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REVIEW ARTICLE

Degenerative Joint Diseases and Neuroinflammation

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■ **Abstract:** Rheumatic and joint diseases, as exemplified by osteoarthritis and rheumatoid arthritis, are among the most widespread painful and disabling pathologies across the globe. Given the continuing rise in life expectancy, their prevalence is destined to grow. Osteoarthritis, a degenerative joint disease, is, in particular, on its way to becoming the fourth leading cause of disability worldwide by 2020, with the rising incidence of obesity in addition to age being important factors. It is estimated that 25% of osteoarthritic individuals are unable to perform daily activities. Accompanying osteoarthritis is rheumatoid arthritis, which is a chronic systemic disease that often causes pain and deformity. At least 50% of those affected are unable to remain gainfully employed within 10 years of disease onset. A growing body of evidence now points to inflammation, locally and more systemically, as a promoter of damage to joints and bones, as well as joint-related functional deficits. The pathogenesis underlying joint diseases remains unclear; however, it is currently believed that cross-talk between cartilage and subchondral bone—and loss of balance between these two structures in joint diseases—is a critical element. This view is amplified by the presence of mast cells, whose dysregulation is associated with alterations of junction structures (cartilage, bone, synovia, matrix, nerve endings, and blood vessels). In addition, persistent activation of mast cells facilitates the development of spinal neuroinflammation mediated through their interaction with microglia. Unfortunately, current treatment strategies for rheumatic and articular disease are symptomatic and do little to limit disease progression. Research now should be directed at therapeutic modalities that target osteoarticular structural elements and thereby delaying disease progression and joint replacement. ■

Key Words: joint diseases, joint pain, neuroinflammation, mast cells, palmitoylethanolamide

INTRODUCTION

Rheumatic or musculoskeletal conditions comprise over 150 diseases and progressive syndromes, which are associated with pain. Among those with the greatest impact on society are osteoarthritis and rheumatoid arthritis.[1,2] Osteoarthritis, also known as arthritis, is considered a degenerative joint disease that affects all articular joints and is associated with degeneration of the joint cartilage and menisci, subchondral sclerosis, and inflammation of the synovial membrane. The

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disease negatively impacts on limb use as cartilage, which has been worn away, results in bones rubbing against each other. This creates friction and causes pain, trauma, and ligament damage. The disease is related to aging and generally affects the joints that are subject to stress, such as the knees, hips, small joints of the hands, and the cervical and lumbar spine.

Rheumatoid arthritis is a chronic systemic disease that affects the joints, connective tissue, muscles, tendons, and fibrous tissue. It occurs in adults during their most productive years, between 20 and 40 years of age, and is a chronic disabling condition that often causes pain and deformity. Its prevalence ranges from 0.3% to 1% of the general population, being higher in women and in industrialized countries. In the latter, at least 50% of those affected are unable to maintain a full-time job within 10 years of disease onset[3,4] (http://www.who.int/chp/topics/rheumatic/en/).

These diseases, in particular osteoarthritis, can no longer be simply labeled as "degenerative" diseases. Growing evidence supports a role of inflammation, not only locally, in promoting damage to joints and bones, as well as joint-related functional deficits. In this review, we will consider key observations, which highlight the contribution of mast cells and microglia in the development of tissue damage and joint-related pain, and the prospects of innovative treatment to slow progression of these diseases by controlling neuroinflammation.

CROSS-TALK BETWEEN ARTICULAR CARTILAGE AND SUBCHONDRAL BONE IS THE BACKBONE OF JOINT DISEASES

Joint cartilage has long been considered the hub of rheumatic and musculoskeletal diseases. However, recent studies now show that other articular joint structures may contribute to disease symptoms and pathogenesis and symptoms affecting the joints. Among these, the subchondral bone seems to play a significant role.[5] The involvement of bone in articular disorders was once thought to be secondary to cartilage damage and, in essence, caused by the need of the junction to adapt. Recent investigations based on magnetic resonance imaging now show that subchondral bone changes such as thickening, reduced flexibility, and density of the trabeculae (often found in the early phase of arthritis) may be significant in the development of osteoporosis and microcrystalline arthropathies. In some cases, changes in the subchondral bone may precede cartilage injury.[6]

