Early intervention for the prevention of blood cancer development

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Abstract: The ubiquitous presence of somatic mutations has been recently documented across healthy tissues. In the hematopoietic system, this process is termed clonal hematopoiesis (CH), a clinically relevant entity associated with increased blood cancer risk. Acquired CH mutations are thought to originate in a single hematopoietic stem cell (HSC) and endow this founder cell with a competitive fitness advantage over normal HSCs, leading to progressive outgrowth and expansion. We and others have found that CH can be identified decades before clinical evolution to overt malignancy and, as such, CH represents an unprecedented opportunity for early intervention and cancer prevention. Malignant transformation may be blocked if we could reduce the fitness of CH HSCs, but we currently lack the requisite understanding of how CH mutations augment fitness. We hypothesize that enhanced self-renewal and aberrant differentiation topologies underlie the fitness advantage of the CH clone, at the earliest stages of neoplastic processes, even before clinically observable changes in blood production are manifest. We will mechanistically determine targetable pathways that underlie augmented fitness and therapy resistance endowed by CH mutations, by deploying innovative single-cell multi-omics platforms that simultaneously capture somatic mutation status, whole transcriptomes, and/or epigenomes in high throughput. These multi-modality single-cell technologies will be applied to novel HSC co-culture systems, lineage-recording murine models of CH, and unique cohorts of primary bone marrow specimens. The proposed studies will fill an essential knowledge gap to provide a path to therapeutically targeting CH**.**