but not abolish protein expression.\textsuperscript{20,21} The significance of proper miRNA synthesis and function is underscored by diseases caused by genetic defects at virtually all steps in miRNA biogenesis and targeting, including miRNA gene deletions/duplications, SNPs in the target mRNA 3’UTR, miRNA “decoys,” and genetic variants in the proteins mediating miRNA biogenesis.\textsuperscript{22-24} Importantly, small differences (as little as a 20% change) in miRNA levels have been shown to cause autoimmune disease and predispose to malignancy.\textsuperscript{25}

\textbf{MiRNAs and megakaryocytopoiesis}
Traditionally, mechanistic studies on hematopoietic cell self-renewal and differentiation have focused primarily on transcription factors. Over the past 6-7 years numerous laboratories have established the essential role of \textit{Dicer} and miRNAs in hematopoiesis, including embryonic stem cell differentiation, erythropoiesis, granulocytopoiesis/monocytopoiesis, and lymphopoiesis. Since the first report by Garzon et al. in 2006, nearly 20 studies have addressed various aspects of miRNAs in megakaryocytopoiesis using megakaryocytes generated from \textit{in vitro} cultured CD34+ hematopoietic stem cells (HSCs) or transformed cell lines with megakaryocytic properties (Table 2). Both unbiased miRNA profiling and candidate miRNA studies have established associations between specific miRNAs and the developmental stage of megakaryocyte progenitors. Functionality has been tested by assessing the effects of candidate miRNAs on \textit{in vitro} and \textit{in vivo} proliferation and differentiation after over-expression or knock-down. Mechanistic assessment of these miRNAs has included target protein knock-down and reporter gene assays using constructs with the putative target 3'UTR. Several of the best-studied miRNAs will be discussed for their role in megakaryocytopoiesis.

\textit{MiR-155 inhibits megakaryocytopoiesis}

Georgantas and colleagues performed both mRNA and miRNA expression profiling on CD34+ HSCs from healthy subjects, and used a bioinformatic approach to predict candidate miRNAs that target mRNAs encoding transcription factors associated with hematopoietic differentiation. MiR-155 was predicted to repress expression of 9 different CD34+ mRNAs that regulate myelopoiesis. MiR-155 expression was dramatically reduced when CD34+ HSCs were differentiated along the megakaryocyte lineage. Forced over expression of miR-155 inhibited K562 (a chronic myelogenous leukemia cell line) differentiation, and reduced CD34+ HSC-derived myeloid and erythroid colony formation \textit{in vitro}. Transplantation of HSCs over-expressing miR-155 into irradiated mice caused reduced numbers of megakaryocytes in...
recipient bone marrow. Although the effect of miR-155 on platelet count has not been studied, these studies provide strong support that miR-155 inhibits megakaryocytopenesis.

**MiR-150 enhances megakaryocytopenesis**

By profiling primary cells from human umbilical cord blood, Lu and colleagues discovered miR-150 levels increased as megakaryocyte-erythrocyte progenitors (MEPs) differentiated toward the megakaryocyte lineage, but not the erythroid lineage. Over-expression of miR-150 enhanced both *in vitro* and *in vivo* megakaryocyte differentiation at the expense of erythroid differentiation, suggesting a critical switching function at the level of the MEP. MiR-150 also knocked down expression of MYB via its 3'UTR, consistent with data showing low c-Myb levels promote megakaryocytopenesis. These findings, coupled with work from the Kaushansky laboratory showing thrombopoietin up-regulates miR-150, underscore a critical role for miR-150 in promoting megakaryocytopenesis.