A recent systematic review, based on the use of nonconventional radiographic techniques, examined the association between disorders of the subchondral bone and joint transplants, pain, or structural progression of osteoarthritis of the knee, hip, hand, ankle, and foot. This analysis confirmed that bone lesions, osteophytes, and changes in bone morphology are associated, independently from each other, with structural progression and joint replacement. Bone lesions and changes in bone morphology were also associated with pain in cases of osteoarthrosis involving the knee, hands, and hip.[5] This meta-analysis points to the existence of a robust cross-talk between subchondral bone and articular cartilage underlying joint diseases.[5] Shared features in patients with rheumatoid arthritis and osteoarthritis include not only subchondral bone resorption but also microarchitecture and periarticular bone remodeling, including the subchondral bone.[7]

Cytokines and trophic factors released during elevated subchondral bone turnover interact with articular cartilage to create a positive feedback loop between the bone healing process and cartilage damage. On the other hand, chondrocytes, in response to stimuli such as inappropriate loads or the presence of subchondral bone catabolic factors, undergo a change in phenotype and begin producing cytokines and chemokines, which act in a paracrine fashion to initiate a vicious cycle leading to degradation of the cartilage itself. Moreover, tissue damage triggers an inflammatory reaction that involves the synovia: Articular mast cells are rapidly activated to drive the inflammatory response and promote restoration of intertissue equilibrium. The close interaction between joint structures shows also how protection or damage to a joint structure can impact other structures. For example, administration of osteoprotegerin prevents not only the loss of trabecular bone but also the cartilage degradation. On the other hand, at the cellular level osteoblasts from patients with osteoarthritis induce a change in chondrocyte phenotype in favor of hypertrophic differentiation and matrix mineralization.[8–11]

ARTICULAR MAST CELLS

Mast Cells as Coordinators of Cross-Talk Between Articular Cartilage and Subchondral Bone, Neuroinflammation, and Pain

Cytokines and growth factors are the principal mediators of cross-talk between subchondral bone, cartilage, and synovia. Not only are mast cells the main source of

these agents, but they also orchestrate neuroinflammatory processes, both low-grade and frank inflammation. At the articular level, mast cells are located mainly in the synovial membrane and joint capsule,[12–17] and elsewhere mostly along blood vessels and nerve endings of the joint.[18] Mast cell density increases in the early stages of joint disease, especially in synovial membranes. Hyperplasia and hyperactivation of mast cells correlate with the appearance of osteoarthritic pathogenic hallmarks (eg, cartilage erosion, and flogistic and painful *poussées*).[14,19–23] Mast cells contribute to all stages of the inflammatory process and to disease pathogenesis in the chronic-evolutive phases.[24–26] Mediators released by joint tissue mast cells have specific actions in joint inflammation and degenerative–destructive processes.[27,28] For example, histamine stimulates synovial fibroblast proliferation, the production of metalloproteinases like matrix metalloproteinase-1 (MMP-1), and the upregulation of histamine H_1 receptors.[29,30] Mast cell tryptase, by inhibiting fibroblast apoptosis, favors their proliferation.[31] Synovial tissue from patients with rheumatoid arthritis or osteoarthritis exhibits marked increases (sixfold to 25-fold) in tryptase type β,[32] which is capable of degrading aggrecan (chondroitin sulfate proteoglycan 1), a principal component of the cartilage matrix. The tetrameric form of tryptase β activates the latent forms of MMP-3 and pro-MMP-13, which are constitutively produced by B synoviocytes, chondrocytes, and other cell types in arthritic cartilage. Aggrecan can be degraded by activated MMPs and its fragments released in the synovial fluid, which, unlike the parent molecule, are unable to bind hyaluronic acid.[33]

