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The Jak/STAT pathway: A focus on pain in rheumatoid arthritis

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ABSTRACT

Pain is a manifestation of rheumatoid arthritis (RA) that is mediated by inflammatory and non-inflammatory mechanisms and negatively affects quality of life. Recent findings from a Phase 3 clinical trial showed that patients with RA who were treated with a Janus kinase 1 (Jak1) and Janus kinase 2 (Jak2) inhibitor achieved significantly greater improvements in pain than those treated with a tumor necrosis factor blocker; both treatments resulted in similar changes in standard clinical measures and markers of inflammation. These findings suggest that Jak1 and Jak2 inhibition may relieve pain in RA caused by inflammatory and non-inflammatory mechanisms and are consistent with the overarching involvement of the Jak-signal transducer and activator of transcription (Jak/STAT) pathway in mediating the action, expression, and regulation of a multitude of pro- and anti-inflammatory cytokines. In this review, we provide an overview of pain in RA, the underlying importance of cytokines regulated directly or indirectly by the Jak/STAT pathway, and therapeutic targeting of the Jak/STAT pathway in RA. As highlighted herein, multiple cytokines directly or indirectly regulated by the Jak/STAT pathway play important roles in mediating various mechanisms underlying pain in RA. Having a better understanding of these mechanisms may help clinicians make treatment decisions that optimize the control of inflammation and pain.

KEYWORDS:

Cytokines; Inflammation; Janus kinases; Pain; Rheumatoid arthritis; STAT

Abbreviations:

DRG: dorsal root ganglion; GM-CSF: granulocyte-macrophage colony–stimulating factor; gp130: glycoprotein; IFN: interferon; IL: interleukin; Jak: Janus kinase; R: receptor; RA: rheumatoid arthritis; STAT: signal transducer and activator of transcription; TNF: tumor necrosis factor; TYK: tyrosine kinase; VEGF: vascular endothelial growth factor

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, immune-mediated, systemic inflammatory disease of the synovial joints that affects approximately 0.5% to 1% of the population worldwide [1]. One of the key manifestations of RA is pain. This symptom is of particular importance to patients [2] and their quality of life, as illustrated by the finding in a multinational survey that being pain free was one of the main indicators of patients with RA having a “good day” [3].

Traditionally, pain in RA was ascribed to peripheral/diarthrodial joint inflammation; however, various clinical studies have shown that patients with RA may continue to experience pain even when inflammation is controlled [4]. Although attributed to subclinical inflammation, residual pain is now thought to be also linked to non-inflammatory mechanisms, as well as contributions from peripheral and central sensitization [5-7]. A better understanding of these mechanisms may help clinicians make treatment decisions that optimize the control of inflammation and pain relief.

Recently reported post hoc findings from a Phase 3 clinical trial (RA-BEAM; NCT01710358) showed that patients with RA who were treated with a Janus kinase 1 (Jak1) and Janus kinase 2 (Jak2) inhibitor (baricitinib) achieved significantly greater improvements in patient-reported pain than patients treated with a tumor necrosis factor (TNF) blocker (adalimumab), despite both treatments being associated with similar changes in standard clinical measures and markers of inflammation, including erythrocyte sedimentation rate, swollen join count, and C-reactive protein levels [8]. This finding in patient-reported pain suggests that Jak1 and Jak2 inhibition may relieve pain in RA caused by inflammatory and non-inflammatory mechanisms and is consistent with the overarching involvement of the Jak-signal transducer and activator of transcription (Jak/STAT) pathway in mediating the action, expression, and regulation of a multitude of pro- and anti-inflammatory cytokines [9-11]. The greater improvement in pain on Jak1 and Jak2 inhibition may be a reflection of effects on multiple

cytokines involved in regulating pain in RA as opposed to a single cytokine in the case of TNF blockade.

To further explore the more pronounced improvement of pain in RA with Jak1/Jak2 inhibition than TNF blockade, we herein provide a brief overview of pain in RA, the underlying importance of cytokines regulated directly or indirectly by the Jak/STAT pathway, and therapeutic targeting of the Jak/STAT pathway in RA.

Methods

This is a descriptive review. Relevant literature was identified by searching PubMed using key search terms, including arthritis, cytokines, cytokine signaling, inflammation, Janus kinases, pain, mechanisms, rheumatoid arthritis, and STAT. Additional literature was identified by searching the reference lists of articles identified in the PubMed search and based on the authors' knowledge of the therapeutic area.

