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Commentary

Progenitor cell-derived smooth muscle cells in vascular disease

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ABSTRACT

Accumulation of vascular smooth muscle cells (VSMCs) in the tunica intima plays a major role in the pathogenesis of atherosclerosis and restenosis following endovascular procedures. Arterial VSMCs are heterogeneous even in the normal vessel wall and display different phenotypes in physiological and pathological conditions. In the classical paradigm, vascular wall injury induces VSMC de-differentiation, proliferation and migration from the media into the intima in response to growth factors and proteolytic agents. Accordingly, VSMCs in atherosclerotic plaques and in restenosis display a de-differentiated or 'synthetic' phenotype compared to a 'contractile' phenotype in the normal media. In contrast, recent studies have identified bone marrow and peripheral blood-derived endothelial and VSMC progenitors that may contribute to intimal formation in atherosclerosis, after arterial injury and in transplant atherosclerosis. The precise frequency of these bone marrow-derived vascular precursor cells is controversial and their role is unknown. In addition, additional data support the presence of a resident progenitor cell subpopulation and its involvement in the response of the adult arterial wall to damage or ischemia. This review will examine the evidence for and the putative role of progenitor cell-derived VSMCs in arterial disease, a necessary prerequisite before deciding whether progenitor cells are therapeutic targets in vascular disease.

1. Introduction

Atherosclerosis is a chronic inflammatory disease, in which risk factors result in dysfunction and damage to the arterial endothelium [1–3]. Endothelial damage permits migration of inflammatory cells and accumulation of lipid, followed by proliferation and migration of vascular smooth muscle cells (VSMCs) from the media into the intima. Following arterial injury to either normal or diseased vessels, proliferation and subsequent accumulation of VSMCs results in further intimal expansion, which can result in restenosis [4]. The classical paradigm of atherosclerosis suggests that accumulation of VSMCs in the tunica intima plays a crucial role in the pathogenesis of atherosclerosis and restenosis following angioplasty or stenting [1–3]. In the original 'response to injury' hypothesis of atherosclerosis, growth factors and proteolytic agents induce VSMC proliferation and migration from the tunica media into the intima, akin to the vessel wall response after mechanical injury [4]. During this process, VSMCs switch from a 'contractile' to a 'synthetic' phenotype, with reduced expression of typical VSMC contractile protein markers and an enhanced response to growth and chemotactic factors [5]. In atherosclerosis, VSMC accumulation in the fibrous cap is monoclonal or oligoclonal [6,7], implying that only a small number of medial VSMCs undergo proliferation. Subsequent studies examining telomere loss indicate that fibrous cap VSMCs have undergone 10–14 more population doublings than cells in the normal media [8], suggesting the existence of a resident arterial subpopulation that contributes to arterial healing in response to injury [9].

More recent studies have questioned the origin of VSMCs comprising atherosclerosis and neointima formation after injury or in transplant disease. In particular, studies in transplantation arteriopathy showed that recruitment of bone marrow or host-derived circulating precursors contributes to the intima after *in situ* SMC differentiation [10]. Similar studies in primary atherosclerosis and after arterial injury demonstrated bone marrow-derived VSMCs in both experimental animals and humans [11–13], although these findings have since been refuted [14,15]. Finally, the presence of cells expressing stem cell antigens in the normal arterial wall suggests the existence of resident progenitor cells capable of contributing to neointima formation [16,17]. Whilst most studies focused on uncovering their origin, the behavior of stem marker-expressing VSMCs and their contribution to vascular remodeling following acute and chronic damage remain largely unknown. In this review we will examine the evidence for arterial VSMC heterogeneity and

Abbreviations: VSMCs, vascular smooth muscle cells, stem cell antigen-1 (sca-1); α-SMA, alpha smooth muscle cell actin; SMMHC, smooth muscle cell myosin heavy chain.

