Molecular Genetics of Coronary Artery Disease

Monographs in Human Genetics

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Robert S. Sparkes, Los Angeles, Calif.

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Candidate Genes and Processes in Atherosclerosis

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Introduction

Atherosclerosis is a disease of large arteries that has fascinated and puzzled physicians and scientists for more than a century. It is the major cause of heart disease and stroke, which together account for more than one third of deaths in Western populations. This volume provides a comprehensive description of our present state of knowledge of the cellular, molecular and physiologic processes underlying atherosclerosis. Because of the interactive nature of many of these processes, it is important to consider them together in attempting to formulate hypotheses concerning the mechanisms underlying atherogenesis.

Perhaps the first breakthrough in understanding the basis of the disease came from the work of Carl Miller in Oslo in the 1930s. He demonstrated that the triad of high plasma cholesterol, xanthomas and premature coronary heart disease (CHD) segregated together in families, providing evidence for a genetic component of the disease as well as a molecular link to cholesterol metabolism. The past two decades, in particular, have witnessed major advances in our knowledge of the cellular and molecular determinants of CHD. The molecular details of familial hypercholesterolemia, the disorder studied by Carl Miller, have been established, and a variety of other ‘major gene’ disorders associated with CHD have been at least partially characterized. Pathologic studies have demonstrated the importance of various blood cells as well as artery wall cells in atherogenesis. Epidemiologic studies have shown that high blood cholesterol is a prerequisite for most forms of atherosclerosis
and have revealed a number of secondary risk factors including hypertension, diabetes, autoimmune disorders and coagulation factor levels. Evidence for an important genetic component in the disease has continued to accumulate, although it is now clear that CHD results from an interaction between genetic and environmental factors.

The volume is divided into 4 sections. The first deals with cellular interactions of the artery wall and blood elements involved in atherogenesis. The chapter by Berliner and Gerrity provides a review of the pathology of the disease, including results from studies of animal models as well as humans. The chapter by Territo et al. discusses the growth factors, cellular adhesion proteins, chemoattractants and other molecules likely to be important in mediating the cellular events associated with various stages of the disease. The chapter by Haberland and Steinbrecher focuses on lipoprotein metabolism in the artery wall, including lipoprotein modification and cellular uptake of lipoproteins. The chapter by Kaner and Hajjar reviews evidence for a viral component in the disease and the possibility that some forms of atherosclerosis result from nonmalignant transformation of arterial smooth muscle cells. The chapter by Denver discusses the nature of hemodynamic forces on the artery wall and possible mechanisms by which they may influence atherogenesis.

The second section of the volume deals with lipoprotein metabolism. A high level of blood cholesterol in the form of low-density lipoproteins (LDL) can be considered the primary risk factor for the disease. In the absence of severe or moderate hypercholesterolemia,
individuals with `secondary' risk factors such as diabetes, hypertension and smoking, rarely develop CHD. The chapter by Schumaker and Lembertas reviews the metabolism of LDL and very-low-density lipoproteins (VLDL). There has been considerable progress in this area, as several major gene effects have been characterized at the molecular level. The chapter by Karathanasis reviews high-density lipoprotein (HDL) metabolism. Low levels of HDL constitute a major risk factor in atherosclerosis, but in contrast to LDL and VLDL the metabolism of HDL and the mechanism by which HDL protects against atherosclerosis remain largely unknown. The chapter by Doolittle et al. discusses triglyceride metabolism. The relationship of plasma triglycerides to CHD has been a controversial subject, but clearly the metabolism of the triglyceride-rich lipoprotein by lipases and other enzymes contributes importantly to the levels of LDL and HDL. The chapter by Berg reviews one of the major risk factors in CHD, high levels of a lipoprotein called Lp(a). This `mysterious' particle resembles LDL in containing a core of cholesteryl esters and a single molecule of apolipoprotein B, but in addition it contains a molecule or two of a large and genetically heterogeneous protein designated apo(a). The levels of Lp(a) vary greatly among individuals, and epidemiologic studies have shown that high Lp(a) levels are strongly associated with CHD. The chapter by Davis et al. provides an overview of cholesterol homeostasis, with emphasis on bile acid metabolism. Cholesterol is obtained from the diet and synthesized by many tissues, but it can be removed only by transport to the liver, where it is oxidized to form bile acids. Thus, it's likely that bile
acid synthesis and circulation play a pivotal role in determining the levels of circulating lipoproteins.

The third section of the book deals with 'risk factors' for the disease. These include:
hypertension (chapter by Burke and Motulsky);
levels of coagulation factors (chapter by Francis); certain autoimmune disorders (chapter by Acton et al.);
diabetes (chapter by Shohat et al.); and the rare disease homocystinuria (chapter by Wilcken and Dudman). With the exception of homocystinuria, these risk factors are complex and genetically heterogeneous. At present, the mechanisms by which they contribute to atherosclerosis are poorly understood, although many hypotheses have been proposed. Thrombosis is usually the final occlusive event in myocardial infarction or stroke, providing a possible explanation for the involvement of coagulation and thrombolytic factors. It's likely that hypertension, immunologic disorders and homocystinuria affect cells of the artery wall in ways that promote lipoprotein accumulation, monocyte entry or smooth muscle cell proliferation. Diabetes has broad effects on lipoprotein cellular metabolism, although which effects are most relevant to atherosclerosis is unclear. As mentioned above, the processes affecting atherosclerosis are highly interactive, and few of the known risk factors are independent. For example, coagulation and thrombolysis are importantly influenced by diabetes, obesity, inflammatory responses and lipoprotein levels.
The final section of the volume deals with the genetics of CHD. While it's clear that

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atherosclerosis has important genetic influences, environmental influences (particularly
diet) are also significant. The differences in the incidence of CHD between Western populations (where the disease is the major cause of death) and most other populations (where CHD is relatively uncommon) appear to result primarily from environmental influences. Thus, Japanese immigrants who adopt a Western life-style have a greatly increased incidence of CHD. Within populations, however, genetic influences appear to predominate. The chapter by Dreon and Krauss reviews the nature of genetic-dietary interactions related to atherosclerosis, a poorly understood but important subject. The chapter by Hayden et al. discusses differences between populations in genes involved in lipoprotein metabolism, a topic of interest not only for understanding population dynamics but also disease diagnosis. The chapter by Mehrabian and Lusis discusses molecular methods for the analysis of CHD. The final chapter by Warden et al. reviews a powerful new approach for analysis of polygenic traits in animal models, an approach which promises to revolutionize understanding of complex genetic diseases.

In conclusion, the processes involved in atherosclerosis are very diverse, and understanding how they contribute to the disease represents a formidable challenge. Nevertheless, the opportunities have never been greater. It is our hope that this volume will be helpful in providing an overview of a large amount of information which must be considered to develop a coherent synthesis for mechanisms involved in the disease.

A.J. Lusis, for the editors