Pain Mechanisms 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" [12]. A specialized class of sensory fibers, termed nociceptors, respond to actual or potential tissue damage that may result from high-intensity mechanical, chemical, or thermal stimulation [13]. Activation of nociceptors most often results in pain providing warnings about changes in homeostatic state, including the inflammatory responses that result from tissue injury [14]. The experience of pain requires integration of nociceptive inputs within the dorsal horn of the spinal cord and at higher brain centers. Emotional states, memories, cultural background, and other factors, including the

assessment of the degree of threat and the neural decision for appropriate behavioral responses, are all a part of the subjective experience of pain [15, 16].

Like other chronic diseases, pain associated with RA is complex and multifactorial (Figure 1) [5-7]. RA is characterized by pain that manifests with different qualities, distribution, and intensity between patients and over time for the same patient. Patients who have RA with well-controlled inflammation may continue to experience pain [7]. Therefore, it is important to understand the inflammatory and non-inflammatory mechanisms underlying pain in RA.

Inflammatory pain mechanisms

At the local joint level, inflammation of the synovium, caused by pro-inflammatory cytokines, can lead to activation, or sensitization, of afferent nociceptive fibers [17], which transmit "pain" signals to the dorsal horn of the spinal cord [18]. Ascending signals then travel via several pathways, including the spinothalamic tract, to the thalamus and to higher processing centers, including the somatosensory, insular, and cingulate cortices and the reticular and limbic systems [18]. Pro-inflammatory cytokines can act directly on mechanosensitive nociceptors, as well as in post-synaptic pathways in the spinal cord and supraspinal circuits, and on non-neuronal elements of the nervous system, including glial and immune cells [19-21].

Non-inflammatory pain mechanisms

Structural changes to the joint environment with ongoing disease may contribute to non-inflammatory pain in RA [5, 6], although whether such changes are major contributors remains uncertain. Damage and/or dysfunction of peripheral nerves, including ectopic discharge and increased excitability of damaged afferent nociceptors, are also likely to contribute to pain with neuropathic qualities [19, 21, 22].

Inflammatory mediators, such as cytokines, can bind to and lower the activation thresholds of transducers for evoked stimuli in primary afferent nociceptors, which leads to increased pain, a primary mechanism of peripheral sensitization [19, 20, 22]. Peripheral sensitization also promotes subsequent amplification of signaling in central circuits at all levels of the neuraxis [22], a process that is referred to as central sensitization (discussed in further detail subsequently).

Persistent afferent pain input, like that associated with a chronic inflammatory condition such as RA, can lead to synaptic changes and dysregulation in the neurons involved in the pain circuitry of the central nervous system, including the brain and the spinal cord [7, 23]. Central sensitization can result from multiple mechanisms, including increased excitatory neurotransmission, diminished inhibitory neurotransmission, or both [24, 25]. Enhanced temporal and spatial summation of repetitive nociceptive inputs also contributes to central sensitization and enhanced pain [24].

For more in-depth information on inflammatory and non-inflammatory mechanisms underlying pain in RA, we refer the reader to several excellent reviews addressing these topics [5-7, 26].

Jak/STAT Pathway

The Jak/STAT pathway is an intracellular signal transduction pathway that can be triggered by numerous cytokines, which can lead to the additional production of pro- and anti-inflammatory cytokines and locally destructive enzymes [9-11]. The involvement of pro- and anti-inflammatory cytokines in the pathogenesis of RA is well established [27]. The roles these cytokines play in mediating RA-associated pain and their relationship to the Jak/STAT pathway, including indirect relationships in the case of interleukin (IL)-1 and TNF, are summarized in Table 1 and Figure 2, respectively. The contributions of the Jak/STAT

pathway to nociception are not well understood; however, multiple cytokine receptors, such as IL-6R, IL-1R, and IL-10R and interferon (IFN)-γR, are expressed on afferent nociceptors, and cytokines acting at these receptors have been implicated in pain modulation (Table 1) [19].

