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Review Article

Osteoarthritis joint pain: The cytokine connection

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ABSTRACT

Osteoarthritis is a chronic and painful disease of synovial joints. Chondrocytes, synovial cells and other cells in the joint can express and respond to cytokines and chemokines, and all of these molecules can also be detected in synovial fluid of patients with osteoarthritis. The presence of inflammatory cytokines in the osteoarthritic joint raises the question whether they may directly participate in pain generation by acting on innervating joint nociceptors. Here, we first provide a systematic discussion of the known pro-algesic effects of cytokines and chemokines that have been detected in osteoarthritic joints, including TNF-α, IL-1, IL-6, IL-15, IL-10, and the chemokines, MCP-1 and fractalkine. Subsequently, we discuss what is known about their contribution to joint pain based on studies in animal models. Finally, we briefly discuss limited data available from clinical studies in human osteoarthritis.

1. Osteoarthritis, a painful joint disease

Osteoarthritis (OA), the most prevalent form of arthritis, is a chronic and painful disease of synovial joints, most commonly the knees, hips, and hands. The prevalence of OA increases with age. OA is a leading cause of disability among older adults in the US [1] and worldwide [2]. Obesity and joint injuries are other major risk factors [3]. The most prominent symptom of OA is pain. Since effective therapies for OA and the associated joint pain are not available, this disease represents an enormous unmet medical need [4,5].

OA pathology is characterized by progressive cellular and molecular changes in all joint tissues, including articular cartilage, subchondral bone, synovium, ligaments, and peri-articular muscles (Fig. 1) [3]. OA was long considered a quintessential "degenerative" joint disease, where mechanical stresses and ageing precipitate cartilage breakdown and bone remodeling – ultimately leading to joint dysfunction. In recent years, however, evidence has been mounting for a critical contribution of inflammatory mechanisms to OA pathogenesis, with a particular role for synovitis [6]. Indeed, synovitis has been shown to correlate with structural progression of OA (cartilage degeneration and osteophyte formation) [7]. Importantly, several studies have demonstrated that pain and joint dysfunction are increased in association with synovitis [7]. In post-traumatic OA, which develops after joint injury and tends to affect younger and middle-aged adults [8], research in animal models and human subjects indicates that several inflammatory cytokines and related inflammatory mediators are elevated following joint injury [9].

2. Cytokines in osteoarthritis

Chondrocytes, synovial cells and other cells in the joint can express and respond to cytokines and chemokines, and cytokines can also be detected in synovial fluid of OA patients (reviewed in [10]). Cytokines that have been implicated in OA pathogenesis include tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, other common γ-chain cytokines such as IL-2, IL-7, IL-15, and IL-21, and chemokines (reviewed in [6,10]). The presence of inflammatory cytokines in the OA joint raises the question whether they may directly participate in pain generation by acting on innervating joint nociceptors. In the current review, we first provide a systematic discussion of the known pro-algesic effects of these cytokines, and then discuss what is known about their contribution to joint pain, based on studies in animal models.

Abbreviations: AIA, antigen-induced arthritis; CNS, central nervous system; DMM, destabilization of the medial meniscus; DRG, dorsal root ganglia; GPCR, G-protein coupled receptor; IL, interleukin; MCP-1, monocyte chemoattractant protein-1; MIA, monoiodoacetate model; NGF, nerve growth factor; NMDA, N-methyl-d-aspartate; OA, osteoarthritis; TNF, tumor necrosis factor; TRG, trigeminal ganglia; TRP, transient receptor potential; TTX, tetrodotoxin; VGSC, voltage-gated sodium channel; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

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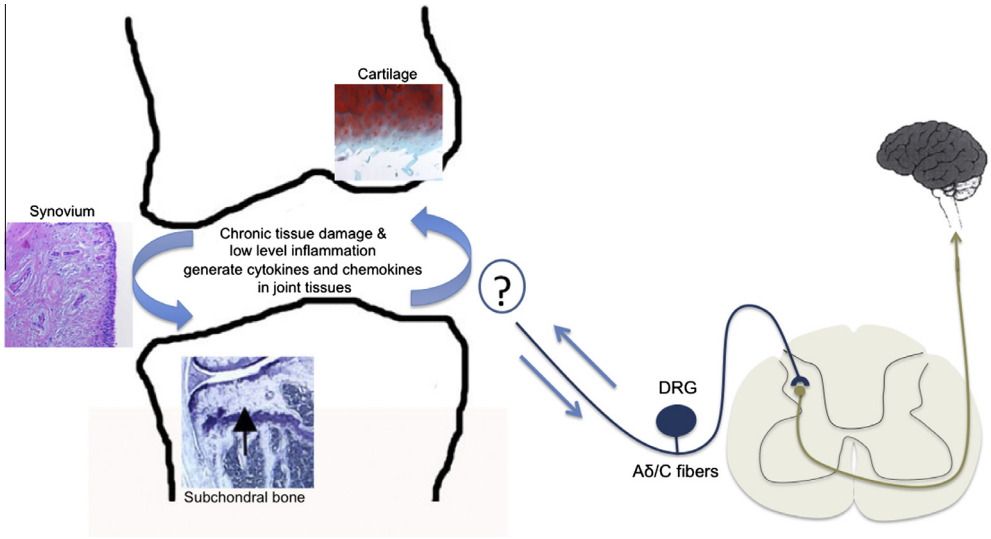

