Atherosclerosis 229 (2013) 23–29

Contents lists available at SciVerse ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Dipeptidyl peptidase-4 inhibition and vascular repair by mobilization of endogenous stem cells in diabetes and beyond

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ARTICLE INFO

Article history:
Received 22 January 2013
Received in revised form
28 February 2013
Accepted 8 April 2013
Available online 18 April 2013

Keywords:
Bone marrow
Atherosclerosis
Endothelium
Angiogenesis
Regeneration

ABSTRACT

Endothelial integrity is maintained by local neighboring cells, but studies in the field of regenerative medicine have highlighted that circulating bone marrow-derived endothelial progenitor cells (EPCs) contribute to endothelial homeostasis in health and disease. In addition, bone-marrow derived smooth muscle precursors may be recruited to the diseased vasculature. Therefore, modulation of vascular stem/progenitor cells holds promises to tackle the development and progression of vascular disease. The dipeptidyl peptidase-4 (DPP-4) ectopeptidase cleaves several proteins, including the incretin hormones that regulate meal-induced insulin release. Another attractive DPP-4 natural substrate is the highly-conserved chemokine SDF-1α, a major regulator of stem/progenitor cell trafficking in the bone marrow and tissues. DPP-4 might also broadly affect bone marrow function, by acting on hematopoietic growth factors. Emerging data indicate that diabetes is associated with impaired bone marrow structure and function, which translates into pauperization of vascular regenerative cells and contributes to vascular disease. DPP-4 inhibition has potentials to tackle these alteration and promote vascular repair. Currently, millions of diabetic patients around the world are being treated with DPP-4 inhibitors and the study of ancillary effects is gaining an increasing interest for the possible cardiovascular benefit of these drugs beyond glucose control. As DPP-4 inhibitors show favorable safety profiles and do not cause hypoglycemia, they are attractive drugs also for non-diabetic patients and may become part of a vascular regenerative pharmacotherapy.

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Contents

1. Vascular repair by adult stem cells

The vasculature contains several types of cells that can be affected by disease processes. Endothelial cells and smooth muscle (SM) cells are the best known actors in vascular biology, although a role for adventitial cells has also been shown. Endothelial dysfunction/damage is considered a primary event paving the way to the development of atherosclerosis and vascular remodeling in general [1,2]. Endothelial integrity is maintained through the contribution of local neighboring cells, but re-coverage of a damaged endothelium may be slow and incomplete. Indeed, endothelial cell functions are impaired by diverse risk factors, such as diabetes, through several biochemical mechanisms [3]: hyperglycemia impairs the migratory activity of endothelial cells, which

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http://dx.doi.org/10.1016/j.atherosclerosis.2013.04.007

is required for reconstitution of a continuous endothelial layer [4]. Studies in the field of regenerative medicine have highlighted that circulating, bone marrow (BM)-derived cells contribute to endothelial homeostasis in health and disease [5–7]. These endothelial progenitor cells (EPCs) represent a heterogeneous cell population involved in endothelial healing and angiogenesis through differentiation into mature endothelial cells and/or an intense paracrine activity [8,9]. EPCs appear to be derived from precursors in the hematopoietic system (the hemangioblast) and share features with adult stem cells, such as clonogenic proliferation, self-renewal and stress-resistance [10,11]. Several pre-clinical studies have demonstrated that provision of EPCs at sites of endothelial damage or ischemia stimulates vascular and tissue repair in murine models of vascular disease (reviewed in Refs. [12,13]). In atherosclerosis, EPCs are believed to prevent endothelial damage and slow down plaque growth [14], although the effects of a pro-angiogenic therapy with EPCs in the late stages of atherosclerosis is controversial [15,16]. In myocardial ischemia, mobilization and recruitment of EPCs is critical to limit infarct size and adverse remodeling, depending on nitric oxide signaling [17,18]. Circulating EPC level and function are nowadays considered important determinants of cardiovascular health, and EPC impairment is associated with traditional cardiovascular risk factors as well as prevalent cardiovascular disease. Moreover, a low circulating EPC level predicts future adverse cardiovascular outcomes [19]. Based on this knowledge, an intense research is being conducted in the cardiovascular field to devise novel strategies to stimulate EPC-mediated vascular repair [20,21]. In addition, to counter shortage of EPCs in patients with cardiovascular disease, replenishment strategies based on cell therapies have become available, proving as safe and potentially effective ways to treat no-option patients [22–24].

