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Arterial smooth muscle dynamics in development and repair

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A B S T R A C T

Arterial vasculature distributes blood from early embryonic development and provides a nutrient highway to maintain tissue viability. Atherosclerosis, peripheral artery diseases, stroke and aortic aneurysm represent the most frequent causes of death and are all directly related to abnormalities in the function of arteries. Vascular intervention techniques have been established for the treatment of all of these pathologies, yet arterial surgery can itself lead to biological changes in which uncontrolled arterial wall cell proliferation leads to restricted blood flow. In this review we describe the intricate cellular composition of arteries, demonstrating how a variety of distinct cell types in the vascular walls regulate the function of arteries. We provide an overview of the developmental origin of arteries and perivascular cells and focus on cellular dynamics in arterial repair. We summarize the current knowledge of the molecular signaling pathways that regulate vascular smooth muscle differentiation in the embryo and in arterial injury response. Our review aims to highlight the similarities as well as differences between cellular and molecular mechanisms that control arterial development and repair.

1. Introduction

Most tissues react to injuries by initiating a complex and multi-faceted response that involves inflammation and activation of diverse cell types that contribute to the healing process. Several tissues can achieve complete restoration of the damaged architecture by either extensive enrolment of stem cells or proliferation of non-specialized cell types. Controversial hypothesis suggests that in some cases adult tissue regeneration recapitulates embryonic developmental mechanisms. Arterial response to injury involves several distinct cell types and although the repair process is efficient, it often results in excessive cell proliferation in the vascular wall that can eventually reduce blood flow and lead to vascular occlusion. The current review aims to provide an overview and compare the mechanisms that regulate vascular smooth muscle differentiation in embryonic development and arterial injury repair. In addition we discuss here why the principal developmental processes that control arterial morphology fail in arterial injury repair and how the knowledge of these mechanisms may offer new opportunities to treat cardiovascular diseases.

2. Cellular architecture of arterial walls

The primary cell types of arterial walls, endothelial cells and vascular smooth muscle cells (VSMCs), have been described since the 19th century. In recent years a great number of additional cell types have been identified, revealing an elaborate morphology of large blood vessels (Fig. 1A). The arterial lumen is covered by a layer of endothelial cells that in addition to providing the primary barrier also secrete vasodilators (i.e. nitric oxide) and vasoconstrictors (i.e. endothelin-1). A thin basement membrane separates the endothelium from the surrounding *tunica intima*. Here a distinct layer of pericyte-like cells forms an interconnected network adjacent to the endothelium (Andreeva et al., 1998; Orekhov et al., 2014; Rekhter et al., 1991). The role of these intimal pericytes remains to be established, but they have been postulated to contribute to atherosclerosis by modifying the local inflammatory microenvironment (Ivanova et al., 2015). The majority of the *tunica intima* is composed of a proteoglycan rich matrix with embedded immature VSMCs (Glukhova et al., 1988; Orlandi et al., 1994). At aortic branch sites a specific population of VSMCs develops early in the embryo and are maintained in immature state until adulthood (Roostalu et al., 2017). These cells make up cushion-like structures at branching sites, but little is known about their function. Intimal cushions have been proposed to play a role in directing blood cells to lateral branches (Fourman and Moffat, 1961), but they may in addition provide strength to the branching sites that are influenced by blood flow turbulences and may even represent a pool of immature cells that can contribute VSMCs to growing arteries. Importantly, arterial branching sites are prone to developing athero-

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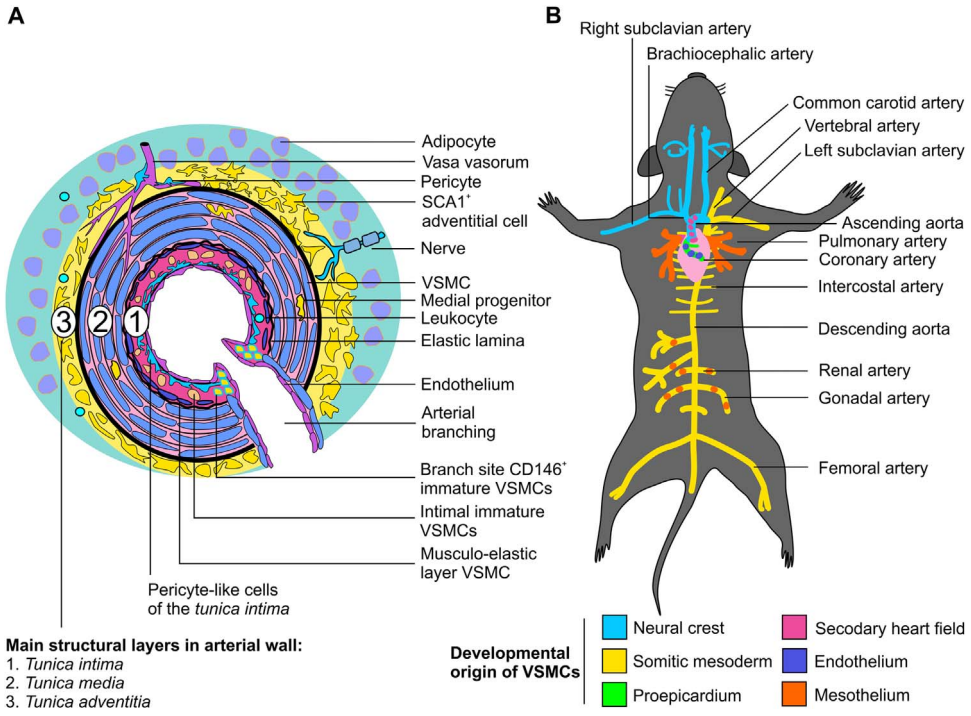

