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Macrophage proliferation appears to drive progression of atherosclerosis

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New insights into the development of vulnerable atherosclerotic plaques could lead to better treatment or prevention of heart attacks and strokes. In a report being published online in *Nature Medicine*, researchers at the Massachusetts General Hospital (MGH) Center for Systems Biology re-evaluated previous assumptions regarding the role of inflammatory cells in atherosclerosis and found that the process relies on proliferation of certain immune cells within plaques and not exclusively on the uptake of cells from the blood.

The prevailing theory of atherosclerosis has been that plaques grow by drawing white blood cells called monocytes in from the circulation. These monocytes then mature into macrophages, cells that ingest lipid and cholesterol molecules but remain within the plaques, leading to the buildup of a fatty core that contributes to the risk of plaque rupture. While it had been believed that each macrophage descended from a single monocyte that had entered a plaque, the MGH team found that proliferation of new macrophages within plaques is a major driver of their growth.

"Currently, there is quite a bit of interest in targeting inflammation as a way to treat vascular disease, and one of the ways to do so is by targeting the cells responsible, says Filip Swirski, PhD, of the MGH Center for Systems Biology, senior author of the *Nature Medicine* report. "We discovered that the atherosclerotic lesion is a very dynamic environment, and even though the macrophages within a lesion are fundamentally derived from monocytes, they do not require constant monocyte input to

sustain their numbers."

In a series of experiments in mice, the MGH-CSB team first found that existing plaques within the aortas of animals fed a high-cholesterol diet showed evidence of a rapid and constant proliferation of macrophages that did not require the presence of monocytes in the blood. Although monocytes were needed for the initiation of atherosclerosis, once plaques had formed, macrophage proliferation became the primary mechanism for the further growth of plaques. The investigators also identified a receptor protein on macrophages that appears to contribute to their proliferation within plaques without the involvement of monocytes. While further study is required to determine whether the same processes occur in humans, the MGH team did find evidence of macrophage proliferation in plaques from human carotid arteries.

"I think this work will force some major re-evaluations," says Swirski, an assistant professor of Radiology at Harvard Medical School. "People have been thinking of targeting monocyte influx to treat atherosclerosis, but they need to consider macrophage proliferation as an additional or alternative approach, especially in established disease. That might actually be better than targeting circulating monocytes, since interrupting pathological processes within the plaques themselves could spare the beneficial immune responses mediated by monocytes."

More information: Local proliferation dominates lesional macrophage accumulation in atherosclerosis, DOI: 10.1038/nm.3258

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