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Editorial

Tendon Stem Cell: A Possible Solution for Tendon Injury Repair and Aging

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EDITORIAL

Tendon injuries due to misuse or overuse as well as age-related degeneration are common clinical problems facing orthopedic surgeons and sports medicine clinicians. Following injury, tendons exhibit an ineffective repair response that is often characterized by scar formation. Severe tendon injuries often require surgical intervention, but the structure and function of repaired tendons remain inferior when compared to non-injured tendons [1]. The repair of injured tendons remains a great challenge, and becomes even more challenging in older patients. Currently, there are no therapies to restore the normal function and structure of injured tendons.

Aging is a major risk factor for tendon injury and impaired tendon healing, suggested by the high prevalence of shoulder disorders in individuals over the age of 60 [2]. Aging tendons undergo structural and biomechanical degenerative changes, accompanied by reductions in the number and functional activities of tenocytes [3]. Tenocytes are cells responsible for producing and remodeling tendon extracellular matrix. The decline of tenocytes weakens the tensile strength and performance of tendon and reduces its ability to adjust to environmental stress and to repair injuries.

Stem cells hold promise for improving tendon repair and regeneration. Bone marrow mesenchymal stem cells (MSCs) and embryonic stem cells (ESCs) have been used as therapeutic tools to repair tendon injuries [4]. However, in some cases, the use of MSCs in tendon repair resulted in ectopic calcification [5], which may be due to the absence of optimal conditions to direct their differentiation to tenocytes [6]. The occurrence of bone formation after transplantation of MSCs may exacerbate the tendinopathy [7]. One of the challenges in using ESC for tissue repair is controlling their differentiation *in vivo*. In this regard, Chen et al. demonstrated differentiation of hESCs via a MSC programming phase by treatment with fibroblast growth factor 2 (FGF2) improved tendon regeneration [10]. However, bone formation was also observed in *in situ* patellar tendon repair [6]. Recent studies support the notion that genetic manipulation can serve to reprogram and change stem cell fate [8]. Alberton et al. have shown evidence of converting human MSCs into tendon progenitor cells by gene transfer of scleraxis [9]. It would be of great interest to know whether such reprogramming can be effective in improving MSC and ESC teno-repair ability to resolve the above issues.

Of interest, tendon stem/progenitor cells (TSPCs) have been identified in human tendon tissues [11] and tissues of other mammalian species [12,13]. This discovery offers new avenues for treating tendon injuries and accelerates its slow repair. Tendon stem cells exhibit higher clonogenicity, proliferation, and multi-lineage differentiation potential when compared to bone marrow derived MSCs [14]. They also appear to have many advantages compared to MSCs; i.e. the percentage of stem cells in tendons are at least three times the number of MSCs [7], and there is no risk for bone formation [11,12]. These studies indicate that tendon stem cells exert good potential to restore the structure and the functions of injured tendons. Despite these findings, aging of tendon stem cells represents a major problem toward the establishment of such cell therapy [15].

Recent studies demonstrated that TSPC self-renewal declines with age [16]. TSPC frequency and proliferation rate are reduced and cell cycle progression is delayed in aged TSPCs. Of note, in aged TSPCs, expression of tendon lineage marker genes is reduced while adipocytic differentiation is increased. Interestingly, reduced expression of CITED2, a multiple-stimuli responsive transactivator involved in cell survival, growth and senescence, is associated with the above changes in aged TSPCs [16]. Additionally, Kohler et al. revealed the existence of premature entry into senescence in aged TSPCs is accompanied by an upregulation of $P16^{INKa4}$, a gene associated with MSC stem cell senescence [17]. Taken together, uncovering the mechanisms and means to rejuvenate aged tendon stem cell may provide a fundamental solution to reversing tendon stem cell aging and improving tendon injury repair.

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