The New and Evolving Science of IL-6 in Rheumatoid Arthritis

The Role of IL-6 in RA Pain

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Mit wegweisenden Therapien
komplexen Erkrankungen begegnen.

SANOFI GENZYME

Dear Colleagues,

This is a very exciting time in the field of rheumatoid arthritis (RA). The more we understand from basic and clinical research about the pathogenesis of RA, the more equipped we are to understand this disease. We now know that cytokines play many key roles in the inflammation that drives RA. One such example is interleukin-6 (IL-6), a multifunctional cytokine that contributes to chronic inflammation in patients with RA.

Regeneron Pharmaceuticals and Sanofi Genzyme are excited to bring you additional educational material describing some of the fundamental immunology as well as clinical pathology we see in our RA patients through a series of scientific monographs entitled *The New and Evolving Science of IL-6 in Rheumatoid Arthritis*. In the first installment, we reviewed the signaling mechanisms of IL-6 that allow it to have widespread effects in RA. In the second installment, we reviewed the contributions of the IL-6 pathway to bone resorption in RA. In the third installment, we reviewed how persistently elevated IL-6 signaling may contribute to both articular and systemic manifestations of RA. In the fourth installment, we reviewed the roles of IL-6 in both innate and adaptive immunity in RA. In this installment, we discuss the role of IL-6 in RA-associated pain.

We hope you find this latest installment informative and engaging.

Sincerely,

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Introduction

The ability to feel pain is an essential feature of the nervous system that allows an organism to detect and interpret noxious stimuli.[1] While physiological pain is a useful tool for safeguarding against damaging stimuli, pathological pain can be a debilitating symptom that significantly impairs health-related quality of life (HRQoL).[2,3] Pain consistently ranks as one of the leading concerns among patients with rheumatoid arthritis (RA), and pain relief is one of the key motivating factors that prompt patients to seek medical care.[2,4] Patient goals are commonly based on the modification of disease symptoms and may include pain reduction, improved function and mobility, and resumption of daily activities.[5] With this in mind, identification of the major players in the pathogenesis of pain is a necessary step toward the development of strategic approaches that can ultimately help patients attain a better quality of life and alleviate the negative impact of pain associated with RA.[6]

As our understanding of RA has advanced over the years, we have a greater appreciation of the immunological complexity that drives this progressive and devastating disease. The development of a growing number of therapeutic agents capable of targeting proinflammatory cytokines underscores the importance of cytokines as mediators of the inflammatory pathways and joint destruction that contribute to the generation and persistence of joint pain.[7-9] Within the proinflammatory milieu that characterizes RA is interleukin-6 (IL-6), a pleiotropic cytokine whose activities not only contribute to the foundation of RA pathogenesis, but also facilitate other aspects of the disease, including inflammatory pain.[8]

Pain in RA

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[10] RA is a chronic inflammatory disease characterized by cartilage/bone damage and disability resulting in significant pain in the joint.[6,11] Pain is a common and dominant symptom of RA that significantly contributes to the overall burden of the disease.[12] It is often recognized as the greatest concern and highest priority among patients with RA, and accounts for a large majority of all physician visits by affected patients.[13,14]

Measures of synovitis and bone erosion by magnetic resonance imaging (MRI) have been found to correlate with patient-reported pain, and improvements in synovitis were generally associated with greater improvements in pain, physical functioning as measured by the Health Assessment Questionnaire (HAQ), and patient global assessment of disease activity (PtGl) scores. Similarly, changes in bone erosion were positively associated with changes in pain and PtGl scores.[15] Nevertheless, RA pain can persist even when disease is in clinical remission (ie, according to disease activity score using 28 joints–C-reactive protein 4 [DAS28-CRP4]

and the American College of Rheumatology/European League Against Rheumatism [ACR/EULAR] remission criteria).[16] More than 60% of patients with RA have reported inadequate pain relief even when their disease was "well-controlled" (based on patient self-reporting), and approximately 70% of patients have expressed a desire to see an improvement in their pain symptoms.[4,17,18]

RA Pain and Psychosocial Functioning

Infectious, neurodegenerative, and autoimmune diseases have profound effects on psychosocial behavior and can manifest in many ways, such as malaise, fatigue, depression, anorexia, hyposomnia or hypersomnia, reduced physical and social activities, and cognitive disturbances.[19] Indeed, in patients with RA, psoriatic arthritis, and ankylosing spondylitis, self-reported health status data revealed that, compared with a selected sample of healthy individuals, these autoimmune inflammatory diseases conferred detrimental effects in all domains of living, especially with regard to physical function, role limitation due to physical health problems, and bodily pain.[20] In RA, the combined effects of pain, fatigue, and functional deficits significantly impair HRQoL, and decline in HRQoL is associated with reduced productivity, work loss, and work disability.[21] Pain is widely considered one of the most debilitating symptoms across many rheumatic diseases, and is a major contributor to a large number of negative personal and social consequences associated with disease progression, including increased healthcare costs, disability, and mortality.[14] To underscore the significance of pain in RA, it was found that the functional capacity scores of patients strongly correlated with pain scores; however, radiographic damage of the small joints did not correlate with pain.[22] Two commonly observed yet unexplained characteristics of RA are the presence of arthralgia preceding joint inflammation and the persistence of joint pain following successful anti-inflammatory treatment.[23] These observations suggest that inflammation and subsequent joint damage may not be the only factors implicated in the pathogenesis of RA-associated pain.[24] Patients with early RA who present with high levels of bodily pain are more likely to report greater disability after 1 year; a high DAS28-P (patient-reported components to DAS28) index, for example, may reflect the contribution of noninflammatory factors (eg, central sensitization) to the persistence of pain and may also predict less improvement in bodily pain.[25,26] In a large study of more than 15,000 patients with RA, self-perceived pain was a stronger predictor of psychosocial health than both disease activity and functional disability.[17] Patients who expressed satisfaction with their level of pain were more likely to report higher satisfaction in other areas of health, including social activity, tension, mood, and fatigue.[18]

