



The biology of atherosclerosis comes full circle: lessons for conquering cardiovascular disease

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Atherosclerosis causes myocardial infarction, ischaemic cardiomyopathy, many ischaemic strokes and jeopardized limbs. Despite enormous progress, atherosclerosis has become the major cause of death worldwide. This Comment intertwines clinical and basic advances in atherosclerosis to illustrate their interdependence, which provides a template for a way forwards to conquer the scourge of atherosclerotic cardiovascular disease.

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Although we have made major strides into the prevention and treatment of atherosclerosis, this disease has expanded globally and now accounts for the majority of deaths worldwide. Much remains to be done to understand fundamental mechanisms of atherosclerosis and to apply advances in prevention and treatment broadly and equitably. This Comment provides a background and context for the *Nature Reviews Cardiology* Series on mechanisms of atherosclerosis. This introduction discusses the milestones of atherosclerosis research, both the clinical discoveries and the laboratory advances, to emphasize their interdependence. Clinical observations often stimulate basic research, which in turn provides the foundation for therapeutic advances that then require recourse to clinical science for application (FIG. 1).

Coronary artery atherosclerosis affected the ancient humans, as demonstrated by a study of Egyptian mummies¹. William Heberden described angina pectoris, the manifestation of chronic coronary artery disease, in an unsurpassed depiction in the eighteenth century². In 1799, Caleb Parry recognized coronary artery disease as a cause of sudden cardiac death³. Coronary artery thrombosis as a cause of acute myocardial infarction emerged in the early twentieth century. In the past century, many pharmacological and mechanical approaches have alleviated the manifestations of coronary artery disease. These advances include LDL-cholesterol-lowering medications, coronary artery bypass graft surgery, percutaneous interventions including angioplasty, and stents of bare metal as well as those that deliver drugs. Arterial hyperplastic responses challenge the durability of the mechanical approaches to alleviating myocardial ischaemia due to coronary artery disease⁴. Therefore, further innovations to limit atherosclerosis and its complications should focus on altering the underlying vascular biology of this disease.

Rudolph Virchow, on the basis of insightful histopathological and anatomopathological observation and deductive reasoning, postulated in the mid-nineteenth century an inflammatory basis of atherosclerosis⁵. He recognized the importance of smooth muscle cell proliferation, cell death and accumulation of ‘cholesterin’ in his examination of human atherosclerotic lesions. Around the same time, Karl von Rokitansky postulated the incorporation of thrombi into the artery wall as a cause of atherosclerosis. Considerable polemic surrounded these then seemingly competing theories. The experimental study of atherogenesis germinated in the observations of Nikolay Anitschkow that feeding a diet enriched in cholesterol could produce lesions recapitulating features of human atherosclerosis in rabbits⁶. The ascendancy of chemical methods led Adolf Windaus to isolate cholesterol from human atherosclerotic plaques⁷. Research into the cell biology of atherosclerosis took wing in the seminal studies of Michael Brown and Joseph Goldstein that elucidated the pathobiological basis of familial hypercholesterolaemia and the LDL-receptor pathway⁸. Akira Endo discovered the statin class of drugs that limit endogenous cholesterol synthesis, augment LDL-receptor expression, lower blood LDL-cholesterol concentration and strikingly reduce atherothrombotic events⁹.

The capacity to culture in vitro the intrinsic cells of the arterial wall, endothelium and smooth muscle fostered further progress into understanding mechanisms of atherogenesis. Russell Ross championed the concept of smooth muscle cell proliferation and generation of extracellular matrix molecules as key events. Michael Gimbrone recognized the role of endothelial-leukocyte adhesion molecules in atherogenesis. Coming full circle, a wealth of experimental studies and observations on human lesions and studies on biomarkers have supported the participation of inflammation in atherosclerosis, as deduced

