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The vascular adventitia: An endogenous, omnipresent source of stem cells in the body

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ABSTRACT

Until a decade ago it was believed that the wall of adult blood vessels exclusively contains terminally differentiated cell types. A paradigm shift was unavoidable since studies from different groups convincingly showed the presence of vascular wall-resident stem and progenitor cells (VW-SCs) which were identified to particularly reside in the sub-endothelial space and the so-called adventitial "vasculogenic zone". Data published during the last decade uncloaked the fact that VW-SCs have the capacity to differentiate into both vascular and non-vascular cell types. Up to date, little is known about the full capacity of VW-SCs, the exact composition of their endogenous niche and the mechanisms that govern their self-renewal, activation and differentiation. The aim of this review is to provide an overview about the current knowledge on VW-SCs and to highlight the impact of this endogenous niche on health and disease. In addition, we will discuss strategies how these adult stem cells could be manipulated in order to activate and expand them, ideally within their niche at sites of tissue damage and subsequently differentiate them into a desired cell type, e.g. an endothelial cell, a macrophage or a muscle cell. This would pave the way towards new pharmacological strategies for endogenous tissue repair and regeneration.

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Abbreviations: BBB, blood–brain-barrier; BM, bone marrow; BM-MSC, bone marrow-derived mesenchymal stem cell; BMP, bone morphogenetic protein; BNP, brain natriuretic protein; CFU, colony forming unit; CNS, central nervous system; CSC, cardiac stem cell; EC, endothelial cell; EC-SP, endothelial cell side population; EPC, endothelial progenitor cell; Flk-1, fetal liver kinase 1; HAEC, human arterial endothelial cell; hITA, human internal thoracic artery; HGF, hepatocyte growth factor; HPC, hematopoietic progenitor cell; HSC, hematopoietic stem cell; HUVEC, human umbilical vein endothelial cell; IGF-1, insulin-like growth factor 1; M-CSF, monocyte colony stimulating factor; MI, myocardial infarction; MVSC, multipotent vascular stem and progenitor cells; PC, pericyte; Sca-1, stem cell antigen 1; Shh, sonic hedgehog; SMC, smooth muscle cell; SPs, side population cells; TAGLN, transgelin; Tie-2, tyrosine kinase with Ig and EGF homology domains 2; VEGFR-2, vascular endothelial growth factor receptor 2; VW-MPSCs, vascular wall-resident multipotent stem cells; VW-SCs, vascular wall-resident stem cells; VW-SMPCs, vascular wall-resident smooth muscle progenitor cells.

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1. Introduction

All vascular wall cells are derived from mesoderm in which the so-called blood islands appear in the third embryonic week at different sites within the conceptus such as the intraembryonic splanchnopleura as well as the extraembryonic yolk sac and placenta. Blood islands harbor hemangioblasts as common ancestor stem cells which differentiate into both vascular endothelial and hematopoietic cells (Risau & Flamme, 1995; Shalaby et al., 1995). Within a few days and still in the third embryonic week the outer layer of blood island hemangioblasts differentiates into endothelial cells (ECs) and forms the first nascent blood vessels such as the dorsal aorta as well as yolk sac vessels, a process referred to as vasculogenesis (Risau, 1997). During maturation such cells undergo further morphogenetic changes such as establishment of inter-endothelial junctional complexes, including the formation of a well-structured basement membrane to which ECs are anchored and which serves as basis for the assembly of vascular mural cells. Only if these morphogenetic processes occur in a well-coordinated fashion regarding space and time, the nascent blood vessels will reach a stabilized state, which enables their survival and allows further morphogenetic maturation events resulting in the typical hierarchic structure of the adult vascular system composed of large, medium-sized or small vessels as well as microvasculature. The final result is a three-layered vessel wall containing tunica intima, media and adventitia. The lumen of all vessels is lined by ECs. ECs together with a thin sub-endothelial space, which is free of microvessels, form the intima. The media is basically composed of smooth muscle cells (SMCs) and contains elastic collagen fibers, which are most abundant in large vessels such as the aorta. For a long time, the adventitia was believed to be a simple connective tissue layer embedding the vessel into the surrounding tissue and containing vasa vasorum and nerve fibers. Both media and adventitia strongly vary in their thickness depending on vessel size and location.

