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RESEARCH ARTICLE

GENETIC DETERMINANTS OF RESTENOSIS: A PATH LESS TRAVELLED

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ABSTRACT

Percutaneous coronary intervention (PCI) with stent placement is a standard treatment for coronary artery disease (CAD). Despite the use of drug eluting stents (DESs), restenosis remains a challenging clinical problem. Restenosis is the maladaptive response of the coronary artery to injury. Oxidative stress, inflammation and neointimal hyperplasia have been implicated in the process of restenosis. However, the molecular and biochemical pathways of restenotic process are not fully understood yet. Furthermore, as restenosis is assumed to be a multigenetic process and genetic predisposition is considered an important risk factor, analysis of the genome-wide gene expression is recommended for better insight of the phenomenon along with comparison among different study groups.

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INTRODUCTION

Cardiovascular diseases (CVDs) refer to disorders of the heart and circulatory system. Though over the last two decades cardiovascular mortality rates have declined in many developed countries, still CVDs represent a major cause of morbidity and mortality worldwide. Even in developing countries, cardiovascular related deaths and diseases have increased at an astonishingly fast rate (Gaziano, 2008 and Reddy, 1998). Epidemiologists in India and international agencies, such as the World Health Organization (WHO) have been sounding an alarm on the rapidly rising burden of CVDs for the past 15 years (Libby, 2002; Reddy, 1993 and 2005). According to WHO, an estimated 17.3 million people died from CVDs in 2008, which accounted for 30% of all global deaths. Based on the global trends, WHO have predicted that, by 2030, almost 23.6 million people will die from CVDs and India will supercede all other nations owing to the highest burden (http://www.who.int/mediacentre/factsheets/fs317/en/index.html).

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CVDs comprise of a broad category of diseases which include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. Among them, CAD is the most important underlying cause of CVD-related deaths (Bachar, 2007). Advancing atherosclerosis leads to narrowing or occlusion of major coronary arteries and their branches, which manifests as CAD thereby resulting in angina, heart failure or myocardial infarction (Koerselman, 2003).

Pathogenesis of CAD

The exact pathogenesis of CAD is not clear and no single theory adequately explains the atherosclerotic process. Two main explanations have been proposed: the lipid hypothesis and the chronic endothelial injury hypothesis. These explanations are probably inter-related and are certainly not mutually exclusive. The lipid hypothesis speculates that elevation in lipid plasma levels promotes lipid penetration of arterial walls. It is considered that this process is instigated by abnormal lipid metabolism or excessive dietary intake of cholesterol and saturated fats, particularly when coupled with a

genetic predisposition. Low-density lipoproteins (LDLs) are the primary atherogenic lipids, whereas high-density lipoproteins (HDLs) have a protective effect and probably help in mobilizing LDLs. When LDLs undergo oxidation in the body, they become harder to mobilize and get locally cytotoxic. This is where the lipid hypothesis and endothelial injury hypothesis potentially overlap (Libby, 2005 and El-Sherif, 2010). According to the latter theory, the initial step in the formation of atherosclerosis is the weakening of the arterial glycosaminoglycans (GAGs) layer. GAGs protect the arterial endothelium and promote its repair. The exposed endothelial cells of the artery are prone to free-radical damage making these sites more permeable to plasma constituents, particularly lipoproteins (Libby, 2005 and El-Sherif, 2010). Besides oxidized LDLs (OxLDLs), several other factors can damage endothelial cells and induce plaque formation. These factors may be immunologic, inflammatory, viral, chemical, mechanical or physical in nature. In response to cell injury, macrophages migrate from circulation into the cells that line the subendothelial layer of the intima CAD accounts for approximately 25% of total deaths in the developed world and 15% in the developing world (Gaziano, 2008). In India, the prevalence of CAD is around 3.9% (Ashavaid, 2004). So, CAD is the leading cause of death globally, where India has the highest burden.

Risk factors

Risk factors for CAD include high blood pressure, high cholesterol levels, smoking, positive family history, diabetes, obesity, physical inactivity, high stress, male gender, alcohol abuse, old age and radiation therapy to the chest as used for certain types of cancer. Sometimes, CAD develops without any classic risk factors. Various other possible risk factors are elevated blood homocysteine, elevated fibrinogen, high CRP, low levels of selenium, high levels of lipoprotein (a) [Lp (a)] and sleep apnea (Bachar, 2007; Ashavaid 2004 and El-Sherif, 2010).

