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MAIN FIELDS OF RESEARCH; ABSTRACT

Hematopoietic Stem Cells (HSC) are multipotent cells that sustain lifelong blood production. Despite their immense turnover, most HSC are quiescent (>90% in steady state). Notably, aged HSCs are more quiescent than young ones, possibly due to altered epigenetic patterns associated with self-renewal and cell differentiation. To study HSC cell cycle kinetics, our group developed a CFSE-based in-vivo tracking method: CFSE covalently binds to cytoplasmic proteins and distributes equally to daughter cells. Results obtained from CFSE in-vivo tracking assays suggest that HSC cycling is regulated by a cell-intrinsic program (e.g. genomic/epigenomic imprinting), as well as by extrinsic signals (e.g. growth factors or pathogen components). However, the exact mechanisms regulating dormancy and activation of HSCs are still elusive.

While research has focused largely on factors that activate HSCs from dormancy to division and self-renewal, our main aim is to enlighten mechanisms that lead to HSC quiescence. We hypothesize that increased proliferative history (long-term steady state cycling, inflammation driven fast-cycling, or enhanced turnover with natural or experimental aging) activates an intrinsic HSC program that drives HSC towards quiescence. Dysregulation of this drive to quiescence in cells with high proliferative history might lead to proliferative exhaustion or alternatively, to accumulation of genetic alterations and blood malignancies.

To understand the regulatory mechanisms involved in proliferative control of the HSC compartment, particularly the elements that drive HSC to quiescence, might allow to ultimately developing means for therapeutic intervention in HSC aging and/or pre-malignant HSC alterations that are observed in an aging population. According to the latest studies, 10% of the aged population is affected by clonal hematopoiesis (CHIP), with increased risk to develop blood malignancies and cardiovascular diseases. This means that timely discoveries and interventions will likely have an impact on the overall life quality of the individuals as well as on the health care system. In addition, we speculate that the findings of this study and insights gained could have relevance to other somatic stem cell systems (i.e. gut, neural, and skin stem cells).

SPECIAL TECHNIQUES AND EQUIPMENT

FACS and FACS sorting, CFSE in-vivo labeling, humanized mice, RNA-sequencing.