Study finds aging of bone marrow accelerates arterial plaque formation

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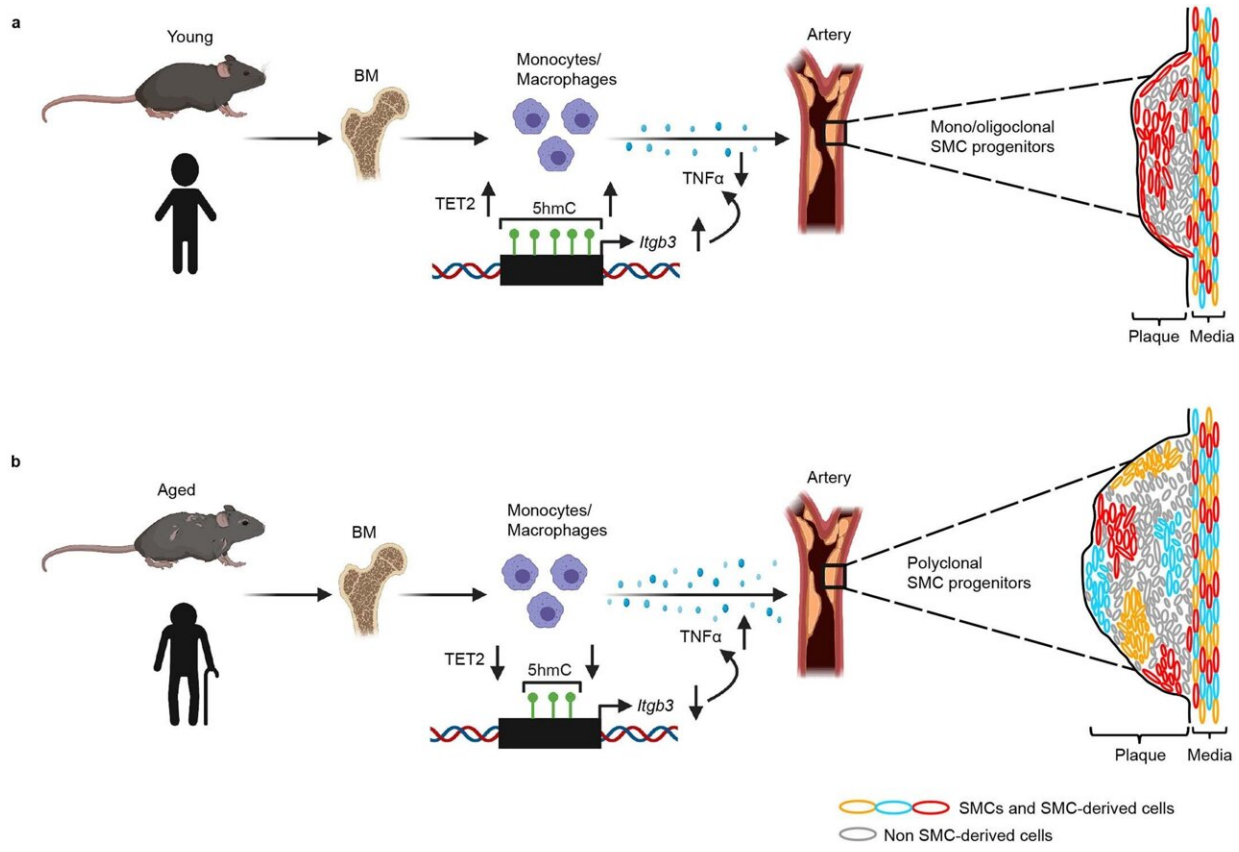

Atherogenesis is depicted in a young (a) or aged (b) host. Aged monocytes/macrophages have decreased levels of the epigenetic regulator TET2, leading to reduction of the 5-hydroxymethylcytosine (5hmC) mark on the Itgb3 promoter. The resulting low integrin β3 levels in aged monocytes/macrophages induces high TNFα levels, facilitating recruitment and expansion of multiple SMC progenitors (polyclonality) in the atherosclerotic plaque and worse disease burden. In contrast, the young control is characterized by mono/oligoclonal SMC expansion in a smaller plaque. Credit: *Nature Aging* (2023). DOI:

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Aged bone marrow promotes the expansion of arterial smooth muscle cells and exacerbates the build-up of fatty deposits in artery walls, a new Yale study has found.

The effects of aging of cells in the bone marrow on arterial smooth muscle cells (SMCs) are not defined. Senior author Daniel Greif, MD and his collaborators used clonal and single-cell analyses to delineate these effects. First author Inamul Kabir, Ph.D., an associate research scientist in the Greif Lab, previously contributed to a study illustrating the progression of fibrotic lung disease. Here, they report that bone marrow from aged individuals promotes the expansion of SMCs and exacerbates atherosclerosis, the build-up of fatty deposits called plaques, in artery walls.

Age is a major risk factor for atherosclerosis, the leading cause of heart attacks and strokes. As we age, mutations accumulate in stem cells in the bone marrow, a process known as clonal hematopoiesis of indeterminate potential (CHIP). These mutated stem cells give rise to dominant clones of white blood cells, such as macrophages, that induce inflammation. CHIP is implicated in adverse cardiovascular outcomes. SMCs and macrophages are key components of atherosclerotic plaques, and the authors previously described that rare SMCs are recruited into and clonally expanded in the plaques.

In their study published Jan. 9 in the journal *Nature Aging*, the research team transplanted bone marrow from aged mice into young, genetically altered atheroprone mice to reveal that the aged bone marrow induces multiple SMCs to enter the plaques, thus exacerbating atherosclerosis. TET2 is a major gene implicated in age-induced CHIP, and from studies

in humans and mice, the authors learned that with aging, decreased levels of TET2 regulates the recruitment to and expansion of SMCs in the plaque.

"We show that aged macrophages express reduced levels of TET2, inhibiting Itgb3 expression, and that decreased integrin β3 in macrophages enhances tumor necrosis factor-α levels, which induces polyclonal expansion of SMCs in the atherosclerotic plaque and worsens disease," the authors wrote. "Thus, our studies put forth deficient regulation of SMC clonal expansion by aged bone marrow-derived macrophages as a critical underlying factor in atherogenesis."

This concept could lead to future therapies to reduce the burden of cardiovascular disease. Further investigation is needed to see if the findings are applicable in the regulation of other cell types and in other diseases, such as liver failure and neurodegenerative diseases.

More information: Inamul Kabir et al, The age of bone marrow dictates the clonality of smooth muscle-derived cells in atherosclerotic plaques, *Nature Aging* (2023). DOI: 10.1038/s43587-022-00342-5

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