Granulocyte colony-stimulating factor acts on lymphoid-biased, short-term hematopoietic stem cells

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Granulocyte colony-stimulating factor (G-CSF) is a cytokine that increases myelopoiesis,1 impairs lymphopoiesis by inhibiting committed progenitor cells,2,3 and enhances hematopoietic stem cell (HSC) mobilization.4 The direct effects of G-CSF on purified subpopulation of HSC remained to be delineated. In this issue of Haematologica, Xie et al.5 investigate the influence of G-CSF on proliferation and the repopulating potential of myeloid-biased, long-term HSC (CD201+CD150+CD48-CD41-CD34-KSL) and lymphoid-biased, short-term HSC (CD201+CD150+CD48-CD41+CD34-KSL).

Understanding the direct influences of G-CSF on HSC could improve our understanding of HSC responses to an increase in G-CSF level caused by inflammation.4 The study by Xie et al. shows that G-CSF acts directly on lymphoid-biased, short-term HSC but not on myeloid-biased HSC. Interestingly, G-CSF cooperates with stem cell factor in driving the expansion of lymphoid-biased, short-term HSC in culture and in maintaining the in vivo repopulating potential of such cultures. These findings suggest that G-CSF-mediated effects on lymphoid-biased, short-term HSC may contribute to the previously noted enhancement of early lymphopoiesis of bone marrow stem and progenitor cells after exposure to G-CSF.7 In contrast, however, G-CSF is also known to instruct bone marrow stromal cells to suppress the function of committed progenitors of B-lymphopoiesis.8 The functional relevance of the G-CSF-mediated priming of early lymphoid progenitor cells and lymphoid-biased HSC7 in association with G-CSF-mediated impairment in the progression of lymphopoiesis from committed progenitor cells8 should be delineated in future studies.

The primary role of G-CSF is currently seen in activation of myelopoiesis to strengthen myeloid immune responses, such as the recruitment of neutrophils during bacterial lung infections.5 However, the simultaneous priming of early lymphoid progenitor cells and lymphoid-biased HSC by G-CSF may also be important to ensure prompt reactivation of lymphopoiesis after the initial induction of myeloid cell-driven immune responses. The sequential coordination of such immune actions by G-CSF seems to be an interesting area of future research.

Understanding direct influences of G-CSF on HSC could also be relevant for our understanding of HSC...
aging. During mouse aging, the number of myeloid-biased HSC increases more than 10-fold, whereas the number of lymphoid-biased HSC shows only a mild (2-fold) increase. Xie et al. revealed that G-CSF improves the maintenance of lymphoid-biased HSC in culture, but does not have direct effects on myeloid-biased HSC. Whether G-CSF could contribute to the in vivo maintenance of lymphoid-biased HSC remains to be seen. Interestingly, in humans, G-CSF levels in the serum were reported to decrease during aging and this decrease was pronounced in patients with Alzheimer disease. The findings of Xie et al. suggest that aging-associated declines in G-CSF level could contribute to the relative reduction in the self-renewal of lymphoid-biased HSC versus myeloid-biased HSC during aging. It would be interesting to investigate whether G-CSF has similar effects on human lymphoid-biased HSC as those on murine HSC described by Xie et al. However, the discrimination between different subtypes of HSC (lymphoid vs. myeloid-biased) has not yet been established in humans.

In addition, it would be of great interest to analyze the influence of other aging-related factors on G-CSF levels and HSC aging. Telomere dysfunction occurs as a consequence of telomere shortening and represents one of the hallmarks of aging. Telomere shortening induces cellular senescence and a strong increase in the secretion of pro-inflammatory cytokines by senescent cells - referred to as the senescence-associated secretory phenotype (SASP). An accumulation of senescent cells have been described to occur in various tissues of primates, including humans, during aging. Interestingly, genetic studies on telomerase knockout mice revealed that G-CSF increases in blood serum as a consequence of telomere dysfunction, which leads to impairments in lymphopoiesis and myeloid-skewed hematopoiesis. This phenotype is very similar to that present in aging humans, which is also characterized by increases in myeloid relative to lymphoid cells in the blood. While studies on human serum showed decreases in G-CSF during aging, future studies should investigate whether the accumulation of senescent cells in bone marrow tissue may lead to increases in G-CSF levels in the micro-milieu of HSC and lymphoid progenitor cells. If G-CSF indeed contribute to the reduction in lymphopoiesis during aging, this could be related to the inhibitory effect of G-CSF on committed lymphoid progenitor cells.

A direct influence of G-CSF on HSC could also be relevant for the clinical usage of G-CSF. It has been shown that macrophage colony-stimulating factor acts directly on HSC to enhance myeloid differentiation, which has positive effects in protecting HSC-transplanted mice from Aspergillus infection. Two of the main applications of G-CSF are to ameliorate chemotherapy-induced neutropenia and to mobilize HSC to be used for mobilized peripheral blood (MPB) transplantation. G-CSF leads to the mobilization of HSC by disrupting the function and maintenance of specific niche cells. It remains to be determined whether direct effects of G-CSF on lymphoid-biased HSC would influence the mobilization of
sub-populations of HSC. If so, the method of mobilization could have an impact on transplantation results. In breast cancer patients who need a transplant of autologous MPB as part of their anticancer therapy, the transplantation of purified HSC improved the survival outcomes compared to those receiving non-purified MPB (https://doi.org/10.1016/j.bbmt.2011.07.009). It remains to be seen whether direct effects of G-CSF on HSC may influence transplantation outcomes.

In brief, the study by Xie et al. provides very interesting new data indicating that G-CSF can act directly on lymphoid-biased but not on myeloid biased HSC. This finding may have implications for our understanding of immune responses, HSC aging, and bone marrow transplantation therapies.

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No conflicts of interest to disclose.

Contributions
YC and KLR wrote the editorial together.

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