

Mechanoflamination in Osteoarthritis Pathogenesis

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Abstract:

Mechanical injury is the most important risk factor in osteoarthritis (OA) development. Although once considered a passive disease of mechanical attrition, injury drives active mechanosensitive intracellular signalling which affects the structural and symptomatic course of disease. Mechanosensitive signalling in cartilage has been elucidated over the years and two principal responses emerge: those that cause the release of growth factors from the matrix and which stimulate repair, and those that drive inflammatory signalling, a process that we have termed “mechanoflamination”. The up-stream activator of mechanoflamination remains unknown, but it results in rapid activation of NFkB and the inflammatory mitogen activated protein (MAP) kinases and this controls the bioavailability of aggrecanase and regulation of nerve growth factor (NGF), causing pain. The precise relationship between mechanoflamination and cartilage repair is currently unclear but it is likely that chronic mechanoflamination will contribute to disease by also suppressing intrinsic tissue repair.

Introduction:

Mechanical load is an undisputed risk factor in the development of osteoarthritis (OA) and arguably the only obligatory factor in the development of disease. The risk can be divided into those cases where excessive mechanical strain is transmitted through a normal joint (obesity, joint malalignment, occupational risk), or where normal load traverses a joint that has lost its mechano-protective mechanisms. Mechano-protection is afforded by having a stable joint (intact ligaments and menisci), by having a healthy thick cartilage (one that is mechano-adapted to the current environment) [1], and by having strong muscle support across the joint and intact gait reflexes [2]. The latter in particular are key contributors to the sizeable risk of disease in elderly populations.

Research over the past 15 years has demonstrated that mechanical load in OA does not simply drive attrition of the articular surfaces, so called ‘wear and tear’. Rather, it induces activation of mechano-sensitive signalling pathways that drive the proteases that initiate the process of joint breakdown. Evidence for this is as follows: (i) mice in which key proteases are deleted are protected from development of OA despite having induced joint destabilisation [3]. (ii) Immobilisation of the joint after induction of OA not only prevents OA development but also abrogates inflammatory gene regulation including the disease-causing proteases [4]. (iii) Mice are protected when key inflammatory signalling pathways that control protease activity are deleted [5,6]. (iv) Targeted killing of the superficial chondrocytes in cartilage protects mice from joint destabilisation-induced OA [7].

The sterile tissue injury response is well described in other organ systems but this has been examined almost exclusively in vascularised tissues where damage to the endothelium is

regarded as a key initiator of the injury response. Endothelial damage leads to an orchestrated response due to activation of platelets and the clotting cascade with consequent release of inflammatory cytokines, recruitment of leukocytes (principally neutrophils, then monocytes) and resolution of tissue damage. Tissue repair by resident and exogenous connective tissue cells then follows [8].

Our group has made significant efforts to understand the molecular basis of the injury response in articular cartilage (Figure 1). Our studies have principally involved studying the response of articular cartilage to mechanical injury following explantation (cartilage cut directly from the intact joint surface), re-cutting (where the tissue is rested in vitro for 48h then re-injured), avulsion (shearing the immature femoral head from the mouse hip) and mechanical compression [9,10]. Articular cartilage is a particularly interesting tissue to study in the context of other tissue injury responses as it is paucicellular (the extracellular matrix makes up around 90% of the tissue), and it lacks blood vessels and nerves thus has no endothelium and no leukocytes. There is only one cell type, the chondrocyte, and this cell must therefore be responsible for receiving and responding to injurious signals transmitted through the matrix. The response to injury is made up of several components, activating both degradative and repair-promoting pathways.

Repair promoting pathways appear to be largely driven by the release of growth factors such as TGF β and FGF2 that are sequestered in the pericellular matrix of cartilage and released immediately in response to injury [11]. The mechanism of this release appears to involve a flux of sodium in the tissue upon compression (unpublished results). In the case of TGF β , sequestration of the latent form is mediated by its covalently bound partner connective tissue growth factor (CTGF, also known as CCN2) that binds to heparan sulfate proteoglycan in the pericellular matrix and allows the latent complex to become activated at the cell surface, through binding to cell surface betaglycan (also known as TGF β R3) [12]. FGF2 appears to be involved in the local recruitment and activation of progenitor cells (FGF2) (manuscript in preparation). Subsequent differentiation of progenitor cells to chondrocytes is most likely mediated by TGF β . In vivo FGF2 is chondroprotective [13] and enhances intrinsic cartilage repair (manuscript in preparation).