Symptoms

Restricted blood flow may not cause any symptoms at first. But various signs and symptoms develop as the plaques continue to accumulate in the coronary arteries. The most often seen symptom is angina pectoris**.**Other symptoms includes hortness of breath, modest increase in heart rate or significant elevation in systolic and diastolic blood pressure (Libby, 2008; Azevedo, 2000 and El-Sherif, 2010).

Diagnosis, Screening and Monitoring

The initial diagnostic approach for CAD encompasses a detailed patient history, complete physical examination and an electrocardiogram (ECG). Once the initial evaluation is performed, laboratory blood tests, stress testingand cardiac catheterization may be necessary to obtain further diagnostic insight. Levels of LDL cholesterol, triglycerides and LDL to HDL cholesterol ratios should be monitored in patients at risk for developing CAD. In addition, they should be assessed for other co-existing disorders which are known to increase the risk (e.g. hypertension, hypercholesterolemia, diabetes and hypothyroidism) (Libby, 2008 and El-Sherif, 2010).

Treatment

The multiple approaches to treat CAD involve lifestyle changes such as diet, exercise, meditation and medications such as antiplatelet agents, hypolipidemic drugs, beta blockers, calcium channel blockers, nitrates, angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (Ashavaid, 2004 and El-Sherif, 2010).

Revascularization

Sometimes more aggressive treatment is needed like interventional or surgical procedures so as torestore and improve the blood flow. The primary revascularization options are PCI and CABG surgery. As CABG requires open-heart surgery, it is often reserved for cases of multiple narrowed coronary arteries. The most common PCI techniques are PTCA and coronary stenting (Dotter, 1964 and Arjomand, 2003).

Restenosis

Restenosis is the maladaptive response of the coronary artery to injury. The simplest and most widely used definition of restenosis is a diameter stenosis of 50% at follow-up. This occurs in 12-60% of the patients within 6 months after intervention, depending on patients' characteristics and the interventional techniques used (Fattori, 2003 and Pache, 2003). Three distinct processes involved in restenosis are: recoil of the vessel, neointimal proliferation and early thrombus formation. The relative contribution of each of these depends on the type of injury (Mintz, 1996). Restenosis, the aphorismic "Achilles heel", remains to be conquered after stenting. For these reasons, there is a growing interest in understanding the biology of restenosis so as to elucidate the underlying mechanisms and thus the predisposing risk factors. Despite the intensive studies performed on restenosis, the factors contributing to its development have not been completely elucidated. Growth factors and cytokines are the major stimuli for proliferation of smooth muscle cells. After an artery is injured, deposition of platelets, leucocyte infiltration, expansion of smooth muscle cells, deposition of extracellular matrix and re-endothelialisation occur. The platelets release platelet derived growth factor (PDGF), transforming growth factor (TGF), epidermal growth factor (EGF) and thrombin, which stimulate the migration, growth and division of smooth muscle cells (Lee, 2004). Increased oxidative stress and oxidizing metabolites generated by impaired redox processes at the site of coronary angioplasty can induce chain reactions that may lead to some of the possible causes of restenosis (Misra, 2008; Azevedo, 2008). Various studies have implicated the role of oxidative stress (Misra, 2005 and Azevedo, 2000), inflammation (Kornowski, 1998), smooth muscle cells (migration, de-differentiation and proliferation) (Lee, 2004). and neointimal hyperplasia (Mitra, 2006) in the development of restenosis. But the relative importance of these mechanisms is not fully defined. Advent of genomics has led to the genomic interrogation of the human restenoticprocess. However, most of the work has focused on the development of risk markers through assessment of single nucleotide polymorphisms (SNPs) and the probing for genes involved in the restenotic process. Current studies have shown only a fraction of genes involved in coronary restenosis. These involve the renin-angiotensin system (Hamon, 2003), platelet aggregation (Wheeler, 2002), inflammatory response (Marculescu, 2003), matrix metalloproteinases (MMPs) (Blankenberg, 2003), smooth muscle cell proliferation, lipids (Gazzaruso, 2003), oxidative stress and nitric oxide (Gorchakova, 2008). As restenosis is assumed to be a multifactorial and multigenetic process, instead of studying

single candidate genes or SNPs, analysis of the whole genome is recommended, which nowadays can be assessed by gene microarrays. Thousands of genes can be monitored simultaneously in parallel fashion with this microarray technology (Gibbons, 2004). Further comparing the profile of different groups and elucidation the role of associated genes is the need of hour.

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