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Review Article

Genetic Susceptibility to Atherosclerosis

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Atherosclerosis is a complex multifocal arterial disease involving interactions of multiple genetic and environmental factors. Advances in techniques of molecular genetics have revealed that genetic ground significantly influences susceptibility to atherosclerotic vascular diseases. Besides further investigations of monogenetic diseases, candidate genes, genetic polymorphisms, and susceptibility loci associated with atherosclerotic diseases have been identified in recent years, and their number is rapidly increasing. This paper discusses main genetic investigations fields associated with human atherosclerotic vascular diseases. The paper concludes with a discussion of the directions and implications of future genetic research in arteriosclerosis with an emphasis on prospective prediction from an early age of individuals who are predisposed to develop premature atherosclerosis as well as to facilitate the discovery of novel drug targets.

1. Introduction

Atherosclerosis is a complex multifocal arterial disease of medium- and large-size arteries involving interactions of multiple genetic and environmental factors. It is characterized by endothelial dysfunction, vascular inflammation, and the buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall [1]. This construction results in plaque formation accumulating on the inner walls of arteries, and as the artery walls thicken, the pathway for blood narrows, and this can decrease or block blood flow diminishing oxygen supply to target organs. Atherosclerosis represents a leading global cause of death and disability [2].

Although environmental factors such as diet or smoking play an important role in atherosclerosis development, genetic factors represent consequential determinant of atherosclerotic cardiovascular disease risk. Advances in techniques of molecular genetics have revealed that genetic disorders significantly influence susceptibility to atherosclerotic vascular diseases. A large number of candidate genes, genetic polymorphisms, and susceptibility loci associated with atherosclerotic diseases have been identified in recent years and, their number is rapidly increasing. Genetically controlled arterial wall properties of carotid arteries influence atherosclerosis susceptibility. The genetic risk of atherosclerosis is conferred in part through known metabolic risk factors such as hypertension, dyslipidaemia, and diabetes mellitus, but together, the known risk features appear to be insufficient to explain the hereditary propensity to atherosclerosis. However, these risk factors alone do not account for the entire contribution to risk of atherosclerotic disease. In recent years, substantial interest in the identification of additional genetic risk factors to atherosclerosis inevitably grows.

Several types of genetic investigations and approaches have been conducted in the last years in order to prove genetic impact of atherosclerotic process.

1.1. Monogenetic Heredity. Single-gene (mendelian) disorders represent the most remarkable examples of the genetic implication to atherosclerosis [3]. Several monogenic diseases elevate plasma levels of LDL by impairing the activity of hepatic LDL receptors, which normally clear LDL from the plasma. Familial hypercholesterolemia was the first monogenic disorder shown to cause elevated plasma cholesterol levels. The primary defect in familial hypercholesterolemia is a deficit of LDL receptors, and more than 600 mutations in the *LDLR* gene have been identified in patients with this disorder [4]. The frequency of this genetic defect is 1 in

1,000,000. Patients with heterozygous familial hypercholesterolemia have only 50% of the normal number of LDL receptors in the liver. Heterozygous persons produce half the normal number of LDL receptors, leading to an increase in plasma LDL levels by a factor of 2 or 3, whereas LDL levels in those who are homozygous are 6 to 10 times normal levels. Homozygous persons have severe coronary atherosclerosis and usually die in childhood from myocardial infarction [5]. Furthermore, deficiency of lipoprotein transport abolishes transporter activity, resulting in elevated cholesterol absorption and LDL synthesis. For example, mutations in the *APOB-100* gene, which encodes apolipoprotein B-100, reduce the binding of apolipoprotein B-100 to LDL receptors and slow the clearance of plasma LDL, causing a disorder known as familial ligand-defective apolipoprotein B-100 [6]. Five different mutations located in this region of the *APOB* gene are reported to cause a high-cholesterol phenotype. One in 1000 people is heterozygous for one of these mutations. These patients are diagnosed as familial defective *APOB* (FDB), which is clinically indistinguishable from familial hypercholesterolemia [4, 7]. Mutations in *PCSK9* have recently been shown to result in Mendelian forms of increased LDL-C levels. *PCSK9* encodes NARC-1 (neural apoptosis regulated convertase), a newly identified human subtilase that is highly expressed in the liver and contributes to cholesterol homeostasis [8].