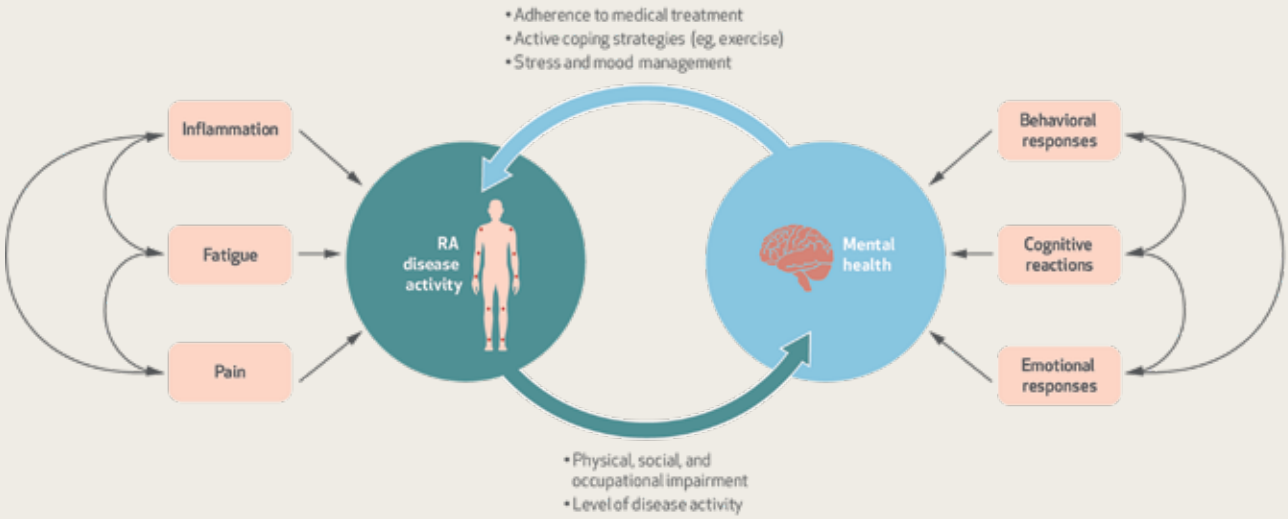

Figure 1. The interconnectivity of disease activity and mental health in patients with RA.[28] Manifestations of RA disease activity and mental health share a bidirectional relationship that shapes the overall patient experience. Pain, fatigue, and inflammation are physical symptoms of RA that are linked to the psychosocial effects of RA, including cognitive, emotional, and behavioral responses. Adapted from Sturgeon JA et al. *Nat Rev Rheumatol*. 2016;12:532-542.

Pain is a complex phenomenon that is influenced by biologic, psychological, and social factors, which in turn can also produce changes that affect responses to pain (**Figure 1**).[27] During both early and established RA, pain is a major contributor to psychological distress, and poor mental health can exacerbate and augment pain.[6,13] Compounding these effects, the cognitive interpretation of pain by patients can also have a significant impact on their mental health.[28]

RA Pain and Depression

Depression is defined as a mood disorder characterized by persistent sadness and a loss of interest in daily activities, and is 2 to 4 times more common in patients with RA than in the general population.[14,29] Major depressive disorder is widely prevalent among patients with RA, and is estimated to affect approximately 13% to 42% of the patient population. A meta-analysis of more than 13,000 patients with RA from a total of 72 studies showed that the prevalence of major depressive disorder was 16.8% (95% CI: 10%–24%) based on the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnostic criteria, while the prevalence of depression was 38.8% (95% CI: 34.0%–43.0%) based on the Patient Health Questionnaire-9 (PHQ-9).[30]

Depression has been linked to elevated levels of pain in patients with RA.[31] A comparison between individuals with RA and healthy subjects revealed a positive association between depression and pain ($z=2.67$, $P=0.0064$).[32] Moreover, the type and severity of pain have also been found to be positively correlated with depressive symptoms.[33] Patients with severe pain were also more likely to report having undergone treatment for depression than those with moderate or mild pain.[18] While some believe that depression develops as a secondary consequence of chronic pain, others have

argued that chronic pain is a manifestation of depression; these opposing theories are perhaps reflective of the bidirectional relationship between pain and depression.[34]