**MiR-146a modulates megakaryocytopenesis**

MiR-146a levels have been reported to dramatically change upon megakaryocytic differentiation of HSCs, but there is conflicting evidence as to the direction of change. Opalinska et al., reported that in murine and human hematopoietic stem cells induced to differentiate into megakaryocytes the expression level of miR-146a increased. However, forced expression of miR-146a had no effect on megakaryocyte colony number (CFU-MK), marker expression or platelet activation. In contrast, Labbaye et al. found that miR-146a decreased in human cord blood stem cells induced to differentiate into megakaryocytes and that forced expression caused a reduction in the number of polyploid cells. Conversely, inhibition of miR-146a by an antagomir caused an increase in the number of polyploid cells. Two recent reports by Starcynowski et al. did not clarify the matter. They report that the level of miR-146a is lower in megakaryocyte/erythroid precursors relative to hematopoietic stem cells, similar to Labbaye et
al., but that forced expression had no effect on platelet number, similar to Opalinska et al. However, when downregulated by decoy targets or anti-miRNA locked nucleic acids (LNA), the CFU-MK and platelet number increases and the ploidy of the megakaryocytes decreases. These apparently conflicting findings may stem from species differences or differing experimental culture conditions (since miR-146a levels vary according to lineage). It is also possible that different experimental conditions result in functionally different levels of miR-146a. This is because Ago proteins preferentially associate with transcripts that contain targets for the highly expressed miRNAs, and mRNAs with a greater number of target sites in their 3' UTR are subject to stricter control. Therefore, differing levels of miRNA expression can result in different mRNA levels and experimental results. Lastly, since SNPs in the 3'UTR binding site as well as the surrounding sequence can significantly alter miRNA effects, it may be necessary to consider the precise mRNA target sequences in these different studies. Recent work by our group and Landry et al. profiling platelets both found miR-146a to be in the top quartile of expressed miRNAs (Fig. 3). An interesting possibility is that the effect of miR-146a is not cell autologous. Opalinska et al. found than the expression levels of tumor necrosis factor α (TNFα), interferon β (IFNβ), and interleukin-1β (IL-1β) were all repressed in macrophages overexpressing miR-146a. In addition, Starcynowski et al. reported that miR-146a directly targets TRAF6, and down regulating it results in increased TRAF6 and interleukin-6 (IL-6) levels. IL-6 has been reported to have an effect on megakaryocyte development, and it is possible that differences in the reports are due to complications resulting from changes in cytokine signaling pathways.

**MiR-34a and megakaryocytopoiesis**

Increased levels of miR-34a have consistently been observed in K562 cells stimulated to differentiate with PMA. When over-expressed in K562 cells, miR-34a inhibited K562 cell proliferation and promoted differentiation. Importantly, miR-34a increased megakaryocyte
colony formation from CD34+ HSCs.\textsuperscript{59} Thus, miR-34a appears to enhance megakaryocytogenesis.

**Other miRNAs and megakaryocytogenesis**

A number of other miRNAs may regulate megakaryocytogenesis, although these miRNAs have been less well studied. Several investigators have observed that more miRNAs were down-regulated than up-regulated during megakaryocytogenesis, but biphasic patterns of expression have also been observed.\textsuperscript{31,45,52} Several studies have linked reciprocal associations between miRNA levels and target mRNA levels – a particularly interesting finding when the mRNA encodes a transcription factor known to be involved in hematopoiesis. Examples include miR-130a and MAFB, miR-10a and HOXA1, and miR-27a and Runx1.\textsuperscript{45,60} Forced expression of the oncomiR miR-125b-2 increased proliferation and self-renewal of MEP and megakaryocyte progenitors\textsuperscript{61} and miR-28 appears to exert a negative effect on megakaryocyte differentiation.\textsuperscript{62} Lastly, both decreasing miR-181 and increasing miR-27a levels have been associated with megakaryocytic differentiation.\textsuperscript{60,63} In the case of megakaryocytic cell lines, such associations should be viewed cautiously since the correlation between miRNA expression in primary megakaryocytes and cell lines may not always be strong.\textsuperscript{64} Figure 2 summarizes the studies of miRNAs in megakaryocytogenesis.

**Platelet miRNAs**

Platelets contain miRNAs\textsuperscript{31,56,65-68} and we and others have used genome-wide profiling to demonstrate normal human platelets express high levels of miRNA (Figure 3).\textsuperscript{56} Microarray profile levels are readily validated using a novel stem-loop RT-PCR that allows quantification of specific miRNAs.\textsuperscript{12} Emerging evidence over the past year suggests platelet miRNAs are
biologically and clinically relevant as 1) potential regulators of platelet protein translation and expression, 2) markers of mature megakaryocyte miRNA levels, 3) biomarkers for hematologic disease and platelet reactivity, and 4) as a tool for understanding basic mechanisms of megakaryocyte/platelet gene expression.