The activity of these mast cell mediators contributes to the marked reduction in viscoelasticity of synovial fluid, due to a reduced concentration and average molecular weight of hyaluronic acid.[34–40] Mast cell–derived β-D-hexosaminidase can also degrade hyaluronic acid during these inflammatory and degenerative processes.[41,42] This enzyme, together with hyaluronidase, plays an important role in the altered catabolism of hyaluronic acid seen in the joint diseases. In particular, β-D-hexosaminidase expression is significantly higher in joint tissues of patients with rheumatoid arthritis and osteoarthritis. These enzymes represent the main glycosidases found in the knee, are able to degrade even hyaline cartilage, and are present both in synovial fibroblasts and mast cells, two types of cells that interact closely during joint inflammatory processes and degeneration.[28,43,44] Mast cells also can influence indirectly the degradation of hyaluronic acid through proinflammatory mediators such as histamine, prostaglandin D2, cytokines, and chemokines, which are able to interact with fibroblasts, synoviocytes, and chondrocytes, thereby influencing hyaluronic acid production by way of its biosynthetic enzymes hyaluronan synthase-1 and synthase-2, as well as degradation mediated by catabolic enzymes.[45–47] In addition, the proinflammatory milieu elaborated by mast cells promotes the formation of reactive oxygen intermediates that contribute to the degradation of hyaluronic acid.[24,25,48,49]

Synovial mast cells interact with blood vessels and nerve endings, and dysregulation can affect their functionality and phenotype.[50] In particular, the rapid release of mast cell histamine can cause tissue edema and consequent destruction of the stromal matrix via activation of endothelial cell H_1 receptors. Moreover, mast cells are a source of numerous growth factors, such as vascular endothelial growth factor, nerve growth factor (NGF), and angiogenin,[51] whose release could contribute to the development of angiogenic processes typical of joint diseases.[25,52,53] The levels of these factors are usually altered in joint tissues of chronic pathologies. NGF, for example, is elevated in synovial membranes and fluid of patients with arthritis; this increase is correlated with mast cell density.[54–58] The proangiogenic effect of mast cell tryptase is favored by its degrading of the extracellular matrix to promote invasion of new vessels. This excessive release of mast cell mediators, along with their proangiogenic, oxidative, and inflammatory effects, sets the stage for the classic manifestations of joint inflammation.[59–61] Experimental models of osteoarthritis show increased vessel density in calcified cartilage, which is especially pronounced in older animals (+100%) compared to young adults (+50%). Angiogenesis is associated with a thickening of subchondral bone, the area from which angiogenesis originates.[11] Mast cell–derived NGF, other than its proangiogenic effect, plays an important role in the development of joint pain and plasticity of sympathetic and somatosensory fibers typical of osteoarthritic joints of patients with bone metastatic pathology.[53,62,63] NGF, interacting with its receptors on sensory nerve endings, triggers a series of processes that profoundly alter cellular activity to amplify pain. In molecular terms, NGF binding to the high-affinity receptor tropomyosin receptor kinase A (TrkA) stimulates synthesis of neuropeptides such as substance P and calcitonin gene-related peptide, together with TrkA itself and transient receptor potential channels. The action of NGF is complemented by participation of the so-called

low-affinity neurotrophin p75 receptor, which facilitates release of these neuropeptides.[64] Antidromic release of such neuropeptides causes tissue neurogenic inflammation,[65,66] an event that, on the one hand, amplifies the ongoing inflammatory process in the joint areas (eg, caused by the attraction, proliferation, and activation of new mast cells) and, on the other hand, feeds the joint neurogenic pain.[67–70] Over the course of osteoarthritis, the direct correlation between synovial neuropeptide concentration, severity of synovitis, and extent of joint pain confirms the intimate inter-relationship between sensory nerve activation and inflammation.[71] In these conditions, and unlike what occurs physiologically, one sees not a single electrical pulse (spike), but rather a series of pulses. Consequently, the threshold of neuronal activation is lowered and the neuron now becomes receptive to stimuli not normally painful (allodynia), an indication of peripheral sensitization.[7]

High levels of NGF contribute to phenotypic changes in dorsal root ganglion neurons and their endings that innervate the joint. The ectopic sprouting of sensory and sympathetic nerve terminals observed in a model of arthritic pain was reduced by administration of anti-NGF antibodies.[63] This plasticity of sensory and sympathetic nerve fibers innervating the knee joint (sprouting) is preserved in the elderly.[53]

