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Lung as a Niche for Hematopoietic Progenitors

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Abstract

Platelets are released from megakaryocytes. The bone marrow has been proposed to be the major site where this process occurs. *Lefrançais* et al. (2017) using state-of-the-art techniques including two-photon microscopy, in vivo lineage-tracing technologies, and sophisticated lung transplants reveal that the lung is also a primary site for platelet biogenesis. Strikingly, lung megakaryocytes can completely reconstitute platelet counts in the blood in mice with thrombocytopenia. This study also shows that hematopoietic progenitors, with capacity to repopulate the bone marrow after irradiation, are present in the lungs. This work brings a novel unexpected role for the lung as a niche for hematopoiesis. The emerging knowledge from this research may be important for the treatment of several disorders.

Keywords

Lung; Hematopoietic stem cells; Origin; Niche

Platelets are tiny discoid, anucleated cell fragments that have a characteristic discoid shape, range from 1 to 3 μm in diameter, and have a life span of 8 to 12 days [1, 2]. Despite of that, platelets are indispensable for processes such as hemostasis, thrombosis, wound healing, angiogenesis, immunity, and inflammation in both health and disease [3–13]. Historically, they were first visualized under a microscope by George Gulliver in the nineteenth century [14]. However, the events that lead to mature platelet production still two centuries later are not completely understood.

Blood platelets are formed from the cytoplasm of rare myeloid cells called megakaryocytes, which are the largest cells residing primarily within the bone marrow [15–17]. Besides the

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bone marrow, there has been mounting evidence suggesting that platelet release could occur in the pulmonary circulation, making the lungs a possible birthplace for platelets [18, 19]. Data supporting this includes the observation that megakaryocytes are also found in pulmonary vascular beds and a higher platelet counts in postpulmonary vessels as compared to pulmonary arteries [20, 21]. In addition, more recent study shows that lung damage reduces circulating platelets, suggesting that lungs may play an active role in the regulation of platelet formation [22]. These studies suggested the presence of a pool of newly formed platelets in the pulmonary circulation.

Understanding the mechanisms by which platelets are produced is a central question in cell biology. In a recent article in *Nature*, Lefrançais and colleagues demonstrated that the lung is a primary site for platelet biogenesis [23]. The authors investigated directly in real time pulmonary platelet production by intravital imaging, using two-photon microscopy and in vivo lineage-tracing technologies to track specifically megakaryocyte and platelets. These experiments revealed that the sources for blood platelets are heterogeneous. Strikingly, platelets are dynamically released from megakaryocytes located in the pulmonary circulation. Furthermore, the authors quantified the contribution of the lungs to platelet production; and it corresponded to approximately half of total platelet biogenesis [23]. Additionally, using state-of-the-art techniques including sophisticated lung transplant experiments, this study showed that lung megakaryocytes can completely reconstitute platelet counts in the blood in mice with thrombocytopenia [23].

Lefrançais and colleagues used RNA-seq to characterize lung and bone marrow megakaryocytes [23]. They described that although the total number of megakaryocytes in the lungs was comparable to that in the bone marrow, lung megakaryocytes had a shift to young immature megakaryocytes (which are more common in neonatal bone marrows) [23, 24]. Future studies should reveal which factors present in the lungs keep those megakaryocytes in the immature state.

Megakaryocytes derive from hematopoietic stem cells (HSCs) that reside mainly in the bone marrow in the adulthood [25]. During early development, before the bone marrow cavities enlarged enough to support hematopoiesis, megakaryopoiesis occurs within the yolk sac, fetal liver, and spleen [26–29]. Surprisingly, Lefrançais and colleagues identified populations of megakaryocytes progenitors and HSCs in the lungs. These progenitors can migrate out of the lungs, repopulate the bone marrow, and contribute to multiple hematopoietic cells [23].

This study brings a new possible role for the lungs as a reservoir for platelets as well as for hematopoietic progenitors.

Perspectives / Future Directions

Interestingly, platelet abnormalities were reported in patients with several pulmonary diseases, such as cystic fibrosis [30, 31], asthma [32–34], pulmonary tuberculosis [35, 36], and pulmonary hypertension [37]. Whether platelets biogenesis in the lungs of those patients is affected remains unknown. Future studies will reveal whether these platelet alterations are due to changes in the pulmonary microenvironment important for platelet biogenesis and

heamatopoeisis in the lungs. Also, are other organs able to compensate platelet production from the lungs in some of those diseases?

