EDITORIALS

CHIP-ping Away at Atherosclerosis

John F. Keaney, Jr., M.D.

Efforts at prevention of cardiovascular disease hinge on the concept of risk factors that, when treated, attenuate the incidence of the disease. Since the concept of cardiovascular risk factors was first proposed in the Framingham Heart Study,[1] many distinct risk algorithms have been developed to target preventive measures in patients who should benefit the most. Among the many risk factors used in these algorithms, age typically emerges as the strongest predictor of cardiovascular risk.

Several explanations have been offered for how age contributes to cardiovascular disease. Aging is associated with the acquisition and exposure duration of other established risk factors for cardiovascular disease, including high systolic blood pressure and increased levels of low-density lipoprotein cholesterol.[2] However, multivariate analyses that adjust for the concomitant burden of other risk factors consistently identify age as an independent predictor of cardiovascular disease. Modifiable risk factors account for only about 12% of the age effect in men and 40% in women.[3] Thus, the aging process itself must promote cardiovascular risk, although the mechanisms that are involved are poorly understood.

Jaiswal et al.[4] now provide new insight into how aging can promote atherosclerosis and cardiovascular events in their investigation of a phenomenon termed clonal hematopoiesis of indeterminate potential, or CHIP.[5] This condition is an age-related disorder characterized by the acquisition of somatic mutations in hematopoietic stem cells that confer on these cells a selective advantage. As a consequence, instead of the normal polyclonal generation of blood cells, mutation-containing clones expand over time and make up an increasing percentage of the stem cells and their progeny and may include granulocytes, lymphocytes, and monocytes. CHIP is rarely found in patients who are younger than 40 years of age, whereas this condition may exist in up to 10% of persons over the age of 70 years.[5] In this older group, hematologic cancers develop at a rate of 0.5 to 1% per year, although the cancers are often not derived directly from the mutation-bearing clones. Patients with CHIP have a higher rate of death from noncancer causes (particularly cardiovascular disease) than do age-matched controls without CHIP.[6]

To address the cause of excess cardiovascular mortality, Jaiswal and colleagues identified CHIP (which they define as clonal dominance of hematopoietic cells bearing pathogenic mutations in any of 74 known driver genes of hematologic cancers) among participants in several prospective and retrospective cohort studies that ascertained cardiovascular disease. In studies involving participants with a mean age of 60 years or older, carriers of CHIP had nearly twice the risk of coronary heart disease as noncarriers. Among younger participants (age, <50 years), CHIP carriers had four times the risk of myocardial infarction as noncarriers. Preclinical coronary disease, as assessed on imaging as coronary-artery calcification, was also associated with CHIP. Finally, four of the most commonly mutated genes in CHIP (*DNMT3A*, *TET2*, *ASXL1*, and *JAK2*) were each individually associated with coronary heart disease, with the *JAK2* V617F mutation carrying 12 times the risk.[4] Thus, CHIP and its common driver genes, in particular, appear to confer an increased risk of coronary heart disease among older persons and a profound relative risk among younger persons.

How do these genes, which are expressed mainly in hematopoietic cells, contribute to atherosclerosis? Jaiswal et al. addressed this question by modeling *TET2* inactivating mutations (the second most common CHIP driver gene) in mouse atherosclerosis. They transplanted *Tet2*-deficient bone marrow into atherosclerosis-prone mice and found that partial or full loss of *Tet2* accelerated atherosclerosis at least partially through enhanced macrophage secretion of CXC family cytokines. It should be noted that an excess of one CXC cytokine (interleukin-8) was observed in clinical specimens obtained from participants with *TET2* mutations. These results generally support the findings of another recent study in mice that modeled CHIP and showed that *Tet2*-deficient bone marrow accelerated atherosclerosis because of excess production of interleukin-1β by monocytes.[7] Thus, available data strongly indicate that at least *Tet2*-driven CHIP promotes atherosclerosis through enhanced inflammation.

Collectively, the work of Jaiswal et al. and others[6-9] supports the hypothesis that CHIP is linked to the clinical events of atherosclerosis and that certain CHIP driver genes are involved in regulating inflammation. Both *TET2* and *DNMT3A* appear to inhibit inflammation,[8,9] so loss-of-function mutations in these genes could plausibly promote inflammatory responses. Similarly, there is a large body of literature suggesting that *JAK2* regulates both inflammation and thrombosis, two important factors in the clinical manifestations of atherosclerosis. Thus, the data provided by Jaiswal and colleagues are consistent with established paradigms that inflammation is an accelerator of atherosclerosis and coronary heart disease. Moreover, their findings should prompt a discourse about studying the use of antiinflammatory agents in patients with CHIP to limit the most common cause of death in these patients — cardiovascular disease.

Important questions remain. We do not know whether all the somatic mutations associated with CHIP work by the same mechanism as *TET2*, so we cannot yet determine whether inflammation is the best therapeutic target for these patients. In addition, we do not know whether CHIP or specific mutations in CHIP driver genes have an effect on other traditional risk factors for cardiovascular disease in a way that might also promote atherosclerosis. Also, since up to 10% of older persons are CHIP carriers, it is worth considering whether this condition has an adverse effect on other chronic illnesses, such as congestive heart failure and type 2 diabetes. Finally, we might need to consider another moniker for this disorder, since emerging data indicate that the clonal hematopoiesis disorder described by Jaiswal et al. no longer has "indeterminate" potential, at least as far as cardiovascular disease is concerned.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

From the University of Massachusetts Medical School, Worcester.

This editorial was published on June 21, 2017, at NEJM.org.

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DOI: 10.1056/NEJMe1706173