It is well known that platelets have mRNA, mRNA splicing machinery and translate mRNA into proteins relevant to hemostasis and inflammation. Notably, platelets stored in Blood Banks increase synthesis of integrin \( \beta3 \). Work from the Provost laboratory has demonstrated that human platelets also contain miRNA processing machinery, including Dicer, TRBP2 and Ago2, and that platelets are able to process pre-miRNA into mature miRNA. Our \textit{in silico} analysis indicates that each platelet miRNA targets an average of 307 distinct mRNAs (range 12-1417; unpublished data), consistent with prior predictions. Thus, platelet miRNAs have ample opportunity to regulate platelet function, although direct evidence has yet to be reported.

As described above, functional miRNA levels change during megakaryocyte differentiation of cultured CD34+ HSCs. It is not difficult to imagine similar changes occurring \textit{in vivo}, but this has not been formally studied. \textit{In vitro} culture conditions lack numerous \textit{in vivo} factors that could alter miRNA levels, including other marrow niche cells, innervation, plasma components, spatial constraints, environmental factors, etc. Hussein et al. attempted to directly assess \textit{in vivo} megakaryocyte miRNA levels by using laser micro-dissection to isolate mature megakaryocytes from patient bone marrow biopsies. The extent to which platelet and mature megakaryocyte miRNA profiles correlate is unknown. As an initial attempt to address this issue, we compared platelet miRNA profiles from 19 healthy subjects with the megakaryocyte miRNA profiles from the 2 patients reported by Hussein. As shown in Fig 4A, there was a significant correlation between the platelet and megakaryocyte miRNAs. We suspect that the true correlation is even stronger because different profiling platforms and RNA preparations were utilized and only 2
megakaryocyte samples were assessed. Furthermore, the megakaryocyte samples were from patients, whereas the platelets were from healthy donors. As expected, when we compared our data set to the platelet miRNAs reported by Landry et al., we found a greater degree of correlation (Fig 4B).

MiRNAs are very stable and compared to mRNAs have superior performance characteristics as biomarkers for disease activity. The first human platelet miRNA profiling study was performed in 2008 by Bruchova et al. as part of a study testing for differentially expressed miRNAs in patients with polycythemia vera. These investigators found that miR-26b was significantly higher in polycythemia vera platelets than in platelets from healthy donors. Landry et al., described how miR-223 could target the mRNA of the ADP-receptor, P2Y12, and that P2Y12 mRNA was found in Ago2 immunoprecipitates in both megakaryocytes and platelets. Our group has investigated associations between miRNAs and platelet reactivity, both to better understand megakaryocyte/platelet gene expression and to identify potential biomarkers for thrombotic risk. Because a SNP in the VAMP8 3'UTR has been associated with coronary artery disease, and because VAMP8 mRNA is differentially expressed between platelets of differing reactivity, we considered whether a miRNA might affect VAMP8 expression. Indeed, miR-96 was shown to knock down VAMP8 mRNA and protein, and in a small number of subjects, miR-96 was differentially expressed between platelets of differing reactivity in a manner that was consistent with its effect on VAMP8 expression. Recent data from our laboratory demonstrates the use of differentially expressed mRNA-miRNA pairs for identifying functional miRNAs, as assessed by the ability of the miRNA to target and knockdown the mRNA was confirmed in cell culture.

