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Review article

The role of endothelial mechanosensitive genes in atherosclerosis and omics approaches

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ABSTRACT

Atherosclerosis is the leading cause of morbidity and mortality in the U.S., and is a multifactorial disease that preferentially occurs in regions of the arterial tree exposed to disturbed blood flow. The detailed mechanisms by which *d-flow* induces atherosclerosis involve changes in the expression of genes, epigenetic patterns, and metabolites of multiple vascular cells, especially endothelial cells. This review presents an overview of endothelial mechanobiology and its relation to the pathogenesis of atherosclerosis with special reference to the anatomy of the artery and the underlying fluid mechanics, followed by a discussion of a variety of experimental models to study the role of fluid mechanics and atherosclerosis. Various *in vitro* and *in vivo* models to study the role of flow in endothelial biology and pathobiology are discussed in this review. Furthermore, strategies used for the global profiling of the genome, transcriptome, miR-nome, DNA methylome, and metabolome, as they are important to define the biological and pathophysiological mechanisms of atherosclerosis. These "omics" approaches, especially those which derive data based on a single animal model, provide unprecedented opportunities to not only better understand the pathophysiology of atherosclerosis development in a holistic and integrative manner, but also to identify novel molecular and diagnostic targets.

Contents

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Abbreviations

WSS	Wall shear stress
GC	Greater Curvature
LC	Lesser Curvature
PCL	Partial Carotid Ligation
LCA	Left Carotid Artery
RCA	Right Carotid Artery
LDL	Low density lipoprotein
d-flow	disturbed flow
OS	Oscillatory Shear Stress
LS	Laminar Shear Stress
EC	Endothelial Cell
NO	Nitric Oxide
ECM	Extracellular Matrix
MMPs	Matrix metalloproteinases
eNOS	endothelial Nitric Oxide Synthase
ApoE	Apolipoprotein E
SSRE	Shear Stress Responsive Element
PECAM1	Platelet Endothelial Cell Adhesion Molecule-1
VEGF	vascular endothelial growth factor
AT1R	Angiotensin Type 1 (AT1) Receptor
TRPCs	Transient Receptor Potential Channels
ERK	Extracellular Signal-Regulated Kinase
GAGs	glycosaminoglycans
PKCα	Protein Kinase C-α
CASK	Calcium/Calmodulin-Dependent Serine Protein Kinase
LINC	Linker of Nucleoskeleton to the Cytoskeleton
SUN	Sad1p, UNC-84
KASH	Klarsicht/ANC-1/Syne Homology
GPCR	G-protein coupled receptor
AngII	Angiotensin II
MAPK	Mitogen Activated Protein Kinases
FAK	Focal Adhesion Kinase
PI3K	phosphatidylinositol-3-OH kinase
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
ROS	Reactive Oxygen Species
IL	interleukin
HDAC	Histone deacetylase
TNFα	Tumor Necrosis Factor α
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
Keap1	Kelch-like ECH-associated protein 1
AP-1	Activator Protein Complex
NFkB	Nuclear Factor kappa B
Klf	Krüppel-like factor
BMP4	bone morphogenetic protein
MCP-1	Monocyte Chemoattractant Protein
TRE	TPA (phorbol ester)-responsive element
15-H-11,12-EETA	15(S)-Hydroxy-11,12-epoxyeicosatrienoic acid
11,12,15-THETA	11(R),12(S),15(S)-trihydroxyeicosatrienoic acid
15-LO	15-lipoxygenase
EV	extracellular vesicles
DNMT	DNA MethylTransferases
RRBS	Reduced Representation Bisulfite Sequencing
CRE	cyclic AMP Response Element
TGFβ	Transforming Growth Factor
miRNA	microRNA
UTR	untranslated region
SOD	Superoxide Dismutase
SIRT1	sirtuin 1
TMAO	trimethylamine oxide
SM	Sphingomyelin

1. Introduction and overview

Although the physical transduction of force to macroscopic objects has been studied exhaustively, the study of the interplay between physical forces and living cells, known as mechanobiology, is relatively young. Furthermore, although the forces at work in the biological system are much more subtle than in more traditionally studied systems, the responses to these forces are arguably more complex. This review focuses specifically on the effects of one particular force, fluid shear stress imposed by blood flow, on the vascular endothelium in the cardiovascular system and its effects on the pathology of atherosclerosis. Finally, this review aims to present how techniques such as “omics” can be used to translate our knowledge of mechanobiology into specific targets that can be developed into therapeutics for atherosclerosis.

2. Vascular fluid mechanics and disease

2.1. Hemodynamics in the arteries

The cardiovascular system is comprised of a heart pump, a low-pressure venous system which brings blood back to the heart, and a high-pressure arterial system which supplies blood to the body's tissues. The arterial system is divided between the lower pressure pulmonary circulation to the lungs and the higher pressure systemic arterial system flowing from the left ventricle of the heart to the aorta and out to the rest of the body. This review is concerned with the arteries functioning in the systemic circulation. The basic arterial wall structure consists of three layers (Fig. 1): the innermost intimal layer comprised of the endothelium, the middle medial layer mainly comprised of smooth muscle cells, and the outermost adventitial layer, comprised of fibroblastic cells. The endothelium is a monolayer of cells which functions as the barrier between the blood and the rest of the vessel wall, as well as a surface to resist blood clotting. Smooth muscle cells mainly act as the mechanical strength needed to support blood pressure-induced stretch. The forces experienced by the arterial wall include the normal stress of blood pressure induced by blood flow, the circumferential stretch induced by cyclic strain driven by the pressure pulse, and the wall shear stress exerted by the blood flowing tangential to the surface of the blood vessel. The focus of this review is the effect of wall shear stress on the endothelium and its role in pathophysiology of atherosclerosis.

Wall shear stress (WSS), the frictional force between the blood