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Review

Diabetic macroangiopathy: Pathogenetic insights and novel therapeutic approaches with focus on high glucose-mediated vascular damage

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ABSTRACT

Diabetic macroangiopathy – a specific form of accelerated atherosclerosis – is characterized by intra-plaque new vessel formation due to excessive/abnormal neovasculogenesis and angiogenesis, increased vascular permeability of the capillary vessels, and tissue edema, resulting in frequent atherosclerotic plaque hemorrhage and plaque rupture. Mechanisms that may explain the premature and rapidly progressive nature of atherosclerosis in diabetes are multiple, and to a large extent still unclear. However, mechanisms related to hyperglycemia certainly play an important role. These include a dysregulated vascular regeneration. In addition, oxidative and hyperosmolar stresses, as well as the activation of inflammatory pathways triggered by a dysregulated activation of membrane channel proteins aquaporins, have been recognized as key events. Here, we review recent knowledge of cellular and molecular pathways of macrovascular disease related to hyperglycemia in diabetes. We also here highlight how new insights into pathogenic mechanisms of vascular damage in diabetes may indicate new targets for prevention and treatment.

1. Introduction

According to the U.S. National Diabetes Statistics Institute, the prevalence of diabetes mellitus (diabetes) in the United States reached 9.3% of the total population in 2014, largely due to an increased prevalence of type 2 diabetes [1]. This number is particularly worrisome because about 20–30% of diabetic patients have prevalent macrovascular complications, including ischemic heart disease, cerebrovascular and peripheral arterial disease [1]. While type 1 diabetes may offer a relatively clean model of pure hyperglycemia-related vascular damage, type 2 diabetes is characterized by multiple metabolic abnormalities, where the independent effect of high glucose is difficult to separate from other components mostly linked to insulin resistance. Indeed, type 2 diabetic patients are particularly prone to develop atherosclerotic cardiovascular disease due to a combined effect of insulin resistance, hyperglycemia and the associated metabolic abnormalities.

Hyperglycemia is primarily responsible for the occurrence of microvascular disease, the primary cause of blindness (retinopathy), end-stage renal failure (nephropathy), peripheral neuropathy and diabetic cardiomyopathy. Hyperglycemia, however, is also known to aggravate macrovascular disease, conferring it a more severe, diffuse, and accelerated pattern [2]. Atherosclerosis in diabetes, and especially in type 2 diabetes, is indeed more aggressive than in the non-diabetic population, being premature, rapidly progressive, and with the involvement of multiple arterial districts at the same time [2]. This is thought to occur in part because the disturbed glucose metabolism in diabetes may modify and increase the impact of other risk factors for atherosclerotic disease. For example, low density lipoproteins (LDL) are susceptible to modification by advanced glycated end products (AGEs), which are modified proteins present in the circulation as well as in the subendothelial matrix in diabetes [3]. Increased lipoprotein oxidation, increased uptake of LDL by the LDL receptor, and platelet hyperaggregability are all perturbed in diabetes. In part, however, disturbed glucose metabolism causes the activation of specific pathways leading to vascular damage.

From a pathological standpoint, diabetic macroangiopathy is indeed characterized by intra-plaque new vessel formation due to excessive or

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abnormal neovasculogenesis and angiogenesis, increased vascular permeability of the capillary vessels, and tissue edema, resulting in more frequent atherosclerotic plaque hemorrhage and plaque rupture, as well as in cardiac microvascular dysfunction [4,5].

Animal models that mimic the interaction of diabetes and atherosclerosis can virtually help identify factors underlying accelerated vascular disease, as well as the initial vascular abnormalities in diabetes. However the results are not immediately applicable to humans. In fact, both type 1 and type 2 diabetes are multifactorial diseases, in which a very complex genetic background interacts with environmental factors, contributing to the development of disease. The limited translability of results from in vitro and animal models to humans reflects the inability of any particular model to reproduce the pathophysiology of the disease in its complexity in humans. Nevertheless, a variety of small and large animal models, as well as in vitro models, have been used, and valuable insights into the molecular mechanisms of diabetic vascular disease have been inferred so far through the use of animal models. They have proven essential for studying the different features or phenotypes of the disease (e.g., hyperglycemia, hyperinsulinemia, insulin resistance, obesity), and their correlation with other factors (mainly environmental, such as diet or physical activity) that can efficiently contribute to the initiation of the disease [6–10]. Such comorbidity models can be used as appropriate tools for investigating the effect of various drugs aimed at preventing and/or attenuating vascular complications in diabetes. An important field of research in which animal models have made a significant contribution is that of nutrient-gene interactions. With the help of nutrigenetics/nutrigenomics, such models have helped to unravel the interactions between obesity and diabetes [7,11–16]. Important data for the early diagnosis of diabetic complications and for a better understanding of the related pathophysiology can now also be obtained by proteomic analyses, performed on body fluids and arterial tissues implicated in macrovascular complications [17].