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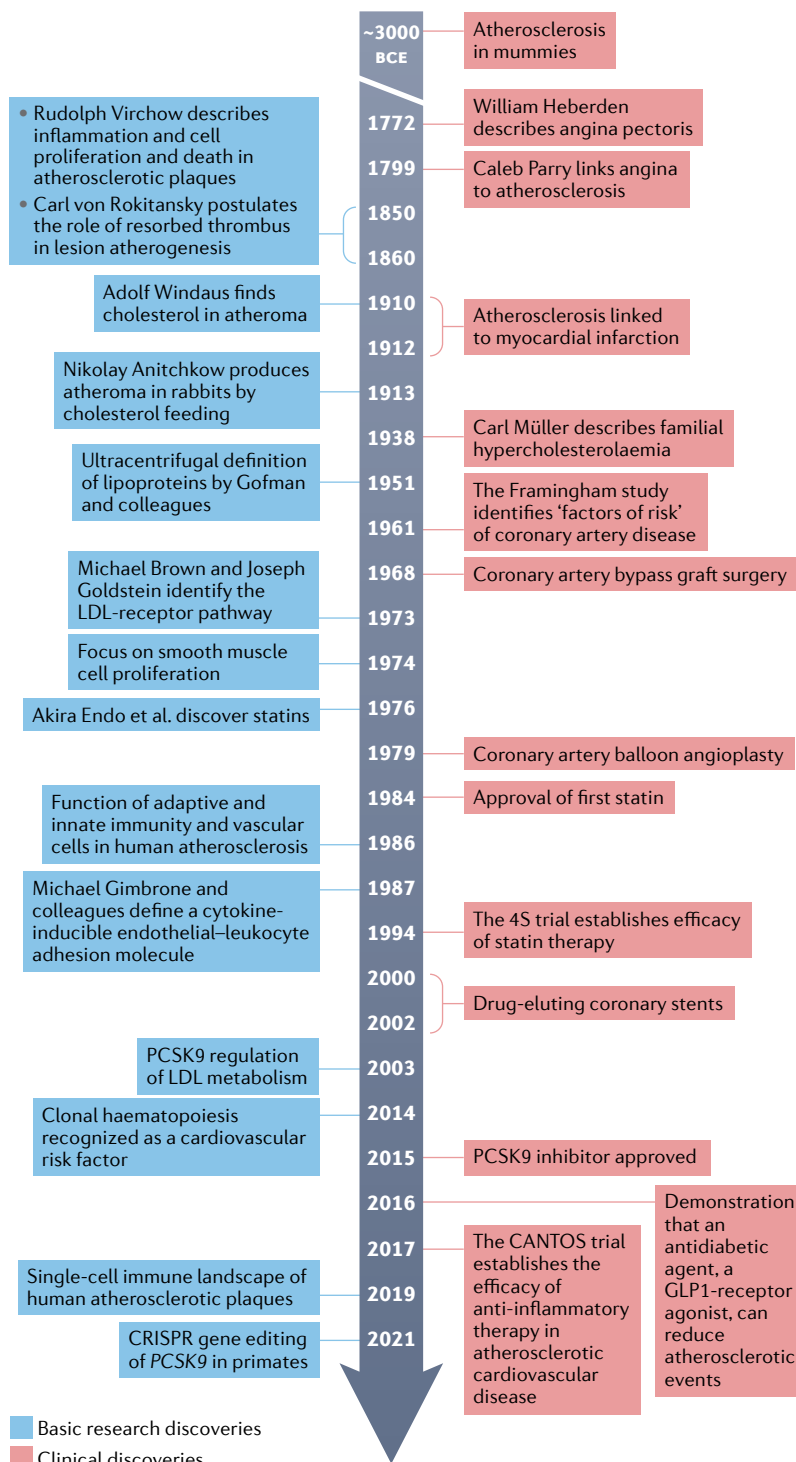


Fig. 1 | Timeline of discoveries in atherosclerosis. The timeline depicts the course of selected clinical observations and advances in the treatment of atherosclerotic cardiovascular disease (red boxes) and key laboratory discoveries on the pathogenesis of atherosclerosis (blue boxes). Note how clinical observations lay the groundwork for laboratory discoveries, which then enable all clinical advances. See the Supplementary information for additional bibliographic documentation for the concepts and studies included in the timeline.

almost two centuries ago by Virchow⁵. Ultimately, studies of selective anti-inflammatory agents have substantiated a role for inflammation and the pro-inflammatory cytokine IL-1 β in human atherosclerosis. Moreover,

studies of human atherosclerotic plaques, either excised or visualized by intravascular imaging, provide support for incorporated thrombus as part of the healing response to disrupted atherosclerotic plaques as a modus of progression of the disease. Indeed, our current understanding incorporates elements of multiple mechanisms of atherosclerosis postulated through the years, providing a synoptic view of the pathogenesis of this common disease that underlies not only myocardial infarction but many ischaemic strokes and peripheral artery disease and its complications, including jeopardized limbs that necessitate amputation.

The application of the fruits of these serial advances in the fundamental understanding of atherosclerosis and its complications could provide more enduring and less invasive intervention to combat atherosclerosis. The biologist and essayist Lewis Thomas viewed measures that treat advanced stages of disease with costly and ethically vexing invasive or mechanical measures as ‘halfway technologies’¹⁰. He articulated the desirability of the application of basic science discoveries to inform the development of clinical strategies that prevent or address the disease at a fundamental level rather than ‘halfway’. The swift translation of the fruits of today’s powerful laboratory research tools to patients by clinical scientists closely allied with basic science investigators promises to continue to provide a path forwards to conquer the scourge of atherosclerotic cardiovascular disease.

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Competing interests

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Supplementary information

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