Commentary

Stem Cell INVESTIGATION

Megakaryocytes regulate the quiescence of hematopoietic stem cells through PF4: 2013 ASH meeting highlights

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Abstract: Hematopoietic stem cells (HSCs) can take one of the three different pathways: quiescence, self-renewal and differentiation. Mechanisms that control the tight balance to maintain lifelong hematopoietic homeostasis have been a major interest of research. Platelet factor-4 (PF4), a weak chemokine, is synthesized exclusively by megakaryocytes and sequestered in platelets. This meeting report highlights a novel study presented at 2013 ASH annual meeting. This study found that megakaryocyte, a progeny of HSC, was involved in maintaining quiescence of HSCs via PF4 in a feedback loop.

Keywords: Hematopoietic stem cell (HSC); platelet factor-4 (PF4); megakaryocytes

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Hematopoietic stem cells (HSCs) can take one of the three different pathways: quiescence, self-renewal and differentiation. Mechanisms that control the tight balance to maintain lifelong hematopoietic homeostasis have been a major interest of research. Non-hematopoietic microenvironmental niches surrounding the HSCs in the bone marrow (BM) have been found to be involved in regulating the dynamic activities of HSCs through paracrine factors (1-3). These niche cells identified thus far include mesenchymal stem cells, osteoprogenitors, vasculoendothelial cells and sympathetic nerves (1-3). Chemokines, cytokines and coagulation factors, such as IL-8, jagged1, notch, CXCR4 and factor VIII, have been implicated in hematopoietic regulation (4-6). *Jagged1*, an angiocrine factor from BM vascular niche cells was demonstrated to regulate homeostatic and regenerative hematopoiesis through Notch-signaling pathways (6).

Platelet factor-4 (PF4), a weak chemokine, is synthesized exclusively by megakaryocytes (Mk) and sequestered in platelets (7). It is found in the α-granules of platelets as a complex with chondroitin 4-sulfate proteoglycan. PF4 was found in high concentrations in the BM fluid. It was found to inhibit hematopoiesis through binding to and inhibiting IL-8 mediated HSC activation (8-10). PF4 is a heparin-binding protein, and has been shown to promote adhesion of HSCs (4,5,11,12).

PF4-cre:iDTR mice

PF4-cre transgenic mouse has been established to express Cre recombinase exclusively in Mk since the *cre* recombinase gene was under the control of PF4 promoter (13). iDTR mouse strain was also created to have transgenic expression of diphtheria toxin receptor (DTR) (14). HSCs have been visualized to be in close contact with Mks by a group led by Dr. Paul Frenette from Albert Einstein College of Medicine, Bronx, New York. To study the involvement of Mk in the regulation of HSC activity, PF4-cre:iDTR mouse strain was generated (15). The expression of DTR in the hybrid PF4-cre:iDTR mouse strain is inducible by Cre recombinase and is therefore limited only in Mk since it is under the control of PF-4 promoter. As a result, megakaryocyte lineage ablation is possible with DT treatment.

Mk regulate the quiescence of HSCs through PF4

At the 2013 ASH annual meeting, this group reported their

study data at the plenary session. The PF4-cre:iDTR mice was treated with DT. After one week DT treatment, a 5.3-fold specific reduction of BM Mk cells were seen (15). This was accompanied by a 11.5-fold increase in the number of HSC cells and a 4.8-fold increase in repopulating capacity. This suggests that Mks normally maintain the quiescence of HSCs. When mice were given injections of recombinant PF4 for a week, there was a 1.5-fold reduction in HSCs. Heparin, which neutralizes PF4, abrogated the reduction of HSCs. Through competitive transplantation, it was shown that HSCs from PF4 treated mice had reduced function, manifested by reduced number of donor cells. This group further proved the PF4 function in maintaining the quiescence of HSCs by analyzing HSC numbers and functions from PF4 transgenic and knockout mice. Therefore, megakaryocyte, a progeny of HSC, was found to be involved in maintaining quiescence of HSCs via PF4 in a feedback loop.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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