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Review

Role of neutrophil-derived matrix metalloproteinase-9 in tissue regeneration

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Summary. Ischemic tissue regeneration depends on neovascularization, the growth of new blood vessels. Bone marrow (BM)-derived cells, including neutrophils, have been shown to contribute to neovascularization during hind limb ischemia and inflammation. Neutrophils produce a broad array of angiogenic growth factors and proteases, which promote remodeling of arterioles into arteries through proteolytic mechanisms. Matrix metalloproteinases (MMPs) have been shown to play a role in the recruitment of neutrophils to sites of inflammation, which requires the extravascular migration of neutrophils through the extracellular matrix. Neutrophils control critical steps during angiogenesis and neutrophil-derived MMPs can promote neoangiogenesis, and collateral growth and perfusion recovery, in part by liberating vital angiogenic growth factors, including vascular endothelial growth factor-A (VEGF-A). This review focuses on the role of neutrophils as key players in the control of the angiogenic process during ischemic tissue regeneration. Aspects of neutrophil regulation, in particular regulation by its major growth factor granulocyte colony-stimulating factor (G-CSF), the role of the unique, readily available, neutrophil-derived MMP-9, and the functional consequences of this MMP-9 activation for angiogenesis, such as MMP-mediated release of biologically relevant cytokines from the matrix and cell surfaces, will be discussed.

Key words: Neutrophil, G-CSF, Angiogenesis, Ischemia, MMP-9

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Introduction

For a long time, it has been known that patients suffering from coronary heart disease can recruit collateral vessels, thereby improving the symptoms of myocardial ischemia (Helfant et al., 1971). It is also well established that an increased demand for oxygen, as occurs during exercise and placental development, can induce the formation of new capillaries. Thus, it seems that the body already possesses an "in-house" rescue system to increase blood flow under ischemic circumstances.

Neutrophils are thought to play an important role in normal physiological angiogenesis (the generation of new blood vessel growth from pre-existing vessels). During the menstrual cycle, angiogenesis occurs in order to support the proliferation and growth of the endometrial tissue. Neutrophils have been shown to be the source of the potent pro-angiogenic factor vascular endothelial growth factor (VEGF-A) in these tissues. In fact, VEGF-A-expressing neutrophils were found in the microvessels of the endometrium during the proliferative stage of the cycle (Mueller et al., 2000). Moreover, in a murine study of endometrial angiogenesis, the proliferation of endothelial cells in mice depleted of neutrophils by using anti-Gr-1 antibodies was reduced

compared to control mice, suggesting that neutrophils affect normal physiological angiogenesis (Heryanto et al., 2004).

Granulocyte colony-stimulating factor: a major growth factor for neutrophils

Under normal conditions, neutrophils are produced solely in the bone marrow (BM) by a process termed granulopoiesis (Christopher and Link, 2007). At steady state, only a small fraction of the total BM neutrophil pool is released into the circulation. Under stress conditions such as infection, peripheral blood neutrophil counts can rise significantly. The principle cytokine that regulates granulopoiesis is granulocyte colony-stimulating factor (G-CSF), a 25 kDa secreted glycoprotein encoded by the *CSF3* gene. G-CSF is widely used in clinical settings to treat or prevent neutropenia. Recently, an autosomal mutation in the *CSF3R* gene was identified in a family with chronic neutrophilia (Plo et al., 2009), in which constitutive activation of the receptor, and hypersensitivity to G-CSF for proliferation and differentiation, led to chronic neutrophilia.

Named for its relatively specific stimulation of the growth of neutrophil progenitor cells in vitro in semi-solid cultures (Burgess and Metcalf, 1980; Nicola et al., 1983), G-CSF induces the commitment of multipotent progenitor cells in the myeloid lineage, from hematopoietic stem cells through to mature neutrophils (Lord et al., 1989; Richards et al., 2003). It was shown that direct infusion of G-CSF into the BM vasculature, using an in situ perfusion of the femoral BM, leads to the selective mobilization of neutrophils (Wengner et al., 2008).

