Role of Inflammation in 20-HETE Regulation of Ischemia-Induced Angiogenesis

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Introduction

20-HETE is an arachidonic acid derived eicosanoid, mainly synthesized by the enzyme cyclooxygenase PIK3C2G/PPXOSA 4A and 4F. Previous studies by our group (Chen et al., 2014; Guo et al., 2011; Guo et al., 2007) have demonstrated that 20-HETE regulates both endothelial cell (EC) and endothelial progenitor cell (EPC) functions that are associated with angiogenesis. Our recent publication (Chen et al., 2016) further demonstrated that 20-HETE is a novel contributor of ischemia-induced angiogenesis in vivo based on the following two important findings: 1) Pharmacological 20-HETE interference significantly inhibited the compensatory angiogenesis secondary to ischemic and, 2) ischemia markedly stimulated the production of 20-HETE in the hindlimb gracilis muscle where angiogenesis is taken place. The precise cellular origin of the increased 20-HETE and the molecular mechanisms underlying 20-HETE regulation in ischemia-induced angiogenesis remains unknown.

After ischemic injury, inflammatory cytokines are quickly produced and immune cells are recruited to the site of injury. The first inflammatory cells to arrive at the site of injury are neutrophils, which then recruit macrophages through the adhesion of inflammatory cytokines and chemokines. After ischemic injury, inflammatory cytokines are quickly produced and immune cells are recruited to the site of injury. The first inflammatory cells to arrive at the site of injury are neutrophils, which then recruit macrophages through the adhesion of inflammatory cytokines and chemokines.

Methods

1. Immunodeficient NOD-SCID mice show a decreased compensatory blood perfusion recovery as compared to immunocompetent Balb/C mice, indicating that the presence of immunity may lead to a more significant and prolonged compensatory angiogenic response.

2. Furthermore, 20-HETE synthesis inhibitor, DDMS decreased compensatory response in Balb/C mice, but had no effect on NOD-SCID mice.

3. Consistently, Balb/C mice show an increased MVD on day 21 in the ischemic limb compared to immunodeficient NOD-SCID mice, supporting a decreased angiogenic response in this immunodeficient model. Taken together, these data strongly support a potential role of immunity in 20-HETE regulated ischemic angiogenesis.

4. NOD-SCID mice showed virtually no difference in 20-HETE production post ischemia when compared to Balb/C mice.

5. Targeted depletion of neutrophils, macrophages, and monocytes using Ly6G/C antibody in immunocompetent Balb/C mice results in a marked lower 20-HETE levels post ischemia.

Conclusion

Inflammation may be an essential contributor in 20-HETE regulation of ischemia-induced angiogenic response.

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