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Assembly, maturation, and degradation of the supraspinatus enthesis

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The development of the rotator cuff enthesis is still poorly understood. The processes in the early and late developmental steps are gradually elucidated, but it is still unclear how cell activities are coordinated during development and maturation of the structured enthesis. This review summarizes current knowledge about development and age-related degradation of the supraspinatus enthesis. Healing and repair of an injured and degenerated supraspinatus enthesis also remain a challenge, as the original graded transitional tissue of the fibrocartilaginous insertion is not re-created after the tendon is surgically reattached to bone. Instead, mechanically inferior and disorganized tissue forms at the healing site because of scar tissue formation. Consequently, the enthesis never reaches mechanical properties comparable to those of the native enthesis. So far, no novel biologic healing approach has been successful in enhancing healing of the injured enthesis. The results revealed in this review imply the need for further research to pave the way for better treatment of patients with rotator cuff disorder.

Level of evidence: Narrative Review

Keywords: Rotator cuff; footprint; fibrocartilage; cytokine; mineralization; healing; inflammation

Rotator cuff (RC) lesions are one of the most common conditions affecting the shoulder. The prevalence of RC tears is age dependent, and the prevalence of both partial- and full-thickness RC tears increases markedly after 50 years of age.[51,83] The etiology of RC diseases is multifactorial, but the supraspinatus (SS) tendon is particularly vulnerable to become injured.[8]

Longitudinal data suggest that tears progress over time.[84] Approximately 30% of surgical repairs will fail, and the failure rate is as high as 90% in patients with large chronic tears.[21,74]

The attachment site of the SS tendon at the footprint of the greater tuberosity of the humerus defines a classic enthesis made of 4 zones (Fig. 1). Degenerative changes may be seen in all 4 zones, and the severity of a lesion depends on the degenerative status of the enthesis and the adjacent tissues involved. The SS tendon makes up the roof of the shoulder joint, with the joint side of the tendon being covered by synovial tissue and the acromial side by bursal tissue.[8,46] It is believed that damage to the enthesis can induce an

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inflammatory reaction in the synovium or bursal tissue characterized by expression of matrix-degrading molecules and increased proliferation and differentiation of osteoclasts. This may cause excessive degradation of the enthesis matrix,[20,44,46,68,76] leading to inadequate enthesis function. The induced imbalance in the enthesis remodeling process is a crucial event in the onset of RC tears and pathologic RC disease.

Both the development and maturation of the native enthesis are poorly understood. Muscle loading (ie, exertion of force on tendon and bone by muscles) is critical for maturation of the developing enthesis, as tissue deformity and diminished mineralization are apparent in mouse models where 1 shoulder has been paralyzed.[76,77] Besides muscle loading, molecular factors are critical for the development of a functional enthesis.[61] Recently, several transcription factors, including scleraxis (*Scx*), SRY-box 9 (*Sox9*), and GLI-Kruppel family member 1 (*Gli1*), have been detected in early progenitor cells of the developing enthesis and are crucial for development.[10,19,20,75] However, many questions remain unanswered as to what drives development and differentiation of the progenitor cells and how this is regulated.

The reparative capacity of the damaged enthesis is inadequate because the repaired enthesis never regenerates its native structure after an SS tendon tear. Instead, excessive scar tissue formation with inadequate biomechanical properties appears at the repair site.[70,71] Attempts to enhance the healing process of damaged RC tendons have thus been directed toward biologic enhancement at the repair site, just as stimulation of the regenerative repair processes also has attracted attention.[6,21] Transforming growth factor β (*TGF-β*) isoforms have received special attention as important mediators in both scarless and scar-mediated healing processes.[6,21]

This review provides an overview of recent knowledge on the developmental steps of the fibrocartilaginous enthesis, the inflammatory response after SS tear, and the early characteristics of enthesis healing after damage, touching on therapeutic applications and considerations about biologic augmentation.

Methods

A comprehensive search for peer-reviewed articles, excluding conference papers or reports, was conducted on the basis of the following MeSH terms: enthesis, rotator cuff, supraspinatus, growth and development, inflammation, scleraxis, SRY-box 9, Indian hedgehog, transforming growth factor β, arthritis, tendinopathy, osteoclastogenesis, tumor necrosis factor, synovial, synovium, RANK, and healing.

The following databases were searched for literature: PubMed, Embase, and Web of Science. The reference section of each article was also inspected to find additional articles. The process yielded 85 articles published from 1986 to September 2017.

Structure and function of the native enthesis

The native SS tendon enthesis develops postnatally and is viewed as a 4-zone structure at maturity (Fig. 1). The tendinous *first zone*

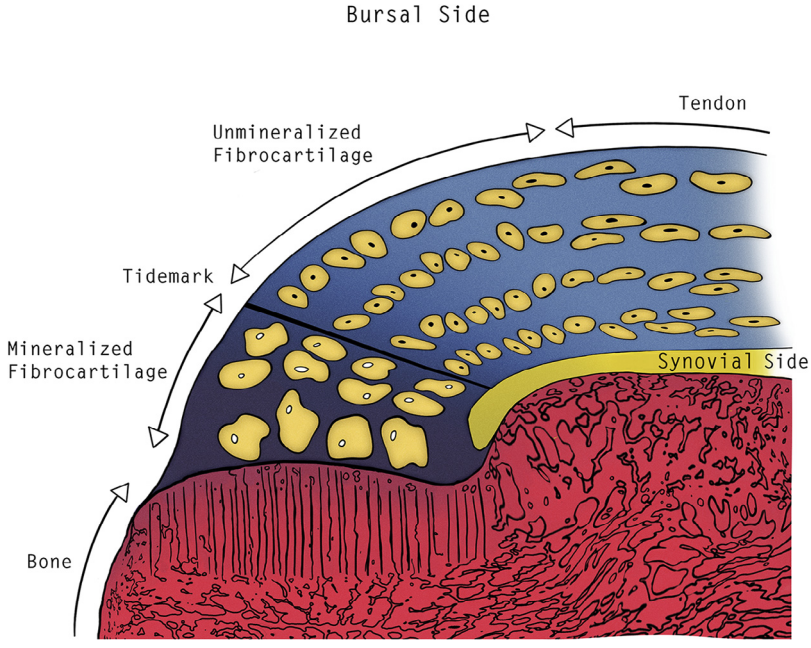

Figure 1 The 4 zones of the fibrocartilaginous enthesis. The tendon zone consists of elongated tenocytes. At the border to the fibrocartilaginous zone, the cells change from elongated fibroblasts to round chondrocytes, stacked in columns. The cells enlarge during the transition from unmineralized to mineralized fibrocartilage. These hypertrophic cells are large cells imbedded in the mineralized matrix, gradually mineralizing the matrix. The mineralized fibrocartilage firmly anchors into the underlying trabecular bone tissue. The tidemark separates the 2 fibrocartilaginous zones.