Clonal Hematopoiesis as a Driver of Adverse Clinical Outcome

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Abstract: Age-related clonal hematopoiesis (CH) was first identified through the finding of non-random X-chromosome inactivation in the blood of healthy elderly women. This observation led us to identify recurrent somatic *TET2* mutations in women with CH. We and others then performed large-scale next generation sequencing studies of unpaired exome data from blood samples obtained from healthy subjects identified somatic mutations in leukemia-associated genes, most commonly in *DNMT3A*, *TET2*, and *ASXL1*, in healthy individuals. These mutations lead to clonal expansion of hematopoietic cells in the absence of clinically overt hematologic transformation. Most recently, we analyzed deep coverage, targeted sequencing data of paired tumor and blood samples from >10,000 patients with advanced cancers. We identified CH in 25% of cancer patients, with 4.5% harboring presumptive driver mutations (CH-PD) with variant allele fraction ≥0.1. CH was associated with increased age, prior radiation therapy and tobacco use. Most importantly, CH and CH-PD led to an increased incidence for subsequent hematologic cancers, and CH-PD was associated with shorter survival from the primary tumor. These studies suggest that CH is a common finding among aging hematopoietic stem cells (HSCs) and that the presence of CH may impact overall outcome and subsequent risk for hematologic malignancies. In this project, we will use a set of complementary genetic and functional studies to assess the factors that drive the development of clonal hematopoiesis and the clinical and biological consequences of mutated blood cells in the setting of cancer patients.