The various functions of ATP binding cassette transporter 1 (ABCA1) became apparent after the discovery in 1999 that mutations in the *ABCA1* gene caused Tangier disease (TD), an autosomal recessive hereditary disorder characterized by severe HDL deficiency, sterol deposition in macrophages and, premature atherosclerosis [9–11]. ABCA1 promotes cholesterol and phospholipid efflux from cells to lipidpoor apolipoprotein (apoA1), the precursor of HDL, and plays a major role in cholesterol homeostasis and reverse cholesterol transport [12]. Sitosterolemia, a rare autosomal disorder, results from loss-of-function mutations in genes encoding two ABC transporters, ABCG5 and ABCG8, which act in concert to export cholesterol into the intestinal lumen, thereby diminishing cholesterol absorption [13, 14].

Very rare hereditary hypercholesterolemia with the prevalence <1 case per 10 million persons is autosomal recessive hypercholesterolemia. The molecular cause is the presence of defects in a putative hepatic adaptor protein, which then fails to clear plasma LDL with LDL receptors [15]. Mutations in the gene encoding that protein elevate plasma LDL to levels similar to those seen in homozygous familial hypercholesterolemia [16].

1.2. Polygenetic Heredity. However, in the majority of cases it is not possible to identify single-genetic determinants, and it is likely that several major genes may contribute to the manifestation of the disease. Most of our success in understanding the genetic basis of common forms of atherosclerosis has come from studies of candidate genes, genes tested for their role in atherosclerosis *in vitro*, *in vivo,* and in association studies [17]. Within the general population, polymorphisms within genes in lipid metabolism, inflammation, and thrombogenesis are probably responsible for the wide range of atherosclerotic diseases. A good example of a candidate gene is *apolipoprotein E* (*apoE*). Yet in the 1970s, Utermann et al. identified the common genetic differences (polymorphisms) of *apoE*, and subsequent studies suggested associations with plasma cholesterol levels and type III hyperlipidemia [18]. The *apoE* gene is located at chromosome 19q13.2. Among the variants of this gene, alleles *E2*, *E3*, and *E4* constitute the common polymorphism found in most populations. Of these variants, *apoE3* is the most frequent (>60%) in all populations studied [19]. The role of *apoE* in plasma lipid metabolism has been studied intensively [20, 21]. The polymorphism has functional effects on lipoprotein metabolism mediated through the hepatic binding, uptake, and catabolism of chylomicrons, chylomicron remnants, very low-density lipoprotein (VLDL), and high-density lipoprotein subspecies [22]. Type III hyperlipidemia is an interesting example of a genetic interaction. Almost all individuals with this uncommon hyperlipidemia are homozygous for the *E2* allele, but most individuals who are homozygous for the *E2* allele do not have the disorder [23]. We can summarize from these observations that other genetic or environmental interactions are required to produce hyperlipidemia in addition to homozygosity for the *E2* allele. Another interesting example is *CYBA* gene polymorphisms, including the *C242T* (rs4673) and the $-930^{A/G}$ (rs9932581) which are implicated in the process of atherosclerosis from a very early stage to the clinical phase of cardiovascular diseases [24, 25]. The *CYBA 242T* allele consistently shows a protective association against the chronic inflammatory process presenting as impairment of endothelial function and the development of coronary artery disease [26]. In addition, the *CYBA* $-930^{A/G}$ gene polymorphisms might modify the effect of smoking and hypertension on early structural alterations on the arterial wall [27, 28].