Several lines of evidence support the hypothesis that the presence of systemic inflammation may contribute to the high prevalence of depression in RA.[29] Many studies have shown that individuals with depression have increased expression of IL-6 compared with nondepressed healthy individuals, whereas decreases in peripheral IL-6 levels have been associated with resolution of psychological distress symptoms in a nonclinical population.[35-38] Patients with depression and a history of poor response to traditional antidepressants have increased plasma concentrations of cytokines such as IL-6 and tumor necrosis factor-α (TNF-α).[29] Moreover, increased expression of inflammatory biomarkers such as IL-6 may be a predictive marker for psychopathological response among patients with major depressive disorder.[39] Further investigation into how systemic inflammation contributes to depression may support the implementation of evidence-based strategies that ease the effects of depression in RA.[29,38]

RA Pain and Fatigue

Fatigue is a common symptom among individuals with rheumatic disease and is strongly associated with the intensity of pain.[40] A majority of patients with RA experience clinically significant fatigue that interferes with their quality of life and physical functioning.[28] In a study of more than 500 patients with RA, 80% had clinically relevant fatigue and more than 50% had high fatigue scores.[40] A patient survey has also shown that pain severity was directly related to fatigue levels.[18]

Although fatigue and pain appear to have a synchronous relationship in established RA, causal directionality between these symptoms has not been established, and it remains unclear whether pain precedes fatigue or vice versa.[41] Several groups have shown that elevated pain was one of the strongest predictors of fatigue, which may be explained by the observation that pain can cause disrupted sleep patterns, a commonly reported occurrence in RA.[42-44] Pain and fatigue impair physical function, negatively impacting patients' ability to participate in social and work activities.[2] Additionally, patients who stopped work because of RA had higher pain scores over time than those who remained employed.[45] Interestingly, compared with individuals with fibromyalgia (FM) or osteoarthritis (OA), patients with RA display relatively stable patterns of daily fatigue, which may be indicative of lower levels of pain in patients with RA compared with the other rheumatic conditions.[46]

While the exact cause of RA-associated fatigue is not entirely known, hormones, metabolic factors, cytokines, psychological factors, and medications may have a contributive role.[47] Prior studies have demonstrated a link between hypothalamic–pituitary–adrenal (HPA) axis dysregulation and the development of fatigue in a variety of

pathologies, including seasonal depression, chronic fatigue syndrome, and FM.[47,48] IL-6, which has an established role in modulating the HPA axis, has been implicated in the development of fatigue.[47] Healthy volunteers (N=16) who were administered IL-6 reported increased levels of fatigue, inactivity, reduced concentration, and sleep disruption, further supporting the link between IL-6 and fatigue.[49]

Classification and Mechanisms of RA Pain

Dynamic and multifaceted, arthritic pain has traditionally been attributed to erosive damage in the joints and bones or to inflammation. It is becoming clear, however, that the presence or severity of pain associated with chronic pathologies cannot be explained merely by tissue damage or by inflammation, which are considered peripheral factors. We now understand that these factors and the central nervous system (CNS) converge to orchestrate the overall experience of arthritic pain. Indeed, current descriptions of the mechanism of arthritic pain take into consideration both peripheral and central contributions to pain.[50] The qualities of pain have often been described as being either acute (eg, short-term) or chronic (eg, ≥3 months), constant or intermittent, localized or widespread, or have been classified by disease type (eg, cancer pain, FM) or anatomical location.[6,50,51] An alternative method of classifying pain would be according to mechanism: nociceptive/inflammatory, neuropathic, or central.[50]

Nociception is a neural process by which nociceptors, peripheral nerve endings that transduce and encode noxious signals, respond to stimuli that exceed a certain intensity threshold.[1,10] Nociceptive pain is triggered by actual or potential damage to tissues resulting in the activation of nociceptive neurons by noxious stimuli.[6,52] Nociceptors, which include fast-conducting myelinated Aδ-fibers and slower unmyelinated C-fibers, have the ability to detect various types of stimuli stemming from chemical, thermal, and mechanical sources.[50,53] In a healthy individual, the nociceptive system can only be activated by the application of noxious stimuli; however, during inflammation, the nociceptive system is sensitized such that inactive nociceptors can assume functional plasticity and respond to a normally innocuous stimulus.[8,54]

The mechanisms of RA-associated pain may vary between the early versus late stages of disease, suggesting that peripheral and central sensitization evolves with disease progression (**Figure 2**).[6] It has been proposed that peripheral and central sensitization of the nociceptive systems is a major determinant of the intensity and persistence of pain associated with RA.[55] While it has been customary to ascribe RA pain to peripheral sensitization and then treat with antirheumatic therapy,