There are 4 protein tyrosine kinases in the Jak family, comprising Jak1, Jak2, Jak3, and tyrosine kinase (TYK) 2 [10, 28-31]. These signal-transduction peptides function as dimers (homo- or heterodimers) when phosphorylated by the binding of a specific cytokine to its membrane-bound receptor [10, 28-30]. Once phosphorylated, the Jak dimers recruit additional signaling peptides, specifically, those from the STAT family [10, 28-31]. The STAT family includes 7 transcription factors: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 [10, 28-32]. Once dimerized (homo- or heterodimers), STAT peptides traverse the nuclear membrane and initiate transcription, usually after recruiting coactivators [10, 31, 32]. STAT-initiated transcription can upregulate the expression of cytokines or other components of immune pathways, which creates a positive-feedback loop [28, 30]. Examples of cytokines and pro-nociceptive factors that are regulated through the Jak/STAT pathway include IFN expression (STAT1); IL-4 secretion from B-cells (STAT2); and CCL5, IL-6, and IL-10 expression (STAT3) (Table 1) [21, 30, 33]. The involvement of these cytokines in pain signaling is implicated by expression of associated cytokine receptors on sensory neurons or neighboring glial cells [19, 20]. In addition, the regulation of cytokine receptors, such as TNF receptor 1 (TNF-R1), glycoprotein (gp130), and IL-1R on neuronal cells, also plays a role in promoting pain (Table 1) [19, 20].

It is important to note that activation of the Jak/STAT signaling pathway can diminish or intensify the pain experience depending on the intracellular mechanisms activated [34]. For instance, the anti-nociceptive cytokine, IL-10, and the pro-nociceptive cytokine, IL-6, activate the Jak1/STAT3 pathway, yet differences in downstream signaling result in anti-nociceptive or pro-nociceptive transmission, respectively [9, 21, 34].

Overview of Cytokine Involvement in RA-Mediated Pain

Several cytokines targeted for the treatment of RA, such as TNF-α, IL-1, and IL-6, have been well characterized in the pathogenesis of RA and associated pain through autoimmunity promotion, chronic inflammatory synovitis, and adjacent joint tissue destruction [35]. Other cytokines, such as granulocyte-macrophage colony–stimulating factor (GM-CSF), IL-4, IL-10, IL-13, and IL-17, are also involved in the modulation of pain and inflammation [20, 34, 36-38] (Table 1).

GM-CSF

GM-CSF signals through a variety of signal transduction pathways, including the Jak2/STAT5 pathway, and can stimulate the release of other pro-inflammatory cytokines and chemokines, such as CCL17 [37]. These additional signaling molecules can directly and indirectly evoke nociception [36]. Of note, GM-CSF has been associated with pain due to bone cancer, inflammation, and arthritis [36, 39, 40]. GM-CSF and CCL17 are readily detectable in the synovial fluid of patients with RA [41, 42]. There is also evidence from animal studies to suggest that GM-CSF may contribute to mechanical hyperalgesia in RA. Specifically, mechanical hyperalgesia was found to be diminished in mice lacking the GM-CSF receptor β-chain [36]. The specific mechanism by which GM-CSF contributes to pain behavior is unclear, but a recent report suggests an indirect mechanism via immune cell-driven transcriptional changes in nociceptive genes may play a role [43].

IL-1β

IL-1β, a pro-inflammatory cytokine, is widely upregulated in RA, including in the synovial milieu [35]. Members of the IL-1 family, such as IL-1β, are major inducers of inflammation and structural damage in arthritis [44]. As a synovial fibroblast-derived factor, IL-1β may help

recruit and activate T cells. IL-1β is also a pro-nociceptive factor and can contribute to hyperalgesia [20].

IL-4, IL-10, and IL-13

The anti-inflammatory cytokines IL-4, IL-10, and IL-13 differ from GM-CSF, IL-1β, and other pro-nociceptive cytokines in that upregulation of these cytokines ameliorates nociception [34]. However, similar to GM-CSF, these 3 cytokines signal directly through the Jak/STAT pathway. More specifically, the IL-4 receptor type I (IL-4R-I) signals through Jak1, Jak3, and STAT6, and the IL-4 receptor type II (IL-4R-II) signals through Jak1, Jak2, TYK2, STAT3, and STAT6 [34]. The IL-10 receptor (IL-10R) signals via Jak1 and STAT3 [9]. IL-4 and IL-13 can activate IL-4R-II, whereas IL-10 activates IL-10R [9, 34]. The Jak/STAT signaling of these anti-nociceptive cytokines raises interesting questions about the balance between pro- and anti-nociceptive cytokines and the net effect on the pain response.

