Sistema immunitario nell'aterosclerosi aa 2024-2025

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Souilhol C et al. (2020) Endothelial responses to shear stress in atherosclerosis: a novel role for developmental genes. Nat Rev Cardiol. Cardiol. 17:52-63.

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Nat Rev Nephrol. 2017 Jun;13(6):368-380. doi: 10.1038/nrneph.2017.51. Epub 2017 Apr 10.

The immunology of atherosclerosis.

Gisterå A, Hansson GK.

Abstract Cardiovascular disease is the leading cause of death worldwide, both in the general population and among patients with chronic kidney disease (CKD). In most cases, the underlying cause of the cardiovascular event is atherosclerosis - a chronic inflammatory disease. CKD accelerates atherosclerosis via augmentation of inflammation, perturbation of lipid metabolism, and other mechanisms. In the artery wall, subendothelial retention of plasma lipoproteins triggers monocyte-derived macrophages and T helper type 1 (T_H1) cells to form atherosclerotic plaques. Inflammation is initiated by innate immune reactions to modified lipoproteins and is perpetuated by T_H1 cells that react to autoantigens from the apolipoprotein B100 protein of LDL. Other T cells are also active in atherosclerotic lesions; regulatory T cells inhibit pathological inflammation, whereas T_H17 cells can promote plaque fibrosis. The slow build-up of atherosclerotic plaques is asymptomatic, but plaque rupture or endothelial erosion can induce thrombus formation, leading to myocardial infarction or ischaemic stroke. Targeting risk factors for atherosclerosis has reduced mortality, but a need exists for novel therapies to stabilize plaques and to treat arterial inflammation. Patients with CKD would likely benefit from such preventive measures.

Nat Rev Cardiol. 2020 Jan;17(1):52-63. doi: 10.1038/s41569-019-0239-5. Epub 2019 Jul 31

Endothelial responses to shear stress in atherosclerosis: a novel role for developmental genes

Celine Souilhol, Jovana Serbanovic-Canic, Maria Fragiadaki, Timothy J Chico, Victoria Ridger, Hannah Roddie, Paul C Evans

Flowing blood generates a frictional force called shear stress that has major effects on vascular function. Branches and bends of arteries are exposed to complex blood flow patterns that exert low or low oscillatory shear stress, a mechanical environment that promotes vascular dysfunction and atherosclerosis. Conversely, physiologically high shear stress is protective. Endothelial cells are critical sensors of shear stress but the mechanisms by which they decode complex shear stress environments to regulate physiological and pathophysiological responses remain incompletely understood. Several laboratories have advanced this field by integrating specialized shear-stress models with systems biology approaches, including transcriptome, methylome and proteome profiling and functional screening platforms, for unbiased identification of novel mechanosensitive signalling pathways in arteries. In this Review, we describe these studies, which reveal that shear stress regulates diverse processes and demonstrate that multiple pathways classically known to be involved in embryonic development, such as BMP-TGFβ, WNT, Notch, HIF1α, TWIST1 and HOX family genes, are regulated by shear stress in arteries in adults. We propose that mechanical activation of these pathways evolved to orchestrate vascular development but also drives atherosclerosis in low shear stress regions of adult arteries.

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Familial Hypercholesterolemia: A Complex Genetic Disease With Variable Phenotypes

Maria Donata Di Taranto [1], Carola Giacobbe [1], Giuliana Fortunato [2]

Abstract Familial hypercholesterolemia (FH) is the most frequent genetic disease and is characterized by elevation of LDL-cholesterol that accumulates in tissues leading to premature atherosclerosis and sometime tendon xanthomas. Main causes of FH are pathogenic variants in the genes encoding the LDL receptor (LDLR), its ligand - the apolipoprotein B (APOB) - or Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9). Rarer causes include variants in genes encoding apolipoprotein E (APOE) and the signal-transducing adaptor family member 1 (STAP1). Genetics of FH is extremely complicated by 1. high heterogeneity, 2. presence of variant clusters and 3. phenotypic variability. In fact, a great variability was observed among patients with the same genetic status: an overlap of LDL-cholesterol levels was observed between heterozygous patients (HeFH) and homozygous FH patients, as well as some HeFH showed a normal lipid profile. A correct pathogenicity evaluation is the first step to correctly define the genetic status helping to identify the variants which really cause the FH. Several phenotypic differences were observed among HeFH patients