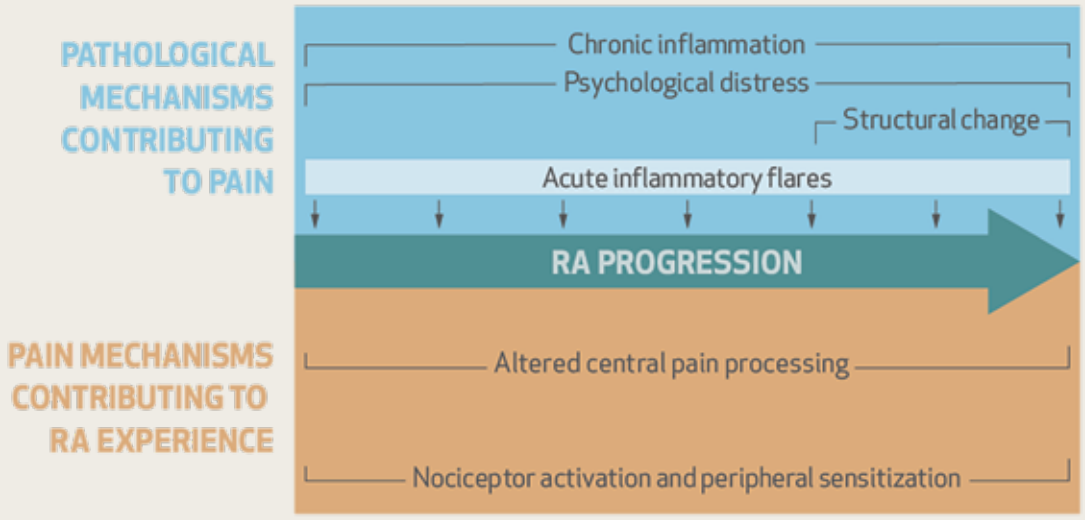

Figure 2. Mechanisms of pain throughout RA progression.[6] The mechanisms contributing to RA pathology and pain evolve throughout the course of the disease. Pathological changes such as chronic inflammation, psychological distress, and structural change to the joint contribute to the mechanisms of RA pain. After the onset of inflammation, alterations to peripheral and central pain processing contribute to the overall RA experience. Adapted from Walsh DA et al. *Nat Rev Rheumatol*. 2014;10:581-592.

observational studies have shown that many patients still continue to experience moderate pain during disease remission, suggesting that a noninflammatory component could also be in play.[16,55] In these cases, it is suspected that centrally mediated aspects of nociception may cooperate with peripheral mechanisms to augment the perception of pain.[50] Indeed, durable changes in the articular environment can lead to peripheral sensitization of nociceptors, resulting in larger cortical responsiveness (ie, alterations in central processing) and a lowered threshold to stimulation of their receptive fields, as has been observed in patients with RA.[6,10,56,57] Peripheral nociceptor input can trigger modification of the central pain pathways, heightening the responsiveness of pain transmission neurons to both noxious and innocuous inputs.[58] Altogether, this would indicate that noxious peripheral stimuli contribute to the perpetuation of central sensitization, and thereby the chronicity of pain.[59,60]

Persistent pain that is associated with injury or disease is often the combined result of damage to peripheral nerve fibers and the accumulation of a milieu of inflammatory signaling molecules (eg, TNF-α, IL-1, IL-6, nerve growth factor-β [NGF-β], leukemia inhibitory factor [LIF]) that are secreted by activated nociceptors or nonneural cells (eg, mast cells, basophils, macrophages, neutrophils, platelets, fibroblasts, keratinocytes) that infiltrate and can persist at the site of injury.[1,13,61]

Chronic pain may be neurogenic in origin and is the consequence of tissue breakdown or changes in the overall integrity of the cartilage, bone, and soft tissue.[60] A wide variety of disorders, including RA, can induce true neuropathic pain originating as a direct consequence of a lesion or disease affecting the somatosensory system.[24,52] In addition to the commonly described "gnawing" or "aching" sensations associated with nociceptive pain, individuals with RA have also reported experiencing neuropathic pain such as "burning" or "prickling."[24] Neuropathic-like pain in the absence of an apparent lesion of the nervous system has also been reported in other rheumatic diseases such as FM and OA, and the prevalence of neuropathic-like pain in patients with RA has been reported to be approximately 17% to 21%.[24] Observational studies have suggested that reduced pressure pain thresholds in RA may be a consequence of central sensitization and were associated with prolonged disease duration and high tender point counts (ACR FM classification criteria requires tender points in at least 11 of 18 specified sites and the presence of widespread pain for diagnosis), possibly reflecting the coexistence of FM.[62-65] This suggests that inflammation in RA can lead to the persistence of pain, and that continuous stimulation of the nociceptive system may lead to central sensitization and reduced pain thresholds.[62]

The Role of IL-6 in Pain

IL-6 is a pleiotropic cytokine that mediates inflammation, immune responses, hematopoiesis, and other processes through a broad spectrum of cells and tissues (**Figure 3**).[66,67] It has been observed that IL-6 levels are markedly elevated in a variety of pathologies associated with increased pain and hyperalgesia. These conditions, which include neuropathies, malignancies, musculoskeletal disorders, and burn injuries, as well as autoimmune and chronic inflammatory disorders, share a common denominator involving tissue tenderness and hypersensitivity.[9]