2. Specific cellular mechanisms of macroangiopathy in diabetes

2.1. Stem/progenitor cells in vascular disease and repair

Pathogenetic mechanisms for vascular dysfunction in diabetes include dysregulated vessel regeneration or impaired function of cells involved in the maintenance of vascular homeostasis and permeability (i.e., endothelial cells, smooth muscle cells, stromal cells, pericytes, inflammatory cells, circulating and tissue-resident vascular stem/progenitor cells, reviewed in [18]). Stem/progenitor cells residing in the vessel wall or circulating in the blood have recently attracted much attention as a mechanism to repair vascular damage and to replace exfoliated endothelial cells. Defects in the number of circulating progenitor cells have been related to cardiovascular risk factors, and have been associated with a more rapid progression of vascular disease [19,20]. Diabetes in general, and the hyperglycemic and insulin resistance components of diabetes specifically [21], have been related to a reduction/loss of function of progenitor cells, as well as to stem cell mobilization defects – a so called bone-marrow “mobilopathy” [22] due to the ineffective egress of stem/progenitor cells from the bone marrow into the peripheral circulation, contributing to the development of vascular disease [19,20]. In particular, hyperglycemia has been shown to negatively affect the growth reserve and repair capacity of the vessel wall [23]. One type of stem cells, mesenchymal stem cells (MSCs), which has been the subject of our own research [24], has been proposed as a potential target of diabetes-related pathogenetic mechanisms [24]. A reduction in the abundance and function of circulating and tissue-resident stem/progenitor cells, including MSCs, have been shown in both type 1 and type 2 diabetes [19,20]. Therefore, macrovascular complications of diabetes may reflect – at least in part – a “stem cell vasculopathy”, whereby the defective stem cell compartment is unable to regenerate dying endothelial or vascular smooth muscle cells, or

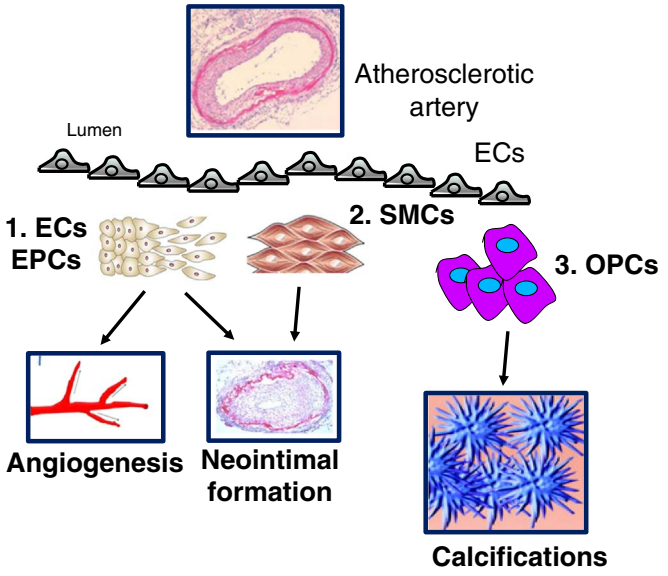

Fig. 1. Cellular mechanisms associated with diabetic macroangiopathy. The figure depicts the main cellular mechanisms underlying arterial calcification, neointimal formation and angiogenesis in the atherosclelrotic aorta. Abbbreviations: ECs, endothelial cells; SMCs, smooth muscle cells; OPCs, osteoprogenitor cells; EPCs, endothelial progenitor cells.

where the dysfunctional stem cell compartment itself contributes to the development of macrovascular complications. In type 2 diabetes, the reduction of vascular stem/progenitor cells is directly related to the degree of glycemic control [25,26], although some reduction is already apparent in subjects with impaired glucose regulation (pre-diabetes) [27–29]. An inverse correlation between the number and function of vascular stem/progenitor cells and blood glucose (fasting and 2 h after an oral glucose tolerance test) has here been shown [27,29]. Whether the reduction and/or dysfunction of stem/progenitor cells is, however, the direct consequence of glucose levels derangements, and to what extent this putative mechanism can be attributed to the hyperosmolar component of hyperglycemia is difficult to unravel. In patients with type 1 diabetes, a reduction of vascular stem/progenitor cells proportional to hemoglobin A1c (HbA1c) levels has been reported (Fig. 1).

2.2. Vascular calcification and macrophage polarization

Calcification may occur either within atherosclerotic plaques or in the tunica media of large and medium-size arteries with several mechanisms. In atherosclerosis, intimal calcified nodules contribute to destabilize the plaque [30,31], while in the peripheral vasculature medial calcification leads to arterial stiffening and raises systolic blood pressure [32,33]. There is a subset of circulating cells positive for the bone protein osteocalcin (OC) and bone alkaline phosphatase (BAP) that have been termed osteoprogenitor cells (OPCs) [34,35]. These cells descend from the myeloid lineage, retaining monocyte/macrophage markers, may recirculate from peripheral tissues, and may differentiate from peripheral blood monocytes, contributing to ectopic calcifications in vivo [35]. In addition to having plaques with a larger necrotic core and significantly greater inflammation, diabetic patients also have more extensive calcifications in the coronary and carotid arteries. In type 2 diabetic patients, coronary artery calcium score (CACs), assessed by computed tomography, had the best prognostic value and offered significantly better accuracy in predicting atherosclerotic events compared to non-invasive markers of atherosclerosis, including brachial artery endothelial function, carotid artery atheroma burden, ankle-brachial index, arterial stiffness [36]. Oxidative stress, changes in the metabolism of minerals, and increased mobilization of OPCs from the marrow to the blood and to the arterial wall are key players of coronary and