



Rotator cuff muscle stem cells: the double-edged sword in the skeletal muscle

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Rotator cuff tear (RCT) is a representative muscle-tendinous disease-causing shoulder pain (1), and recently, its prevalence rate is remarkably increasing by an aging population and various sports activities (2,3). For RCTs, surgical repair is prevalent and has been a commonly accepted treatment, especially when the conservative management was failed (4). Nevertheless, failure of rotator cuff healing after repair is common and is one of major post-surgical complications (5), though the arthroscopic repair techniques have been advancing steadily. Most of all, fatty degeneration in muscle is a critical detrimental cause of poor functional outcome due to its irreversible property (6,7). Although the precise mechanisms of muscle fatty infiltration are not fully determined yet, numbers of studies have assumed that muscle fat accumulation is caused by adipogenic differentiation of the stem cells in muscle (8-10).

Stem cells have the potential to differentiate into multilineage of tissues and can theoretically be stimulated to undergo transition to a preferred lineage such as bone, cartilage, tendon, and muscle, thus recreating a specific tissue (11). Therefore, recently, various stem cell-based therapeutic approaches have been attempted to repair the injured tissue (12). But, as above mentioned, satellite cells can also differentiate into adipocyte by various degenerative factors including aging, muscle injury, mechanical unloading, and hormonal imbalance (13-16). Thus, understanding of the fine-tuned balance of stem cell differentiation has considerable interest in biological

augmentation of rotator cuff healing.

In “*The Journal of Bone and Joint Surgery (American volume)*”, Schubert *et al.* reported that rotator cuff satellite cells are more disinclined to myogenic differentiation, rather prone to adipogenic differentiation compared with that from gastrocnemius muscles (17). By isolation of the specifically labeled satellite cells from rotator cuff muscle and gastrocnemius muscles in tamoxifen-stimulated *Pax7^{CreERT2}:R26R^{tdTomato}* mice, they evaluated the potential of satellite cells to differentiating into myogenic or adipogenic lineage. The rotator cuff satellite cells revealed a 23% reduced myogenic capacity and a 4.3-fold increased adipogenic differentiation compared with gastrocnemius satellite cells. Although there was no significant difference in gene expression of desmin and myomaker, the expression of myogenic regulatory factor 4 (MRF4), the late-muscle differentiation marker was remarkably decreased (an 87% reduction) in rotator cuff satellite cells. With respect to adipogenic differentiation, the representative adipogenic transcription factor peroxisome proliferator-activated receptor gamma (PPAR γ) and a carrier protein for fatty acids fatty acid binding protein 4 (FABP4) were significantly increased in rotator cuff satellite cells (a 12-fold and a 65-fold increase, respectively). However, there was no significant differences in the expression of adiponectin and CCAAT-enhancer-binding protein-alpha (C/EBP α) between the groups. They also identified rotator cuff muscle-specific 180 hypomethylated regions and 175 hypermethylated

regions compared with gastrocnemius by evaluation of any epigenetic difference between both groups of satellite cells. Gene ontology analysis of relevant biological processes and molecular function predictions of the differentially methylated regions revealed that the top 15 genes revealing higher methylation differences are associated with embryonic development and limb morphogenesis. They also suggested that the molecular functions of high-ranked genes are closely related to transcription-factor activity and lipid metabolism regarding adipogenesis.

Although this study presents very interesting and meaningful findings that satellite cells in rotator cuff muscle have distinct differentiation potential compared with that from other type of muscles such as the gastrocnemius muscles, there are several concerns to be considered. Because they cultured the isolated satellite cells in adipogenic media only and analyzed the capacity of both myogenic and adipogenic differentiation, this examination seems asymmetric assessment showing only the susceptibility of both satellite cells against adipogenic condition. In addition, the proportion of satellite cells between rotator cuff and gastrocnemius muscles should be considered due to the fact that the satellite cells are a functionally heterogeneous population showing many differences in their gene expression profile, myogenic differentiation tendency, and pluripotency to assume non-myogenic fates (18).

In general, for an efficient repair of tissue damage, muscle stem cells are activated by muscle injury and undergo self-renewal process (19) However, in certain cases, they can enter the adipogenic process by activation of the crucial transcription factors C/EBP α or PPAR γ . The fate decision of stem cells is ultimately derived from an imbalance between myogenic and adipogenic environment. In view of this context, the important thing is what kind of factors decide the fate of stem cell to select which edge of the sword. To identify the potent molecule(s) associated with a myogenic or adipogenic capacity of the satellite cells, they examined a limited number of molecules with regard to each differentiation. Various transcription factors or molecular mediators are known to be involved in decision of stem cell fate. It has been known that myogenic differentiation 1 (MyoD) and myogenic factor 5 (Myf5) are master regulators of skeletal muscle formation during embryogenesis and postnatal myogenesis (20). However, such myogenic regulatory factors also known to be involved

in muscle regeneration. MyoD expression is nearly absent in quiescent satellite cells, while its expression is augmented in activated muscle stem cells by muscle injury or exercise (21). Up to date, a variety of myogenic regulatory factors and their upstream regulators in the field of skeletal muscle formation and regeneration are elucidated (22). Muscle fatty infiltration is induced by the ectopic fat accumulation in damaged muscle and thought to be caused by a defect of proper muscle regeneration process after injury (10,23). Therefore, identification of the molecular mediators involved in muscle regeneration or intramuscular fat accumulation seems to be a promising direction.

Recently, biologic augmentation for rotator cuff repair has been attracting the attention due to its promising potential to regenerate damaged tissues effectively, and various approaches have been tried to improve the outcome of rotator cuff surgeries. Among them, stem cell-based therapies have shown encouraging results to replenish damaged tissue for better healing. However, paradoxically, they are plagued by the limitation, their pluripotency. Stem cells can differentiate into various cell types and they can also spread to other areas of the body causing undesired mutations or alteration of their genetic profile. Therefore, comprehensive understanding of the properties of muscle stem cells and various biologic approaches need to be preceded first before consideration for human clinical trials.

On the other hand, a recent study reported that RCT-induced muscle fatty infiltration is intermediated by FABP4, unlike adipogenesis of muscle stem cells (24). In that study, authors suggested that *FABP4* gene expression is induced by RCT through direct binding of hypoxia inducible factor 1 (HIF1) to the *FABP4* promoter, which leads to ectopic fat accumulation in injured muscle. As an extended study, they also evaluated that the muscle injury-induced ectopic fat accumulation is repressed noticeably by FABP4 inhibitor, and that FABP4 inhibitor further improves muscle tensile strength (25). Thus, the application of other approaches besides stem cell-based therapy would be a considerable way to improve muscle degeneration with respect to RCT.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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