Mice with a genetic deletion of either G-CSF or the G-CSF receptor (G-CSFR) have few neutrophils in their blood or BM. Furthermore there is evidence to suggest that, under homeostatic conditions, G-CSF regulates both granulopoiesis and neutrophil mobilization from the BM (Lieschke et al., 1994; Semerad et al., 2002). The latter effect has been attributed to an indirect effect of G-CSF that functions via a reduction in stromal cell-production of stromal derived factor-1 (SDF-1) and a down-regulation of CXCR4 expression on neutrophils (Semerad et al., 2002; De La Luz Sierra et al., 2007; Kim et al., 2006).

G-CSF- and G-CSFR-deficient mice are also characterized by an increased mortality from neutrophil-associated infections, a susceptibility to bacterial pneumonia and a propensity to develop reactive amyloidosis with age (Lieschke et al., 1994; Liu et al., 1996; Seymour et al., 1997; Semerad et al., 2002). Within tissues, human neutrophils are usually identified on the basis of their nuclear morphology coupled with their positive staining for myeloperoxidase. In murine tissues, neutrophils are usually identified by expression of the cell surface marker Gr-1 and lack of F4/80 (monocyte/macrophage marker) expression.

Ischemic tissue regeneration

Neovascularization in humans can be fulfilled by vasculogenesis, angiogenesis, or arteriogenesis. Although the latter does not refer to de novo formation of vessels but rather to enlargement of pre-existing arterioles, most authors use the term neovascularization for all three entities. Vasculogenesis refers to the in situ formation of blood vessels from circulating endothelial progenitor cells, a process found in the embryo, but also detected in the adult (Takahashi et al., 1999; Hattori et al., 2001). In the embryo, angioblasts migrate, lengthen, interconnect, and establish a primitive vascular network. Angiogenesis induced by ischemia and hypoxia describes the process of new blood vessel growth from pre-existing vessels. Since, in both the embryo and the adult, this process leads predominantly to the development of small capillaries, angiogenesis is unable to fully restore the function of larger vessels. Arteriogenesis is characterized by the enlargement of arteriolar anastomoses to collateral vessels through growth and proliferation. These vessels can grow to such an extent that they can even assume the role of a large artery when occluded. This process depends on the following conditions: (1) The existence of an arteriolar network that connects the preocclusive with the postocclusive microcirculation; (2) Activation of the arteriolar endothelium by elevated fluid shear stress; (3) Proliferation of endothelial and smooth muscle cells; and (4) Invasion (but not incorporation) of BM–derived cells.

Role of matrix metalloproteinases in neo-vascularisation

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that degrade various components of the extracellular matrix (ECM). Members of the MMP family include collagenases, gelatinases, stromelysins, matrilysins and membrane-type MMPs. Plasma proteins (e.g. α-2 macroglobulin) and tissue inhibitors of metalloproteinases (TIMPs) are the primary endogenous inhibitors of MMPs. The regulation of MMP production and activity takes place primarily at the levels of gene transcription, pro-MMP activation, and endogenous inhibition. MMPs are formed as inactive proenzymes and are activated by proteolysis in the extracellular fluid (Visse and Nagase, 2003). The balance between MMPs and TIMPs plays a major role in physiologic and pathologic vascular remodeling, and angiogenesis (Raffetto and Khalil, 2008). Deregulation of MMP activity has been associated with vascular diseases such as atherosclerotic plaque formation, abdominal aortic aneurysms, and limb ischemia (Hobeika et al., 2007).

MMPs break down the surrounding tissue, consequently allowing inflammatory cells, including

monocytes and neutrophils, to further invade the vascular wall, thereby enabling paracrine signaling between the endothelium and the perivascular cells, and creating space for the growing vessel (Polverini et al., 1977). Gelatinases strictly regulate microvascular permeability and basement membrane remodeling during the early inflammatory response, whereas concomitant leukocyte recruitment is mediated by these proteases in a stimulus/cytokine-specific manner (Reichel et al., 2008).

