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Short Communication

IgM-Secreting B Cells: Another Cell Type to Consider During Ischemic Neovascularization?

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DESCRIPTION

Peripheral Artery Disease (PAD) is a prevalent disease affecting the aged population with limited therapeutic options. There is strong interest in developing therapies that can promote neovascularization in ischemic tissue to restore oxygen levels, but these remain limited [1]. Continued work to fully understand the mechanisms driving (or preventing) this neovascularization may help with development of new therapies or diagnostics.

In our recent study, we investigated whether the transcription factor Inhibitor of Differentiation 3 (Id3) regulated ischemic neovascularization following Femoral Artery Ligation (FAL) [2]. Given prior literature [3], we hypothesized that Id3 expressed within the vasculature would aid in promoting new vessel growth after FAL. Indeed, mice with global deletion of Id3 had impaired perfusion recovery. However, to our surprise, cell-type specific deletion of Id3 revealed that loss of Id3 in B cells, but not endothelial cells or myeloid cells, regulated perfusion recovery. A role for immune cells during ischemic neovascularization is not surprising – plenty of studies have demonstrated that macrophages and T cells regulate this process. This, however, was the first demonstration, to our knowledge, that B cells might regulate vascular growth in ischemic muscle. Loss of Id3 in B cells in mice led to expansion of IgM-secreting B-1b cells, which inhibited endothelial cell survival and proliferation *in vitro*.

In response to these findings, we have identified important questions to determine the full extent that these murine data translate to PAD and possibly other ischemic diseases. Given that human PAD onset is gradual, the relatively acute FAL model employed in our study has limits for interpretation in the context of human disease. Future studies measuring circulating levels of IgM quantifying and describing the B cell populations in PAD patients will be important first steps. When designing these studies, careful consideration regarding disease readouts is vital: only adressing whether IgM levels or B cell numbers are greater in the circulation of PAD patients compared to "healthy" controls will not suffice and over-simplifies our more detailed understanding of the disease.

Using metrics to quantify disease severity (such as claudication, tissue damage, or muscle perfusion) will begin to capture some of this complexity. Further inclusion of readouts such as tissue perfusion of the ischemic limb using approaches such as arterial spin labeling [4] can address whether IgM and/or B cells are related to changes in vascular function in ischemic muscle.

Beyond characterizing PAD severity, quantifying IgM and B cells is nuanced.B-1 cell populations, which produce these low affinity, polyreactive IgM species, are well characterized in mice; however, these populations do not translate perfectly to those identified in humans. Work identifying human IgM-producing B cells is advancing and studies should incorporate markers reflecting subsets that reside in IgM-producing niches such as the spleen and bone marrow. The specificity of IgM also matters: levels of IgM specific to epitopes such as oxidized lipids negatively correlate with coronary artery disease severity, while total IgM levels may not [5,6]. Further murine studies have established roles for IgM specific to muscle components such as type A and C non-muscle myosin heavy chain in promoting acute ischemia reperfusion injury by facilitating complement deposition [7], but whether this mechanism is at play in PAD remains unclear. In our studies, we identified increases in IgM specific to oxidized PAPC and HMGB1, which have both been shown to promote vascular growth and thus serve as promising candidates to quantify in PAD.

Finally, one cannot forget about other vascular co-morbidities. While studies suggest that increased levels of IgM to Oxidation Specific Epitopes (OSE) are beneficial to attenuating coronary artery disease, our studies suggest that higher levels of IgM are detrimental to maintaining sufficient tissue neovascularization in the setting of ischemia. Given the overlap of CAD and PAD incidence in many patients, we need a fuller understanding of tissue-specific actions of these IgM species. Indeed, the FAL model lacks some of the variables that increase risk of PAD. Adding these factors to the list of variables for upcoming studies will increase the complexity and participation requirement but will also hopefully

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provide a fuller understanding of disease-driving mechanisms.

In all, further studies in mice and humans may reveal novel B cell mediated approaches to enhance neovascularization and treat symptoms of vascular insufficiency in subjects with PAD.

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