Encapsulated Induced Pluripotent Stem Cell-Derived Mesenchymal Stromal Cells Enhance Muscle Function and Angiogenesis in Diabetic Critical Limb Threatening Ischemia

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Critical Limb-Threatening Ischemia (CLTI), the end stage of peripheral arterial disease (PAD), represents a significant healthcare challenge, as it is marked by diminished blood flow to the legs, leading to tissue necrosis and eventual amputation. Since 2010, there has been a 50% increase in non-traumatic major amputations related to PAD. Previous studies have revealed that autologous bone marrow cell therapy fails to prevent amputations in diabetic patients with limited revascularization options. However, allogeneic bone marrow-derived mesenchymal stromal cells (MSCs) have shown promise in stimulating angiogenesis in the muscles of diabetic patients. Induced pluripotent stem cell (iPSC)-derived MSCs might offer superior benefits, including reduced senescence.

This study explores the potential of clinically approved human iPSC-MSCs, sourced from Cynata Therapeutics and encapsulated in alginate hydrogel, to enhance muscle regeneration in a diabetic CLTI mouse model. CLTI was induced by ligation/excision of the common femoral artery in male polygenic diabetic TALLYHO mice. iPSC-MSCs or a vehicle control were injected into the gracilis muscle of the ischemic limb seven days post-ligation. Treated limbs exhibited increased blood perfusion, improved muscle function, reduced pathology, and heightened angiogenesis.

Quantitative real-time PCR was employed to assess changes in mRNA expression related to muscle regeneration. Seven days post-iPSC-MSC injection, the gastrocnemius and tibialis muscles demonstrated elevated mRNA expression for VEGF-A, MyH3, Mrc1, and Foxp3 compared to vehicle-treated muscles, signifying enhanced angiogenesis, muscle cell regeneration, M2-biased macrophage expression, and increased T regulatory cells. The observed rise in Mrc1 and Treg cells also suggested decreased inflammation in the treated muscle.

These findings underscore the efficacy of encapsulated Cynata MSCs in fostering muscle regeneration and angiogenesis in diabetic mice, meriting further investigation to evaluate their potential for limb preservation in diabetic patients with CLTI.