During embryonic development, blood cell production (hematopoiesis) is not limited to one site but can be found in a range of locations which vary with the developmental age [38–40]. This occurs due to the migration of hematopoietic progenitors throughout the conceptus. This migration requires the formation of supportive microenvironments, termed hematopoietic niches [41]. Hematopoietic activity can be identified in the extraembryonic yolk sac; dorsal aorta-gonad-mesonephros (AGM region); placenta; vitelline and umbilical arteries; fetal liver; spleen; and in the skeletal muscle surrounding the developing long bones [38, 39, 42–53]. Hematopoietic progenitors from the fetal liver subsequently migrate via the circulation finally to the bone marrow preceding birth, and the bone marrow becomes the predominant location for hematopoiesis throughout the adult life [54]. The presence of hematopoietic progenitors in the lungs raises questions about their ontogeny [23]. When these progenitors appear in the lungs? Are they present during early stages of the embryonic development? From which site they come to the lungs?

Extramedullary hematopoiesis refers to the presence of hematopoietic progenitors and the development of blood cells in extramedullary (outside the medullary spaces of the bone marrow) sites. It usually reflects a pathologic state, being rare in adults under physiologic circumstances. For example, extramedullary hematopoiesis occurs in the spleen and liver in hypoxia conditions due to increased erythropoietin production, and during immune responses after infections [55]. It also may happen as a result of failed bone marrow hematopoiesis. Extramedullary hematopoiesis has been also observed in other organs, less often affected, including lymph nodes [56] and kidneys [57–59]. Excessive extramedullary hematopoiesis may lead to inflammatory diseases, while inadequate extramedullary hematopoiesis leads to insufficient production of blood cells. Lefrancais and colleagues revealed the presence of hematopoietic progenitors in the lungs under physiologic conditions [23]. Whether the numbers of progenitors would increase under some pathologic conditions will be revealed in future studies. As those, from now on, will take into consideration the lungs as an organ with capacity to host extramedullary hematopoiesis (Fig. 1).

HSCs represent a functionally heterogeneous cell population in their degree of self-renewal [60, 61]. Self-renewal heterogeneity is manifested by distinct capacities of long-term (LT-HSC), intermediate-term (IT-HSC) and short-term repopulating HSCs (ST-HSC) [62], that have been distinguished by differential abilities to engraft in vivo into irradiated hosts and to maintain multilineage hematopoiesis for extended time periods and/or by serial transplantation [63]. Lefrancais and colleagues found the presence of ST-HSCs in the lungs, but not of LT-HSCs [23]. This may be due to the cellular components of the lung microenvironment. It has been shown previously that LT-HSCs require specific cells in their niches for their maintenance in a quiescent state [64]; and whenever this niches are disrupted, LT-HSCs may leave these sites [65].

The concept of a “stem cell niche” was proposed by Schofield forty years ago, who hypothesized that HSCs in bone marrow are prevented to mature by influences from the surrounding cellular microenvironment [66]. Now it is known that the tissue

microenvironment plays a central role in hematopoiesis. Nevertheless, most of what we currently know about the cellular and molecular interactions in the HSCs niches is based on studies done in the bone marrow.

In the adult bone marrow, a niche supporting HSCs was identified in close proximity to blood vessels and has been called perivascular niche [64, 67, 68]. The perivascular niche is heterogeneous and contains endothelial cells, smooth muscle cells, and pericytes. Pericytes have been anatomically defined by their perivascular location in the blood vessel wall in close contact with endothelial cells [69–82]. In addition to physical stabilization of blood vessels, pericytes are cells with high plasticity, and may contribute to the formation of several tissues [76]. Besides their ability to function as stem cells, recent studies show that pericytes can also regulate the function of other stem cells. For instance, pericytes are essential cellular components of the niche for HSCs in the bone marrow [65, 70]. A recent study revealed by imaging of the adult mouse bone marrow that the majority of dormant HSCs are situated close to arterioles; and genetic depletion of arteriolar pericytes results in migration of HSCs away from the arterioles, switching them into non-quiescent status [64]. Even more striking, this pivotal study led to the proposal that arteriolar pericytes form a special niche for quiescent HSCs, promoting their dormancy, essential for HSC maintenance in the bone marrow [64].

During embryonic development, perivascular niches for hematopoietic progenitors have been also described to be present in other organs such as spleen [67] and placenta [83]. Moreover, a recent report revealed that HSCs expand around fetal liver portal vessels, and pericytes from these vessels are essential for this expansion [54]. These studies suggest that blood vessels provide an adaptive niche, serving hematopoiesis at multiple developmental stages.

