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Midkine controls natural bypass growth by regulating the bioavailability of VEGF

Cardiovascular occlusive diseases such as stroke, myocardial infarction or perivascular artery diseases (PAD) are a major personal and social burden. According to the World Health Organization, vascular occlusive diseases are the leading cause of death worldwide. Current state of the art treatments comprise percutaneous transluminal angioplasty (PTA), percutaneous transluminal coronary angioplasty (PTCA), or, if these options are not feasible, bypass surgery. However, from the clinic it is well known that some patients do not need such surgical interventions, since they profit from the growth of a natural bypass (Fig. 1).

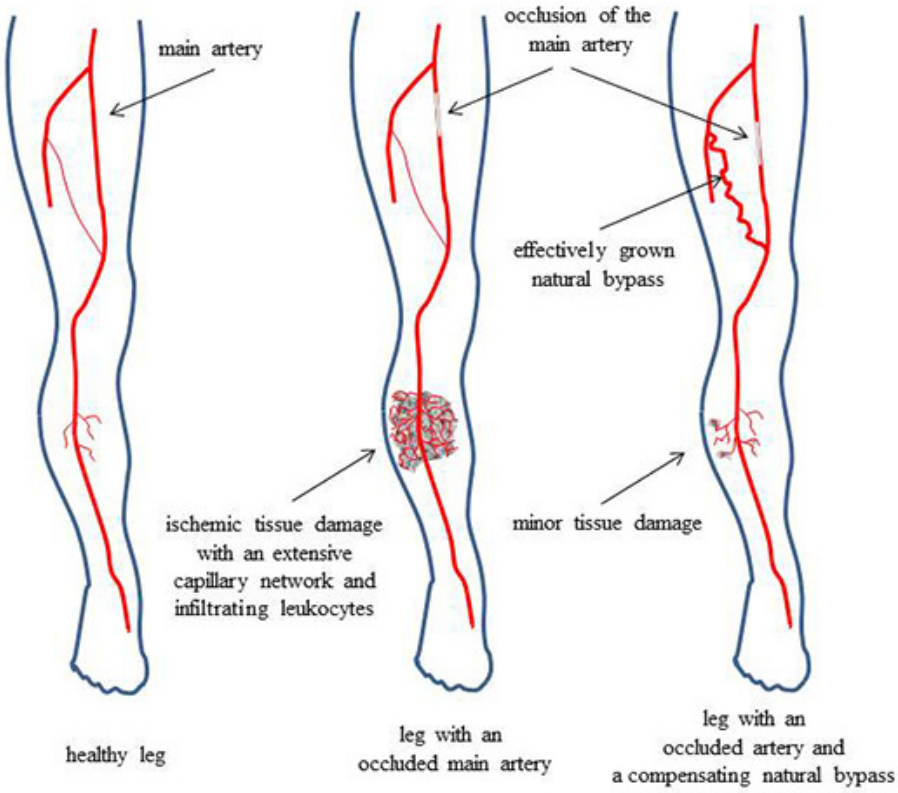

Fig. 1. (From Chillo et al., 2016 with the permission of Cell Reports)

This process called arteriogenesis is triggered by blood driven fluid shear stress. Upon slow progression of a stenosis, blood flow is redirected into pre-existing collateral arterioles circumventing the occluded artery. Due to the increased blood flow, the endothelium of the pre-existing arterioles becomes activated, finally resulting in the growth of the vessel. Much effort has been made to understand the molecular mechanisms of arteriogenesis, presenting the basis for the development of non-invasive treatment options aiming to promote natural bypass growth in patients. According to the current state of science, arteriogenesis is a matter of innate immunity. It relies on a local and temporary inflammation process, which consecutively involves the action of