**Summary and future directions**
MiRNAs have an established role in hematopoiesis and megakaryocytopoiesis and platelet miRNAs have potential as tools for understanding basic mechanisms of megakaryocyte/platelet gene expression. Genome wide association studies have identified orphan loci not in or near protein-coding genes, and at least one such variant proved to be caused by a mutation in a miRNA gene. It is likely that additional megakaryocyte/platelet disease-producing genetic variants in miRNA biogenesis will be identified. Very exciting opportunities exist for future translational research involving miRNAs in megakaryocytopoiesis and platelet biology. Environmental stresses and aging can affect miRNA levels, and it will be important to test whether these factors influence miRNA-mediated megakaryocyte/platelet physiology. Gene therapy approaches are utilizing tissue-specific or developmental stage-specific miRNA expression to avoid off-target effects. For example, Gentner and colleagues have incorporated miRNA target sequences into an expression vector that results in suppressed ectopic gene expression in HSCs but enhanced expression in mature hematopoietic cells. MiRNAs can be released via shed microvesicles, raising the possibility of platelet-mediated delivery of miRNAs to targeted vascular sites. Platelets have been engineered to ectopically deliver recombinant factor VIII and reduce bleeding, perhaps P-selectin bearing platelet microvesicles could target miRNAs to PSGL-1 expressing leukocytes at sites of inflammation. Other potential directions include manipulating platelet miRNAs to modify platelet lifespan or the platelet storage defect in banked platelets.
Authorship

LE and PB wrote the manuscript and analyzed and interpreted data.

Conflict of Interest Disclosures

The authors have no conflicts of interest to disclose.
References


Table 1. MicroRNA dysregulation and hematologic disease

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<th>Hematologic Disorder</th>
<th>Implicated miR</th>
<th>References</th>
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<tr>
<td>Acute Leukemia</td>
<td>miR-125b-2, miR-29b, miR-181a, miR-204</td>
<td>61,86-89</td>
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<td>Chronic leukemia</td>
<td>miR-15a, miR-16-1, miR-155, miR-29b, miR-181a, miR-328</td>
<td>58,90-96</td>
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<td>Myeloproliferative Disorders</td>
<td>miR-150, let-7a, miR-182, miR-26b, miR-143, miR-145, miR-223, miR-26b, miR-30b, miR-30c</td>
<td>31,65</td>
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<td>Myelodysplasia</td>
<td>miR-145, miR-146a</td>
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<td>Lymphoma</td>
<td>miR-21, miR-155, miR-17-92 cluster</td>
<td>97-99</td>
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<td>Study</td>
<td>miRNA Action</td>
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<tr>
<td>Georgantas et al. 29</td>
<td>Over expression of miR-155 in K562 cells caused a block in megakaryocytic differentiation.</td>
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<tr>
<td>Garzon et al. 45</td>
<td>miRNA profile of in vitro differentiated CD34+ bone marrow (BM) cells. Identified miR-130a targets MAFB and miR-10a targets HOXA1</td>
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<td>O'Connell et al. 40</td>
<td>Over expression of miR-155 in transplanted BM lead to a decrease in erythrocytes, MKs, and lymphocytes.</td>
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<td>Guimaraes-Sternberg et al. 63</td>
<td>Calcium release suppresses pre-miR-181a in Meg-01 cells. A miR-181a analogue blocked Ca2+-induced differentiation and induced apoptosis.</td>
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<td>Labbaye et al. 50</td>
<td>The PLZF transcription factor represses levels of miR-146a which in turn targets CXCR4 expression. Forced expression or repression alters megakaryocyte (MK) development (See text for details).</td>
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<tr>
<td>Lu et al. 47</td>
<td>Expression of miR-150 drives MK-erythroid precursors towards the megakaryocytic fate in murine BM transplant experiments.</td>
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<tr>
<td>Barroga et al. 49</td>
<td>Thrombopoietin induces expression of miR-150 in UT-7/TPO cells, which in turn, targets expression of the transcription factor c-Myb.</td>
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<td>Romania et al. 46</td>
<td>miR-155 levels decrease during megakaryopoiesis in cultured human cord blood. Enforced expression of miR-155 impairs MK proliferation and development.</td>
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<td>Hussein et al. 74</td>
<td>miRNA profile of laser-dissected MKs from primary myelofibrosis essential thrombocythemia patients.</td>
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<td>Navarro et al. 59</td>
<td>miR-34a is rapidly increased during TPA-induced differentiation of K562 cells into MKs. Over expression of miR-34a enhances MK differentiation in HSCs and regulates c-Myb expression.</td>
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<td>Ben-Ami et al. 60</td>
<td>TPA induces Runx1 binding to the miR-27a regulatory region and causes an increase in miR-27a in K562 cells. miR-27a, in turn, targets and suppresses Runx1 levels.</td>
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<tr>
<td>Giradot et al. 62</td>
<td>miR-28 targets the thrombopoietin receptor, MPL. Enforced expression prevents MK differentiation in CD34+ cells and is overexpressed in a fraction of platelets in patients with myeloproliferative diseases.</td>
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<td>Opalinska et al. 52</td>
<td>miR-146a increases during MK development. See text for details.</td>
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<td>Starcynowski et al. 53</td>
<td>Enforced expression of miR-146a in transduced BM cells has no effect on platelet number. See text for details.</td>
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<tr>
<td>Klusmann et al. 61</td>
<td>miR-125b-2 is overexpressed in Down Syndrome - acute megakaryoblastic leukemia. miR-125b-2 overexpression induces proliferation and differentiation of MK and MK/erythroid precursors.</td>
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<td>Ichimura et al. 58</td>
<td>PMA treatment in K562 cells increases miR-34a levels. miR-34a, in turn, targets mitogen-activated protein kinase kinase 1 (MEK1) and represses proliferation.</td>
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<tr>
<td>Starcynowski et al. 51</td>
<td>miR-145 and miR-146a are mediators of the 5q-syndrome phenotype. See text for details.</td>
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FIGURE LEGENDS

