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Review

Diabetic microangiopathy: Pathogenetic insights and novel therapeutic approaches

Rosalinda Madonna [a,b], Carmela Rita Balistreri [c], Yong-Jian Geng [b], Raffaele De Caterina [a,*]

[a] Center of Excellence on Aging (CesiMet), Institute of Cardiology, Department of Neurosciences, Imaging and Clinical Sciences, "G. d'Annunzio" University, Chieti, Italy
[b] The Texas Heart Institute, Center for Cardiovascular Biology and Atherosclerosis Research, Department of Internal Medicine, The University of Texas Health Science Center at Houston, Houston, TX, United States
[c] Department of Pathobiology and Medical Biotechnologies, University of Palermo, Palermo, Italy

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ABSTRACT

Diabetic microangiopathy, including retinopathy, is characterized by abnormal growth and leakage of small blood vessels, resulting in local edema and functional impairment of the depending tissues. Mechanisms leading to the impairment of microcirculation in diabetes are multiple and still largely unclear. However, a dysregulated vascular regeneration appears to play a key role. In addition, oxidative and hyperosmolar stress, as well as the activation of inflammatory pathways triggered by advanced glycation end-products and toll-like receptors, have been recognized as key underlying events. Here, we review recent knowledge on cellular and molecular pathways of microvascular disease in diabetes. We also highlight how new insights into pathogenic mechanisms of vascular damage in diabetes may indicate new targets for prevention and treatment.

Contents

Abbreviations: AGEs, advanced glycation end products; PKC, protein kinase C; DAG, diacylglycerol; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; ECs, endothelial cells; VSMCs, vascular smooth muscle cells; vWF, von Willebrand Factor; MAPK, mitogen-activated protein kinase; MMPs, matrix metalloproteinases; PARP, poly-ADP-ribose polymerase; NF-κB, nuclear factor–kappa B; TLR, toll-like receptors; EPCs, endothelial progenitor; MCP, monocyte chemoattractant protein; SDF, stromal cell derived factor; Ang, angiopoietin; DPP-4, dipeptidyl peptidase-4; SMPCs, smooth muscle progenitor cells; BMP6, Bone morphogenetic protein 6; TNF, tumor necrosis factor; FOXO1, Forkhead box O1; CREB, cAMP-responsive element binding; PDGF, platelet-derived growth factor; TGF-β, Transforming growth factor β signaling; HMGB1, high mobility group box 1; IL, interleukin; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; LPS, lipopolysaccharide; AQP1, Aquaporin-1; COX, Cycloxygenase; NFAT, nuclear factor of activated T; TonEBP, Tonicity-responsive binding-protein; FGF, fibroblast growth factor.

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* Corresponding author at: Institute of Cardiology, Department of Neurosciences, Imaging and Clinical Sciences, and Center of Excellence on Aging (CesiMet), "G. d'Annunzio" University - Chieti-Pescara C/o Ospedale SS. Annunziata, Via dei Vestini, 31, 66100 Chieti, Italy. Tel.: +39 0871 41512; fax: +39 0871 402817.
E-mail address: rdecater@unich.it (R. De Caterina).

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1. Introduction

Macro- and microvascular complications are important causes of morbidity and mortality in patients with type 1 (T1DM) and type 2 diabetes (T2DM). The pathogenesis of vascular dysfunctions in diabetes is incompletely understood [1,2]. Hyperglycemia, a key feature of diabetes, is known to exacerbate macrovascular disease, but is also considered the main mechanism setting the stage for the onset of microvascular diseases, now the leading cause of blindness (retinopathy), end-stage renal failure (kidney disease), diabetic cardiomyopathy and peripheral neuropathy. One mechanism, possibly an important final common pathway, through which hyperglycemia causes or aggravates micro- and macrovascular damage, is oxidative stress caused by high glucose. It induces endothelial damage by triggering the polyol pathway, the formation of advanced glycation end products (AGEs), and the activation of the protein kinase C (PKC)-diacylglycerol (DAG) and hexosamine pathways (reviewed in [1,2]). The link between reactive oxygen species (ROS), vascular endothelial growth factor (VEGF) signaling and retinal neovascularization in a condition mimicking hyperglycemia, is the focus of the research work by Park and co-authors published in this issue of *Vascular Pharmacology* [3]. Here, the authors found that betaine (trimethylglycine), a natural specific type of *zwitterion*, known to improve visual acuity, has antioxidant properties and inhibits pathological neovascularization of human retinal microvascular endothelial cells exposed to high glucose levels, by attenuating ROS production, and subsequently suppressing both the VEGF receptor (VEGFR)-2 signaling pathway and VEGF production [3]. Betaine was, here, reported to act on the hyperosmolar component of hyperglycemia [4], a biophysical mechanism known to contribute to the development of microvascular disease in diabetes [5–7]. Thus, betaine would act on one pathway leading from hyperglycemia to microangiopathy.

