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Review Article

Atherosclerosis: Current perspectives

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ABSTRACT

Atherosclerosis is among greatest concerns of contemporary medical science and care, and its dangerous sequel are common knowledge. Atherosclerosis is not just state of excessive activation of innate but involvement also of adaptive immune responses. Adipose tissue cytokines and their diverse shared biological traits with the immune system counterparts orchestrate an immune mediated inflammatory process. Medical progress in transcriptomics and epi-genetics has primarily been driven in recent years by the subclinical chronic inflammation implied in atherosclerosis. Contemporary evidence based medicine has added obligation to individualized address implying molecular approach to diagnosis and management. The context of new knowledge on pathogenesis and rational remediation is pertinent to update clinical approach to atherosclerosis and its complications. The present narrative attempts to incorporate some current perspects for discussion.

1. Introduction

A century ago in 1914, Anitchkow explained role of cholesterol in development of atherosclerosis and gave cholesterol fed rabbit model of atherosclerosis. Atherosclerosis is a complex, partly physiological phenomenon that commences in early childhood. The growth and localization of individual plaque determines its pathological significance. Endothelial dysfunction, vascular smooth muscle cell proliferation/invasion/secretion, matrix fragmentation, collagenization and glycation are characteristics of aging arterial phenotype that creates a microenvironment enriched with reactive oxygen species (ROS) for pathogenesis of arterial disease. This nich creates an age associated arterial secretory phenotype.[1] Chronic stresses which require significant cell renewal, frequently disturb tissue homeostasis, with causal contribution to chronic diseases as atherosclerosis, diabetes and cancer.[2]

1.1. *Epigenetics perspective*

The perturbations in cellular function may be mediated by epigenetic mechanisms.[3] Diet, smoking, physical activity and other environmental exposures alter epigenetic marks and processes. Nutrition and lifestyle factors impact upon major cellular stressors, e.g. inflammation, metabolic stress and oxidative stress. Opportunities for developing novel interventions to prevent, delay or treat the complex diseases can emerge from epigenetic understanding. As an example, genome-wide analysis of DNA methylation marks (which vary between

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individuals and within individual over a substantial time period) has revealed genetic loci which are associated with adiposity.[4]

Different rates of chronic disease afflictions in different ethnic groups have genetic bases. The same is important also to explain very high chronic disease prevalence in society. The implied genes may have been useful in earlier stages of evolution that drastically differ from present. Genes which allow the fetus to successfully adapt to under-nutrition are likely to be favored by natural selection, even though they may lead to disease and premature death in later life.[5] It is alarming that proportion of obese women getting pregnant is consistently on rise and obesity associates deleterious consequences to baby.[6,7] Over-nutrition associates stress in utero and may epigenetically mark the developing fetus, with long term consequences for patterns of gene expression, cell function and health. The genes involved in regulating appetite and satiety are differently regulated, a mechanism potentially risky for promoting obesity.[8] While most epi-genetics research is currently devoted to fetal and early postnatal life, the possibility of lifelong epi-genome plasticity in response to dietary or other exposures needs examination.

1.2. *Perspective on master metabolic switch, the PPARs*

PPAR nuclear receptor superfamily has three isoforms alfa (PPARa), beta/delta (PPARb), and gamma (PPARr), playing important role in regulation of metabolism of carbohydrates, lipids and protein. Effective strategies aiming at prevention and elaboration of therapeutic actions on obesity, diabetes and its complications may be based on PPAR mechanisms of metabolic regulation. PPARb was seen to regulate expression of genes for proteins involved in uptake and storage of fatty acids and retinol.[9] Vitamin A deficiency was found to increase PPAR expression and modified the regulation of expression of genes for enzymes regulating mitochondrial energetic.[10] Study in rat showed vitamin A and E regulate gene expression of carbohydrate and lipid metabolism and also ameliorate changes associated with obesity induced by high fat diet.[11]