Vascular disease is not simply the result of endothelial pathologies. Smooth muscle cells play major roles in the development and progression of several types of vascular lesions, including atherosclerosis, restenosis and stiffening. In atherosclerosis, proliferation of SM cells, along with their differentiation into a non-contractile and secretive phenotype, accounts for a large part of the plaque volume [25]. While large SM-rich plaques are believed to be stable and less prone to rupture owing to a thick fibrous cap, an exaggerated SM hyperplasia is detrimental after mechanical injury, leading to neointima formation and restenosis after vascular intervention. The exact origin of plaque SM cells is not entirely clear: while the medial layer is supposed to be the main source of neointimal SM cells, migration of immature cells from the adventitia and trans-differentiation into a SM-like phenotype has been shown [26]. In addition, several studies indicate the existence of circulating, bone-marrow derived SM cell precursors that are recruited to the diseased vasculature [27,28]. The protective versus harmful function of SM progenitors is debated and likely diversified according to the underlying vascular disease. While SM progenitor cell injections reduced atherosclerotic lesion size and improved lesion stability [29], inducing apoptosis of lesional BM-derived SM cells substantially decreased plaque size [30]. Interestingly, data suggest that common ancestor cells from the hematopoietic system can give rise to both EPCs and SM progenitor cells [31]. A switch between the endothelial and SM differentiation of such progenitors is thus likely responsible for both impaired endothelial repair and excess lesion growth [32–34].

With this background, we can anticipate that modulation of vascular stem/progenitor cells holds promises to counter the development and progression of vascular disease. While sophisticated cell therapy approaches may require extensive cell manipulation and complex protocols of injection/infusion, re-directing endogenous stem cells for vascular repair represents an attractive and novel strategy. Knowledge on the molecular pathways that regulate such cells is thus critical to devise therapeutic interventions. Specifically, mechanisms and factors that regulate EPC mobilization from the BM to the peripheral blood are of great interest for their ability to promote EPC-mediated vascular repair [35].

2. The biology of DPP-4

The dipeptidyl peptidase-4 enzyme is an ectopeptidase that cleaves a dipeptide (X-Pro and, less efficiently, X-Ala) from the N-terminus of several proteins [36]. It exists as a soluble or a membrane-bound form, the latter being also known as CD26. In addition to its enzymatic activity, CD26 acts as adenosine deaminase (ADA) co-activator and is expressed by several leukocytes subsets [37] and by endothelial cells. Whether CD26 has any intracellular signal transduction activity is unknown, but data in vitro suggest that this might be possible [38]: studies using crosslinking anti-CD26 antibodies have shown multiple tyrosine phosphorylation events occurring downstream [39]. The factors that regulate DPP-4/CD26 expression and function are largely under-investigated. Expression by endothelial cells appears to be induced by inflammatory stimuli, especially in the microvasculature [40]. DPP-4 activity has several natural substrates, easily predicted from the amino-acid sequence, including hormones, cytokines, chemokines and neuropeptides [41]. While cleavage is supposed to inactivate these substrates, the physiologic significance of cleavage by DPP-4, if any, cannot be predicted, as the mere removal of 2 N-terminal residues may have no impact on protein function or receptor binding. Technical challenges arise when trying to determine quantitatively the amount of a test substrate that is cleaved by DPP-4, as commercially-available kits are rarely specific for the intact or cleaved forms.

The interest in DPP-4 biology has recently gained increasing attention because one of the most important DPP-4 substrates is the hormone GLP-1. GLP-1 is produced by intestinal neuroendocrine cells in response to a meal ingestion and, in turn, potentiates insulin release from beta cells (so-called “incretin effect”). However, native GLP-1(7-36) is rapidly and efficiently cleaved by DPP-4 into the inactive GLP-1(9-36), which no longer stimulates the GLP-1 receptor and might even inhibit it [42]. In type 2 diabetes (T2D), dynamic secretion of GLP-1 is impaired and serum DPP-4 activity is increased by about 40% [43]. Therefore, pharmacologic DPP-4 inhibition has been designed as a way to boost the incretin effect and lower plasma glucose in type 2 diabetic patients. The existence of off-target, non-glycemic effects of DPP-4 inhibition has been hypothesized based on the many natural substrates of the enzyme, that can potentially affect several biological functions, well beyond metabolism and GLP-1 signalling. Currently, millions of patients around the world are treated with DPP-4 inhibitors and the study of these ancillary effects is gaining an increasing interest for the possible additional cardiovascular benefit they entail beyond glucose control [44,45]. The potential benefits of DPP-4 inhibition in myocardial ischemia/reperfusion injury have been recently reviewed [46]. Although DPP-4 inhibitors have demonstrated fairly good safety profiles in short and mid-term studies, surveillance of eventual long-term adverse effects mediated by unexpected DPP-4 targets is as well important.

3. DPP-4 and stem cell regulation

The SDF-1α/CXCR4 axis. One of the most attractive DPP-4 natural substrates is the highly-conserved chemokine SDF-1α (also known as CXCL12), a major regulator of stem cell trafficking in the BM and tissues [47]. SDF-1α exerts its functions by binding to the receptor CXCR4, which undergoes homodimerization, interaction with inhibitory $G_{\alpha i}$, phosphorylation by JAK2/JAK3 kinase and downstream phosphorylation of STAT factors. Cleavage of SDF-1α(1-67) by

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