Molecular bases of hematopoietic stem cell renewal

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Hematopoietic stem cells (HSC) are multipotent cells that give rise to all blood cells and exhibit self-renewal capacity that is required for long-term support of hematopoiesis. Several intrinsic and extrinsic signals are required for asymmetric division and maintenance of the HSC reservoir throughout life. Of those, signals from thrombopoietin, interferons and integrins will be discussed in the context of myeloid- and lymphoid biased HSCs.
Significant insight has been gained in the process of physiologic and pathologic HSC renewal by the discovery of the molecular bases of human myeloproliferative neoplasms Polycythemia Vera, Essential Thrombocythemia and Myelofibrosis. These conditions are clonal diseases of the HSC, which start by acquisition of one of the three main types of driver mutations, which lead to constitutive activation of the JAK2-STAT5/STAT3/STAT1 pathway. In turn, this pathway allows committed myeloid progenitors to survive, proliferate and differentiate in the absence of cytokines such as Epo, Tpo or G-CSF, explaining the excessive production of red blood cells, platelets and granulocytes in the chronic phase. With time, a significant fraction of patients evolve to severe conditions, myelofibrosis and secondary acute leukamia. Our laboratories contributed to the discovery of JAK2 V617F and mutants of MPL/TpoR (TpoR W515 mutants) and we recently elucidated thepathogenic mechanism of calreticulin mutants, which are associated with 30% of Essential Thrombocythemia and Myelofibrosis patients. Mutants in the exon 9 of calreticulin genes, represented by deletions and insertions, always change the frame to +1, creating a constant new sequence that mediates specific binding to the extracellular domain of TpoR in the secretory pathway and at the surface. This binding event leads to constitutive TpoR activation.
The HSCs carrying driver mutations acquire clonal dominance and are responsible of the majority of production of peripheral blood cells, with the exception of T cells which have long half-life and persist for years in non-mutated form. With disease progression, mutated HSCs are amplified clonally, and non-mutated HSC decrease in number, while they become completely unable to enter blood-forming circuits. Several mechanisms have been uncovered, some involve inflammatory molecules, especially, TNF, others involve adhesion molecules, but apparently the most important mechanisms involve pathologic feedback from committed progenitors to HSCs. Mutations in epigenetic regulators such as TET2, EZH2, ASXL1, DNMT3a have been detected in clonal HSCs, and some like TET2 can be detected in clonal hematopoiesis of unknown significance associated with the advanced age. The role of these mutations in amplifying the HSCs and the downstream genes involved in niche interactions and also in progenitor-HSC feed back will be discussed. Knowledge obtained in such systems can be translated to induced pluripotent cells stimulated to differentiate into hematopoietic cells in order to establish better protocols of generation and especially amplification of HSCs for novel transplant avenues.