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Skeletal and cardiac muscle pericytes: Functions and therapeutic potential

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ABSTRACT

Pericytes are periendothelial mesenchymal cells residing within the microvasculature. Skeletal muscle and cardiac pericytes are now recognized to fulfill an increasing number of functions in normal tissue homeostasis, including contributing to microvascular function by maintaining vessel stability and regulating capillary flow. In the setting of muscle injury, pericytes contribute to a regenerative microenvironment through release of trophic factors and by modulating local immune responses. In skeletal muscle, pericytes also directly enhance tissue healing by differentiating into myofibers. Conversely, pericytes have also been implicated in the development of disease states, including fibrosis, heterotopic ossication and calcification, atherosclerosis, and tumor angiogenesis. Despite increased recognition of pericyte heterogeneity, it is not yet clear whether specific subsets of pericytes are responsible for individual functions in skeletal and cardiac muscle homeostasis and disease.

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Abbreviations: αSMA, alpha smooth muscle actin; ADAM12, disintegrin and metalloproteinase domain-containing protein 12; Ang, angiopoietin; AP, alkaline phosphatase; CD, cluster of differentiation; C/EBPδ, CCAAT/enhancer binding protein delta; Cox2, cyclooxygenase 2; CXCR, CXC chemokine receptors; EMT, epithelial to mesenchymal transition; GFP, green fluorescent protein; GLI1, glioblastoma 1; FAP, fribro-adipogenic progenitor; HMOX1, heme oxygenase 1; ICAM1, intercellular adhesion molecule 1; IFNδ, interferon gamma; IL, interleukin; IP10, inducible protein 10; LIF, leukemia inhibitory factor; MCP1, monocyte chemoattractant protein 1; MIF, migration inhibitory factor; MSC, mesenchymal stem cell; NG2, neural/glial antigen 2; NF-κB, nuclear-factor kappa-B; PDGF, platelet-derived growth factor; PDGFRβ, platelet-derived growth factor beta; TGFβ, transforming growth factor beta; Tie2, tyrosine kinase with immunoglobulin-like and EGF-like domains 1; TNFα, tumor necrosis factor alpha; VE-cadherin, vascular endothelial cadherin; VEGF, vascular endothelial growth factor; vSMCs, vascular smooth muscle cells; YFP, yellow fluorescent protein.

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1. Introduction

Pericytes are perivascular cells that are found in abundance in all vascularized organs where they regulate numerous functions, including vessel growth, permeability, and contractility (Cappellari & Cossu, 2013). In skeletal muscle, pericytes appear to play additional roles in tissue regeneration, including differentiation into myofibers (Dellavalle et al., 2007). Pericytes are however also implicated in the development of fibrosis, heterotopic ossification, atherosclerosis, and tumor angiogenesis, diseases that represent some of the most frequent causes of morbidity and mortality in the western world (Collett & Canfield, 2005; Fang & Salven, 2011; Henderson et al., 2013; Matthews et al., 2016). Despite these critical roles in tissue physiology and disease, relatively little is known about skeletal muscle and cardiac pericytes (Armulik et al., 2011). The key barrier to our understanding of pericytes is the lack of truly specific markers and thus a lack of consensus on pericyte identity. With increasing recognition of pericyte heterogeneity, it is not yet clear whether subsets of pericytes are responsible for individual pericyte functions. Approaches that combine genetic lineage tracing, anatomical location, and expression of surface markers have facilitated an improved understanding of pericyte roles in health and disease. In this review, we outline current concepts in anatomy, molecular markers, and developmental origins of skeletal and cardiac muscle pericytes. We report proposed roles of skeletal and cardiac muscle pericytes in organ homeostasis and in the response to muscle injury and disease. Finally, we discuss the potential of pericytes from these organs as therapeutic agents of regeneration and repair.