Besides NGF, many other mast cell mediators (tryptase, bradykinin, adenosine triphosphate, and prostaglandin E2) may activate their cognate receptors on sensory endings, thereby contributing to development of peripheral sensitization through mechanisms such as phosphorylation of the transient receptor potential vanilloid 1 receptor.[64,72,73] In the case of joint diseases, persistent peripheral sensitization may also result from an abnormal mechanical stress-irritative nerve fiber joint caused by stretching/compression induced by osteochondrophytes, bone microfractures, and bone marrow hypertension, which can induce chronic pain as, for example, in osteoarthritis. Persistent sensitization of peripheral neurons is the first phase of central sensitization. In fact, neuronal hyperexcitability is followed by excessive release of neurotransmitters not only from peripheral terminals but also from those that connect to the dorsal horn of the spinal cord. This results in a "transfer" of hyperexcitability to second-order neurons and activation of immune cells in the spinal cord, the microglia. The main evidence supporting the role of mast cells in the onset and progression of joint diseases is reported in Table 1.

Mast Cells as Interlocutors of Microglia and Promoters of Central Sensitization

The mast cell–microglia axis supports central and peripheral nervous system inflammation and the aberrant processes of chronic pain in joint diseases. Peripheral mast cells interact with spinal and supraspinal ganglionic microglia directly through chemical mediators and indirectly through somatosensory neurons.[66,76,77]

A growing body of literature supports the existence of spinal and supraspinal neuroinflammation in articular diseases.[78–88] For example, at the spinal level microglia pass from the quiescent to the activated state, astrocytes increase in number, and the production of proinflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α) rises, suggesting that changes in glia are both morphological as well as functional.[89,90] In a model of osteoarthritis, spinal levels of IL-1β increase, while its inhibition reduces pain. Moreover, induction of abnormal IL-1β expression in the spinal cord induces a condition similar to arthritis. These results confirm the existence of cross-talk between the spinal cord and articulation and demonstrate that both peripheral signals can cause changes at the spinal level and central immune alteration can modify peripheral processes.[91] Central sensitization has also been observed in patients with osteoarthritis, where pain thresholds to pressure and prick stimuli are lower than in healthy subjects,[78,92] and is unrelated to radiological findings, suggesting that central sensitization is the factor that contributes most to osteoarticular pain.[78] The main evidence supporting the existence of spinal and supraspinal neuroinflammation in joint diseases is reported in Table 2.

In short, joint pain is not a single typology but rather is associated with different mechanisms primarily of a nociceptive/inflammatory and neuropathic nature.[93–97] Development of the neuropathic component can be facilitated by an abnormal mechanical-irritative stress acting on the joint's nerve fibers, resulting, for example, from stretching/compression due to osteochondrophytes, bone microfractures, bone marrow hypertension due to variations in blood flow to trabecular bone, and muscle spasms. The persistence of these factors can lead to neuropathic pain, especially in the elderly, a situation in which mechanical-irritative stress can occur alongside age-dependent degeneration of proprioceptive sensory innervation.[98,99] Mast cells appear also to be directly involved in neuropathic

Table 1. Main Evidence Supporting the Role of Mast Cells in the Onset and Progression of Joint Diseases

Condition/Articular Tissue	Main Results	References
Normal human synovial tissue	Tissue MCs represent nearly 3% of cellular population of the synovia	12
Normal rat synovial tissue	MCs are present just beneath the lining cells and in the subsynovial and periarticular connective tissues and around the arteriole	18
RA/cartilage–pannus junction	MCs have been identified at sites of cartilage erosion	13
RA and other rheumatic diseases/synovia	More synovial MCs/vessels are present in patients with RA and other rheumatic diseases vs. those without joint disease MCs are not functionally different from pulmonary or intestinal mucosal MCs Mice lacking their tryptase/heparin complexes have attenuated arthritic responses MC tryptase secretion into RA synovial fluid is higher than OA synovial fluid Tryptase has a strong anti-apoptotic effect on RA synovial fibroblasts	14, 15, 31, 45
OA synovia	In OA, MCs constitute 0.8% of all the cell profiles present in the synovia In the subsynovial layer of patients with OA, MCs were higher than those in patients suffering from RA NGF increases in the synovia of patients affected by arthritis as well as in animal models	16, 22, 54
OA cartilage	Immunopositive staining for histamine receptors H1 and H2 and for the enzyme histidine decarboxylase in human articular chondrocytes in OA cartilage was higher than in controls Tryptase enhances release of vascular endothelial growth factor from OA chondrocytes Tetramer-forming tryptases are MMP convertases that mediate cartilage damage and the proteolytic loss of aggrecan proteoglycans in arthritis Inhibition of hexosaminidase activity in cultured articular chondrocytes and chondrosarcoma cells results in accumulation of hyaluronic acid	30, 33, 41, 47
SpA, RA, OA, synovial fluid, and tissue	MCs were elevated in the synovial fluid of OA patients as compared to RA patients MCs are the major IL-17–expressing cell population in the SpA synovium In dogs with chronic lameness, the level of NGF in synovial fluid was found to be significantly higher than that found in healthy dogs Multiple factors in synovial fluid act as MC chemoattractants, 2 of which are SCF and TGF-β The synovitis score is significantly correlated with the number of MCs	17, 27, 58, 61, 74, 75
Tendinosis/patellar tendinosis tissue	Increase of MCs in tendinosis tissue vs. control; number of MCs correlated with the vessel area fraction and with symptom duration	21
OA serum	NGF concentrations were significantly higher in children with juvenile chronic arthritis than in controls	56
NGF-induced arthritis	Intra-articular NGF injection induces an increase of MCs in the synovium	55
MC knockout mouse	Depletion of MCs during the preclinical phase results in a significant reduction of arthritis	74