The lung is a highly complex organ comprised of more than 40 different cell types involved in both respiratory and nonrespiratory functions [84]. It remains completely unknown which of those cell types are important supporters of the pulmonary genesis of platelets and hematopoiesis.

Interestingly, HSCs are reportedly located in close proximity to megakaryocytes within the bone marrow [85–87]. Thus, some studies suggested a complex interaction between megakaryocytes and HSCs. Additionally, thrombopoietin was originally identified as a growth and differentiation factor for megakaryocytes [88, 89], but subsequently also proven to have an essential role in self-renewal of HSCs [90, 91]. Abnormal megakaryopoiesis in mice with mutations in the Myb or p300 genes causes reduction in HSC numbers in the bone marrow due to decrease in thrombopoietin levels combined with the impaired responsiveness of HSCs to thrombopoietin [92]. More recent findings identified a direct HSC regulation by megakaryocytes in steady state hematopoiesis in the bone marrow [85, 86, 93]. Ablation of megakaryocytes reduces HSC engraftment and proliferation [86, 94]. Thrombopoietin administration to megakaryocyte-depleted mice restores HSC function [86], suggesting thrombopoietin as one of the mechanisms for megakaryocytes regulation of HSCs. Megakaryocytes produce high levels of TGFβ, which regulate HSCs [95]. Conditional deletion of *Tgfb1* in megakaryocytes increases HSC activation and proliferation [93]. In

homeostatic conditions, megakaryocytes maintain HSC quiescence through TGFβ signaling; while under stress megakaryocytes promote HSC expansion via FGF-1 production [93]. Strikingly, megakaryocytes physically associate with approximately 20% of HSCs in the bone marrow [85]. Overall, these observations confirm that megakaryocytes serve as HSC-derived niche cells directly regulating HSC function. Nevertheless, it remains to be studied whether megakaryocytes are important cellular components of the pulmonary HSC niche.

A megakaryocyte-biased HSC subset has been identified through the use of high endogenous von Willebrand factor (vWF), a blood glycoprotein responsible for platelet aggregation, expression was reported in bone marrow cells [96, 97]. Whether HSCs present in the lungs are primed toward a specific lineage remains unknown.

Pulmonary pericytes were described more than forty years ago [98]. They cover the blood vessels of both the peribronchiolar and the alveolar regions of the lungs [99–101]. The ratio of pericytes to endothelial cells is approximately 1:10 in the lungs [102]. Whether pericytes have important role in the maintenance of HSCs in the lungs remains unknown. Thus, ongoing and future work will clarify what is their exact involvement of pericytes and other pulmonary cells in the lung HSC niche. Future clarification of the interactions between HSCs and their microenvironment in the lung will also contribute to exploit lung HSCs clinical potential.

Several cytokines are essential for HSC retention in the bone marrow, including stem cell factor (SCF), C-X-C motif chemokine 12 (CXCL 12), angiopoietin-1, transforming growth factor-β (TGFβ), and thrombopoietin [103–112]. Whether those molecules expressed by specific pulmonary cells are important for lung hematopoiesis remains to be elucidated. This may be addressed by using cell-specific inducible CreER drivers crossed to cytokines-specific floxed mice. In the resulting mice, specific citokynes could be deleted specifically in different cell types in the lungs and pulmonary hematopoiesis can be analysed. For instance, by similar methods, it was recently demonstrated that CXCL12 from arteriolar pericytes is essential for HSCs maintance in the bone marrow [65].

Over the last years, murine studies have contributed to our knowledge of the HSC regulation in their niches. The high homology in cells and molecules that form the bone marrow HSC niche in mice and humans highlight the importance of the mouse as a model to study the mechanisms of HSC maintenance. However, to identify whether some of the mechanisms discovered by Lefrancais and colleagues are unique to mouse lungs [23], additional studies in the human lungs must be performed.

The mechanisms of murine and human HSCs maintenance in the bone marrow are highly similar [113, 114]. Nevertheless, Lefrancais and colleagues did not explore human tissues [23], and nothing is known about blood cell production in the human lungs. Therefore, data about the murine hematopoietic niche in the lungs must be carefully translated into data about the human pulmonary hematopoietic niche. Do platelet biogenesis and hematopoiesis also occur in the lungs in human patients? Furthermore, similar to what has been shown in mice [23], are human lungs also contributing to 50% of blood platelets? What about the contribution to the total of neutrophils, B and T cells production? In this fast expanding

field, more knowledge of the adult human pulmonary niche will be crucial for a better understanding of the mechanisms underlying several hematopoietic disorders.