carrying different variant types (null or defective) or variants in different affected genes. Patients with a null variant in LDLR gene showed higher LDL-cholesterol levels and higher risk for coronary artery disease than patients with a defective variant. Pathogenic variants in several lipid-related genes causing different dyslipidemias were found among FH patients acting as both modifying factors (worsening the phenotype) and confounding factors (needing a differential diagnosis to be discriminated from FH). This review aims at depicting the complex genetic basis of FH.

Nat Rev Immunol.12:204

The immune system in atherosclerosis.

Hansson GK, Hermansson A.

Abstract Cardiovascular disease, a leading cause of mortality worldwide, is caused mainly by atherosclerosis, a chronic inflammatory disease of blood vessels. Lesions of atherosclerosis contain macrophages, T cells and other cells of the immune response, together with cholesterol that infiltrates from the blood. Targeted deletion of genes encoding costimulatory factors and proinflammatory cytokines results in less disease in mouse models, whereas interference with regulatory immunity accelerates it. Innate as well as adaptive immune responses have been identified in atherosclerosis, with components of cholesterol-carrying low-density lipoprotein triggering inflammation, T cell activation and antibody production during the course of disease. Studies are now under way to develop new therapies based on these concepts of the involvement of the immune system in atherosclerosis.

Nat Rev Immunol. 2010 Jan;10(1):36-46. doi: 10.1038/nri2675. Epub 2009 Dec 4.

Macrophage death and defective inflammation resolution in atherosclerosis.

Tabas I.

Abstract A key event in atherosclerosis is a maladaptive inflammatory response to subendothelial lipoproteins. A crucial aspect of this response is a failure to resolve inflammation, which normally involves the suppression of inflammatory cell influx, effective clearance of apoptotic cells and promotion of inflammatory cell egress. Defects in these processes promote the progression of atherosclerotic lesions into dangerous plaques, which can trigger atherothrombotic vascular disease, the leading cause of death in industrialized societies. In this Review I provide an overview of these concepts, with a focus on macrophage death and defective apoptotic cell clearance, and discuss new therapeutic strategies designed to boost inflammation resolution in atherosclerosis.

Nature 2008; 454:470-7

Integration of metabolism and inflammation by lipid-activated nuclear receptors.

Bensinger SJ, Tontonoz P.

Abstract The nuclear receptors known as PPARs and LXRs are lipid-activated transcription factors that have emerged as key regulators of lipid metabolism and inflammation. PPARs and LXRs are activated by non-esterified fatty acids and cholesterol metabolites, respectively, and both exert positive and negative control over the expression of a range of metabolic and inflammatory genes. The ability of these nuclear receptors to integrate metabolic and inflammatory signalling makes them attractive targets for intervention in human metabolic diseases, such as atherosclerosis and type 2 diabetes, as well as for the modulation of inflammation and immune responses.

Cell. 2015 Mar 26;161(1):161-72. doi: 10.1016/j.cell.2015.01.036.

A century of cholesterol and coronaries: from plaques to genes to statins.

Goldstein JL[1], Brown MS[2].

Abstract

One-fourth of all deaths in industrialized countries result from coronary heart disease. A century of research has revealed the essential causative agent: cholesterol-carrying low-density lipoprotein (LDL). LDL is controlled by specific receptors (LDLRs) in liver that remove it from blood. Mutations that eliminate LDLRs raise LDL and cause heart attacks in childhood, whereas mutations that raise LDLRs reduce LDL and diminish heart attacks. If we are to eliminate coronary disease, lowering LDL should be the primary goal. Effective means to achieve this goal are currently available. The key questions are: who to treat, when to treat, and how long to treat.

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