MCs, mast cells; RA, rheumatoid arthritis; OA, osteoarthritis; MMP, matrix metalloproteinase; SpA, spondylarthritis; NGF, nerve growth factor; SCF, stem cell factor; TGF-β, transforming growth factor-β.

pain.[100,101] In fact, direct nerve fiber damage—whether of a traumatic, degenerative, or compressive nature—triggers, via release of neuropeptides[95], mast cell degranulation. Massive release of mast cell mediators, such as histamine and NGF, enhances and supports electrophysiological alterations of nerve fibers, leading to their sensitization (Figure 1).

POTENTIAL NEW TARGETS FOR THE TREATMENT OF DEGENERATIVE JOINT DISEASES

Current treatment options for rheumatic and articular disease, such as nonsteroidal anti-inflammatory drugs, are mainly symptomatic and have limited efficacy on disease progression, apart from nervous sensitization, when used precociously. New treatment options that target osteoarticular structural elements can delay disease progression and joint replacement. Some new drugs have been shown effective in reducing pain and in preserving joint structures; however, clinical development of most has stopped, mainly because of adverse effects. Thus, treatment options for osteoarthritis remain very limited.[102]

The ideal treatment should preserve joint structure, improve patient quality of life, and possess a good safety profile. Real hope for new therapeutic solutions for articular diseases is now focused on the so-called "disease-modifying drugs".[86,87,103] At the cellular level, mast cells and microglia represent very attractive targets, as their modulation allows one not only to attack peripheral and central neuroinflammation and reduce pain but also to promote restoration of tissue

Table 2. Main Evidence Supporting the Existence of Spinal and Supraspinal Neuroinflammation in Joint Diseases

Conditions	Main Results	References
Human OA	Negative correlations between pain intensity and PPT were found (more pain, more sensitization) Temporal summation to repeated pressure stimulation and conditioning pain modulation, representing central pain mechanisms, are present in patients with painful knee OA Specific serologic biomarkers are associated with pain sensitization mechanisms in patients with different degrees of knee pain	78, 85, 88
MIA-OA	[3H]PK11195 binding in the ipsilateral (injured) lumbar spinal cord was increased by approximately 25% in MIA-OA Dorsal horn neuron activation and microglial activation but not reactive astrocytes are present 2 weeks after intra-articular MIA injection At day 28, microglia activation was significantly correlated with distal allodynia	81, 90, 93
Adjuvant-OA	Higher numbers of IL-1β, IL-6, and TNF-α mRNA-expressing cells are present in adjuvant-OA rats vs. control rats The number and immunostaining intensity of microglia and astrocytes increase in the spinal cord	89
CIA	Mechanical hypersensitivity in the early phase of CIA is associated with central sensitization that is dependent upon microglial-mediated release of IL-1β in the spinal cord CIA-induced mechanical hypersensitivity was paralleled by significant microglial and astrocytic activation, alongside T-cell infiltration, in the spinal cord Central changes in the dorsal horn of the spinal cord are readily detectable, including significant microgliosis and enhanced release of the pronociceptive peptide CGRP from nociceptor central terminals CGRP release evoked by dorsal root stimulation was higher in the dorsal horn on day 18 in rats with CIA compared to control rats. Prolonged intrathecal administration of CGRP(8-37) attenuated established mechanical hypersensitivity and reduced spinal microgliosis Microglial inhibitors attenuated mechanical hypersensitivity and spinal microglial response in rats with CIA CGRP receptor antagonist to the lumbar spinal cord attenuates both mechanical allodynia and spinal microgliosis	94, 95
CAIA	Following the induction of CAIA, spinal astrocytes and microglia displayed time-dependent signs of activation, and inhibition of glial activity reversed CAIA-induced mechanical hypersensitivity	96