Other pathways, besides hyperosmolarity, are, however, recognized to contribute to diabetic microangiopathy. These include a dysregulated vessel regeneration and impaired function of vascular cells (*i.e.*, endothelial cells (ECs), vascular smooth muscle cells (VSMCs), stromal cells, pericytes, inflammatory cells, circulating and tissue-resident vascular stem/progenitor cells), all involved in the maintenance of vascular homeostasis and permeability [8,9]. The present review summarizes recent advances in the research of cellular and molecular pathways of microvascular disease in diabetes, provides insights into pathogenic mechanisms of vascular damage in diabetes, and indicates potential new targets for prevention and treatment strategies. This review should thus help putting the original work by Park et al. [3] in the broader context of the available pertinent literature.

2. Pathologic features of diabetic microvascular damage

Diabetic microvascular disease is pathologically characterized by abnormal growth and permeability of microcirculatory vessels [10]. Arterioles, capillaries and venules are the smallest functional unit of the microvascular bed. Unlike macrovessels, the specific role of which is to convey blood to the microcirculation in all organs and tissues, microvessels have specific roles in oxygen and micronutrient delivery. Permeability to small molecules, regulation in the physical dimensions and functional properties of the basement membrane are main microcirculatory features, which vary in different types of microvascular beds, such as the glomeruli, the retina, the myocardium, the skin and the muscle [10]. Apoptotic death of podocytes and pericytes are specific changes in diabetic microvessels, occurring in the kidney and in the retina, respectively [11]. In particular, in the diabetic retina pericytes undergo accelerated apoptosis, thereby contributing to an increase in vascular permeability and retinal edema [12]. Furthermore, the loss of pericytes activates a disordered capillarization, consisting of acellular capillaries and micro-aneurysms, which are responsible for impaired perfusion and consequent tissue hypoxia, as well as dysregulated neovascularization [12]. These aspects will be now described in greater detail.

3. Cellular and molecular pathways in diabetic microvascular disease

Endothelial cell damage and malfunction are common in diabetes, and contribute to the progressive loss of microvascular repair mechanisms [13]. Over the past decade, there has been increasing evidence that the integrity of the vascular wall is maintained by diversified cell populations, dedicated to endothelial repair and angiogenesis [8,9,14,15]. Diabetic patients often show deterioration of those cell types, especially in the presence of other cardiovascular complications [13,16]. Since hyperglycemia negatively affects the growth reserve of progenitor cells and the cellular capacity of vessel wall repair, vascular complications of diabetes may reflect a “stem cell vasculopathy”, in which the defective stem cell compartment is unable to regenerate dying ECs or VSMCs, or in which the dysfunctional stem cell compartment itself contributes to the development of the disease (Fig. 1).

3.1. Endothelial cells and vascular smooth muscle cells

Several studies have shown that exposure to high levels of glucose leads to a series of biochemical, structural and functional changes in mature vascular ECs and VSMCs, which can be summarized as follows [2,17]: 1) biochemical changes: accumulation of advanced glycation end-products (AGEs); increased production of the procoagulant protein von Willebrand Factor (VWF); increased apoptosis, induced by increased oxidative stress; increase in intracellular Ca^{2+}; mitochondrial dysfunction; changes in intracellular metabolism of fatty acid; activation of the mitogen-activated protein kinase (MAPK) signaling pathways; and reduced phosphorylation/activation of protein kinase B (also known as Akt); 2) structural changes: increased production of extracellular matrix proteins, collagen and fibronectin, and of related enzymes (*i.e.*, matrix metalloproteinases, MMPs); 3) functional changes: reduction in cell proliferation and migration; impairment of endothelium-dependent vasodilatation, linked to decreased production of vasodilators and increased production of vasoconstrictors; induction of ischemia and neo-angiogenesis [17]. In human retinal ECs, both the poly-ADP-ribose polymerase (PARP) and the nuclear factor–kappa B (NF-κB) signaling play central roles, as described below. Diabetic injury activates PARP, which in turn induces NF-κB activation preferentially through the toll-like receptor (TLR) signaling pathway, and causes cell apoptosis [18]. Similar to the NF-κB pathway, but with opposite biological effects, the evolutionarily conserved Notch-1 pathway, centered around Notch-1, a member of the Notch family of receptors involved both in stem/progenitor cell fate and orientation, and in the life cycle of adult cells, plays a key role in EC function regulation and VSMC proliferation, differentiation, and apoptosis [19]. The existence of a fine interaction between these signaling pathways has been suggested, and growing evidence indicates a complex cooperation between Notch-1, TLR-4 and NF-κB [19]. Recent studies have found that apoptosis is increased in diabetic mice and in human retinal ECs treated *in vitro* with high glucose, through the activation of PARP and cleaved caspase-3, as well as through the reduced expression of Notch-1 and p-Akt. Notch-1 signaling participates in the interaction of PARP and the p50 NF-κB component, and inhibits PARP- and p50-mediated apoptosis. Thus, Notch-1 signaling protects human retinal ECs from PARP- and NF-κB-induced apoptosis occurring under high glucose [20]. In addition, human retinal ECs and VSMCs show aberrant expression of the Notch-1 ligand jagged 1, and abnormal angiogenesis [21].

The Wnt signaling pathway also plays a fundamental role in multiple physiological and pathological processes in ECs, including angiogenesis and inflammation [22]. The loss or gain of function of Wnt pathway components causes abnormal vascular development and angiogenesis. Mutations in Wnt co-receptors, such as Frizzled, or in other upstream