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A new role of mast cells in arteriogenesis

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ABSTRACT

Arteriogenesis is defined as the growth of functional collateral arteries from pre-existing arterio-arteriolar anastomoses. The role of mast cells in arteriogenesis is largely unexplored. Recent evidences suggest that mast cells together with other inflammatory cells, including monocytes-macrophages, lymphocytes, NK cells and endothelial precursor cells (EPCs) may be involved in this process. This review article analyzes the literature concerning this new aspect of biological activity of mast cells.

1. Arteriogenesis

Arteriogenesis is defined as the growth of functional collateral arteries from pre-existing arterio-arteriolar anastomoses. It is induced as a consequence of stenosis or occlusion of a major artery. Arterial occlusions often occur in patients who have one or more cardiovascular risk factors, influencing arteriogenic capacity, together with hypercholesterolemia, hypertension, tobacco use, hyperglycemia, obesity, and advanced age all impair collateral artery development (de Groot et al., 2009).

Atherosclerosis leads to progressive narrowing and occlusion of conductance arteries, and arterial occlusion prompts an adaptive response of the organisms to compensate for perfusion deficits. Altered blood flow through collateral anastomoses is the initial trigger. The increase in shear stress promotes vessel enlargement, which is stimulated by activation of nitric oxide (Pipp, 2004; Tronc et al., 1996).

Two phases of arteriogenesis are described, the proliferating and remodeling phases. Proliferation of the endothelium is followed by smooth muscle cell proliferation, disruption of the lamina elastica interna, migration of vascular smooth muscle cells to form a new neointima, tissue lysis, and cell death of the perivascular tissue to create the space for the growing and expanding new artery. In postnatal life, arteriogenesis refers to anatomic transformation of preexisting arterioles with increasing lumen area and wall thickness, due to a thick muscular layer and purchasing of visco-elastic and vasomotor capacities (Conway, 2001).

Arteriogenesis differs from angiogenesis in several aspects, the most important being the dependence of angiogenesis on hypoxia and the dependence of arteriogenesis on inflammation. Arteriogenesis occurs in non-hypoxic tissue. In fact, after occlusion of the femoral artery, it is detectable neither an increased expression of hypoxia inducible factor-1 alpha (HIF-1α) RNA nor an up-regulation of the HIF-1 controlled vascular endothelial growth factor (VEGF)-gene expression (Deindl et al., 2001).

There are almost two different modalities of formation of collateral arteries: i) artery-to-artery anastomosis bypass the capillary bed to provide blood flow to tissues served by an occluded artery. Numerous connections have been demonstrated between branches of the same and of different coronary arteries in human hearts. ii) arteriole-to-arteriole anastomosis, interconnecting small portion of arterioles of neighboring arterial trees.

In physiological conditions, as a result of chronic exercise or muscle loading, there is an increase in the number and length of distal arterioles, with extension of an arterial tree (Hansen-Smith et al., 2001), while in pathological conditions, arteriogenesis is associated to a degradation of the basement membrane by matrix metalloproteinase2- and -9 (MMP-2 and MMP-9) (Cai et al., 2000), a modification of smooth muscle cells from a contractile to a proliferative phenotype associated with loss of desmin (Wolf et al., 1998) and an inflammatory reaction around vessels.

2. Factors involved in angiogenesis and arteriogenesis

VEGF/VEGF receptor-2 (VEGFR-2) signaling pathway controls endothelial cell function in both angiogenesis and arteriogenesis. Arterial differentiation occurs in angioblasts exposed to higher VEGF concentration, whereas angioblasts less exposed differentiate into venous vessels (Simons and Eichmann, 2015).

