What Makes a Stem Cell and How Does It Go Bad

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Our current studies focus on the origin and nature of leukemia. Hematopoietic stem and progenitor cells (HSPCs) traverse complex differentiation landscapes, following well-defined trajectories for lifelong production of mature blood cell. Serendipitous findings proved that AML originates from clonally expanded human HSC that had acquired a single leukemic mutation in that generated a pre-leukemic HSC (Nature 2014). Through large cohort studies, these studies have shown that preL- HSC can be found in the general population and define individuals at risk for progression to AML up to a decade in advance and thereby providing a rationale for prevention strategies in AML (Nature 2018). In this presentation, I will highlight new studies we have undertaken that have identified a novel human HSC that retains memory of repeated inflammatory insult and these are linked to aging and HSC clonal expansion. This new class of HSC is termed HSC-inflammatory memory (HSC-iM) that retain memory of repeated inflammatory exposures providing a reservoir that selects for CH mutations thereby setting the stage for leukemic progression. This gives insight into the role that inflammation plays as the first non-genetic leukemogenic hit that arises in the HSC (cell of origin). These findings provide an opportunity for targeting AML in the pre-leukemic phase to prevent AML from arising. In a second line of investigation of leukemic origins I will focus on how leukemia has long been considered a caricature of normal development. Now single cell advances have provided a rich resource to begin to define the cellular states that define normal and leukemic development. In acute myeloid (AML) or B-lineage leukemia (B-ALL), certain genetic mutations may distort these differentiation trajectories through inappropriate induction of aberrant self-renewal, lineage biases, or differentiation blocks. While many studies have evaluated how specific driver mutations perturb hematopoiesis, a comprehensive understanding of the genotype-to-phenotype relationships across a wide spectrum of leukemia cases remains elusive. We first developed a single-cell reference atlas of human hematopoietic differentiation that was enriched for primitive HSPC from fetal, neonatal and adult sources as well as an added focus on early B lineage development. In AML used this atlas to map 1.2M single-cell transcriptomes from more than 300 AML samples. In B-ALL we mapped 130K cells from 89 samples. In both cases, the leukemic classification from the single cell studies was then interrogated in large bulk datasets of >2000 cases using deconvolution. In AML, this revealed phenotypic convergence upon 12 recurrent patterns of aberrant differentiation, linked to genetic driver alterations as well as differences in cellular origins and LSC identities. In B-ALL, we found that 25% of samples reflected signatures enriched for HSPC allowing us to develop a new classification termed “Multipotency Score” that was associated with poorer survival. The same genetic driver could result in samples with high or low multipotency suggesting that the cell of origin and/or transformation influences the leukemogenic process.