REFERENCES


HEMATOPOIESIS & STEM CELLS

Comment on Köhler et al, page 290

Visualize eHPCs in different zones

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In this issue of *Blood,* Köhler and colleagues developed a time-lapse intravital imaging method to observe BM cells within long bones of live mice, and found that aged eHPCs localized more distantly to the endosteum than young eHPCs.

The hematopoietic stem cell (HSC) niche is composed of specialized bone marrow (BM) stromal cells that play important roles in regulating adult stem cell self-renewal and differentiation.1 Thus far, at least 3 types of stromal cells including osteoblastic, sinusoidal endothelium, and CXCL12 abundant reticular (CAR) cells have been shown to be involved in the regulation of HSCs.2-5 However, these studies relied on use of genetic knockout models impacting on specific niche cell types, or immunostaining to localize putative HSCs within the marrow environment. Both of these methods have limitations. The former does not precisely define localization of HSCs, and the latter does not reveal their function.6,7 Furthermore, the identification of HSCs requires multiple markers that are feasible using flow cytometry on cells in vitro, but difficult for performing immunostaining on HSCs within intact marrow environments. To monitor the dynamic interaction between the HSC and its niche, new technology was necessary.

Recently, 2 labs have developed imaging technologies using 2-photon microscopy that allow for observation of HSCs in their niches in real time, both in vivo and ex vivo. Lo Celso and colleagues have monitored the behavior of individual hematopoietic stem and progenitor cells (HSPCs) in the calvarium BM of live mice.6 Xie and colleagues have established a new method for ex vivo imaging stem cells (EVISCs) to trace the homing of purified green fluorescent protein (GFP) HSC or young eHPC to different zones of the BM. In this study, the authors observed that aged eHPCs localized closer to the endosteum than young eHPCs. The authors suggest that this observation is likely due to differences in the expression of molecules on the surfaces of these cells, such as integrins and other adhesion molecules.

The illustration shows the endosteal zone and central marrow zone in transplanted mice which donor eHPCs come from young and aged mice. Fig showed young eHPCs located closer to endosteum compare to aged eHPCs, and protrusion movements and cell surface increased in aged eHPCs.
other improved, such as observing the behavior of endogenous HSCs and successfully conducting lineage tracing studies in vivo, this new method is ready to address many important biological questions.

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REFERENCES

Comment on Kryczek et al, page 357

Does IL-17 promote tumor growth?

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Chronic inflammatory conditions may augment tumor growth, but in this issue of Blood, Kryczek and colleagues find that endogenous IL-17 may not be one of the contributing factors.

The association between chronic inflammatory conditions and the development of cancer was postulated by Rudolph Virchow in 1863. Indeed, many cancers arise at the sites of chronic irritation by chemical compounds or physical factors, infections, or autoimmune diseases through a plethora of mechanisms. Subsequent tumor progression is associated with invasion of surrounding tissues that causes further inflammatory changes, triggering recruitment of myeloid and lymphoid immune cells into the tumor microenvironment. Host cells can then release factors that contribute to either tumor progression or tumor inhibition. The precise regulation of the balance between cancer-promoting and antitumor factors involved in this process has yet to be understood, but overall it appears that the immune system does a rather poor job in eliminating the established tumors on its own.

It is postulated that proinflammatory cytokines, including IL-6 and IL-23, contribute to the carcinogenesis and tumor growth directly or indirectly via STAT3-related mechanism. These cytokines induce the differentiation of CD4+ T cells into the Th17 subset, whose name derives from the capacity to produce IL-17. Th17 cells are closely related to induced FOXP3+ regulatory T cells (iTregs), as both are generated in the presence of TGF-β that is readily available in the tumor bed and is considered a potent immunosuppressant. Other sources of IL-17 include CD8+ T cells, γδ T cells, and natural killer (NK) cells. IL-17–secreting cells have been identified in many types of human cancers and murine models. Their exact roles in cancer remain unclear. Th17 cells have been linked to tissue damage associated with many autoimmune diseases, graft-versus-host reaction, and allo-graft rejection. IL-17 elicits diverse proinflammatory effects including induction of GM-CSF, TNF-α, IL-1β, IL-6, and IL-23, as well as production of matrix metalloproteinases and various chemokines. IL-17 attracts neutrophils into the site of inflammation, contributing to end organ destruction in autoimmunity.

Transfection of IL-17 into human tumor cell lines augmented the progression of the...
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