Fig. 1. Cellular composition and developmental origin of arteries. A, Schematic cross section of aorta, demonstrating distinct cell types in the vascular wall. **B,** Developmental origin of VSMCs in mouse arteries. The current understanding of VSMC embryonic origin is extrapolated on adult mouse vasculature with the color scheme indicating the embryonic source. The right subclavian artery arises from pharyngeal arch artery, which recruits neural crest cells to VSMC fate. The left subclavian derives from the descending aorta, which recruits mesodermal cells to VSMC differentiation. VSMCs in many arteries originate from multiple cell types. In many internal organs they can arise from somitic mesoderm as well as mesothelial cells. In coronary arteries both proepicardium and endothelial cells contribute to the smooth muscle layer.

sclerotic lesions, demonstrating their importance in the context of cardiovascular medicine (VanderLaan et al., 2004). The outer section of the *tunica intima* is composed of elastic fibers and spindle-shaped contractile VSMCs (Rekhter et al., 1991). It is separated from the overlying *tunica media* by internal elastic lamina. The *tunica media* is the most prominent part of the arterial wall and is made of concentric layers of mature VSMCs. The elastin-based matrix that surrounds VSMCs enables expansion and contraction of large arteries during systole and diastole. The relative abundance of collagen and other extracellular matrix molecules to elastin and particularly the architecture in which they pattern the vessels define the biomechanical properties of arteries (Cheng and Wagenseil, 2012).

Tunica media is enclosed by loosely packed adventitial layer that harbors several distinct cell types. Our current understanding of the *tunica adventitia* composition is still often limited to identifying cells by relatively non-specific surface markers, making it impossible to distinguish discrete cell lineages from distinct differentiation stages of a single cell lineage. The most widely accepted markers for adventitial cells are SCA1 (Stem cell antigen-1) and CD34 that identify cells around most mouse arteries (Hu et al., 2004; Passman et al., 2008). Similar $CD34^+$ cells are enriched at the interface of *tunica media* and *tunica adventitia* in human arteries (Invernici et al., 2007; Zengin et al., 2006). Intriguingly, Sainz *et. al.* found $SCA1^+$ cells in the *tunica media* (Sainz et al., 2006), suggesting that adventitial cells are capable of penetrating deeper into the arterial wall or there are progenitors of adventitial cells that arise from VSMCs (discussed below). Typical adventitial cells are in a poised state of smooth muscle differentiation as they lack characteristic VSMC markers, but express both transcriptional activators and repressors of VSMC differentiation (Passman et al., 2008). Consequently, activation of these cells for example *in vitro* or in transplantation to vein grafts leads to VSMC differentiation (Hu et al., 2004; Passman et al., 2008; Shen et al., 2016). In addition to smooth muscle differentiation these cells can *in vitro* commit to endothelial cell fate (Hu et al., 2004; Invernici et al., 2007; Pasquinelli et al., 2007; Passman et al., 2008; Sainz et al., 2006; Zengin et al., 2006).

Several lines of evidence suggest that there are even more multipotent progenitor cells in the adventitia. A sub-population of adventitial cells expresses markers of mesenchymal stromal cells (CD44 and CD90) (Corselli et al., 2012; Klein et al., 2011). As $CD34^+$ adventitial cells also upregulate these stromal cell markers *in vitro* (Campagnolo et al., 2010; Hoshino et al., 2008; Pasquinelli et al., 2007), it is possible that they represent the same linage at different stages of activation and differentiation. These stromal-like cells are capable of VSMC, chondrogenic and adipogenic differentiation (Corselli et al., 2012; Hoshino et al., 2008). The development of adventitial cells relies on Sonic Hedgehog signaling and hence one of the most promising genes to identify this cell population is GLI1, a Sonic Hedgehog pathway transcription factor (Kramann et al., 2015; Passman et al., 2008). $GLI1^+$ cells express typical adventitial markers SCA1, CD34 and to a variable degree diverse mesenchymal stromal cell (CD29, CD44, CD90) as well as immature VSMC markers, indicating possible lineage continuity between adventitial cells. $GLI1^+$ cells can differentiate into VSMC, fibroblasts and osteoblast-like cells (Kramann et al., 2016). There are also progenitor/stem cells in the *tunica adventitia* that are characterized by the expression of SRY-Box 10 (SOX10), SOX17, S100β as well as mesenchymal stromal markers CD44 and CD29, but lacking in CD31, CD34, CD146 and SCA1. This cell population, *in vitro,* can be differentiated into VSMCs, Schwann cells, peripheral neurons, chondrocytes, osteoblasts and adipocytes (Tang et al., 2012).

A dense capillary network of *vasa vasorum* surrounds larger human arteries to supply blood to the adventitia and *tunica media*. Hence, endothelial cells and associated pericytes are found frequently in the adventitia. Pericytes can be distinguished by Neural-glial antigen 2 (NG2) and CD146 expression and *in vitro* can differentiate into VSMCs as well as various mesenchymal cell types (Billaud et al., 2017; Crisan et al., 2008). *In vivo* plasticity of pericytes has remained difficult to establish due to the lack of specific lineage tracing transgenic

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