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Brian J. Kwee, Erica Budina, Alexander J. Najibi, David J. Mooney

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CD4 T-cells Regulate Angiogenesis and Myogenesis

Brian J. Kwee[a,b], Erica Budina[a], Alexander J. Najibi[a,b], David J. Mooney[a,b]

[a]John A. Paulson School of Engineering and Applied Sciences, Harvard University, Cambridge, MA 02138, USA
[b]Wyss Institute Biologically Inspired Engineering, Harvard University, Boston, MA 02115, USA

Abstract

Ischemic diseases, such as peripheral artery disease, affect millions of people worldwide. While CD4+ T-cells regulate angiogenesis and myogenesis, it is not understood how the phenotype of these adaptive immune cells regulate these regenerative processes. The secreted factors from different types of CD4+ T-cells (Th1, Th2, Th17, and Treg) were utilized in a series of *in vitro* assays and delivered from an injectable alginate biomaterial into a murine model of ischemia to study their effects on vascular and skeletal muscle regeneration. Conditioned medium from Th2 and Th17 cells enhanced angiogenesis *in vitro* and *in vivo*, in part by directly stimulating endothelial sprouting. Th1 conditioned medium induced vascular regression *in vitro* and provided no benefit to angiogenesis *in vivo*. Th1, Th2, and Th17 conditioned medium, to varying extents, enhanced muscle precursor cell proliferation and inhibited their differentiation *in vitro*, and prolonged early stages of muscle regeneration *in vivo*. Treg conditioned medium had a moderate or no effect on these processes *in vitro* and no discernable effect *in vivo*. These findings suggest that Th2 and Th17 T-cells may enhance angiogenesis and myogenesis in ischemic injuries, which may be useful in the design of immunomodulatory biomaterials to treat these diseases.

Keywords

T-cells; Angiogenesis; Myogenesis; Biomaterial; Regenerative medicine

1. Introduction

Ischemic diseases, such as coronary and peripheral artery disease (PAD), are a leading cause of morbidity and mortality worldwide. PAD, in particular, is estimated to affect over 200 million people worldwide [1]. Due to the chronic loss of blood flow, PAD often leads to loss of skeletal muscle strength [2] and, in severe cases, tissue necrosis and limb auto-amputation. A number of molecular and cellular therapies, including delivery of pro-angiogenic factors or infusion of bone-marrow-derived mononuclear cells, have been explored pre-clinically and in the clinic to restore blood flow and function to ischemic limbs. To date, however, these therapies have not passed FDA approval, as they have not demonstrated substantial improvements in randomized clinical trials [3].

It is increasingly appreciated that immune cells play a key role in promoting vascular regeneration and recovery in response to injuries, including those involving ischemia. Macrophages, in particular, have been extensively studied for their ability to promote