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Mini review

Thrombospondin-1 and CD47 regulation of cardiac, pulmonary and vascular responses in health and disease

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ABSTRACT

Cardiovascular homeostasis and health is maintained through the balanced interactions of cardiac generated blood flow and cross-talk between the cellular components that comprise blood vessels. Central to this cross-talk is endothelial generated nitric oxide (NO) that stimulates relaxation of the contractile vascular smooth muscle (VSMC) layer of blood vessels. In cardiovascular disease this balanced interaction is disrupted and NO signaling is lost. Work over the last several years indicates that regulation of NO is much more complex than previously believed. It is now apparent that the secreted protein thrombospondin-1 (TSP1), that is upregulated in cardiovascular disease and animal models of the same, on activating cell surface receptor CD47, redundantly inhibits NO production and NO signaling. This inhibitory event has implications for baseline and disease-related responses mediated by NO. Further work has identified that TSP1-CD47 signaling stimulates enzymatic reactive oxygen species (ROS) production to further limit blood flow and promote vascular disease. Herein consideration is given to the most recent discoveries in this regard which identify the TSP1-CD47 axis as a major proximate governor of cardiovascular health.

Contents

1. Introduction

The clinical manifestation of cardiovascular disease (CVD) are many and include myocardial infarction, pulmonary hypertension (both with subsequent heart failure), peripheral arterial disease and poor wound healing, renal failure requiring dialysis or transplantation, and

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cerebrovascular events including stroke and hemorrhage (Centers for Disease and Prevention, 2011, 2013; Go et al., 2013). CVD remains the leading cause of morbidity and mortality in the Western world, superseding communicable diseases and malignancy (http://www.cdc.gov/nchs/fastats/lcod.htm). In CVD multiple pathophysiologic changes have been demonstrated in the macro and microcirculation that combine to decrease tissue blood flow and perfusion (Dinerman et al., 1993).

Loss of signaling from the biogas nitric oxide (NO) in vascular cells and blood vessels is a common finding in and contributor to CVD (Napoli and Ignarro, 2009). Decreased NO production or biochemical interactions between preformed NO and other reactive moieties (such as superoxide) account for some of the observed disease-associated loss of NO signaling (Chirkov and Horowitz, 2007; Heinrich et al., 2013). Thrombospondin-1 (TSP1) is a secreted matricellular protein upregulated by vascular cells after injury and in chronic disease. It alters cell responses through binding to cell receptors (Lawler, 2000). Increasingly, molecular evidence demonstrates a pivotal role for TSP1, through interaction with its high affinity receptor CD47, in controlling vascular cell responses in a NO-dependent (Roberts et al., 2012) and -independent manner, limiting blood flow and tissue perfusion in health and disease. In this review we will highlight the broadening role for the involvement of TSP1 and CD47 in CVD.

1.1. The importance of NO to vascular health

NO production is systematically regulated by three nitric oxidase synthases (neuronal, inducible and endothelial) that mediate conversion of L-arginine to L-citrulline (Moncada and Higgs, 1993; Bredt and Snyder, 1994). NO binds many intracellular proteins covalently at cysteine and tyrosine residues modifying their structure and function (Derakhshan et al., 2007a,b). One such interaction with the heme moiety of soluble guanylyl cyclase (sGC) leads to arterial vasodilation (Ignarro et al., 1987). Physiological levels of NO are essential to vessel structural integrity as it promotes endothelial and vascular smooth muscle cell health (Isenberg et al., 2005b, 2006a,b,c, 2009c). Endothelial-derived NO rapidly diffuses into the vessel wall acutely regulating arterial tone. In VSMC, NO reduces calcium availability for myosin light chain (MLC) kinase-mediated phosphorylation of MLC2 to inhibit vasoconstriction (Lincoln et al., 2001). Diffusion of NO into the vessel lumen decreases αIIbβ3 integrin activation and inhibits platelet aggregation and inflammatory cell adhesion to the vessel wall (Radomski et al., 1991). In addition to an inhibitory effect on inflammatory cell adhesion (Bath, 1993), these *in vitro* findings are consistent with the inherent anti-atherogenic role of NO (Shabani et al., 1996; Weller and Finnen, 2006; Schaffer et al., 2007; Blecher et al., 2012) (Fig. 1).