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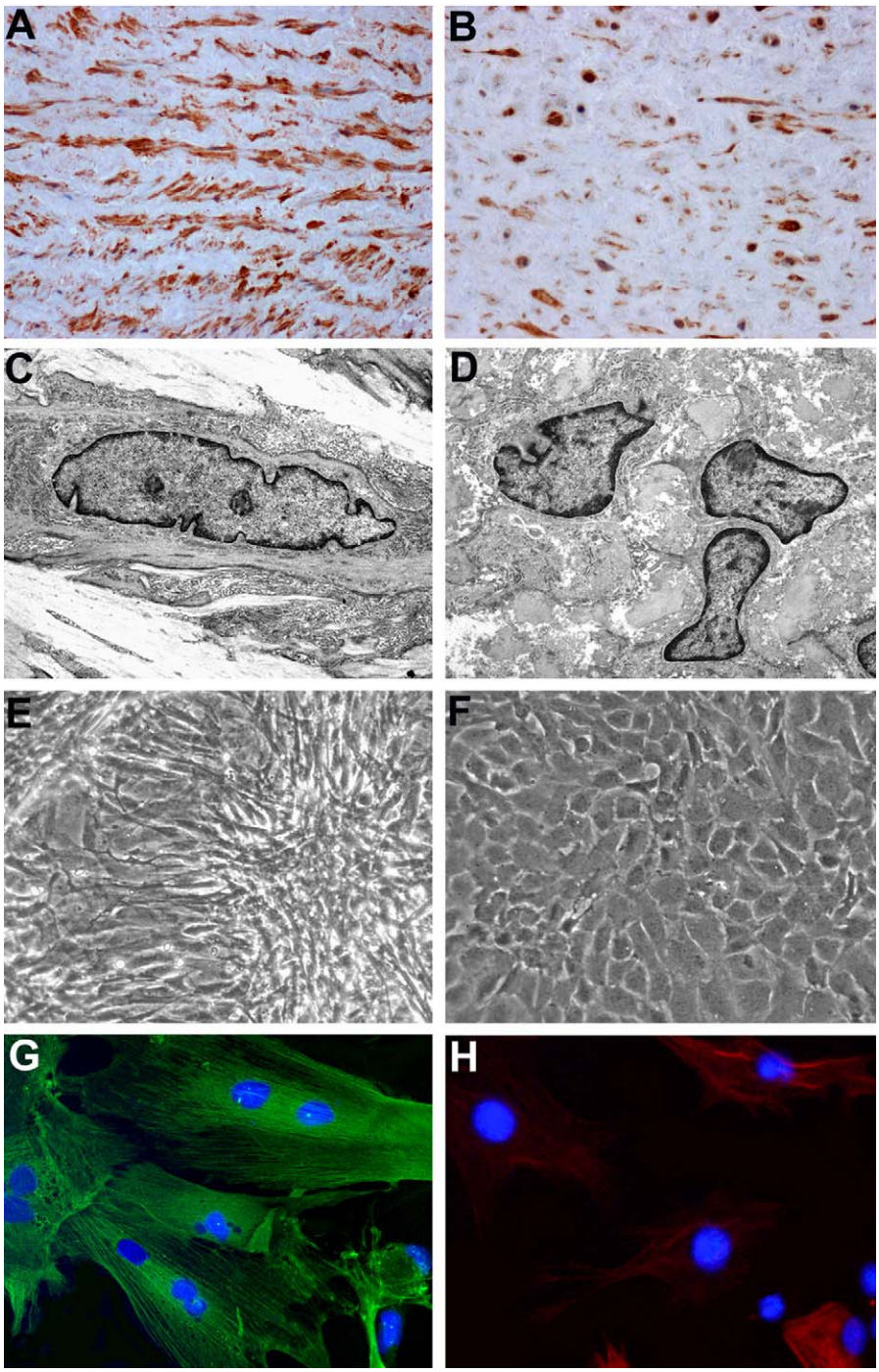

Fig. 1. Phenotypic heterogeneity of vascular smooth muscle cells. (A and B) Immunostaining of human aortic formalin-fixed sections stained with an antibody to anti-smooth muscle myosin heavy chain for VSMCs in (A) tunica media (B) diffuse intimal thickening in 54-year-old man. (C and D) Transmission electron photomicrographs showing (C) elongated rat aorta normal media VSMC SMC and (D) neointimal VSMCs SMCs fifteen days after ballooning. (E) Cultured rat aortic normal media VSMCs with the classical "hill-and-valley" confluent growth pattern, compared with (F) the monolayered and epithelioid appearance of neointimal VSMCs obtained fifteen days after ballooning. Immunofluorescence reveals that (G) rat aortic normal medial VSMCs display abundant typical α-smooth muscle actin cytoplasmic fibers, whereas they are reduced in (H) neointimal VSMCs. Original magnifications, A and B: 200×, C and D: 4000×, E and F: 100×, G and H: 400×.

the existence of VSMC progenitor cells and the contribution of stem cell-derived VSMCs to the development of vascular disease.

2. The heterogeneity of vascular smooth muscle cells

2.1. Vascular smooth muscle cells display different phenotypes

VSMCs within the normal media are heterogeneous. VSMC heterogeneity is manifest by 'contractile' and 'synthetic' phenotypes [18–20], which are typical of VSMCs of the normal and pathologic arteries, respectively (Fig. 1). These phenotypes are also seen *in vitro*; for example two populations are obtained from the post-injury rat aorta and carotid artery: a spindle-shaped phenotype, with the classic "hill-and-valley" growth pattern typical of cultured normal medial VSMCs and an epithelioid phenotype, with cells growing in a monolayer with a cobblestone morphology at confluence that is typically isolated from the neointimal tissue fifteen days after balloon injury [20,21]. Clones