Evidence of involvement of nuclear peroxisome proliferator activated receptors is found in pathogenesis of chronic diseases stemming from metabolic disorder.[12–16] Environmental factors as diet interact with genetic background to modulate metabolic promoters and this relationship is affected by polymorphism in PPAR-alfa (PPARa). The Relationships between polyunsaturated fatty acid (PUFA) intake and lipid parameters exhibit differences among ethnic groups by effect of PPARa genetic variants. Influence of allele frequencies of PPARa SNPs (single nucleotide polymorphisms) on genotype–diet interactions was thus, indicated in relation of n6 or n3 fatty acid intake and total and LDL serum cholesterol concentration.[17] Other PPAR-gamma (PPARr) and PPARa genotype interactions have also been described, in reference to relation of dietary intakes with plasma lipids.[18] PPARa is involved in homeostasis of lipids in the fasted as well as postprandial state of fat rich diet. Lifestyle, drugs and dietary modifications, including consumption of foods that can activate PPARa can affect its metabolic responses. The genetic variant determines specificity of these effects. Disease risk associating the variants depends on such interaction background. Diet can have long lasting effect on PPARa gene expression and parental exposures may induce unique epigenetic effects that underlie complex disease.[19]

2. Pathogenesis

Atherosclerotic process is preceded by endothelial inflammation provoked by atherogenic risk factors and begins with uptake of modified LDL-cholesterol at certain sites. Smooth muscle proliferation and formation of extracellular matrix around the developing fatty deposit, leads to atheroma or atherosclerotic patch. Such plaque is prone to break away and trigger thromboembolism and clinical manifestations.

2.1. *Involvement of immune mechanisms*

Atherosclerosis is chronic inflammatory process associated with enhanced serum levels of inflammation parameters, including C-reactive protein in particular. As seen in chronic inflammation, atherosclerotic vessels produce hydrolytic enzymes, adhesion molecules, cytokines and growth factors. The patho-physiology of atherosclerosis comprises of various important steps. These include, enhanced endothelial permeability, expression of adhesion molecules, monocyte immigration and adhesion, foam cell formation and fatty streaks.

Health and disease homeostasis depends largely upon the recognition and response to damage associated molecular patterns (DAMPs) derived endogenously, or the exogenous pathogen associated molecular patterns (PAMPs). In the maintenance task appropriate innate and adaptive immune responses, degree of inflammation and sets of mediators, are implicated. Increasing numbers of endogenous host origin danger signals are being identified, including the oxidized-modified LDL. Increased lipid per-oxidation in the vessel endothelium generates oxidation specific epitopes. These epitopes on oxidized lipoproteins and on the surface of dying cells and circulating micro-particles, have potential to react with germline encoded pattern recognition receptors (PRRs) present on both immune and nonimmune cells. Robust pro-inflammatory and pro-thrombotic responses may be then triggered.[20]

TLRs (Toll Like Receptors, the molecular pattern recognizing receptors) are important for development of atherosclerosis and are expressed in atherosclerotic lesions.[21] Oxidized LDL up-regulates TLR expression in macrophages. TLR-NFkB pathway is activated in the lesions, transcripting genes related to inflammation and cell proliferation, critical to atherogenesis.[22] These ultimately lead to synthesis and release of antimicrobial peptides and inflammatory cytokines that provide critical link to adaptive immune response.[23] Pro-inflammatory cytokines with Th1 type cytokine Interferon-gamma (IFNr), being a key mediator, play major role and a systemic chronic low grade immune mediated inflammation (scLGI) is recognized to culminate in to atherosclerosis.

Cascades of systemic inflammatory mediators activating the endothelium have cytokines, such as IL1 and TNF-alfa as proximal components. These lead to endothelial dysfunction and alter the balance within lymphocyte subpopulations. The later contain distinct arsenals of secretory mediators, such as interferons, interleukins and chemokines. Lymphocyte