In both developmental and adult arteriogenesis VEGF activation of extracellular signal regulating kinase ½ (ERK ½) induces endothelial

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cell proliferation, network formation and increased vessel lumen size. The activation of this signaling is modulated by neuropilin-1 (NRP-1) (Lanahan et al., 2013; Ren et al., 2010) while transforming growth factor alpha (TGF-α), VEGF, and fibroblast growth factor-2 (FGF-2) stimulate angiogenesis through proliferation of endothelial cells, TGF-β, granulocyte macrophage-colony stimulating factor (GM-CSF), monocyte chemoattractant protein-1 (MCP-1) and FGF-2 stimulate arteriogenesis through proliferation of smooth muscle cells (van Royen, 2001). FGF-2 and platelet-derived growth factor (PDGF) stimulate both angiogenesis and arteriogenesis. Kastrup (2001) demonstrated elevated levels of circulating angiogenic factors in ischemic injury (ischemic heart disease, stroke, or limb ischemia). Fluid shear stress stimulates arteriogenesis; biomechanical forces exerted by blood flow on the endothelium are involved in modulation of endothelial cell phenotype and blood vessel remodeling (Topper and Gimbrone Jr, 1999). Pulsatile shear stress (Buschmann et al., 2010; Li et al., 2005) and circumferential stress (Zheng et al., 2008) activates the cascade of events that leads to development of a collateral circulation (Arras et al., 1998; Sack et al., 1994; Scholz et al., 2002). Laminar shear stress has been shown to induce a variety of endothelial activation genes, which leads to a general predisposition to arteriogenesis while distributed shear stress tends to suppress endothelial activation genes, which results in quiescence combined with a general anti-apoptotic and anti-inflammatory state. In vivo studies suggest that arteriogenesis can occur when the mechanical environment both inside and outside the cell is changing (Egginton et al., 2001), while other studies have supported this model by suggesting that increases in shear rate function as the primary signal for arteriogenesis (Resnick et al., 2003).

The increased flow causes endothelial cell proliferation, with luminar expansion and release of platelet endothelial cell adhesion molecule (PECAM)-1 (Chen et al., 2010), MCP-1, -intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). The up-regulation of adhesion molecules is critical in induction of collateral growth through the recruitment of leukocytes, including monocytes, as well as resident macrophages (Takeda et al., 2011), which, in turn, promote arteriogenesis secreting MMPs, chemokines and growth factors (Ribatti et al., 2007).

3. Inflammatory cells in arteriogenesis

Monocytes are recruited by MCP-1 and by the major MCP-1 receptor, the CC-chemokine receptor-2 (CCR-2) (Heil, 2004). Their binding to the collateral surface is mediated by integrin receptors including macrophage-1 Ag (Mac-1) and lymphocyte function-associated Ag-1 (LFA-1). After adhesion, they migrate in the deeper parts of the collateral wall. Monocytes-macrophages are involved in the proliferation of the vascular wall and in the vascular wall remodeling by releasing growth factors, proteases, and chemokines (Arras et al., 1998; Kusch et al., 2002). Macrophages accumulate along collateral artery within 12 h after ligation and disappear over time (Scholz et al., 2000).

CCR-2 is expressed also on activated T-cells and lymphocytes appear in proximity to growing collaterals (Stabile, 2003). CD4-positive cells deletion resulted in impaired revascularization after hind limb legation (Stabile, 2003). CD8-positive cells are first recruited to the collateral vessel and then influence CD4-positive cells and monocytes recruitment through the release of interleukin-16 (IL-16) (Stabile, 2005). Also natural killer (NK) cells are involved in the development of collateral artery (van Weel et al., 2007).

Controversial is the role of the bone marrow-derived progenitors recruited to growing vessels in arteriogenesis (Kinnaird, 2004; Ziegelhoeffer, 2004), while endothelial precursor cells (EPCs) are incorporated into activated endothelium; in fact, they possess the ability to migrate, colonize, proliferate, and, ultimately, differentiate into endothelial lineage cells acquiring mature endothelial cell characteristics (Hur et al., 2003).