Fig. 1. Nociceptors (medium-sized myelinated Aδ fibers and small unmyelinated C-fibers) detect noxious signals in the innervated tissues and carry them to the dorsal horn of the spinal cord. The cell bodies of these pseudo-unipolar nociceptors are located in the dorsal root ganglia (DRG) and extend axons to the periphery as well as centrally to the dorsal horn, where the first synapse occurs. In osteoarthritis, all joint tissues participate in driving progressive structural joint damage, including the articular cartilage, subchondral bone, and the synovial membrane. Ongoing chronic tissue damage and low-level inflammation generate cytokines and chemokines that may directly act on innervating nociceptors. The precise nature of this interaction in the arthritic joint has not been elucidated.

3. Nociceptive actions of cytokines

Tissue injury generates noxious stimuli that are sensed by specialized receptors on nociceptors, which are small-diameter unmyelinated C-fiber or medium-diameter thinly myelinated Aδ-fiber sensory neurons that carry pain signals from peripheral tissues to the central nervous system (CNS) (Fig. 1). The cell bodies of these pseudo-unipolar nociceptors are located in the dorsal root ganglia (DRG) and trigeminal ganglia (TRG), and extend axons to the periphery and viscera as well as centrally to the dorsal horn of the spinal cord. The first synapse occurs in the dorsal horn either with interneurons or with supraspinally projecting neurons, which then carry nociceptive information to higher levels of the neuraxis such as the thalamus and cortex.

The major cytokines that are expressed in association with tissue damage and inflammation can affect the pain response at numerous points along the neuraxis. Many cytokines, for instance, can excite DRG neurons directly by a variety of mechanisms, often through very rapid effects that do not require gene transcription but are likely to involve regulation of important conductances such as voltage-gated sodium (VGS) and transient receptor potential (TRP) channels. Moreover, these same cytokines may also have rapid electrophysiological effects on second-order neurons in the dorsal horn. Molecules such as TNF-α, IL-1β, and IL-6 can be produced by cells in the joint, by sensory neurons or associated glial cells in the DRG, and by microglial cells in the dorsal horn. Whatever the cellular source of the cytokines produced in response to injury, increases in sensory neuron excitability are likely to be one of the first cytokine-induced effects that underlie chronic pain. Below, we review the major biological effects on the pain pathway by those cytokines that have been implicated in OA pathogenesis.

3.1. TNF-α

TNF-α has been shown to influence and coordinate the inflammatory response in almost all tissues. Cytokine signaling is organized as a cascade (a primary cytokine acting upon a receptor that leads to expression of one or more secondary cytokines and so on), and TNF-α is often observed near the top of such signaling cascades. In addition to its effect on peripheral tissues, there is good evidence that TNF-α can influence the excitability of nociceptors either directly or through the expression of downstream cytokines – or both. TNF-α can be produced by DRG neurons and can also act on them through a variety of mechanisms, as will be discussed. Some of the long-term changes in nociceptor excitability require alterations in gene transcription and protein expression. However, it is also clear that TNF-α can produce very rapid changes in neuronal excitability that do not seem to require alterations in gene transcription [11] but are the result of the regulation of ion channels that in turn regulate nociceptor electrogenesis, including voltage-gated sodium channels (VGSC) and TRP channels expressed by sensory nerves [12]. Perfusion of DRG with TNF-α produces a rapid increase in the firing rate of both A- and C-fibers [13] and also elicits a rapid increase of calcitonin gene-related peptide (CGRP) release from the peripheral terminals of nociceptors [14]. It appears that the excitatory effects of TNF-α result from the modulation of several important conductances. For example, the ability of an intradermal injection of TNF-α into the plantar surface of the hindpaw to produce thermal, but not mechanical, sensitization is abolished in TRP subfamily V member 1 (TRPV1) knockout mice [11]. This suggests that another conductance might be responsible for the TNF-α-induced mechanical pain hypersensitivity. Indeed, it was observed that application of TNF-α to DRG neurons in culture increased the amplitude of the tetrodotoxin (TTX)-resistant sodium current in these cells [11]. Activation of TNF-α receptors produces a wide array of signaling options, including activation of the MAPK pathway [11]. For example, inhibitors of p38 MAPK selectively abolished TNF-α induced mechanical pain hypersensitivity and enhancement of the DRG TTX-resistant sodium current suggesting a model in which the rapid effects of TNF-α might involve activation of TNFR1 expressed by nociceptors leading to enhanced mechanical hypersensitivity mediated by p38-induced phosphorylation of TTX-resistant sodium current subunits, together with thermal hypersensitivity produced by actions on TRPV1. Although it is clear that TNF-α can rapidly excite nociceptors by a number of mechanisms, the cytokine also produced increased TRPV1 protein expression when applied to cultured DRG neurons through extracellular signal-related kinase rather than p38 signaling [15]. However, this effect required