The notion that the mature vessel wall can serve as a niche for stem and progenitor cells is relatively new and was particularly developed over the last decade (Alessandri et al., 2001; Hu et al., 2004; Tavian et al., 2005; Zengin et al., 2006; Invernici et al., 2008; Passman et al., 2008; Tilki et al., 2009; Campagnolo et al., 2010; Klein et al., 2011; Psaltis et al., 2014). Mainly, two zones were reported to harbor stem and progenitor cells: the intimal sub-endothelial zone and the vascular adventitia. Some publications have also reported the presence of progenitor cells in the vascular media (Tang et al., 2012). Furthermore, several groups have demonstrated that pericytes (PCs) have the potential to serve as stem and/or progenitor cells when detached from the capillary wall. (Crisan et al., 2008; Campagnolo et al., 2010) (Wong et al., 2015). In conclusion, the published data suggest the presence of a heterogeneous stem and progenitor cell population within the vessel wall, being present not only in large and medium-sized vessels, but also in microvessels. Considering the fact that the total length of vessels spanning the human body was calculated to range between 80,000 to 100,000 km, one can imagine the extraordinary dimension of this stem cell niche. Moreover, the presence of blood vessels in nearly all tissues and organs underlines its local accessibility in health and disease. Regardless of their location in the sub-endothelial zone or adventitial layer, vascular wall-resident stem and progenitor cells (VW-SCs) have been shown to differentiate not only into vascular, but also non-vascular cells such as macrophages or follicular dendritic cells (Zengin et al., 2006; Campagnolo et al., 2010; Ergun et al., 2011; Krautler et al., 2012; Vono et al., 2012; Psaltis et al., 2014). In vivo studies demonstrate that adventitial progenitor cells contribute to neointima formation and their differentiation potential can be modified by drug application (Wong et al., 2013). This review aims to provide a comprehensive overview of the current knowledge about VW-SCs on both a basic and translational research level and to briefly discuss their clinical potential in regenerative, cardiovascular and oncological medicine.

2. Vascular wall stem cell niches and markers

The hierarchically organized vascular system is composed of large, medium-sized and microvessels (Fig. 1A). In all parts, a basically three-layered wall structure with the innermost intima, the middle media and the outermost adventitia is present (Fig. 1B). In contrast to the intima, the thickness of both the media and adventitia varies depending on vessel type, size and location in the body. As mentioned above different niches have been described within the vessel wall that serve as a reservoir for multipotent stem cells as well as developmentally more restricted precursor cells: the sub-endothelial space of the intima which serves as interface between vessel wall and blood, the muscular layer of the media and the vascular adventitia, representing the interface between vessel wall and surrounding tissue. Among them, the adventitia appears to be the most versatile niche, harboring different types of stem and progenitor cells with the potential to differentiate into vascular and non-vascular cell types, e.g. macrophages, dendritic cells and cells of mesenchymal lineage.

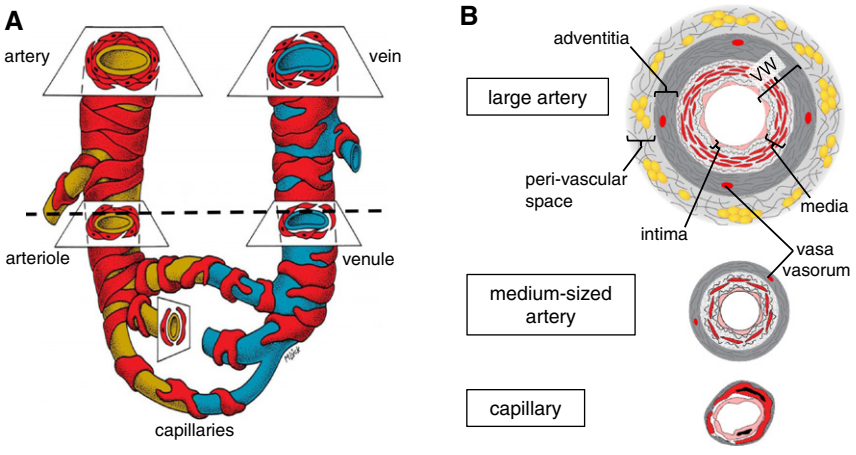

Fig. 1. Hierarchy and basic structure of the vessel system. Macro vessels (arteries and veins) and micro vessels such as arterioles, capillaries and venules (**A**) are the major parts of the vascular system. Microscopically, the wall of large and medium-sized blood vessels exhibits three layers: tunica intima (pink), media (red) and adventitia (gray) containing the vasa vasorum (**B**). The so-called peri-vascular space contains fat (yellow) and connective tissue (**B**). The capillary wall also displays an intima (pink) which is covered by a single discontinuous mural cell layer from the outside containing pericytes (red) (**B**). Particular attention should be paid to distinguish the tunica adventitia from the peri-vascular space. In contrast to the adventitia the peri-vascular space does not display the circular organization and thus, should not be confounded with it.