OA, osteoarthritis; PPT, pressure pain thresholds; MIA-OA, monosodium iodoacetate in the knee joint; IL, interleukin; TNF-α, tumor necrosis factor-α; mRNA, messenger RNA; CIA, collagen-induced arthritis; CGRP, calcitonin gene-related peptide; CAIA, collagen antibody-induced arthritis.

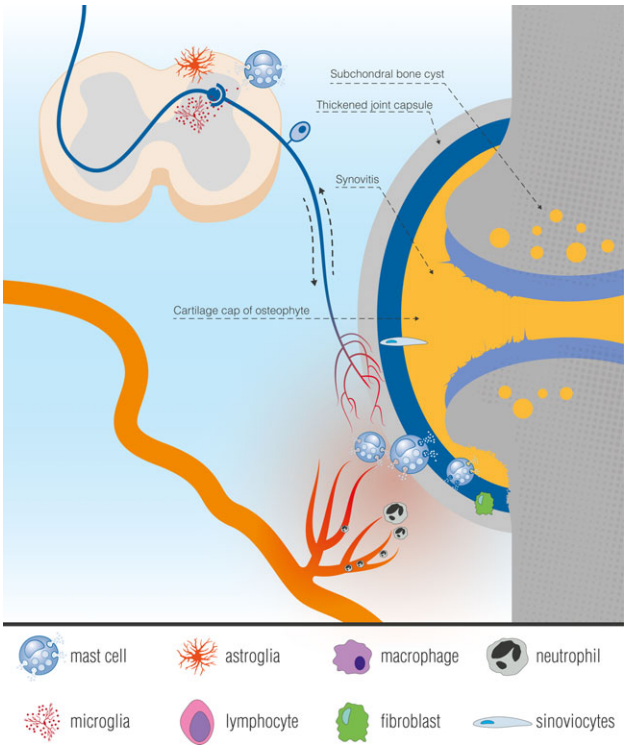

Figure 1. Schematic representation of the contribution of mast cells and microglia to degenerative joint diseases and neuroinflammation. At the articular level, mast cells are located mainly in the synovial membrane and joint capsule, and elsewhere mostly along blood vessels and nerve endings of the joint. Peripheral and central mast cells are likely play a crucial role in the shift of acute to chronic pain by interacting with other immune cells and somatosensory nerve terminals. In the periphery, persistent mast cell activation promotes the recruitment of other immune cells such as lymphocytes at the lesion site, amplifying inflammatory processes and causing a sensitization of peripheral nociceptors and spinal somatosensory neurons. In the CNS, mast cells amplify neuroinflammatory processes by promoting glial cell activation, which coordinates inflammation at the spinal level and central sensitization of central somatosensory neurons.

homeostasis, thereby limiting disease progression. Among disease-modifying drugs targeting the mast cell–microglia axis are the *N*-acylethanolamines,[55,104] such as *N*-palmitoylethanolamine (palmitoylethanolamide or PEA). PEA is an endogenous fatty acid amide-signaling molecule and a congener of the endocannabinoid anandamide.