Importantly, IL-6 is a key driver of both the chronic inflammation and the articular and systemic manifestations that characterize RA.[68] The biological activity of IL-6 is mediated through its unique receptor system and is achieved through 2 distinct mechanisms: classical (*cis*-) and *trans*-signaling.[68] *Cis*-signaling is facilitated by the membrane-bound IL-6 receptor (mIL-6R), which forms a complex with IL-6 and subsequently associates with glycoprotein 130 (gp130), which then initiates intracellular signaling.[66,69] mIL-6R is predominantly expressed on hepatocytes, neutrophils, monocytes/macrophages and some lymphocytes, thereby limiting *cis*-signaling to certain cell types.[66,68] In contrast, *trans*-signaling is mediated by a soluble form of IL-6R (sIL-6R), which is generated

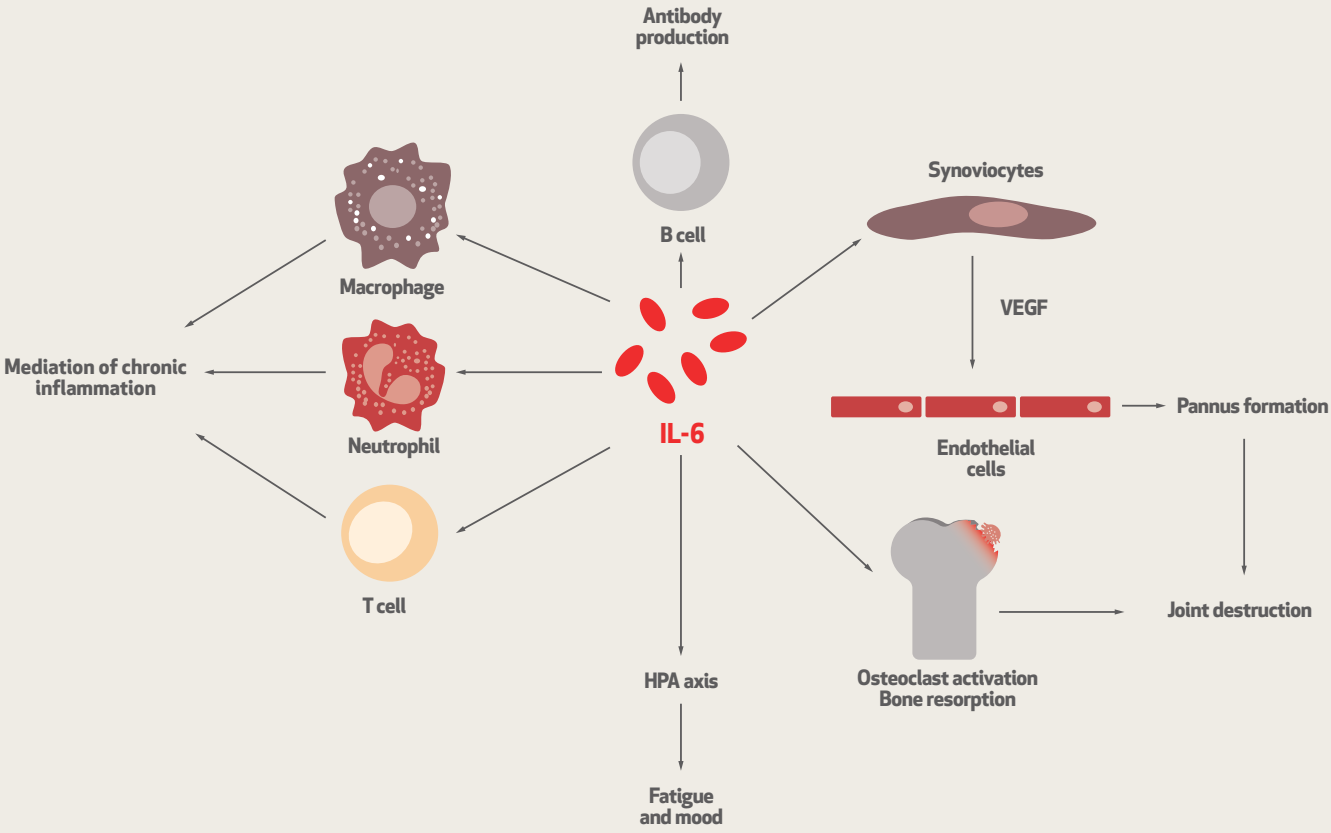

Figure 3. IL-6 modulates several aspects of RA pathogenesis.[68] IL-6 promotes chronic inflammation in RA by modulating the activity of a variety of immune cells such as macrophages, neutrophils, and T cells; IL-6 also stimulates mature B cells to produce antibodies. In addition, IL-6 mediates joint destruction by stimulating pannus formation through the increased expression of vascular endothelial growth factor (VEGF) and by augmenting bone resorption through the activation of osteoclasts. Through its effects on the HPA axis, IL-6 can also regulate fatigue and mood. Adapted from Dayer JM et al. *Rheumatology (Oxford)*. 2010;49:15-24.

