

## Inflammation in Post-traumatic Osteoarthritis: How does it Start?

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Traumatic injuries to weight-bearing joints (knees, ankles, hips, spine) may greatly increase the risk for the early onset of osteoarthritis (OA) in a younger and more active population. Different from idiopathic primary OA, this type of joint degeneration is secondary to intraarticular trauma and is defined as post-traumatic OA (PTOA). Studies have shown that ACL rupture, meniscus tear, patellar dislocation, shoulder dislocation, and ankle instability are injuries that frequently occur to athletes and place patients at great risk of developing PTOA [1]. A study conducted by Brown and colleagues indicated that PTOA accounted for approximately 12% of the overall prevalence of symptomatic OA in lower extremities in the United States. Correspondingly, the aggregate financial burden specifically of PTOA is \$3.06 billion annually, or approximately 0.15% of the total U.S. health care direct cost outlay [2].

The main cause of PTOA symptoms (joint pain, stiffness, and even disability) is the irreversible degradation of cartilage in affected joints. However, the molecular mechanism underlying this degenerative process still remains unclear. Studies from PTOA patients and animal or explant models have reported production of inflammatory mediator, activation of inflammatory pathways and immune cell infiltration after joint injury [3]. This overwhelming inflammatory response may get out of control, which results in further joint tissue damage and the loss of joint function.

In an *ex vivo* PTOA explant model, activation of proinflammatory MAP kinases was observed in the impact zone of cartilage within 24 hrs after a single blunt impaction to the explant was applied. This kinase activation spread to neighboring areas with time. Specific inhibitors to those kinases could prevent impacted cartilage from losing extracellular matrix. Those results implied that mechanical insults to cartilage might trigger inflammatory responses in chondrocytes, the only cell type in cartilage [4].

Another study using the same explant model revealed that the generation of extracellular matrix protein degradation products, fibronectin fragments (Fn-fs), could be the upstream effectors of the inflammatory pathways in chondrocytes of mechanically injured cartilage. The authors proposed that Fn-fs could be one of the inflammatory mediators that ignite inflammation in injured joints and are responsible for the spreading of local cartilage injury to eventually cause the breakdown of the whole tissue [5].

In addition to Fn-fs, reactive oxygen species (ROS) might be another set of initiators of mechanical injury induced joint inflammation. Coleman et al. reported that injurious loading on cartilage could stimulate mitochondria to produce abnormally high levels of ROS [6]. This oxidative stress created by ROS may lead to the opening of inter-endothelial junctions and promotes the migration of inflammatory cells across the endothelial barrier into the joint space. The role of ROS in trauma induced inflammatory damage to the joint was further demonstrated in an *in vivo* PTOA rabbit model. Riegger, *et al.* reported that administration of N-acetyl cysteine, an antioxidant fighting against ROS, could mitigate initial inflammatory response and alleviate cartilage degeneration after blunt trauma to knee cartilage [7].

In summary, inflammation plays a critical role in PTOA pathogenesis. Both Fn-fs and ROS might serve as initiators of joint inflammatory responses to mechanical insults. Nonetheless, more investigations need to be done to elucidate the exact molecular mechanisms leading to joint destruction in PTOA.

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