Chapter 1

Vascular biology of atherosclerosis

Peter F. Bodary, Daniel T. Eitzman

Introduction

The pathogenesis of atherosclerosis has been the subject of thousands of articles published over the past several decades. Currently over 5000 papers per year are being published related to atherosclerosis. To identify only eight articles from this vast literature that have had great impact on our understanding of the biology of atherosclerosis is a difficult task. It will be impossible to do justice to the hundreds of investigators that have shaped the field as it is currently viewed. Most of the fundamental concepts shaping the field of atherosclerosis were generated by pathologists through observational studies. The current view of atherosclerosis probably began with the work of Rudolph Carl Virchow, a professor of pathology, who published “Cellular Pathology” in 1858. Virchow put forth the novel notion that cells were affected by outside stimuli and that diseased cells arose from other diseased cells. Virchow suggested that the atherosclerotic lesion resulted from lipid accumulation and cellular proliferation in the arterial wall. During the same time period (1852), von Rokitansky suggested that atherosclerotic lesion development was preceded by fibrin deposition and that persistence of fibrin deposits might contribute to the formation of an atherosclerotic lesion. Many other pathologists preceding and during this time period had made similar observations and it is difficult to determine who should be credited with the original observations. Suffice it to say, many pathologists have described atheromatous changes in the vasculature but experimental data to support specific hypotheses were lacking during this time period. This review will therefore focus on papers from the more “modern era” of vascular biology.

The modern biology of atherosclerosis arguably began with a series of seminal primate studies described by Russell Ross. In 1973, Ross and Glomset described the cellular composition of atherosclerotic lesions and proposed a critical role for the vascular smooth muscle cell in atherogenesis. Ross and Harker went on to propose the “response to injury hypothesis” to explain the development of atherosclerotic plaques and establish the critical role of hyperlipidemia in the initiation and progression of atherosclerosis. In 1981, Ross Gerrity established the role of the monocyte in atherogenesis using a hypercholesterolaemic swine model. This work de-emphasized the contribution of the vascular smooth muscle cell in the growing atherosclerotic lesion and stressed the importance of foam cells derived from monocytes. In 1983, Erling Falk studied human autopsy specimens and demonstrated that coronary thrombosis developed when plaque rupture occurred at a site of pre-existing coronary stenosis. Further characterization of the “vulnerable plaque” composition was provided by Michael Davies from an autopsy series of patients who died suddenly of ischaemic coronary disease. Seymour Glagov and co-workers introduced the concept of vascular remodelling when he demonstrated that the vascular wall could actually enlarge to accommodate atherosclerotic lesion growth. Further elucidation of the complexity of atherosclerotic lesions was provided by Herbert Stary when he published results of an autopsy series that included infants through young adults. These studies demonstrated that growth of the atherosclerotic plaque begins very early in life and progresses through various stages of complexity. Following the establishment of the contribution of lipids to atherosclerosis by several investigators, Brown and Goldstein elucidated the major pathway responsible for cholesterol homeostasis. This work would earn them the Nobel prize and lead to therapeutical breakthroughs towards the battle against atherosclerotic vascular disease.
Atherosclerosis and the arterial smooth muscle cell

Author

Ross R, Glomset J

Reference

Science 1973; 180: 1332–1339

Abstract

Proliferation of smooth muscle is a key event in the genesis of the lesions of atherosclerosis.

Summary

In this paper, Russell Ross reviews the current data regarding the vascular smooth muscle cell in atherosclerosis. “Proliferation of smooth muscle is a key event in the genesis of the lesions of atherosclerosis”. At the time this paper was written, little was known about the genesis of atherosclerosis. Previous studies had demonstrated that blood pressure, smoking and plasma lipid concentrations could influence the development of clinical symptoms of atherosclerotic vascular disease but the sequence of pathological events at the cellular level was largely unknown.

Focal accumulation of intimal smooth muscle cells was argued to be critical to the early stages of atherosclerosis. Ross argued that “the accumulation of smooth muscle cells necessarily precedes or accompanies both the deposition of lipid and the accumulation of extracellular connective matrix, because the lipid deposits occur either within smooth muscle cells or outside them in association with connective tissue matrix components which are secretory products of smooth muscle cells”. Ross stated that smooth muscle cell proliferation began when a breach of endothelial integrity occurred that would allow substances present in the plasma to stimulate cellular proliferation. Studies supporting these observations included the tendency of vascular smooth muscle cells to accumulate in the intima at arterial branch points, where endothelial permeability appeared to be increased. Stemerman and Ross had also demonstrated experimentally using macaques that vascular lesions could be induced by denuding the femoral artery vascular endothelium with balloon catheters. Three months after injury, the lesion contained as many as 15 layers of smooth muscle cells surrounded by collagen and immature elastic fibers. These lesions were described as identical in appearance to the “fibromusculoelastic” lesions seen in man. Ross also reviews evidence (in vitro and in vivo) that lipids appear to influence proliferation of vascular smooth muscle cells and that vascular smooth muscle cells are responsible for production of extracellular matrix.

Key message

Vascular smooth muscle cell proliferation plays a critical role in the development and growth of atherosclerotic lesions.

Strengths

The identification of vascular smooth muscle cells and the time course of proliferation and matrix production following vascular injury greatly enhanced the understanding of vascular lesion...