those with prior late loss (n = 81), but these subgroup analyses are hypothesis generating at best.3 An ongoing randomized controlled trial will hopefully shed further light on the potential benefit of LMWH to prevent recurrent pregnancy loss in thrombophilic women (www.trialregister.nl #NTR 3361). The bottom line is that we need further research to explore whether LMWH can improve live birth rates in women with thrombophilia. However, until this research is completed, LMWH should not be offered to women outside of clinical trials based on the weak association highlighted above and the lack of good-quality evidence to support benefit.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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Endogenous miR-29a regulates HSC function in mammals

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In this issue of Blood, Hu et al identify a critical role for endogenous miR-29a in hematopoietic stem cell (HSC) homeostasis, including the regulation of HSC proliferation and survival.1

HSCs must strike a careful balance between self-renewal and differentiation into hematopoietic progenitor populations, and the molecular mechanisms that control these events are still being elucidated. There is emerging evidence that microRNAs (miRNAs) might be well suited to regulate these decisions due to their ability to modulate gene expression networks and confer robustness to developmental systems. Consistent with this, recent work has found that a subset of mammalian miRNAs, including miR-29a,miR-126,miR-155, and miR-125a/b, are expressed in HSCs and sufficient to alter HSC biology following their overexpression or inhibition in vivo. In some cases, including miR-29a and miR-125a/b, enforced expression triggered myeloproliferative disorders and eventual leukemic transformation in mice, indicating that these miRNAs could also be functionally relevant in human acute myeloid leukemia (AML)

Although overexpression of some HSC miRNAs results in hematopoietic engraftment phenotypes during competitive reconstitution experiments, there is little genetic evidence to date demonstrating that specific endogenous miRNAs are important for normal HSC function beyond a recent study that found an HSC protective role for miR-146a during chronic inflammation.6 However, as hematopoietic-specific deletion of Dicer (which is required for miRNA biogenesis) results in impaired stem cell engraftment and hematopoietic reconstitution,1 there is a fundamental need to determine which endogenously expressed miRNAs promote

[Diagram of HSCs and miR-29a regulation]
stem cell functions during steady-state conditions.

In the current study, Hu et al.\(^1\) find that mice lacking miR-29a/b-1 bicistron have reduced HSC numbers correlating with enhanced HSC proliferation and cell death and reduced multilineage engraftment following competitive bone marrow reconstitution (see figure). Although this mouse strain is deficient in both miR-29-a and miR-29-b1, only expression of miR-29a was able to rescue this hematopoietic phenotype. Providing mechanistic insight, transcriptional profiling of miR-29a/b-1−/− mice with Dnmt3a+/− mice to specifically reduce Dnmt3a levels in HSCs lacking miR-29a/b-1. This provides genetic evidence that this particular DNA methyltransferase, a known regulator of HSCs,\(^7\) is a functionally relevant target of miR-29a in this context.

In addition to expanding our understanding of how miR-29a has evolved to modulate HSC biology under physiological circumstances, the connection between miR-29a and Dnmt3a also provides important mechanistic insight into how miR-29a might epigenetically influence AML phenotypes. Dnmt3a acquires loss-of-function somatic mutations that result in reduced DNA methylation in a high percentage of AML patients with intermediate-risk cytogenetic profiles or FLT3 mutations, and is associated with a poor prognosis.\(^8\) As miR-29a directly targets Dnmt3a,\(^9\) this may prove to be an important step during the oncogenic process in certain types of AML.

With the identification of miRNAs that drive malignant phenotypes and recent progress in developing various methods to target specific miRNAs therapeutically, miRNAs such as miR-29a may one day be an effective target to treat AML. However, the decision to pursue miR-29a targeting as a means to mitigate AML might prove to be complicated, as a seemingly paradoxical role for exogenous miR-29 family members in blocking AML cell line growth has also been reported.\(^10\) This implies that the miR-29 family may play varying roles in AML depending upon the cellular context and possibly the stage of disease where its expression becomes perturbed. Thus, further work is needed to unravel these complexities to both better understand its biology and enable intelligent targeting approaches in the clinic.

The discovery that endogenous miR-29a plays an indispensable role in HSCs through a mechanism involving repression of Dnmt3a is an important step toward defining the molecular circuitry underlying HSC biology. It also justifies additional genetic studies to continue exploring other candidate miRNAs that may have imperative functions in this vital cellular compartment.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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**PLATELETS AND THROMBOPOIESIS**

Comment on Di Buduo et al, page 2254

**Platelet biogenesis wears silkworm cocoons**

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In this issue of Blood, Di Buduo et al report an artificial scaffold of the bone marrow niche whereby Bombyx mori silkworm cocoons appeared to coordinate several factors required for megakaryopoiesis and platelet biogenesis.\(^1\)

A single bone marrow megakaryocyte (Mk) in the body produces >2000 platelets.\(^2\) By recapitulating the chemical and physical signaling that promotes Mk differentiation, maturation, and the release of proplatelets and platelets into the blood stream in vivo, experimental trials ex vivo have tried but failed to achieve similar numbers.\(^3,4\) Building on these ex vivo systems have been designs that incorporate switching the culture from 2-dimensional to 3-dimensional (3D) culture environments, for example, using scaffolds made of polyester fabric, hydrogel, or

polydimethylsiloxane (PDMS) along with cytokines, extracellular matrix, or endothelial cells.\(^5,7\) 3D environments likely make for more surface area, which could permit more proplatelets to interact with the endothelial wall, increasing the number of platelets acquired.

A series of bioreactor systems that better mimic the bone marrow environment by including extracellular matrix components, surface topography, stiffness, cytokines, and shear stress is also being investigated. Di Buduo et al,\(^1\) to obtain higher production efficiency...
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Ryan M. O'Connell