

## Molecular Mechanisms during Tendon Injury: A Review Article

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**Abstract:** Tendon injuries are common injuries which usually occurred by open injury. These injuries can lead to single; multiple or other structures injuries like blood vessels, bone and other soft tissues. Knowledge of molecular mechanism of injury and drugs which affected of them may get the examiner to better diagnosing and in consequence better treatment. Tendinopathy is the result of imbalance between protection and pathologic processes, after any trauma to tendons. As this important need, we concluded a review article which molecularly surveys the tendone injury. The goal of this review study is to guide orthopedic surgeons and sports physicians to select better approaches and to design better future studies that are less limited.

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### 1. Introduction

Tendon injuries are common injuries which usually occurred by open injury (1). These injuries can lead to single; multiple or other structures injuries like blood vessels, bone and other soft tissues (2). Sport is another important cause of tendon damages which may be due to overstressed whom named as close injuries. The complete tearing of a tendon is responsible for immediate loss of its function, which may be state permanent unless it is repaired. Pain swallowing, and difficulty in moving a finger is the symptoms. Partial tears in tendons cannot detect obviously and may be ignored. Assessment of tendon injuries requires careful systematically examination and testing other tissues which may be injured along with tendon injury. Position of level of injury is important aspect too (3). However, many of partial injuries may involve but not detected. Most of tearing tendons need repairing but in some conditions probably it manages by a period of splinting. Good rehabilitation after tendon repair is crucial. Repaired tendon weaker than normal and can snap if over-stressed. However, there are also controversial aspects in diagnosis and treatment of injuries (4). Knowledge of molecular mechanism of injury and drugs which affected of them may get the examiner to better diagnosing and in consequence better treatment. As this important need, we concluded a review article which molecularly surveys the tendone injury.

### 2. Molecular Survey of Tendon Injury

When tendon is injured, the inflammatory phase begins after occasioning the hematoma and platelet activity. Having secreted the inflammatory mediators, the neutrophils invade the tissue and phagocyte the tissue debris. Inflammatory mediators and secreted factors from cells have advantages and disadvantages in the healing of injured tissue. Oxidants, secreted from aggregated neutrophils, damage and degenerate the tissue. The inflammatory phase combines with degeneration in injured tissue. These macroscopic changes contain poorly demareated with loss of tendon structure. The injured tendon begins gray and amorphous. Microscopically, the degenerative changes contain hypoxic, hyaline, mucoid, myxoid, fibrinoid and fatty degeneration (5, 6). Cellular density is also different in different part of degenerated tissue. Degenerative fiber of collagen type I are calcified or filled with lipid cells (Tendolipomatosis). The normal tendon contains more collagen type I but injured tendon contains more collagen type III and fewer cross-links (7, 8). Corticosteroids, through inhibiting the neutrophil aggregation, and decreasing the inflammatory mediators and oxidants, can help the tissue in healing rapidly. Concurrent with degenerative changes, neovascularization also occurs in injured tendons (9, 10). The wound and inflammation cause the excretion of growth factors which are involved in neovascularization, proliferation of fibroblasts and tenocytes, and collagen synthesis. Growth factors such as Growth and Differentiation Factor (GDF), Scleraxis (Sex), Fibroblast Growth Factor (FGF) have roles in collagen synthesis and tendon

morphogenesis (11). Studies show increasing level of lactate in injured tendons, due to anaerobic status which accelerates the expression of Vascular Endothelial Growth Factor (VEGF) (15, 16). VEGF have roles in angiogenesis, up regulation of expression of Matrix Metalloproteinase (MMP), and increasing of extracellular matrix degradation (9, 12). When the neovascularization has occurred, the nerves migrate to new vessels (13). This confirms the theory of the relation of pain and neovascularization.

Concurrent with neutrophil aggregation, tissue hypoxia and neovascularization, fibroblasts enter into injured tendon. Fibroblasts synthesise the collagens and increase the mechanical performance of the tendon. Collagen fibrillogenesis contains three phases (14). 1; the collagen molecules firstly aggregate near fibroblast and make the immature fibrils (collagen fibrillogenesis). 2; these fibrils are placed end-to-end for making a longer fibril (linear growth) 3; and then are placed laterally near each other to have a greater diameter (lateral growth). The fibrils make fibers and finally the large fibers, while increasing the cross-links to get the tendon properties. In the chronic phase of tendinopathy, the fibroblasts change to contractile cells (myofibroblasts) due to extension tissue remodeling. Myofibroblasts have smooth muscle actines in their cytoplasm and make a force for wound contracture. These cells make the long contracture in pretendinous adhesions, so the vessels are affected and vasoconstriction occurs. Due to insufficient microcirculations and hypoxia, new microvessels are produced. Other events occur in chronic tendinopathy too. Repeated mechanical stretching causes an increase of PGE2 in injured tendon. PGE2 inhibits the collagen type I synthesis (15). PGE2 also has catabolic effects on injured tendon (16).

Because of the cascade properties of these processes and the overlapping of the events, the corticosteroids have direct and indirect effects on different aspects of the processes. For example, corticosteroids inhibit the production of PGE2 and preserve tendons from structural damage. The effects of corticosteroids will actually not be limited to special cells. Their effects are extent in all processes. In the repair phase many molecules are involved: MMPs, Thrombospondin Motifs (ADAMTs), and their tissue inhibitors (TIMPs) (17). The expression of MMP-9 and MMP-13 increases 7-14 days after injury. However, the amount of MMP-2, MMP-3 and MMP-14 remains high till the 28th day. These results indicate that MMP-9 and MMP-13 only have a role in collagen degradation. and MMP-2, MMP-3 and MMP-14 have roles in collagen degradation and collagen remodeling (17). The events which occur during regular exercises with reference to athlete

physical performance have beneficial effects. These exercises increase the collagen synthesis. Some studies use microdialysis techniques for assessing the collagen turnover, and have indicated that the exercise increases the production and degradation of collagens and that the production was greater (18). The result of this would be that the tendon becomes more powerful, with more elastic potency opposite the injury. During exercise, both dynamic and isometric, the microcirculation increases in the tendon and its surroundings. When the force to the tendon is higher than physical performance, the collagen begins to slide past and the cross-links are cut. These microtraumas cause weakness in the tendon and damage to pretendinous soft tissues, including vessels. On the other hand, there are other mechanisms which may do damage to the tendon. During exercise, the tendon temperature increases and it may rise to 43-45 °C, however experimental studies have shown that a temperature higher than 42.5 °C may kill the fibroblasts and degrade the tendon (19). During exercise, the damaging and repairing mechanisms are actually occurring simultaneously. During the healing process, MMPs, ADAMTs, NOs, GDFs and Scx are over-expressed. The damaging process includes over-expression of MMP-3 and increase in secretion of endothelial growth factors, platelet-derived growth factors, as well as leukotriene and PGE2 (20). So the tendinopathy is the result of imbalance between protection and pathologic processes, after any trauma to tendons.

### 3. Conclusion

tendinopathy is the result of imbalance between protection and pathologic processes, after any trauma to tendons. However, future studies in regard to specifying of drugs which can reduce the inflammation phase are warranted.

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