by proteolytic cleavage by ADAM metallopeptidase domain 17 (ADAM17) or translation from differentially spliced mRNA.[66] Because gp130 is ubiquitously expressed, *trans*-signaling allows most cell types to respond to IL-6, including neurons.[70-75] In fact, it has been shown that gp130 in nociceptive sensory neurons may be a key player in the induction and persistence of pain.[76] Because its unique signaling mechanism occurs via gp130, IL-6 can act on nociceptive neurons, suggesting a potential role for this proinflammatory cytokine in the induction and persistence of pain.[77,78]

The empirical evidence supporting a role for IL-6 in human pain has been steadily growing.[6] Not only is IL-6 expression positively associated with pain scores, assessed using the visual analog scale (VAS), but IL-6 levels were also significantly higher among patients who reported having severe pain (VAS score ≥5 cm) than in those with less severe pain (VAS score <5 cm).[79] In addition, patients with RA who were subjected to psychophysical testing displayed elevated levels of serum IL-6 in the presence of noxious stimuli (ie, mechanical, heat, and cold) compared with healthy controls.[80]

Peripheral Effects of IL-6

The neurons of the peripheral and central nervous systems exhibit a high degree of plasticity during inflammation, undergoing a series of functional, chemical, and structural alterations that result in lowered pain thresholds and increased responsiveness.[81,82] Proinflammatory cytokines play an important role in mediating disease processes as well as in pain generation by directly acting on the nociceptive system.[8] The level of peripheral cytokine production is largely dependent on the state of immune activation; during acute or chronic inflammation and tissue damage, the immune system is activated, resulting in the increased production and release of cytokines by macrophages.[83] Indeed, in the initial stages of RA, the inflamed synovium is marked by a notable increase in the presence of cytokines, growth factors, and chemokines in the synovial fluid. Proinflammatory mediators (eg, prostaglandins and bradykinin) and cytokines (eg, TNF-α, IL-1, NGF-β, and IL-6) can sensitize peripheral nerves through specific cell surface receptors, contributing to the generation and maintenance of pain.[6,13,84] Moreover, intra-articular administration of soluble gp130 (sgp130) in rats has been shown to neutralize the IL-6/sIL-6R complex and arthritis-induced pain in a model of antigen-induced arthritis, further supporting a potential role for IL-6 in pain.[85]

Intra-articular injection of various proinflammatory cytokines into the knee joint has shown that different cytokines can have distinct effects on the responsiveness of nociceptive sensory neurons (**Table 1**).[8] For example, TNF-α, which is a major component of the inflammatory network and mediates mechanical and thermal hyperalgesia, can

Cytokine	Responsiveness of Aδ-fibers to mechanical stimulation	Responsiveness of C-fibers to mechanical stimulation
TNF-α	↑	↑
IL-6	≈ (on average)	↑ (difficult to reverse)
IL-1β	↓	↑

↑ Enhancement ↓ Reduction ≈ No effect

Table 1. The effects of proinflammatory cytokines on the responsiveness of sensory neurons.[8] Intra-articular injection of cytokines into the normal knee joint variably affects the responsiveness of nociceptive sensory neurons (ie, Aδ- and C-fibers) to mechanical stimulation of the joint. Adapted from Schaible H-G. *Arthritis Res Ther*. 2014;16:470.

induce persistent sensitization to benign stimuli by increasing the responsiveness of nociceptive C- and Aδ-fibers in animal models.[8] Moreover, addition of TNF-α was shown to transiently sensitize rat cutaneous nociceptors to heat in vitro, implicating a role for this cytokine in thermal hyperalgesia.[72] Conversely, IL-1β, which is abundantly expressed in RA and contributes to both pain and hyperalgesia, has the opposite effect on C- and Aδ-fibers—while IL-1β sensitizes nociceptive C-fibers of the joint to mechanical stimuli, it reduces the mechanosensitivity of Aδ-fibers.[86,87] Data showed that intraplantar injections of IL-1β in rats induced hyperalgesia and transient spontaneous discharge in response to thermal stimuli.[88] Lastly, injection of IL-6 or coinjection of IL-6 plus sIL-6R into the normal knee joint of anesthetized rats was found to lead to long-term sensitization of nociceptive C-fibers to mechanical stimulation, while Aδ-fibers remained unaffected; these data also suggest a role for IL-6 in mechanical hypersensitivity.[89]

Central Effects of IL-6

Proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 play key roles in both RA pathogenesis and in the generation and maintenance of pain.[8,13] In addition to stimulating peripheral sensory neurons, these cytokines also create exaggerated pain states by promoting central sensitization through their actions in the spinal cord.[90] From a mechanistic standpoint, TNF-α and IL-6 regulate excitatory and inhibitory neurotransmission, respectively, while IL-1β modulates both types of synaptic transmission in superficial dorsal horn neurons, enhancing pain by central mechanisms.[90] Further support for the role of IL-6 in centrally mediated pain was provided in several in vivo studies, in which intrathecal and intracerebroventricular administration of IL-6 was sufficient to induce either hyperalgesia or allodynia in rats.[82,91] Furthermore, application of IL-6 together with sIL-6R into the knee or the spinal cord of rats increased sensitization of spinal neurons to mechanical stimulation, indicating a role for peripheral and spinal IL-6 signaling in inflammation-evoked central sensitization and hyperalgesia.[8,92]