2. Pericyte anatomy

Pericytes are periendothelial mesenchymal cells that reside within the microvasculature, sharing a basement membrane with underlying endothelial cells (Armulik et al., 2011) (Fig. 1). Classically described to be present on capillaries, there is considerable evidence to suggest that pericytes are ubiquitous in higher order vessels such as pre-capillary arterioles, post-capillary venules, and veins while conspicuously absent in the lymphatic vasculature (Campagnolo et al., 2010; Norrmen et al., 2011). Given their periendothelial distribution, pericytes are frequently confused with vascular smooth muscle cells (vSMCs), which reside in this location on arterioles. In contrast to arteriolar vSMCs, pericytes have a nearly rounded cell body with numerous finger-like projections that extend longitudinally spanning the abluminal surface of several endothelial cells. These primary processes extending along the length of the capillary give rise to secondary processes that run perpendicular to the primary processes, partially encircling the capillary with tips of secondary processes making connections with endothelial cells (Armulik et al., 2005, 2011). In addition to forming connections with underlying capillary endothelial cells, pericytes connect with endothelial cells in neighboring capillaries with fine processes that traverse the intercapillary space cells (Armulik et al., 2011). In vitro studies of isolated cardiac pericytes have demonstrated that these cells are also capable of forming connections with other pericytes likely *via* gap junctional proteins such as connexins (Nees et al., 2012). Dye transfer studies have demonstrated rapid transfer of dye from pericytes to endothelial cells as well as between adjacent pericytes suggesting that pericytes along with endothelial cells likely form a functional intercommunicating unit in the vasculature (Larson et al., 1987). In comparison, pericytes do not form robust connections with vascular smooth muscle cells. Although the physiologic significance of pericyte–pericyte and pericyte–endothelial connections are not clear, the functional coupling of pericytes to endothelial cells and not vascular smooth muscle cells likely represents a mechanism for pericyte-mediated regulation of the vasculature independent of vascular smooth muscle cells.

Pericyte density varies between different organs as does the area of the abluminal endothelial surface that they cover (Armulik et al., 2011). Pericyte density and coverage appears to correlate with endothelial barrier properties (brain > lungs > muscle) (Armulik et al., 2011), endothelial cell turnover (large turnover equates to less coverage), and orthostatic blood pressure (larger coverage in lower body parts) (Diaz-Flores et al., 2009; Armulik et al., 2011). The brain is thought to be organ with the greatest density of pericytes with an endothelial cell–pericyte ratio between 1:1 and 3:1 (Sims, 1986; Mathiisen et al., 2010). By contrast, skeletal muscle vasculature has substantially fewer pericytes covering endothelial cells with an endothelial–pericyte ratio of approximately 100:1 (Diaz-Flores et al., 2009). The pericyte content of the cardiac microvasculature is thought to be closer to that of the cerebral vasculature with endothelial–pericyte ratios of 2:1–3:1 (Nees et al., 2012). It is estimated that there are approximately 3.6×10^7 pericytes/cm^3 of left ventricular

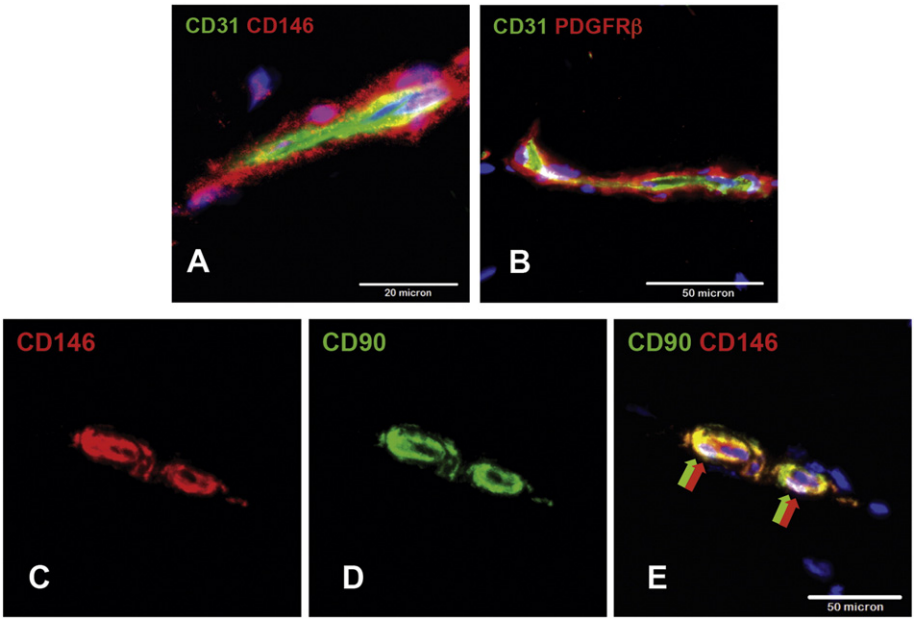

Fig. 1. Immunohistochemistry demonstrating the intimate relationship of pericytes to endothelial cells. (**A**) Adult mouse skeletal muscle pericytes expressing CD146 and PDGFRβ surround CD31$^+$ microvascular endothelial cells. (**B**) Adult human skeletal muscle pericytes co-expressing CD90 and CD146 surround CD146+ microvascular ECs.