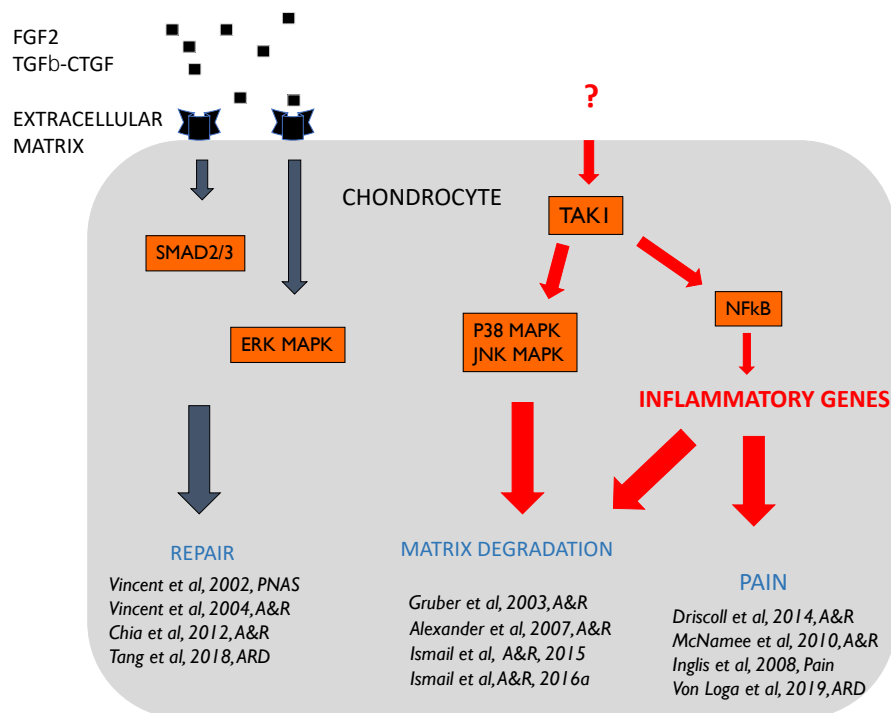


Figure 1. Injury-activated pathways in articular cartilage. Pathways activated in chondrocytes upon simple cutting injury of articular cartilage. Mechanoflammentation drives TAK1-dependent pathways that lead to pain and matrix degradation in vitro and in vivo. The up-stream mediator of this response is unknown. Release of matrix sequestered growth factors drives tissue repair responses.

The inflammatory response to mechanical injury, so called “mechanoflammentation”, involves the activation of the TGFβ-activated kinase 1 (TAK1) which lies up-stream of the inflammatory mitogen activated protein kinases, p38 and c-Jun N-terminal kinase (JNK) and NFκB signalling. TAK1 can also be activated by classical inflammatory mediators such as IL1, TNF and TLR ligation but none of these are involved in the injury response and the pattern of ubiquitination of TAK1 that marks its upstream activation is quite distinct from that seen with IL1 or TNF [14]. TAK1 activation drives disease relevant pathways involving control of aggrecan degradation in vitro and in vivo [5] [6] through the activation of the JNK2 isoform specifically. It also drives induction of nerve growth factor (NGF) [15], a key mediator of pain in murine and human OA [16-18]. Interestingly our data point to NGF being made in vivo in the articular cartilage itself albeit only late in disease once the basal layer of cartilage is breached [15]. The upstream activator of injury is currently unknown but does not appear to involve a soluble factor (Saklatvala, personal communication).

How the balance of pro-degenerative and pro-repair pathways after injury is controlled remains unclear although our previous work has hinted at qualitative differences in the type of load being important. Specifically, shear stress at the surface is more likely to activate mechanoinflammatory responses and compressive load more likely to drive chondroprotection [4]. It is also of interest to note recent work from others that implicates a reciprocal relationship between TAK1 and YAP/TAZ-dependent repair pathways in OA [19]. Suppression of mechanoflammentation in OA may therefore not only inhibit matrix turnover and pain but may indirectly promote intrinsic repair signalling.

Mechanoflamination could also be an important part of the repair response; tissue remodelling being a requirement of subsequent successful repair. In other systems temporal control of the inflammatory response to injury appears to be critical in affecting a good repair outcome. Chronic tissue inflammation predicts a poor outcome and is frequently seen in the elderly, at sites of mechanical stress (e.g. pressure sores) and in diabetics [8]. Injury to vascularised and innervated tissues is usually painful and patient symptoms will tend to limit mechanical stress at the damage site. Whilst there may be some short-term perceived benefit from articular cartilage being insensate, this may inadvertently lead to a chronic mechanoinflammatory response that limits the intrinsic repair response. This may account for why off-loading the joint through a procedure known as joint distraction, where the joint is kept apart by an external frame, may help to break the cycle of chronic mechanoflamination and shift the balance in favour of repair [20]. Although some structural benefit is being seen with intra-articular anabolic agents such as FGF18 [21], it seems likely that greater clinical benefit will be realized when used in combination with therapies that also target mechanoflamination; either through correcting the mechanical environment of the joint or by interfering with mechanoinflammatory signalling.

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