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Christina Zhu

Karina Skylar

Yori Endo

Mohamadmahdi Samandari,

Mehran Karvar

See next page for additional authors

Authors

Christina Zhu; Karina Skylar; Yori Endo; Mohamadmahdi Samandari,; Mehran Karvar; Azadeh Mostafavi; Jacob Quint; Chiara Rioldi; Wojciech Swieszkowski; Joshua Mauney; Shailesh Agarwal; Ali Tamayol; and Indranil Sinha

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159. AEROBIC EXERCISE AND SCAFFOLDS WITH HIERARCHICAL POROSITY SYNERGISTICALLY PROMOTE FUNCTIONAL RECOVERY POST VOLUMETRIC MUSCLE LOSS

Christina Zhu, BS, BA[1,2], Karina Sklyar[1], Yori Endo, MD[1], Mohamadmahdi Samandari, PhD[3], Mehran Karvar, PhD[1], Azadeh Mostafavi, PhD[4], Jacob Quint, MS[3], Chiara Rinoldi, PhD[5], Wojciech Swieszkowski, PhD[6], Joshua Mauney, PhD[7], Shailesh Agarwal, MD[1], Ali Tamayol, PhD[3], Indranil Sinha, MD[1]

[1]Brigham and Women's Hospital, Boston, MA, USA, [2]Texas Tech University Health Sciences Center, Lubbock, TX, USA, [3]University of Connecticut, Farmington, CT, USA, [4]University of Nebraska-Lincoln, Lincoln, NE, USA, [5]Institute of Fundamental Technological Research Polish Academy of Sciences, Warsaw, Poland, [6]Warsaw University of Technology, Warsaw, Poland, [7]University of California Irvine, Irvine, CA, USA.

PURPOSE: Volumetric muscle loss (VML) is a composite loss of skeletal muscle tissue (greater than 20%) that heals with minimal muscle regeneration, substantial fibrosis, and subsequent functional deficits. Standard treatment, involving free functional muscle transfer and physical therapy, cannot restore full muscle function following VML. Tissue engineered scaffolds, 3D structural templates that mimic native extracellular matrix, are promising to enhance functional muscle formation and recovery. Bioprinted 3D scaffolds are engineered using bioinks, created from scaffolding material, cells, and growth factors, to replicate skeletal muscle architecture with precise control over their spatial deposition.

METHODS: The present study evaluates a 3D-printed foam-like scaffold for the treatment of VML in a murine model. This colloidal foam-like scaffold was developed to have high porosity to improve tissue ingrowth, in contrast to dense polymeric scaffolds that routinely resulted in very poor tissue ingrowth, and sufficient stiffness to maintain its shape. A handheld 3D bioprinter using an *in-situ* printing strategy allowed for direct printing and crosslinking of the scaffold into the muscle defect without suturing. Direct adhesion to the remnant muscle creates a temporary 3D microenvironment to support cellular infiltration and proliferation for endogenous skeletal muscle regeneration and improved muscle function. The scaffold was additionally engineered with microparticles of insulin-like growth factor 1 (IGF-1), a myogenic factor known to promote skeletal muscle progenitor cell proliferation and differentiation that is notably reduced in VML. The hierarchical pores created by the foaming method allowed for sustained release of IGF-1 and thereby enhance muscle regeneration by promoting cellular permissibility of proliferating cells.

RESULTS: At eight weeks following VML injury to the gastrocnemius, gross imaging of the muscle demonstrated significant tissue in-growth and improved muscle repair in the foam group compared to the VML untreated group. Histological analysis confirmed *de novo* muscle regeneration in the foam group. Similarly, strength assessment of ankle plantarflexion demonstrated a significant 1.2-fold increase (p=0.02) in torque and a significant 1.8-fold increase (p=0.01) in tetanic force in the foam group compared to the VML untreated group. Additionally, the scaffold demonstrated a significant 50% reduction (p=0.0005) in fibrosis, measured by collagen deposition area, and a significant 2.3-fold increase (p=0.01) in neuromuscular junction innervation in the regenerated tissue of the foam group compared to the VML untreated group. To evaluate the effects of exercise on the VML murine model, synergistic incorporation of aerobic running in the foam group resulted in a significant 25% improvement (p=0.04) of *in situ* gastrocnemius strength and a significant 30% improvement (p=0.02) in maximal distance of running, compared to the VML untreated with exercise group.

CONCLUSION: Taken together, the combination of this 3D-bioprinted highly porous foam-like scaffold and exercise training demonstrated improved muscle regeneration, reduced fibrosis, and increased functional recovery. This may be an effective clinical treatment option for patients following VML injury in the future.

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