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"The aged dormant HSC compartment under homeostatic and stressed conditions"

Adult hematopoiesis is responsible for the production of billions of mature blood cells every day. It is a hierarchically organized process that almost exclusively occurs in the red bone marrow. At the top of this hierarchy sits an extremely rare cell population, the so-called dormant hematopoietic stem cells (dHSCs). These cells were identified using long-term label retention assays (label-retaining cells, LRCs) and are characterized by the expression of a combinatorial set of cell surface markers (Wilson et al., 2008; Foudi et al., 2009; Takizawa et al., 2011; Qiu et al., 2014). dHSCs are highly quiescent cells dividing only 4 to 5 times per lifetime of a mouse. We have recently shown that dHSCs are defined by a low metabolic state which is gradually up-regulated upon lineage commitment (Cabezas-Wallscheid et al., 2017). Regulators of the dormant HSC state include cell-intrinsic signaling pathways as well as soluble components produced by bone marrow cells. For instance, stress-signals such as interferons, lipopolysaccharide or stress-conditions including chemotherapy are known to cause HSC proliferation, thereby altering their homeostatic dormant status (Essers et al., 2009; Baldridge et al., 2010; Walter et al., 2015). In contrast to the factors that can activate and promote HSC exit from dormancy, little is known about the mechanism maintaining HSC quiescence. Importantly, dysregulation of this fine-tuned system may lead to aberrant hematopoiesis such as leukemia.

The goal of this project is to use our recently described mouse model that marks reversibly dormant HSCs avoiding label retaining assays (Cabezas-Wallscheid et al., 2017) to address i) the evolution of the dHSC compartment from young towards aged hematopoiesis; and ii) how the aged dormant HSC compartment returns to quiescence upon stress conditions. These are key biological questions that so far have not been addressed due to the lack of suitable tools.

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