It is well established that disease-related symptoms associated with chronic inflammatory diseases such as RA display circadian rhythms.[93] Symptoms of RA, such as joint stiffness, functional disability, and joint pain, are often most prominent in the early morning and result from diurnal disruptions of the neuroendocrine and immune systems.[94,95] The HPA axis modulates the inflammatory activity of the immune system and, during acute proinflammatory events, it responds by increasing the levels of circulating adrenocorticotropic hormone (ACTH) and cortisol, effectively suppressing the production and release of proinflammatory cytokines such as TNF-α, IL-1, and IL-6 (**Figure 4**).[96] In RA, however, chronic inflammation downregulates HPA axis activity, resulting in reduced availability of cortisol and an inability to dampen the proinflammatory activities of cytokines.[94] Similar to hormones, cytokines exhibit circadian rhythms that correspond to the peaks and troughs of RA-associated functional disability and pain. Levels of cytokines such as TNF-α and IL-6 have been shown to be elevated during the very late-night hours, followed by depressed

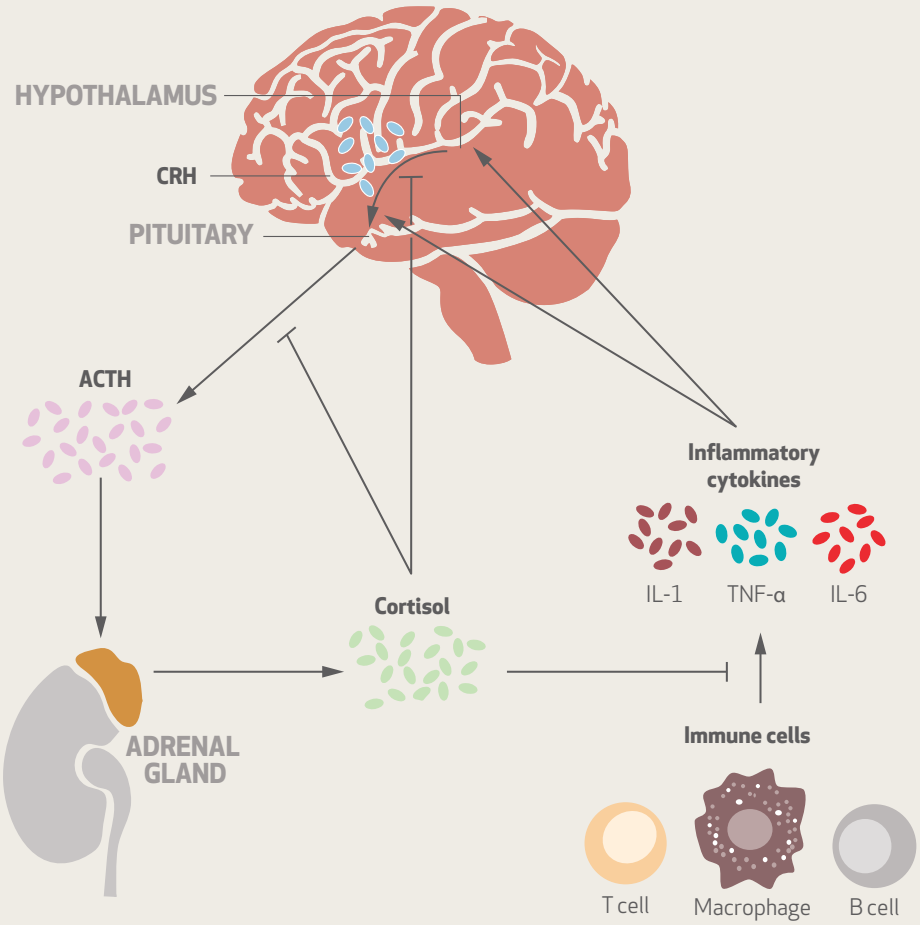

Figure 4. Interaction between the HPA axis and the immune response.[96] Activation of the HPA axis leads to the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which subsequently induces the production of ACTH in the pituitary gland. ACTH enters the peripheral circulation and stimulates the adrenal gland, resulting in the release of cortisol into the bloodstream. Cortisol then inhibits the activity of the HPA axis by abrogating CRH and ACTH secretion through a negative feedback mechanism. During an infection, immune cells such as T cells, macrophages, and B cells produce proinflammatory cytokines that activate the HPA axis. The resulting release of cortisol suppresses the further production and release of these cytokines. Adapted from Malek H et al. *Comput Biol Med.* 2015;67:1-12.

levels after noontime in patients with active RA, paralleling the cycles of heightened inflammation in the evenings followed by stiffness, functional joint disability, and pain in the morning.[93,95]

