Abstract


Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease.


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BACKGROUND: Clonal hematopoiesis of indeterminate potential (CHIP), which is defined as the presence of an expanded somatic blood-cell clone in persons without other hematologic abnormalities, is common among older persons and is associated with an increased risk of hematologic cancer. We previously found preliminary evidence for an association between CHIP and atherosclerotic cardiovascular disease, but the nature of this association was unclear.

METHODS: We used whole-exome sequencing to detect the presence of CHIP in peripheral-blood cells and associated such presence with coronary heart disease using samples from four case-control studies that together enrolled 4726 participants with coronary heart disease and 3529 controls. To assess causality, we perturbed the function of Tet2, the second most commonly mutated gene linked to clonal hematopoiesis, in the hematopoietic cells of atherosclerosis-prone mice.

RESULTS: In nested case-control analyses from two prospective cohorts, carriers of CHIP had a risk of coronary heart disease that was 1.9 times as great as in noncarriers (95% confidence interval [CI], 1.4 to 2.7). In two retrospective case-control cohorts for the evaluation of early-onset myocardial infarction, participants with CHIP had a risk of myocardial infarction that was 4.0 times as great as in noncarriers (95% CI, 2.4 to 6.7). Mutations in DNMT3A, TET2, ASXL1, and JAK2 were each individually associated with coronary heart disease. CHIP carriers with these mutations also had increased coronary-artery calcification, a marker of coronary atherosclerosis burden. Hypercholesterolemia-prone mice that were engrafted with bone marrow obtained from homozygous or heterozygous Tet2 knockout mice had larger atherosclerotic lesions in the aortic root and aorta than did mice that had received control bone marrow. Analyses of macrophages from Tet2 knockout mice showed elevated expression of several chemokine and cytokine genes that contribute to atherosclerosis.

CONCLUSIONS: The presence of CHIP in peripheral-blood cells was associated with nearly a doubling in the risk of coronary heart disease in humans and with accelerated atherosclerosis in mice. (Fundied by the National Institutes of Health and others.).

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