Figure 1. MicroRNA biogenesis and function. (A) The canonical miRNA biosynthesis pathway, described in text. Drosha, an RNase type III endonuclease; DGCR8, DiGeorge syndrome critical region 8; Dicer, another RNase type III endonuclease; TRBP, TAR RNA-binding protein; RISC, RNA-induced silencing complex; Ago, Argonaute 2; ORF, open reading frame. (B) The seed region of the miRNA (bp 2-8) bind to complementary sites on the 3’ UTR of target mRNAs where it predominantly causes a decrease in mRNA levels, but may also inhibit translation.

Figure 2. MicroRNAs and megakaryocytopoiesis. This cartoon summarizes the miRNAs known to participate in megakaryocytopoiesis. Megakaryocytes (MK) originate from self-renewing hematopoietic stem cells (HSC), which differentiate progressively into common myeloid precursors (CMP), megakaryocyte/erythroid precursors (MEP) and megakaryocyte precursors (MP). The height of the triangles indicates the level of the miRNA, with some miRNAs decreasing during megakaryocytopoiesis, and others increasing. There is conflicting evidence regarding the role of miR-146a. Levels of miR-125b-2 do not change during progression from MEP to MP.

Figure 3. Variation in levels of platelet miRNAs. Levels of individual human platelet miRNAs are displayed, arbitrarily ordered from lowest to highest expression (unpublished data). As examples, the expression levels of miRNA-150, miRNA-155, miRNA-126, and miRNA-146a are highlighted in green. 750 human miRNAs were profiled from leukocyte depleted platelet RNAs from 19 human volunteers using the miRCURY™ LNA Array Version 11.0 (Exiqon, Vedbaek,
Denmark). Expression levels ranged over four orders on magnitude. The background level is indicated by the horizontal dashed line.

**Figure 4. Correlation between human platelet and megakaryocyte miRNAs.** MiRNA expression levels were determined in platelets from 19 healthy donors by microarray (our unpublished data) and in patient megakaryocytes by QRT-PCR. The miRNAs that were queried in both studies were rank ordered and plotted. Statistical significance was calculated by Pearson Rank Correlation. Dotted line represents 1:1 ratio of rank. Panel A, platelet miRNAs correlated with megakaryocyte miRNAs. Panel B, platelet miRNAs from the author’s laboratory correlated with platelet miRNAs from the Provost laboratory (Landry et al. 56).
Figure 1
Figure 2
Figure 3
Figure 4
MicroRNAs in platelet production and activation

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