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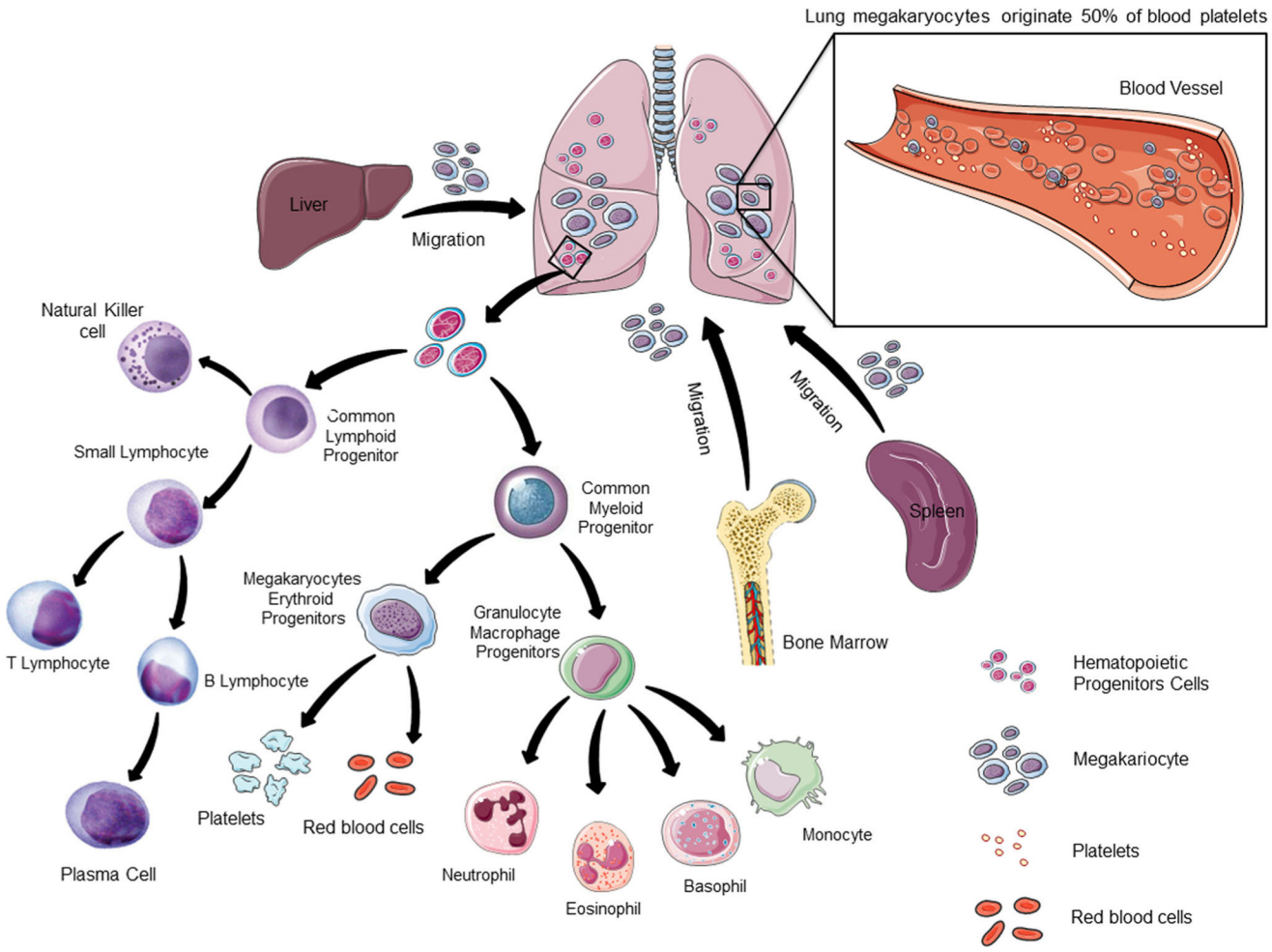

Fig. 1.

Lung as a Primary Site for Platelet Production and Hematopoiesis. It is well accepted that bone marrow is an important site for platelet biogenesis and hematopoiesis. Extramedular hematopoiesis can occur in other organs, such as liver and spleen. The study of Lefrançais and colleagues now reveales that megakaryocytes circulate through the lungs and release platelets [115]. Platelet biogenesis in the lung represents 50% of its total production. Lefrançais and colleagues also showed that the lung is a reservoir for hematopoietic progenitors, including HSCs. With the appearance of state of art technologies, future studies will reveal in detail the components of the lung hematopoietic niche