Two members of the MMP family in particular, MMP-2 and MMP-9, have been implicated in the angiogenic response to ischemia (Heissig et al., 2003). The direct contribution of MMP-9 to angiogenesis and vascular performance is thought to involve MMP-9-catalytic activity that results in either the cleavage of ECM components such as native and denatured collagens (Van den Steen et al., 2002; Hamano et al., 2003), the processing of various cytokines and chemokines such as CXCL5, CXCL6 and CXCL8 (IL-8) (Van den Steen et al., 2000), or the release of angiogenic growth factors such as VEGF-A (Bergers et al., 2000; Heissig et al., 2005; Lee et al., 2005). MMP-9 can also inhibit tumor angiogenesis by generating the inhibitory factor angiostatin. Angiostatin is produced by the action of several MMPs (MMP-2, -3, -7, -9, and -12) on plasminogen (Patterson and Sang, 1997).

Many animal studies that investigate angiogenesis in critical limb ischemia use the mouse hind limb ischemia model with unilateral femoral artery ligation. After occlusion of a major artery, the ischemic limbs revascularize via the distinct mechanisms of arteriogenesis and angiogenesis. These transformations in the macrovasculature and microvasculature require changes in both the cellular and extracellular components of blood vessels and their surrounding tissues. An increase in MMP-9 activity in the gastrocnemius ischemic muscle tissue was observed three days after femoral artery ligation in mice (Muhs et al., 2004). Which cell types are the sources of MMP-9? Inflammatory cells are good candidates, as they typically infiltrate the ischemic muscle. The main source of MMPs in the ischemic muscle is probably neutrophils and, in fact, the increment of neutrophilic infiltrate parallels the elevation of MMPs. It is also conceivable that platelets may make some contribution to raised plasma MMP levels, given that platelets release relevant amounts of MMPs upon activation in vivo and that, in vivo, platelet activation is a hallmark of peripheral artery diseases (Falcinelli et al., 2007).

Role of neutrophil-derived MMP-9 in tissue regeneration

Neutrophil granules contain large amounts of MMP-9. Moreover, serine proteases released by these cells activate MT1-MMP, a membrane bound MMP that activates pro-MMP-2, leading to an increase in active MMP-2. Neutrophils are unique in that they can release TIMP-1 free *pro*MMP-9 and that they can chemically activate latent *pro*MMP-9 (Sopata and Dancewicz, 1974; Opdenakker et al., 2001). Thus, even in the absence of any transcriptional induction, ischemic tissue-infiltrating neutrophils are capable of rapidly releasing pre-stored *pro*MMP-9, making it immediately available to exert its vascular remodeling and/or pro-angiogenic action. Human neutrophil *pro*MMP-9, delivered in vivo as a purified zymogen, has been shown to be potently angiogenic at low to sub nanomolar levels (Ardi et al., 2009). A recent study demonstrated that neutrophil *pro*MMP-9, unencumbered by TIMP-1, undergoes activation in vivo and catalytically induces angiogenesis via an FGF-2/FGFR2 pathway (Ardi et al., 2009). Neutrophil depletion has been shown to block the naturally occurring activation of MMP-9 in ischemic tissues in models of limb ischemia and of middle cerebral artery occlusion/perfusion (Romanic et al., 1998; Justicia et al., 2003; Muhs et al., 2004).

MMPs promote angiogenesis by regulating matrix-bound growth factors such as VEGF-A. MMP-9 has been shown to proteolytically process and potentiate specific neutrophil-attracting cytokines, including IL-8 (Van den Steen et al., 2000), and to proteolytically release cell-recruiting factors such as the kit ligand (Heissig et al., 2002, 2003, 2007, 2009; Yang et al., 2004), of which the latter can increase circulating neutrophils by stimulating myelopoiesis (Fig. 1).

