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The Role of Muscle-Derived Stem Cell-Enriched Scaffolds for Treating Volumetric Muscle Defects

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Wang et al. recently investigated the role of muscle-derived stem cell (MDSC)-enriched scaffolds for muscle regeneration in a preclinical model of volumetric muscle loss (VML).¹ The use of MDSCs to treat VML as a result of trauma, extirpative therapy or reconstructive surgery highlights a novel tissue engineering strategy with great translational appeal. We believe, however, that specific issues in the methodology preclude interpretation and translation of study results.

The C57BL/6J mice used in the study are weaned beginning at 4 weeks of age, and grow rapidly, increasing their body weight approximately 31% from 4 to 8 weeks.² As such, it remains unclear as to why the authors chose such young mice of varied age (4 – 8 weeks). Strategies to limit rapid muscle growth as a confounder, such as stratification or matching according to age or weight are not reported and we do not know to which groups these animals were randomized. Collectively, it is hard to imagine that not stratifying groups of animals with large differences in growth rates did not confound the muscle regeneration data.

The lack of a healthy control group, and selection of the contralateral limb as a control and surrogate marker for normal muscle volume presents another challenge. The surgical defect creates a functional impairment on the ipsilateral limb and resultant alteration of hindlimb kinematics. As such, the ipsilateral hindlimb will be underloaded, as the contralateral hindlimb will be subjected to compensatory overloading while adapting to new

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physiological and biomechanical demands. In combination with factors mentioned above, it is likely that the observed increase in volume is confounded by these contralateral hypertrophic changes.

Unfortunately, there also appear to be some inconsistencies in the methods of volume measurements. The outline in figure 2C (scaffold + MDSCs) includes a contour deformity and a portion of the femur which is not included in figure 2A. This discrepancy in measurement undoubtedly contributed to the increased ratiometric data in this group. Additionally, the data provided also suggest MDSC-enriched scaffolds are capable of achieving increases in cross-sectional area (CSA), however, a volume increase is reported. Although figure 2 shows an increase in CSA, the authors use this as a surrogate marker for volume, yet no calculations for muscle volume are presented. Had CSA been multiplied by muscle fiber length, muscle volume would have been easily estimated. Micro-computed tomography would have also given insight into potential volumetric changes however, images were only taken at the study conclusion, thereby preventing pre/post volumetric comparisons.

Interestingly, Aguilar et al. recently showed that the pathologic response to VML impairs endogenous and exogenous regenerative processes in the acute setting.³ Importantly, this may explain the lack of colocalization of green fluorescent protein-expressing MDSCs with regenerated muscle fibers noted by Wang et al. Lastly, the goal of treating VML is to ultimately restore muscle function. Although the authors acknowledge this as a limitation, the lack of kinematic and kinetic data reduces the significance and impact of this potentially innovative approach.

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