An alternative genetic approach is conducting genomewide linkage studies to find atherogenesis-regulating quantitative trait loci (QTL). In addition, recently, the availability of whole genome sequences in humans and mice, especially the abundant SNP and haplotype information, has made it possible to perform genomewide association studies in order to identify responsible genes. Genomewide association is thought to be more powerful than genomewide linkage analysis to detect common alleles at a locus, but it is less powerful if the extreme phenotypes of interest are due to the segregation of many relatively rare alleles at that locus [29]. Recent experimental studies have revealed certain genetic background of LDL oxidation in the vessel wall, initiating the formation of an early fatty streak lesion consisting mainly of macrophages. Subsequently, a series of lipid-modifying enzymes have been identified in the vessel wall, capable of generating inflammatory mediators, which can further stimulate plaque growth by enhancing cellular influx [30]. One of the lipid-modifying enzymes that have generated a lot of interest recently is 5-lipoxygenase (5LO) which is produced by macrophages and is an important enzyme in the conversion of the lipid molecule arachidonic acid into leukotrienes. Hence, *5LO* may serve as a gene driving chronic inflammation and thereby the progression of atherosclerotic plaques.

In line with this hypothesis, *5LO* has recently been shown in genetic and knockout studies in mouse to play a major role in promoting plaque growth [31]. Based on these findings in mice, polymorphisms in the promoter ofso *5LO* have been studied in patients and were correlated with the progression of lesion formation based on measurements of the thickness of the vessel wall [32]. These seminal observations place genes interacting with *5LO* in a prime position as candidate genes for coronary artery disease (CAD). Among those genes is *ALOX5AP*, encoding 5LO-activating protein (FLAP). A recent study by Helgadottir et al. from deCODE genetics elaborated successfully on this clinical question, by performing a linkage study in a large set of Icelandic families [33]. Sum of 296 families were studied, including 713 patients with myocardial infarct, generating a highly susggestive linkage peak to a locus on chromosome 13q.

Subsequently, this chromosomal region was further investigated by association analysis with 120 microsatellite markers in a study including around 800 cases and controls. This screen resulted in the detection of a haplotype spanning two genes including *ALOX5AP*. The study by Dwyer et al. has also investigated the role of gene-environment interactions by studying the effect of diet on *5LO* promoter polymorphisms [32]. First, a subgroup of carriers of a particular promoter variant was identified, which showed increased carotid artery intima-media thickness. Second, it was shown in these allele carriers that dietary arachidonic acid, the substrate for *5LO*, increased the production of inflammatory mediators, as compared to subjects that were fed a "marine" diet with N-3 fatty acids. Another gene identified in human linkage studies of myocardial infarct, named, *myocyte-enhancing factor 2A* (*MEF2A*), is expressed in endothelial cells of coronary arteries. A 21-base pair deletion was identified in exon 11 in all ten living members within the family, and not in family members and an additional 119 individuals with normal angiograms, strongly suggesting that the deletion is responsible for myocardial infarct in this large family [34]. *MEF2A* mutations may be a rare cause of myocardial infarct because they are present in less than 2% of a US population of 207 patients [35]. Furthermore, adiponectin has thought to have variety of metabolic effects on obesity, insulin sensitivity, and atherosclerosis. To identify genes influencing variation in plasma adiponectin levels, Ling et al. performed genomewide linkage and association scans of adiponectin in two cohorts of subjects [36]. The genomewide linkage scan was conducted in 789 family members of Turkish and southern European and 2,280 northern and western European. A whole genome association (WGA) analysis was carried out on approximately 1,000 subjects with dyslipidemia and 1,000 overweight subjects with normal lipids. In conclusion, these results support an effect of DNA variation at the *ADIPOQ* locus (the adiponectin structural gene) influencing plasma adiponectin levels. However, the degree to which DNA sequence variants at this locus influence health and disease remains to be seen. Furthermore, these analyses indicated that SNPs at the *ADIPOQ* locus were the most strongly associated with adiponectin variation throughout the entire genome.