In a purified system MMP-3, -7, and -9 can cleave matrix-bound isoforms of VEGF-A, thus releasing soluble active fragments that display a peculiar neoangiogenetic potential (Lee et al., 2005). We have shown that G-CSF stimulation of neutrophils increases the release of VEGF-A and stimulates hind limb ischemic tissue regeneration, a process that mainly depends on the VEGF/VEGFR1 pathway (Ohki et al., 2005). In a recent study, we demonstrated that neutrophils from G-CSF-treated wildtype, but not MMP-9 deficient mice, promoted ischemic tissue regeneration in an HL ischemic model, due to impaired recruitment of neutrophils into the circulation and a reduction in their local influx into ischemic tissues (Ohki et al., 2005; Sato et al., 2009). Of interest, neutrophil-derived VEGF189 has been shown to be both chemotactic and chemokinetic for neutrophils, implicating an autocrine amplification mechanism that results in sustained VEGF release at inflammatory sites (Ancelin et al., 2004).

The increasing evidence of a role for neutrophils in tumor angiogenesis suggests that agents designed to reduce either neutrophil numbers or their biological activity within the tumor environment may be useful for anti-tumor therapy [reviewed in (Tazzyman et al., 2009)]. Tumor-associated neutrophils can stimulate tumor angiogenesis by producing proangiogenic factors, including VEGF, IL-8, and certain proteases such as MMPs (Coussens et al., 2000; Yang et al., 2004). The RIP1-Tag2 transgenic mouse model is a well-

characterized in vivo model of multi-step pancreatic carcinogenesis, in which insulin-induced expression of the simian SV40 large T antigen oncogene leads to dysplastic pancreatic islets, some of which become angiogenic and later form malignant tumors. It was found that angiogenic islets within lesions of these tumors contained neutrophils (Nozawa et al., 2006). Depletion of neutrophils in these animals by anti-Gr-1 therapy at the early stages of tumor development reduced the number of dysplastic islets undergoing angiogenesis due to suppression of VEGF:VEGF-receptor association, a signature of MMP-9 activity. Taken together, these studies strongly suggest that neutrophils play a role in the regulation of non-malignant and malignant angiogenesis.

Conclusions

Therapeutic angiogenesis in patients experiencing ischemic diseases has become a challenging goal for clinical research. In contrast to promising results from animal studies, VEGF-A and FGF-2 failed to induce significant improvement in a number of clinical phase I trials, (Seiler et al., 2001; Simons and Ware, 2003). On the other hand, it has been shown that treatment of critical limb ischemia in humans with BM-derived mononuclear cells induces active and durable neoangiogenesis in the ischemic and distal part of the treated limb. However, this effect may not prevent amputation in patients with very severe ischemia. The fact that proliferation lasted more than 2 months after cell injection suggests that this therapeutic approach could trigger a self-sustained angiogenic response in this propitious ischemic environment (Van Huyen et al., 2008).

Neutrophils were once an ignored cell type in the field of tissue regeneration. However, there is now an increasing body of evidence to show that neutrophils are capable of directly affecting neoangiogenesis and tissue regeneration through the release of neutrophil-derived factors (Fig. 1). Genetic lesions that alter the function of neutrophils and their release of MMPs may impinge on the ability of the body to mount a proper angiogenic response following ischemic stress or tumor growth. Given the evidence that neutrophils display pro- and anti-angiogenic characteristics, more research is required to understand the conditions under which pro- or anti-angiogenic effects can be expected. Nevertheless, using molecules which improve neutrophil recruitment into ischemic tissue may prove a beneficial and feasible therapeutic strategy to complement more traditional pro-angiogenic therapies for the treatment of ischemic

