Musings

Musings on genome medicine: cholesterol and coronary artery disease

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Abstract

Cholesterol levels and not inflammatory markers are the major variables that pose a risk of coronary artery disease. Diabetes greatly increases the risk at any cholesterol level. Coronary artery disease and cancer are linked by a common protein - an apoptotic protein that also functions as a regulator of insulin secretion.

Although it is difficult for a pair of hematologists/oncologists to admit, cardiologists teamed with public health aficionados and pharmaceutical companies have made a huge dent in the death and disability rates induced by atherosclerosis and coronary artery disease (CAD). The relatively puny successes of our brethren in oncology pale by comparison (although we have definitely turned the corner). In this month's Musings, we address the role of cholesterol in CAD.

Much of the success in atherosclerosis and CAD has derived from changes in life style that have been informed by increasing awareness of the risks of saturated fat and cholesterol in the diet and a better understanding of the hazards of diabetes, obesity, hypertension and smoking. Here emerge interesting similarities (and differences) between CAD and cancer. Cancer incidence is only slightly influenced by diet and not all by hypertension, but obesity influences cancer incidence and over 30% of cancer incidence is due to tobacco use. Curiously, diabetes and cancer are unexpectedly linked, as we discuss below. Furthermore, hypertensive heart disease, CAD and cancer are particularly dangerous illnesses in African Americans, which strongly supports a genetic basis for both diseases.

Although the role of cholesterol in the genesis of atherosclerosis and CAD seems obvious today, the pathway to that recognition has been littered with obstacles. Confusion about the primary (and indeed uniquely essential) role of plasma cholesterol levels in the genesis of CAD stems from misinterpretation of the results of the Framingham Heart Study. The overlap of cholesterol levels in individuals who did or did not have CAD prompted William Castelli, an experienced observer, to state: 'cholesterol levels by themselves reveal little about a patient's coronary artery disease risk' [1]. Although Castelli recognized that almost every individual with a blood cholesterol level greater than 300 mg per deciliter did have CAD, he failed to note that no individual in the Framingham cohort with a cholesterol level lower than 140 mg per deciliter developed CAD.

Clearly, the problem we face is quite simple; we accept cholesterol levels that induce a high risk of CAD as 'normal'. In fact, if one plots CAD risk as a function of cholesterol level, a near-linear relationship emerges [2,3]: the lower the cholesterol level and the longer the low level is maintained, the lower the risk. It is frustrating to read accounts in major journals that other factors, for example vague indices of inflammation such as C-reactive protein [4-6], might have any important primary role in the pathogenesis of heart disease. It is certainly true, as demonstrated years ago by Ross and Agius [7], that invasion of the intimal cells of arteries by cholesterol is associated with macrophage activation, and the release of damaging cytokines within the

intima would certainly result in inflammation of the vessel wall. Atherosclerosis, through activation of macrophages, can actually cause ulcerating lesions in the great vessels. So inflammation clearly has a role, but positing that it has a primary role in the disorder is not supported by the data.

Atherosclerosis is a chronic disease that often begins in childhood when excess plasma low density lipoprotein (LDL) particles, consisting predominantly of cholesterol esters and a protein called ApoB100, accumulate in plasma and spill over into vessel walls [8,9]. Approximately 70% of cholesterol absorbed from the diet or synthesized in the liver by 3-hydroxyl-3-methylglutaryl coenzyme A reductase (HMGCoA reductase, the target of statins) is carried in the circulation on LDL particles. These circulating particles deliver lipids to cell membranes via LDL receptors that dump the particles into lysosomes in which the cholesterol esters are processed and from which the free cholesterol is transferred to cell membranes. A paucity of lipoproteins leads to cholesterol deficiency in the cell membrane and concomitant cell deformity and dysfunction, the Bassen-Kornzweig syndrome [10]. An excess of LDL production or a deficiency of lipoprotein receptors leads to accumulation of LDL-cholesterol particles in the circulation [8]. These excessive particles are engulfed by 'scavenger' receptors, particularly on macrophages. The macrophages turn into foam cells and release toxic cytokines. The process of atherosclerosis is thus initiated.

Appallingly, CAD is readily detectable in a high proportion of otherwise 'healthy' teenage American males on a high-salt, high-fat, meat diet [11], just as rabbits fed cholesterol rapidly develop the disease [12]. The rate and extent of atherosclerosis is therefore influenced by diet, and both are markedly accelerated by inactivating mutations in LDL receptor genes and mutations in the *ApoB* genes that interfere with the binding of LDL to the LDL receptor [8]. The two mutations are uncommon but dominant.

African Americans have a higher incidence and severity of heart disease than Caucasian Americans, even when diabetes, obesity and smoking are taken into account [13]. But African Americans with inactivating mutations of *PCSK9*, a gene whose product inhibits the synthesis of LDL receptors, have much lower rates of heart disease, as defined by myocardial infarction, sudden death or need for revascularization [14]. This recent observation provides overwhelming evidence that LDL-cholesterol levels are the key to CAD. Evidence of inflammation, such as increased serum levels of C-reactive protein, are a secondary consequence of atherosclerosis and may be of some predictive value in particular circumstances, but these are epiphenomena and therefore relatively unimportant. The medical focus must be on cholesterol.

The high incidence of CAD in diabetes is not entirely understood, but it is certainly related, at least in part, to cholesterol levels, and is perhaps enhanced by elevated triglycerides. It is tempting to propose that glycosylation of endothelial cells and/or macrophages may also have a role and may enhance atherosclerosis at any level of LDL, but that is purely speculative. Far less speculative is the remarkable cell biological and biochemical link between cancer incidence and diabetes (and thus CAD) recently discovered by Danial, Walensky and their colleagues [15]. These investigators [15] have observed that BAD, an apoptosis promoting protein that contributes to cancer development when it is inactivated, has a major role in insulin production. A chemically stabilized peptide derived from BAD stimulates glucokinase and thus insulin production in type 2 diabetic rodents and normalizes their glucose tolerance curves. Here we observe a perfect example of 'the wisdom of the body'. The same gene is used to prevent cancer and diabetes with its concomitant CAD, three of the most important diseases of mankind. Furthermore, the study demonstrates that the chemically stabilized peptide approach may turn non-receptor proteins into drug targets.

Although enormous progress has been made in the management of the CAD epidemic that has plagued 'developed' societies since the 20th century and although new avenues of research are regularly opening, we remain troubled by a vexing problem. If CAD does not occur below an LDL cholesterol level of 140 mg/deciliter, why do we fail to maintain our citizens as close to that level as reasonable by diet if possible and with statins if not? At what age should we begin that approach? We know that many teenagers on a standard American diet already have the disease. Therefore, we must start early, but how early? Children need cholesterol for proper brain development. These are the issues that should be front and center. We should not be distracted by epiphenomena.

Abbreviations

CAD, coronary artery disease; HMGCoA, 3-hydroxyl-3-methylglutaryl coenzyme A reductase; LDL, low density lipoprotein.

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