platelets, neutrophils, mast cells, T cells and monocytes. Recently, a mechanosensing complex involving the action of the vascular endothelial growth factor receptor 2 (VEGFR2) has been identified to be relevant for the translation of the mechanical force, i.e. fluid shear stress, into diverse biological and biochemical signals resulting in collateral artery growth. Vascular endothelial growth factor A (VEGF-A), a ligand of VEGFR2, is a potent inducer of angiogenesis, the sprouting of capillaries. However, capillaries cannot substitute for the loss of an artery as capillaries are not able to conduct blood through the body, but only locally supply tissue with blood. Whether VEGF-A also plays a role in arteriogenesis has been discussed controversially for a long time. Neither VEGF-A nor its receptor VEGFR2 is differentially expressed in (growing) collaterals. Moreover, administration of VEGF-A promoted arteriogenesis, if it all, only to a minor degree in animal models and in patients. Recently, it was shown that the source of VEGF-A for angiogenesis are neutrophils, and later on that leukocytes such as neutrophils and monocytes are also the source of VEGF-A for arteriogenesis. We were now able to show that the bioavailability of leukocyte derived VEGF-A is regulated by midkine. Midkine is a retinoic inducible cytokine, which is expressed during embryogenesis and under inflammatory conditions in adult organisms. Using a murine hindlimb model of arteriogenesis, our results evidenced that midkine mediated levels of VEGF-A are necessary and also sufficient to promote shear stress induced vascular cell proliferation and hence collateral artery growth by regulating the expression nitric oxide synthases (NOS) (Fig. 2).

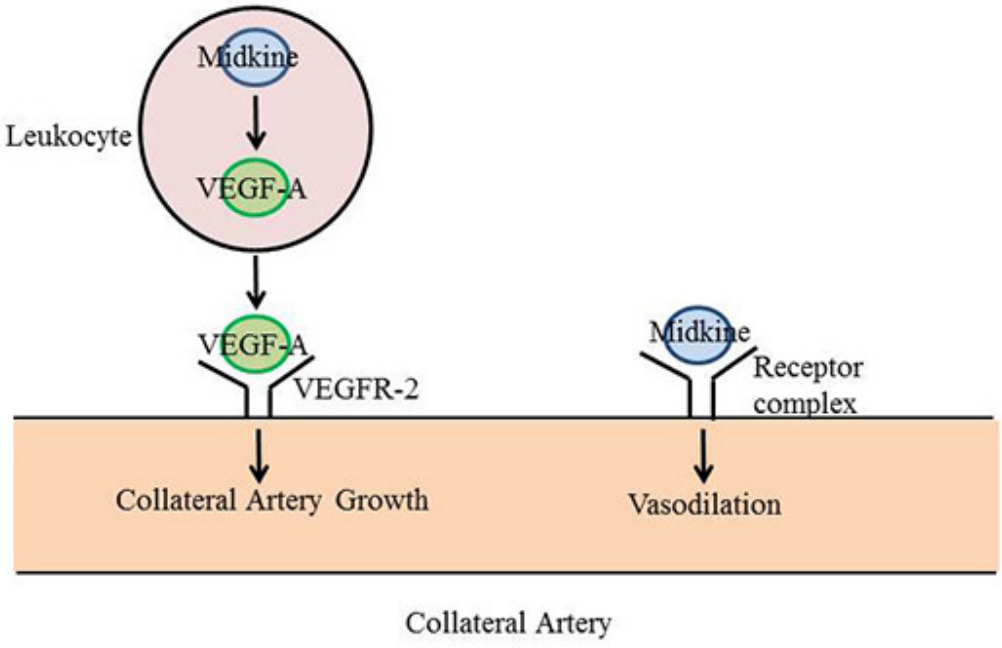

Fig. 2. (Adapted from Lautz et al., 2018 with the permission of EBioMedicine)

During arteriogenesis, VEGF-A induced VEGFR2 homodimer signaling is tightly regulated by the co-receptor Neuropilin-1. Accordingly, the question arises whether auxiliary factors such as extracellular RNA mediating the interaction of VEGF-A with VEGFR2 and Neuropilin-1 and promoting local inflammation might enhance the otherwise limited effect of exogenously administrated VEGF-A in terms of promoting

arteriogenesis. However, further investigations are necessary to resolve this question. Interestingly, our study on midkine revealed that application of this cytokine resulted in long-term vasodilation, probably by activating NOS via a multi-receptor-complex (Fig. 2). Hence, midkine might present a drug superior to currently available vasodilators such as nitric oxide donors, which only show a limited effect due to rapid tolerance.

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Publication

Midkine Controls Arteriogenesis by Regulating the Bioavailability of Vascular Endothelial Growth Factor A and the Expression of Nitric Oxide Synthase 1 and 3.
Lautz T, Lasch M, Borgolte J, Troidl K, Pagel JI, Caballero-Martinez A, Kleinert EC, Walzog B, Deindl E
EBioMedicine. 2018 Jan