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Review

Cytoprotective pathways in the vascular endothelium. Do they represent a viable therapeutic target?

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ABSTRACT

The vascular endothelium is a critical interface, which separates the organs from the blood and its contents. The endothelium has a wide variety of functions and maintenance of endothelial homeostasis is a multi-dimensional active process, disruption of which has potentially deleterious consequences if not reversed. Vascular injury predisposes to endothelial apoptosis, dysfunction and development of atherosclerosis. Endothelial dysfunction is an end-point, a central feature of which is increased ROS generation, a reduction in endothelial nitric oxide synthase and increased nitric oxide consumption. A dysfunctional endothelium is a common feature of diseases including rheumatoid arthritis, systemic lupus erythematosus, diabetes mellitus and chronic renal impairment. The endothelium is endowed with a variety of constitutive and inducible mechanisms that act to minimise injury and facilitate repair. Endothelial cytoprotection can be enhanced by exogenous factors such as vascular endothelial growth factor, prostacyclin and laminar shear stress. Target genes include endothelial nitric oxide synthase, heme oxygenase-1, A20 and anti-apoptotic members of the B cell lymphoma protein-2 family. In light of the importance of endothelial function, and the link between its disruption and the risk of atherothrombosis, interest has focused on therapeutic conditioning and reversal of endothelial dysfunction. A detailed understanding of cytoprotective signalling pathways, their regulation and target genes is now required to identify novel therapeutic targets. The ultimate aim is to add vasculoprotection to current therapeutic strategies for systemic inflammatory diseases, in an attempt to reduce vascular injury and prevent or retard atherogenesis.

Contents

Abbreviations: AMPK, AMP-activated protein kinase; bFGF, basic fibroblast growth factor; Bcl-2, B cell lymphoma protein; CRE, cAMP response element; CO, carbon monoxide; CV, cardiovascular; DAF, decay-accelerating factor; Dlk1, Notch inhibitor delta-like 1 homolog; EC, endothelial cells; eNOS, endothelial nitric oxide synthase; GR, glutathione reductase; HDAC, histone deacetylase; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; HO-1, heme oxygenase-1; ICAM-1, intercellular adhesion molecule-1; IFNγ, Interferon-γ; IL, interleukin; Keap1, kelch-like ECH-associated protein; KLF, Krüppel-like factor; LDL, low-density lipoprotein; LPS, lipopolysaccharide; LSS, laminar shear stress; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; MCP-1, monocyte chemotactic protein-1; miRs, Micro-RNAs; MnSOD, manganese superoxide dismutase; mTOR, mammalian target of rapamycin; NO, nitric oxide; NQO1, NAD(P)H:quinine oxidoreductase 1; NF-κB, nuclear factor- κB; Nrf2, NF-E2-related factor-2; OSS, oscillatory shear stress; PDGF, platelet-derived growth factor; PI-3K, phosphinositide-3-kinase; PKC, protein kinase C; PLGF, placental growth factor; RA, rheumatoid arthritis; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; Trx-1, thioredoxin reductase-1; TNF-α, tumour necrosis factor-α; VEGFA, vascular endothelial growth factorA; VSMC, vascular smooth muscle cells; VCAM-1, vascular cell adhesion molecule-1.

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1. Introduction

The importance of endothelial homeostasis for health is often underestimated. The vascular endothelium provides an effective, regulated barrier between the circulating blood and the tissues, which sustains blood flow and an anti-coagulant, anti-adhesive surface. This constitutive role is combined with a rapid response mode. The latter requires endothelial activation. This process, which has been reviewed elsewhere in detail, comprises Type I and Type II activation [1]. Type I is an acute response independent of new gene transcription, with typical mediators including histamine and thrombin. In contrast, Type II activation is more delayed, longer in duration and requires gene transcription. It is well represented by endothelial responses to tumour necrosis factor-α (TNF-α) and interleukin-1 (IL-1) and leads to the upregulation of cellular adhesion molecules E-selectin, vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1. These endothelial responses facilitate the coagulation cascade, angiogenesis, control of vascular tone and permeability and regulation of the leukocyte adhesion cascade [1,2]. Therefore it is unsurprising that factors which compromise endothelial function predispose to vascular diseases.