1.2. The integral role for TSP1 and CD47 in controlling NO signaling

Thrombospondin-1 (TSP1) is a large matricellular glycoprotein stored preformed in platelet α-granules (Lawler, 2000). TSP1 is released from platelets on activation (Baenziger et al., 1971). TSP1 is also produced and secreted by multiple primary cells (vascular smooth muscle (Isenberg et al., 2006a), endothelial (Phelan et al., 1998) and epithelial cells (Rogers et al., 2012), fibroblasts (Dameron et al., 1994) and keratinocytes (Wikner et al., 1987)) in response to stress as well as by innate immune cells (dendritic cells, macrophages (DiPietro and

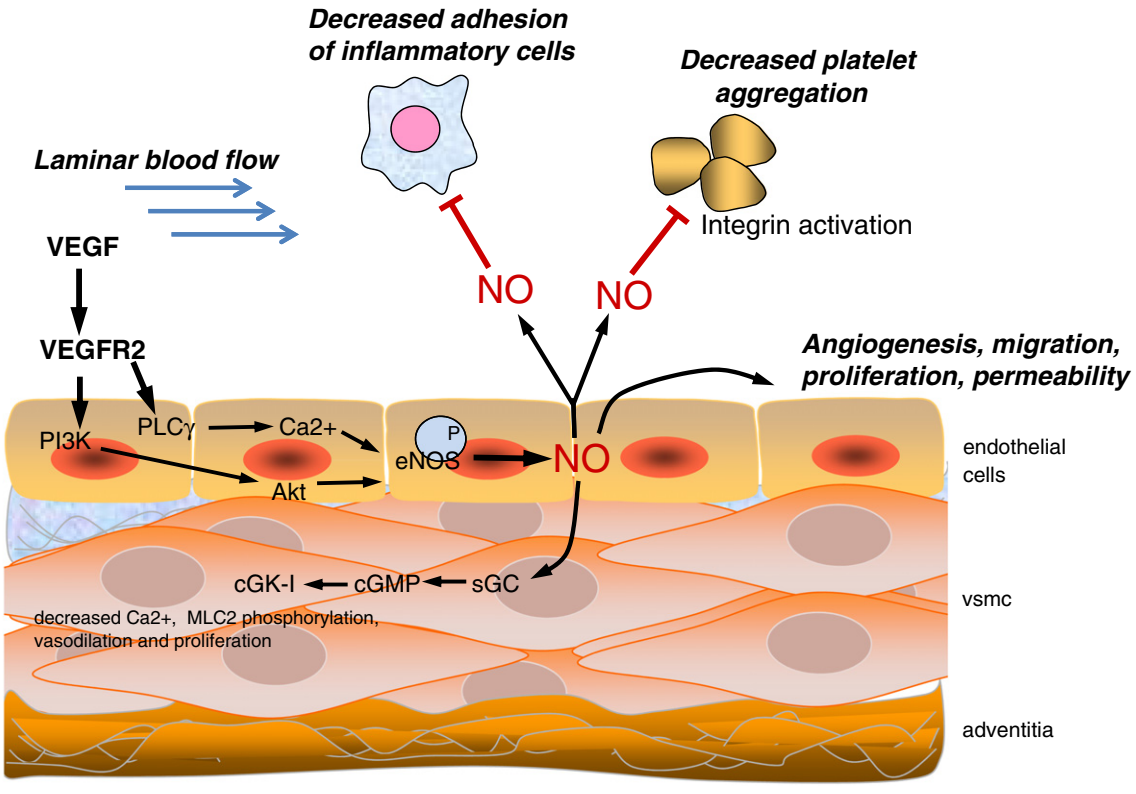

Fig. 1. Nitric oxide (NO) signaling within arteries targets multiple cells types to promote blood flow. Endothelial nitric oxide synthase (eNOS) reacts to hormones, including VEGF, and to the mechanical signal of laminar blood flow to increases production of the reactive nitrogen species NO. As a biogas, NO rapidly crosses cell membranes to activate the intracellular target soluble guanylyl cyclase (sGC) stimulating increased production of cyclic guanosine monophosphate (cGMP) itself a signaling intermediate. NO stimulates endothelial cell angiogenesis and suppresses expression of adhesion proteins on cell membranes. NO also acts distal to the site of production. In the artery lumen, NO decreases production of inflammatory cell cytokines and suppresses integrin signaling and platelet aggregation. In the wall of arteries NO acutely inhibits vascular smooth muscle cell contraction to dilate blood vessels and chronically suppresses cell overgrowth and hypertrophy, thus preserving vascular diameter and blood flow.