IL-6

IL-6, a pro-inflammatory cytokine and one of the principal mediators of systemic inflammation in RA [45], can directly activate the Jak/STAT3 pathway [9, 34]. In addition to playing a major pro-inflammatory role in the pathogenesis of RA, findings from various in vitro and in vivo studies indicate that IL-6 plays an important role in regulating pain in joints [45]. The effect of IL-6 on pain is mediated peripherally and at the dorsal root ganglion (DRG). Specifically, IL-6 is able to exert effects by the binding of sIL-6R and trans-signaling via gp130, which is expressed at various locations in the nociceptive system, including neurons, glial cells, and DRG [45]. Of interest, findings from preclinical studies suggest that IL-6 family cytokines may play a role in neuronal survival and differentiation via trans-signaling [46] and in neuronal regeneration [47]. In addition, IL-6 has also been implicated in mediating pain in various other conditions, including bone cancer, spinal cord or peripheral nerve injury, and peripheral neuropathy due to chemotherapy [48].

IL-17

The expression of IL-17A, a pro-inflammatory cytokine, is increased in the synovial fluid of patients with RA [49, 50]. In experiments using rodent models, injections of IL-17 induced hyperalgesia [51], whereas mice lacking the gene for IL-17A displayed the opposite—a lack of mechanical hyperalgesia after artificially induced inflammation [52]. There is limited evidence that IL-17A may signal via the Jak-STAT pathway. Specifically, findings from a study in astrocytes suggests that IL-17A may signal via Jak2, STAT1, and STAT3 [38]. Activation of this pathway has been demonstrated to increase vascular endothelial growth factor (VEGF) expression [38]. Given this finding, and preclinical findings showing that downregulation of VEGF receptor 2 can be anti-nociceptive in models of inflammatory arthritis [53], IL-17A may signal directly via the Jak/STAT pathway and VEGF to modulate neuronal activity. Finally, IL-17 receptors are expressed on sensory neurons, suggesting a role for IL-17 in nociception [7].

TNF-α

TNF-α is a ligand for TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2), both of which have been detected in the DRG in animal studies [20]. Further evidence from animal studies indicates that binding of TNF to either of these receptors contributes to hyperalgesia in chronic inflammation [54]. TNF-α can promote synaptic plasticity and induce pain through actions at multiple regions of the nervous system, including the spinal cord, thalamus, periaqueductal gray, and the amygdala [55, 56]. Synaptic plasticity associated with central sensitization can also promote chronic pain [24]. TNFR1 has also been implicated in mediating neuropathic pain [57], while expression of TNFR1, TNFR2, and TNF-α are upregulated after peripheral nerve injury [58]. Moreover, a reduction in TNF-α has been shown to reverse connectivity in the upper circuitry of the central nervous system and ultimately lessen a chronic pain state [55].

Therapeutic Targeting of the Jak/STAT Pathway

Direct inhibition of Jak/STAT signaling of pain-modulating cytokines

Most cytokines associated with RA pathogenesis and pain are affected directly (via signaling through the Jak/STAT pathway) or indirectly (via enhancement by or a decrease in upstream or downstream signaling through the Jak/STAT pathway) by the Jak/STAT pathway. Examples of direct Jak/STAT inhibitors indicated for RA are tofacitinib (Jak1/Jak3 inhibitor) [59-62], baricitinib (Jak1/Jak2 inhibitor) [63, 64], and upadacitinib (Jak1 inhibitor) [65, 66]. Other Jak/STAT inhibitors, such as ruxolitinib (Jak1/Jak2 inhibitor), are also available but are not approved for RA [67]. Each of these therapies is a competitive inhibitor of adenosine triphosphate that transiently and reversibly prevents the phosphorylation and activation of Jak and, therefore, interrupts STAT downstream signaling [11]. In contrast, approved biologics indicated for RA target IL-6 receptors directly [35, 68]. However, these cytokine-specific therapies only mitigate the cytokine-specific effects, whereas the Jak/STAT pathway remains intact. Direct inhibition of the Jak/STAT pathway, however, could mitigate the effects of the multiple pro-nociceptive and anti-nociceptive cytokines that signal through the pathway (Table 1).