Endothelial dysfunction is an imprecise term and represents the common end-point of a variety of upstream insults [3]. It is a recognised feature of diseases as diverse as diabetes mellitus, familial hyperlipidemia, sepsis, chronic renal impairment, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Dysfunction follows excessive endothelial cell injury, which predisposes to apoptosis and impaired homeostatic responses. A common feature is the excess generation of reactive oxygen species (ROS) that consume nitric oxide (NO). This in turn generates peroxynitrite and leads to the oxidation of tetrahydrobiopterin and its subsequent uncoupling from endothelial nitric oxide synthase (eNOS) [4]. Additional disease-specific factors that may contribute to endothelial dysfunction include hyperglycemia, advanced glycation end-products, pathogenic antibodies, complement-mediated injury, modified-low-density lipoprotein (LDL), inflammatory cytokines such as TNF-α and activated leukocytes. The associated local inflammatory response drives a vicious cycle of events which, if uncontrolled, leads to barrier breakdown and increased endothelial permeability to monocytes and LDL, which accumulate in the sub-intimal space and initiate fatty streak formation [5,6]. Post-transplantation, immune-mediated endothelial dysfunction results in accelerated arteriosclerosis [7].

Given that endothelial dysfunction is an early adverse biomarker that can be detected by non-invasive techniques [8], therapeutic reversal represents a key clinical goal. However, effective strategies for this have not been easy to identify. This review aims to integrate basic science advances in the understanding of molecular mechanisms regulating endothelial protection, with potential clinical therapeutic strategies aimed at optimising endothelial function and repair.

2. Inflammation and cardiovascular disease

The integral role of chronic inflammation in atherosclerotic plaque development is well recognised [9]. In addition to acting as a catalyst for intense research efforts, this pathogenic observation has encouraged different clinical disciplines to share their insights with respect to atherosclerosis. Thus cardiologists liaise more closely with rheumatologists, renal physicians, endocrinology/metabolic medicine experts and imaging specialists. The recognition that patients suffering from RA or SLE, chronic renal failure, diabetes mellitus and the metabolic syndrome are at risk from premature cardiovascular events provides an opportunity to advance understanding of the underlying molecular mechanisms.

2.1. Pathology of atherogenesis

Excellent recent reviews have described in detail the complex cellular interactions, immune and inflammatory processes that drive atherogenesis and atherothrombosis [9–11]. Pro-inflammatory cytokines including TNF-α and interleukin-1 (IL-1) induce expression of endothelial adhesion molecules including VCAM-1, and act in concert with chemoattractants such as monocyte chemotactic protein-1 (MCP-1, CCL-2) to facilitate the egress of monocytes and T cells from the bloodstream into the developing atherosclerotic plaque. Subsequent proliferation and maturation of monocytes into macrophages is followed by their uptake of LDL via cell surface scavenger receptors to create foam cells [11]. Locally activated vascular smooth muscle cells (VSMC), dendritic cells, mast cells and B cells are present in the developing atherosclerotic plaque. Subsequent apoptosis of VSMC and foam cells leads to the accumulation of cell debris and cholesterol crystals to create a necrotic lipid core which is retained by an overlying fibrous cap.

The importance of cellular adaptive immunity and particularly the pivotal regulatory role of T cells in atherogenesis has emerged over the last decade. Interferon-γ (IFNγ) is a critical pro-atherogenic cytokine. In contrast, the regulatory T cell subset may work in the opposite direction [12]. Similarly B cells may be important, with outcomes reflecting the balance between B1 cells, which are reported to be protective, and B2 cells which may accelerate atherogenesis [9,13,14].

2.2. Atherothrombosis – endothelial erosion and plaque rupture

Atherosclerotic plaques may impair arterial blood flow and induce tissue ischemia. Life-threatening events are typically the result of atherothrombosis leading to myocardial infarction or stroke, with the latter due to plaque embolisation and occlusion of a distal cerebral artery [5].

Changes in the plaque that predispose to atherothrombosis include endothelial erosion and plaque rupture. Plaques are typically covered by arterial endothelium, which is exposed to high levels of shear stress, and circulating pro-inflammatory mediators including TNF-α, IL-1β and eicosanoids. The inflammatory milieu predispose to endothelial cell apoptosis and loss of endothelial monolayer integrity. Endothelial erosion is a recognised feature of plaques obtained from up to 40% of patients suffering coronary thrombosis [15]. Erosion exposes the pro-thrombotic basement membrane. Plaques with this phenotype are typically less inflamed, incorporate proliferating VSMC and undergo significant