Metabolic crosstalk between the endothelium and macrophages during recovery from hindlimb ischemia

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Angiogenesis, the formation of new blood vessels from existing ones, is initiated by the secretion of growth factors – the vascular endothelial growth factor VEGF is the best described one - from a hypoxic environment. To grow under low oxygen conditions, ECs have unique metabolic characteristics. Indeed, even though they are located next to the blood stream - and therefore have access to the highest oxygen levels - ECs are highly glycolytic. However, when they need to sprout into avascular areas and form new vessels, they upregulate glycolysis even further to fuel migration and proliferation. Suppression of glycolysis via inhibition of the glycolytic regulator PFKFB3 (phosphofructokinase-2/fructose-2,6-bisphosphatase isoform 3) in endothelial cells prevents blood vessel growth in the retina of the mouse pup and also in various models of pathological angiogenesis. While we now know that ECs are metabolically preconditioned to rapidly form new vessels, it remains an outstanding question whether this also holds true in muscle and whether endothelial metabolism can become a target for the treatment of peripheral artery disease.

We recently could show that EC specific loss of PFKFB3 reduced revascularization of the mouse ischemic hindlimb and impaired muscle regeneration. This was caused by the reduced ability of macrophages to adopt a proangiogenic and proregenerative phenotype. Mechanistically, we found that endothelial cells metabolically communicate with macrophages to drive M2-like polarization of macrophages during recovery from ischemia. In summary, we have identified angiocrine metabolic properties of ECs during muscle regeneration from ischemia.