2. Genetic Models for Atherosclerosis

The use of genetic models has greatly assisted investigations of the natural history, mechanisms, and potential therapy for atherosclerosis. In the past several years, the advent of molecular techniques has enabled investigators to produce additional novel genetic models of disease that have further enhanced the study of vascular biology and medicine. Particularly valuable models in vascular diseases investigations are inbred genetic strains, transgenic animals, gene targeting by homologous recombination, and *in vivo* gene transfer [37]. Distinct types of experimental design that has used inbred mouse strains which differ in their predisposition to atherosclerosis has revealed more precise whether differences in lipid profiles were restricted to particularly dietary terms or reflect an underlying genetic factors that contribute to atherosclerotic susceptibility. The most often used mouse models of atherosclerosis were a high-fat model in which inbred mice are fed a high-fat and cholesterol diet, *ApoE*-deficient mice fed either chow, a Western diet, and *Ldlr*-deficient mice fed either a Western diet or a high-fat and cholesterol diet [38]. In order to exempt dyslipidemia as a crucial factor for the development of atherosclerosis, one of the first investigators in this particular area, has used *apoE*-deficient mice strains, extensively studied mouse model of atherosclerosis that develops atherosclerosis on a chow diet [39–41]. The authors bred *apoE*-deficient mice that had C57BL/6J or strain susceptible to atherosclerosis and C3H/HeJ, a prototypical atherosclerosis mouse resistant strain. The study demonstrated that in mice with an *apoE*-deficient background that were fed a chow diet, there were not major differences in plasma lipids. Nevertheless, The same study has revealed that mice with the C57BL/6J background developed markedly more atherosclerosis than mice with C3H/HeJ background, indicating that differences in atherosclerosis susceptibility do not reside in differences in plasma lipid level. There are variety of cell types involved in atherosclerotic process, including endothelial cells, smooth muscle cells, monocytes, macrophages, and T lymphocytes. Genetic variation that affects some of these cell types could influence susceptibility to atherosclerosis. In a second series of experiments, Shi and collaborators have analyzed the cellular compartments that have a role in genetic susceptibility to atherosclerosis in mice [39]. They have generated chimeric mice by performing bone marrow transplantation of C57BL/6J bone marrow into C3H/SW mice and C3H/SW marrow into C57BL/6J mice. They have proved that C56BL/6J mice that received C3H/SW bone marrow were not protected from atherosclerosis, and C3H/SW mice that received C57BL/6J bone marrow did not develop increased atherosclerosis. General conclusion of this study is that atherosclerosis development was determined by the genotype of the host rather than the genotype of bone marrow donor, suggesting that genetic differences in atherosclerotic susceptibility are not conditioned by the hematopoietic cells. Some novel studies have yielded similar results [42]. Sequentially *ex vivo* studies of endothelial cells isolated from C57BL/6J mice showed substantial induction of a limited panel of proinflammatory genes (*MCP-1*, *M-CSF*, *VCAM-1*, and *heme*

oxygenase-1) in response to minimally modified LDL (MM-LDL), where endothelial cells from C3H/HeJ mice did not. These results suggest the plausibility that the differences in atherosclerotic susceptibility between these two mice strains relate to genetic difference in the proinflammatory response of endothelial cells to a specific inflammatory stimulus, MM-LDL.

3. Conclusions

Beyond the traditional risk factors, less well-established risk factors for atherosclerosis development are being firmly evaluated in recent years. The outcome of these efforts will not only unveil the molecular basis of atherosclerosis but also allow prospective prediction from an early age of individuals who are predisposed to develop premature atherosclerosis as well as to facilitate the discovery of drug targets and individualized medications against the disease. Our understanding of the pathogenesis of this process has evolved in the last few decades, guiding our efforts to find treatments. The relatively recent appreciation that inflammatory response plays a key role in atherogenesis implies that inhibiting inflammation may provide new anti-atherosclerosis therapy.

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