Peripheral arterial disease (PAD) is widespread in Canada, affecting about 800 000 people. This disease is due to systemic atherosclerosis leading to a narrowing of arteries. In PAD, arteries supplying the lower extremities are not able to provide enough blood to the peripheral tissues. Restricted blood perfusion is often observed in the legs, which results in a reduced supply of oxygen and nutrients within distal skeletal muscle. The skeletal muscle in the lower limbs then become ischemic and cannot not function properly, in particular in response to physical activity. If blood flow is not restored, this circulatory problem can ultimately lead to limb amputation.

Restriction in oxygen supply usually stimulates angiogenesis the formation of new capillaries, the minute blood vessels in our tissue, from pre-existing blood vessels. The angiogenic process aims to enhance or to restore blood perfusion. Although patients with PAD encounter reduced levels of oxygen in their skeletal muscle, no change in the density of capillaries is observed. This suggests that angiogenesis is inhibited within the ischemic muscle. Our recent work published in Angiogenesis has revealed a molecular mechanism that could explain why angiogenesis fails to occur in the muscle of patients with PAD. We used a translational approach from in vitro to in vivo studies together with an analysis of biopsies from PAD patients. We observed an up-regulation of FoxO1, a transcription factor able to modify the phenotype of cells, in the ischemic muscle. Our results demonstrate that FoxO1 increases in the vascular compartment, particularly in the endothelial cells that form the wall of blood vessels. The increase in FoxO1 promotes the production of the anti-angiogenic factor thrombospondin-1. Our results shows that an enhanced activity of FoxO1 within the endothelial cells retrains blood flow recovery and hinders angiogenesis in the lower limb during ischemia.

Altogether our work suggests an important role for the endothelial expression of FoxO1 in the physiopathology of PAD.

Reference: Roudier E, Milkiewicz M, Birot O, Slopack D, Montelius A, Gustafsson T, Paik JH, DePinho RA, Casale GP, Pipinos II, Haas TL. Endothelial FoxO1 is an intrinsic regulator of thrombospondin 1 expression that restrains angiogenesis in ischemic muscle. Angiogenesis. 2013 Oct;16(4):759-72.

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