Tripartite interactions between arteries, nerves and immune cells shape atherosclerosis

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Atherosclerosis is a chronic inflammatory disease of medium and large-size arteries that affects millions of people. Atherosclerotic plaques emerge in the inner intimal layer of arteries and plaque instability triggers clinically significant cardiovascular disease including heart attack and stroke. As plaques lack innervation, the impact of neuronal control on atherosclerosis remains unknown. However, the immune system responds to plaques by forming leukocyte infiltrates in the outer connective tissue coat of arteries, i.e. the adventitia. Because the peripheral nervous system uses the adventitia as its principal conduit to reach distant targets, we hypothesized that the peripheral nervous system may directly interact with diseased arteries via adventitia immune cells to sense and affect atherosclerosis.

We identified crosstalk between arteries, nerves, and immune cells as a key component that drives atherosclerosis by using detailed aorta imaging, gene expression analyses, tissue clearing approaches, retrograde virus tracing, in-vivo ultrasound plaque imaging, extracellular nerve recording, systemic and local sympathetic denervation, normo- and hyper-lidemic mouse models, and human cardiovascular tissues. Surprisingly, wide-spread vascular neuroimmune interfaces arose in murine and human atherosclerosis: diseased adventitia segments showed expanded axon networks including growth cones at axon endings near immune cells and media smooth muscle cells. Murine vascular neuroimmune interfaces established a structural artery-brain circuit: abdominal adventitia nociceptive afferents entered the central nervous system through spinal cord lower thoracic dorsal root ganglia, and were traced to higher brain regions including parabrachial and central amygdala neurons; and sympathetic efferents projected from medullary and hypothalamic neurons to the adventitia through spinal intermediolateral neurons and both celiac and sympathetic chain ganglia. Moreover, central and peripheral components of the artery-brain circuit were activated in parallel to disease progression. When this crosstalk is disrupted by systemic or local sympathetic denervation, plaque-associated immune cell aggregates in the adventitia are destabilized, plaques shrink and become more stable. In summary, our data demonstrated that the tripartite interactions between arteries, nerves and immune cells shape atherosclerosis, and suggested that these unexpected interactions could be targeted to treat atherosclerosis.

Reference:

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