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KILLER CLONES: CLONAL HEMATOPOIESIS AS A NEW CAUSAL RISK FACTOR FOR CARDIOVASCULAR DISEASE

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Abstract

Somatic DNA mutations accumulate with age in many tissues and lead to genomic mosaicism. However, the causal role of genomic mosaicism in the diseases of the elderly other than cancer remains relatively unexplored. Large exome sequencing studies in humans have shown that aging is associated with an increased frequency of acquired mutations in pre-leukemic "driver" genes within hematopoietic cells. These "driver" gene mutations provide a competitive growth advantage to the mutant hematopoietic cell and therefore allow its clonal expansion (i.e. clonal hematopoiesis). Unexpectedly, these somatic mutations have been found to be associated with greater risk of coronary heart disease and stroke, suggesting a previously unrecognized link between somatic mutations in the hematopoietic system and cardiovascular disease. One of the genes that is frequently mutated in clonal hematopoiesis is the epigenetic regulator *TET2*. Using *TET2* as a test case, we explored whether the expansion of mutant hematopoietic cells promotes atherosclerosis in hyperlipidemic mice. More recently we have extended these analyses to additional cardiovascular disease processes and additional driver gene mutations including *DNMT3A* and *JAK2*^{V617F}. Overall, these findings support the concept that clonal hematopoiesis represents a new mechanism of cardiovascular disease that shares features with hematologic malignancy, and that evaluating an individual's clonal hematopoiesis status could add to the predictive capabilities of the traditional risk factors. Further research in the area of hemato-vascular biology could provide a mechanistic framework for the development of personalized medicines for cardiovascular disease that are tailored for individuals who carry specific somatic mutations in their hematopoietic cells.

Keywords

Hematopoiesis, genomic mosaicism, somatic mutations, cardiovascular disease, TET2, DNMT3A, JAK2^{V617F}