Interestingly, the psychosocial effects associated with RA, such as fatigue and depression, have been attributed to dysregulation of the HPA axis.[83,97] Compared with normal subjects, patients with chronic fatigue syndrome showed a significant reduction in basal evening total plasma cortisol, low 24-hour urinary free cortisol excretion, and elevated basal levels of ACTH, indicating impaired activation of the HPA axis.[98]

In depressive disorders, the feedback mechanism that counters hyperactivity of the HPA axis is dysregulated, and this may be mediated, in part, by proinflammatory cytokines that disrupt the inhibitory effect of corticosteroids on the HPA axis.[83] More specifically, it has been suggested that the activity of inflammatory cytokines such as IL-1 and IL-6 mediates fatigue, mood disorders, and pain, all of which have been clinically associated with RA.[99]

RA-Related Pain and Disease Assessment

Important clinical considerations of pain include a rheumatologic diagnosis as well as the underlying mechanism of pain generation.[60] The multifactorial nature of pain calls for an interdisciplinary strategy that can assess a patient's overall experience with pain, including onset, pattern, duration, location, and intensity in the context of physical function, psychosocial function, and quality of life.[100] The quantitative measurement of pain can be performed using a variety of instruments (**Table 2**).[6,100] Ultimately, a critical evaluation of clinical signs and symptoms, together with results from laboratory tests and imaging studies, are necessary to assess the predominant mechanisms of pain.[6,100]

Although pain significantly affects patients' assessments of RA disease activity, it does not necessarily equate with heightened inflammatory activity from the disease, and may, in part, account for the discordance between patients' and physicians' perceptions of RA disease activity.[101,102] Discrepancies between a patient's global assessment and the evaluator's global assessment have been attributed to differences in the perception of pain and joint swelling.[103] Although physicians predominantly rely on RA-specific outcomes such as joint count for determining global assessment scores, patients place more importance on indicators of general health, such as pain, when evaluating their overall disease experience.[101,102] Thus, while increased pain may worsen a patient's experience of RA

Questionnaire	RA in validation population?	Severity			Impact			
		Sensory	Emotional	Quality	Periodicity	Functional	Psychological	Quality of life
SF-36 bodily pain section	Yes	Yes	No	No	No	Yes	No	Yes
EQ-5D pain dimension	Yes	Yes	No	No	No	No	No	Yes
AIMS	Yes	Yes	Yes	No	No	Yes	Yes	Yes
VAS	Yes	Yes	No	No	No	No	No	No
McGill Pain Questionnaire	Yes	Yes	Yes	Yes	No	No	No	No
RAPS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
WHYMPI	Yes	Yes	Yes	No	No	Yes	Yes	Yes
painDETECT	No	Yes	No	Yes	Yes	No	No	No

AIMS, Arthritis Impact Measurement Scales; EQ-5D, European Quality of Life—5 dimensions; RAPS, Rheumatoid Arthritis Pain Scale; SF-36, 36-item Short Form Health Survey; WHYMPI, West Haven–Yale Multidimensional Pain Inventory.

Table 2. Assessing the dimensions of RA pain.[6] The qualities of RA pain can be assessed using a variety of validated questionnaires. Adapted from Walsh DA et al. *Nat Rev Rheumatol*. 2014;10:581-592.

disease activity, a higher swollen joint count may result in a worse evaluator perception.[103] In addition to the effect that pain produces on measures of disease activity, it also imposes a great influence on patient-reported outcomes and quality of life.[101] Considering the substantial associations between pain, sleep disturbance, and emotional health, measures of HRQoL have become increasingly important in assessing patient-reported outcomes.[101,104] A meta-analysis of 27 randomized controlled trials demonstrated a significant correlation between psychological care and improvements in pain, depression, and physical activity among patients with RA, which highlights the interdependent relationship between the physical and psychosocial manifestations of RA.[105] Other studies have confirmed that improvements in the physical and mental domains of HRQoL are associated with better outcomes in physical function.[104] In summary, patient-reported measures may provide important contributions to physician-assessed measures with regard to disease outcomes.[104]

Conclusions

Pain is a significant symptom in RA with far-reaching consequences that impact the psychological well-being and physical and social functioning of patients. As such, pain is a critical dimension to consider in the clinical evaluation and optimal care of patients with RA.[6,60] Although much remains unknown regarding the immunopathology of RA and its symptoms, mounting lines of evidence suggest that the mechanisms of RA-associated pain are multimodal in origin and can be attributed to cytokine-driven inflammation, peripheral and central pain processing, and structural changes in the joint.[6,81] In recent years, IL-6 has emerged as a central contributor to the inflammation that characterizes RA based on experimental models.[85] As a component of the inflammatory milieu that infiltrates the synovium during RA pathogenesis, IL-6 potentially enhances pain by modulating nociceptive responses and by promoting peripheral and central sensitization.[8,68,82] Furthermore, IL-6 levels have been associated with several types of psychosocial dysfunction as a result of RA pain, including depression and fatigue.[35,47] In summary, the findings of these studies underscore the physiologic relevance of IL-6, not only in the pathogenesis of RA, but in the generation and maintenance of acute as well as chronic arthritic joint pain.[85]

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