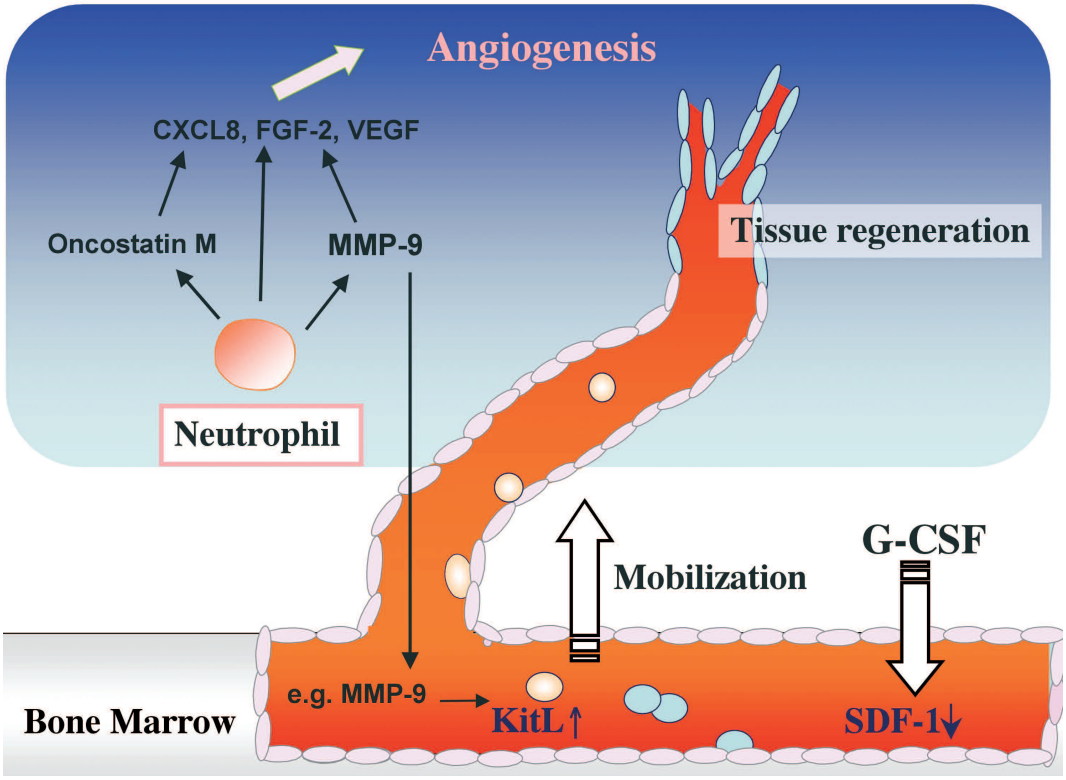

Fig. 1. Neutrophil-derived MMP-9 in neoangiogenesis. Administration of G-CSF increases the number of circulating and ischemic tissue-residing neutrophils. Neutrophil mobilization has been attributed to an indirect effect of G-CSF that functions via a reduction of stromal derived factor-1 (SDF-1) production by stromal cells and a down-regulation of neutrophil CXCR4 expression. G-CSF-activated neutrophils show degranulation of VEGF-A and CXCL8 (IL-8). Ischemic tissue-infiltrating neutrophils are capable of rapidly releasing the pre-stored tissue inhibitors of metalloproteinase-free pro matrix metallo-proteinase-9 (*pro*MMP-9) making it immediately available for exertion of its vascular remodeling and/or pro-angiogenic action. Similarly, neutrophil-derived MMP-9 can liberate pro-angiogenic growth factors (VEGF-A and FGF-2) that are sequestered in the extracellular matrix, or it can induce the influx of various cell-attracting cytokines or chemokines, including CXCL8 and kit ligand (KitL). These potent pro-angiogenic factors then act directly on the nearby vasculature to promote ischemic tissue regeneration.

patients. Integration of molecular, cellular and genetic studies with animal models will further clarify the involvement of neutrophil-derived MMPs in the regulation of angiogenesis.

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