In synovial fluid, PEA is normally present in elevated amounts (1,500 pmol/mL), which are drastically reduced in patients with osteoarthritis or rheumatoid arthritis,[73] suggesting a protective role in these conditions. In experimental models of joint disease, changes in PEA levels were also detected in the spinal cord.[80] These results point to a dysregulation in PEA metabolism in articular diseases and suggest that PEA supplementation may prove beneficial in these situations. In support of this hypothesis, administration of PEA or inhibition of endocannabinoid degradation ameliorates

collagen-induced arthritis in mice.[105,106] Moreover, PEA administration exerts anti-inflammatory and analgesic effects in different conditions of chronic inflammation,[107,108] modulates mast cell degranulation,[109] and reduces activation of spinal cord microglia.[110–113] Clinically, PEA reduces chronic and neuropathic pain associated with numerous pathological conditions[103,114] and reduces pain and improves function in patients with temporomandibular disorders.[115,116] Importantly, PEA possesses an optimum tolerability profile, conditions fundamental for chronic treatment of the elderly.[86,87,117,118]

Both membrane and nuclear receptors appear to be important targets for controlling disease progression. Among membrane receptors, endocannabinoids may be of particular interest, as they play a key role in bone formation, resorption, and growth. Both cannabinoid receptors CB1 and CB2 are present in the skeleton, with CB1 being expressed on nerve endings and CB2 on osteoblasts, osteocytes, and osteoclasts.[119,120] Both cannabinoid receptors are expressed on hypertrophic chrondrocytes.[121] The CB2 receptor is also expressed by synovial tissue fibroblasts of patients with rheumatoid arthritis[122,123] and on immune system cells like mast cells.

CB1 and CB2 receptor agonists have a protective role in joint diseases, with CB1 intervening in bone remodeling and age-dependent bone loss. The CB2 receptor also protects against bone loss, such as that linked to menopause, and its presence on immune cells endows it with immunomodulatory and anti-inflammatory activities as well. Therefore, molecules that activate the CB2 receptor, either directly or indirectly, such as PEA, are good candidates for the treatment of rheumatic diseases.

Among nuclear receptors, peroxisome proliferator-activated receptors alpha and gamma (PPARα, PPARγ) have been proposed as potential targets for joint diseases. Interestingly, PEA has agonist activity toward PPARα. Diverse studies suggest that PPARγ agonists also reduce the synthesis of inflammatory and catabolic agents to prevent cartilage lesions. Mice genetically modified to lack PPARγ develop, in adulthood, a form of osteoarthritis characterized by increased degradation of cartilage, hypocellularity, fibrosis, synovial inflammation, and an increased expression of catabolic factors including MMP-13 and other MMPs. Activity of the latter leads to a reduced expression of collagen type II and aggrecan and a high number of apoptotic chondrocytes.[124] PPARγ protects cartilage by inhibiting mammalian target of rapamycin (mTOR), a serine/threonine kinase and negative regulator of autophagy.[125] Inhibition of mTOR and intracellular kinases that promote cellular metabolism, growth, energy consumption, and differentiation prevents development of osteoarthritis by reducing chondrocyte apoptosis and increasing autophagy.[126]

Autophagy is a key mechanism in maintaining cellular homeostasis and for removing dysfunctional cellular organelles and macromolecules. Autophagy is prolonged in cases of catabolic or nutritional stress. It should be noted that articular chondrocytes, which live isolated in gaps, are not removed by specialized cells of the hematopoietic system such as macrophages. For this reason, autophagic processes are critical for maintaining chondrocyte integrity and cartilage homeostasis.

CONCLUSIONS

Rheumatic and joint diseases remain among the most common and widespread painful and disabling pathologies worldwide, whose prevalence is expected to grow mainly due to the rise in life expectancy. Pain associated with joint disease stems from both inflammatory and neuropathic components, the latter appearing to contribute substantially to the intensity and quality of the algic events. While the pathogenesis of joint diseases is still not completely clear, general consensus favors an underlying cross-talk between cartilage and subchondral bone. Loss of balance between these two structures in joint diseases is amplified by the presence of mast cells, whose dysregulation is associated with alterations of all junction structures (cartilage, bone, synovium, matrix, nerve endings, and blood vessels). In addition, persistent activation of mast cells facilitates the development of spinal neuroinflammation mediated by their interaction with microglia. At present, these diseases lack a satisfactory therapeutic solution. Drugs that are disease-modifying, that is, those capable of counteracting disease progression, represent the future direction of research. Molecules targeting cannabinoid receptors and PPARs are among the potential therapeutic avenues for these new therapies.

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