4. Mast cells in arteriogenesis

Mast cells reside in close proximity to vessels, making them key players in wound healing, tissue remodeling, fibrosis and angiogenesis. Mast cells are localized in the perivascular spaces of arteries (Wolf et al., 1998), where they synthesize vasoactive substances and growth factors (Ribatti and Crivellato, 2011), involved in arterial remodeling (Cao et al., 2003). Wolf et al. (1998) suggested a larger presence of mast cells during the initiation and growth phases, when these cells are able to release a large amount of proteolytic enzymes, cytokines and growth factors able to stimulate endothelial cell migration and proliferation, with a disappearance as the collateral vessels mature.

In 2005, Heissig and co-workers (Heissig et al., 2005) demonstrated in mast cell deficient mice that these cells play a significant role in neovascularization after hindlimb ischemia through secretion of VEGF and MMP-9. They proposed a mast cell-mediated mobilization of progenitor cells from bone marrow during ischemia that could be enhanced by low-dose radiation. In fact, mast cells express the stromal cell derived factor-1 alpha (SDF-1α) receptor CXCR-4 as well as the stem cell factor (SCF) receptor c-kit and both ligands are able to recruit stem cells promoting neovascularization. SCF is required for the differentiation and maturation of mast cells; in fact, mice carrying a mutation in their c-kit gene result in complete mast cell deficiency (Kitamura et al., 1978). Moreover, mast cells stimulate arteriogenesis recruiting neutrophils as well as monocytes and T cells.

Chillo et al. (2016) used an experimental murine hindlimb model in which femoral artery ligation resulted in collateral artery growth in the upper limb (Limbourg et al., 2009). They demonstrated that mast cells degranulate around growing collateral arteries. Moreover, pharmacological activation of mast cells with compound 48/80 (c48/80) and the c-kit ligand SCF, which triggers mast cell maturation and recruitment, enhanced perfusion recovery and arteriogenesis (Chillo et al., 2016). C48/80 treatment enhanced mast cell degranulation and reduction of the number of detectable mast cells around the collateral arteries. Combined administration of c48/80 and diprotin A (dip A, a protease inhibitor acting as an inhibitor of dipeptidyl aminopeptidase IV) further increased perfusion recovery, whereas combined treatment with c48/80, dipA, and SCF showed no further additive effect (Chillo et al., 2016). Finally, Cromolyn (an inhibitor of the release of mediators of inflammation induced by specific antigens as well as not specific mechanisms, from mast cells) treatment abolished the stimulating effect of dip A and c48/80, indicating that the majority of recruited cells were mast cells that promoted arteriogenesis by their degranulation products (Chillo et al., 2016).

Mast cells play a crucial role also in the development of atherosclerotic plaque through the release of a large amount of inflammatory mediators, including histamine, heparin, proteases, and cytokines, contributing to the initiation and progression of atherosclerosis and ultimately, leading to the destabilization and rupture of advanced atherosclerotic plaque (Kovanen and Bot, 2017; Ribatti et al., 2008).

5. Arteriogenesis and angiogenesis factors stored in mast cell granules

Mast cells produce several pro-angiogenic factors, including FGF-2, VEGF, IL-8, tumor necrosis factor alpha (TNF-α), TGF-β, and nerve growth factor (NGF) (Ribatti and Crivellato, 2011).

Mast cells migrate in vivo and in vitro in response to VEGF and placental growth factor-1 (PlGF-1) (Detmar et al., 1998; Detoraki et al., 2009; Gruber et al., 1988). Granulated murine mast cells and their granules are able to stimulate an intense angiogenic reaction in the chorioallantoic membrane (CAM) assay, partly inhibited by anti-FGF-2 and -VEGF antibodies (Ribatti et al., 2001). Intraperitoneal injection of the degranulating c48/80 causes a vigorous angiogenic response in the rat mesentery window angiogenic assay and in mice (Norrby et al., 1986; Norrby et al., 1989). Histamine and heparin stimulate