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Editorial
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Atherosclerosis: Caused by Mutated Old Blood Cells

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Editorial

It might be natural that as people are getting old, age-related somatic mutations are accumulated even in healthy individuals; however, it might be a surprise that frequency of age-related mutations in hematopoietic cells reaches almost 10% or 20% in healthy individuals older than 70 years, or 90 years, respectively [1,2]. As expected, age-related clonal hematopoiesis is associated with increased risk of hematologic cancer [1,2]. Furthermore, the serious problem is that presence of somatic mutations (mainly in three genes: *DNMT3A*, *TET2*, and *ASXL1*) is associated with increased risk of coronary heart disease in humans [2].

Why are age-related mutations in blood cells associated with risk of coronary heart disease? Based on the fact that monocyte-macrophage lineage in blood cells is involved in atherosclerosis, one possibility is that hematopoietic cells (ex. M1/M2-macrophages) may be responsible for coronary heart disease. In fact, *TET2*-deficiency promotes monocyte-macrophage differentiation [3]; *ASXL1*-deficient cells have impaired capacity of granulomonocytic differentiation [4]; furthermore, *DNMT3A*-loss impairs differentiation of hematopoietic stem cells [5].

Very recently, a paper published in Science [6] demonstrated using a mouse model that somatic *TET2* mutations in blood cells play a causal role in atherosclerosis. *TET2*-deficient macrophages showed an increase in NLRP3 inflammasome mediated IL-1β secretion leading to atherosclerosis, which can be inhibited by an NLRP3 inhibitor [6]. This paper is interesting enough, and this finding should be translated into human trials; people with somatic *TET2* mutations would be picked up, and then current status on atherosclerosis should be evaluated. If possible, NLRP3 inhibitor could be administered to these people in order to treat atherosclerosis or to prevent onset of atherosclerosis.

These results indicate that atherosclerosis can be promoted by mutated old blood cells, which would make us consider the safety issues on clinical trials using hematopoietic cells. For example, in Lancet paper, Patel et al. [7] report promising outcomes of cell therapy for heart failure using ixmyelocel-T that contains expanded MSCs and M2-macrophages. The potential concerns with this study are that it should be explored in individuals harboring somatic mutations (i) whether quantity of M2-macrophages (ex. ratio of M2/M1) decreases, (ii) whether quality of M2-macrophages (ex. secretion of cytokines) remains unchanged, (iii) whether new additional mutations occur during ex vivo expansion culture for 15 days, and (iv) whether any adverse events (ie. exacerbation of heart failure) occur after injection of ixmyelocel-T, compared to individuals without mutation; these things are suggested to be addressed in the near future. It would be also interesting to stratify participants according to presence or absence of mutations in blood cells. If possible, inclusion criteria could be revised according to the presence of mutations in blood cells.

In addition to M2-macrophages, innate lymphoid cells (ILCs) have recently been recognized as powerful effectors of innate immunity and tissue remodeling. If ixmyelocel-T contains ILCs, it might also be essential to examine whether ILCs (with or without mutations) are involved in atherogenesis.

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