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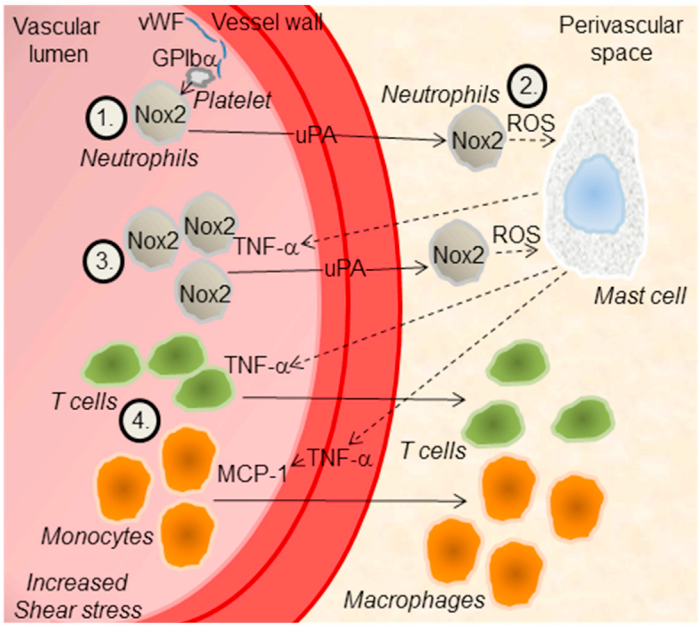
Perivascular Mast Cells Govern Shear Stress-Induced Arteriogenesis by Orchestrating Leukocyte Function

Graphical Abstract



Highlights

- Arteriogenesis is mediated by coordinated action of innate immune cells
- Mast cells orchestrate leukocyte function in arteriogenesis
- Platelet GPIbα is decisive for shear stress-provoked mast cell activation
- Shear stress-induced mast cell activation is mediated by neutrophil-derived ROS

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In Brief

Increased fluid shear stress is the triggering force for the growth of natural bypasses. How this mechanical load is translated into collateral artery growth is an enigma. Chillo et al. find that mast cell activation governs arteriogenesis by orchestrating leukocyte function.

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Perivascular Mast Cells Govern Shear Stress-Induced Arteriogenesis by Orchestrating Leukocyte Function

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SUMMARY

The body has the capacity to compensate for an occluded artery by creating a natural bypass upon increased fluid shear stress. How this mechanical force is translated into collateral artery growth (arteriogenesis) is unresolved. We show that extravasation of neutrophils mediated by the platelet receptor GPIbα and uPA results in Nox2-derived reactive oxygen radicals, which activate perivascular mast cells. These c-kit$^+$/CXCR-4$^+$ cells stimulate arteriogenesis by recruiting additional neutrophils as well as growth-promoting monocytes and T cells. Additionally, mast cells may directly contribute to vascular remodeling and vascular cell proliferation through increased MMP activity and by supplying growth-promoting factors. Boosting mast cell recruitment and activation effectively promotes arteriogenesis, thereby protecting tissue from severe ischemic damage. We thus find that perivascular mast cells are central regulators of shear stress-induced arteriogenesis by orchestrating leukocyte function and growth factor/cytokine release, thus providing a therapeutic target for treatment of vascular occlusive diseases.

INTRODUCTION

Arteries transport oxygenated blood from the heart to every individual organ of the body. Accordingly, occlusion of a major artery by thrombus formation or stenosis results in substantially reduced perfusion of distal organs, leading to ischemic damage or even necrosis of the affected tissue. Current options to treat vascular occlusive diseases such as myocardial infarction, stroke, or peripheral artery disease are percutaneous transluminal angioplasty (PTA) or bypass surgery. However, the body can create natural bypasses from pre-existing arteriolar anastomoses. This so-called arteriogenesis constitutes a tissue and even life-saving process, as it can compensate for the loss of a major peripheral or coronary artery. Promoting arteriogenesis in ischemia-related diseases may present a non-invasive alternative therapeutic approach to established clinical interventions.

Arteriogenesis is a complex, multi-factorial process (Deindl and Schaper, 2005) that involves the proliferation of endothelial cells (ECs) and smooth muscle cells (SMCs) as well as the recruitment of leukocytes, especially monocytes, which provide a variety of growth-promoting factors to the growing blood vessel (Arras et al., 1998). It is, therefore, not surprising that the therapeutic use of single growth factors or cytokines to support arteriogenesis did not meet expectations in clinical studies. To effectively promote arteriogenesis in patients, it is important to identify the molecular mechanisms naturally triggering the process of collateral artery growth.

Mast cells reside in the perivascular space of arteries (Wolf et al., 1998) and produce several vasoactive substances and growth factors (Hiromatsu and Toda, 2003; Rao and Brown, 2008), some of which have been described to contribute to arterial remodeling (Cao et al., 2003; Ito et al., 1997). The functional role of these c-kit$^+$/CXCR4$^+$ cells in arteriogenesis is currently unclear. Moreover, how fluid shear stress, which is the driving force for arteriogenesis (Pipp et al., 2004) and is sensed directly by vascular ECs, is translated into the activation of perivascular mast cells remains unresolved. Here we dissect the underlying