Indirect inhibition of pain-modulating cytokines that do not signal through the Jak/STAT pathway

Some RA-pain–mediating cytokines, such as IL-1β and TNF-α, do not signal directly through the Jak/STAT pathway [69]. There is evidence that inhibition of the Jak/STAT pathway can indirectly alter the effects of these non-Jak/STAT–signaling cytokines. For example, TNF-α indirectly involves the Jak/STAT pathway by inducing an autocrine loop that includes IFN-β or IL-6 [69]. In addition, TNF-stimulated synoviocyte activation can be affected by Jak-dependent pathways [70]. Ultimately, therapies that promote Jak inhibition might be more effective in mitigating pain than would a single cytokine inhibitor because multiple cytokines implicated in pain signal directly and indirectly through the Jak/STAT pathway (Table 1).

Discussion

Pain in RA is complex, in part because it involves multiple driving mechanisms that may differentially occur over time in individual patients and because each patient may have a different subjective pain experience. Nevertheless, nociceptive activation almost always promotes pain, even when joint inflammation is limited, and approaches that can normalize the thresholds for activation of nociceptors or diminish central transmission would be desirable for the development of therapies for patients with RA. Thus, mechanisms mitigating peripheral or central sensitization, or both, may be considered as therapeutic strategies (emphasizing the different nature of pain) for developing treatments directed specifically at pain associated with RA.

As highlighted herein, multiple cytokines directly or indirectly regulated by the Jak/STAT pathway play an important role in mediating various mechanisms underlying pain in RA. Hence, patients who achieve a measured clinical response to a given treatment, particularly with respect to reductions in swollen joint counts and acute-phase reactants, but who are not developing a satisfactory improvement in their pain, might derive additional benefit from switching to or incorporating a treatment targeting the Jak/STAT pathway.

The reduction in clinical measurements of inflammation appears broadly similar among biologics and Jak inhibitors in treating RA. The prospective comparison of baricitinib versus adalimumab [8], however, suggests that there are differences in favor of baricitinib in the magnitude and speed of pain relief between these 2 agents. These differences were most apparent in subjects with the highest baseline pain [8]. This finding is hypothesis generating and suggests that some agents may have an additional independent effect on non-inflammatory pain (perhaps via a direct effect on nociceptors or more proximal pain receptors). Whether this difference is specific to these 2 representatives of their class is unclear.

Additional research is warranted to better understand the mechanisms underlying pain in RA, including the various contributions of inflammatory and non-inflammatory mechanisms to overall pain in individual patients. An understanding of these mechanisms will help clinicians better determine effective individualized treatments for the underlying pathology and manifestations, such as pain, that are of significant importance to patients.

Jak inhibitors seem to impact many cytokine pathways that amplify pain. Therefore, future research should address various remaining questions, such as the following: Which Jak/STAT pathway-targeting therapies will be most effective in treating RA pain? It is presently unknown if the specific inhibitory profile, that is the relative inhibition of Jak1/Jak2/Jak3/TYK2, results in a differential pain response; this is an area for future exploration. Will future Jak/STAT inhibitors cross the blood-brain barrier, and, if so, what are the implications of this for RA-related pain? Although current Jak inhibitors are reported not to cross the blood-brain barrier in animal models, it is conceivable that the human blood-brain barrier becomes permeable to some degree in the context of a marked systemic inflammatory response. Another remaining question is will it be possible to better improve pain outcomes in patients with RA via a single treatment that targets multiple mechanisms or will multiple/combination treatments prove more efficient? The answer to this question will depend on the overall risk:benefit ratio observed with any treatment strategy that targets multiple pathways. It must also be remembered that whatever the diverse mechanisms promoting nociceptive transmission, and any signal modification by spinal and descending modulatory mechanisms, the perceived unpleasantness of afferent signals will result from engagement of cognitive brain regions and will also be influenced by psychosocial factors. Understanding these influences will help formulate management plans for which non-pharmacological interventions may also need to be considered.

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FIGURE LEGENDS

Fig. 1. Overview of the different mechanisms contributing to pain in rheumatoid arthritis (RA). Data from [5].

Fig. 2. Overview of Janus kinase (Jak)/signal transducer and activator of transcription (STAT) pathway-regulated cytokine involvement in mediating pain in rheumatoid arthritis (RA). Some cytokines, such as interleukin (IL)-1β, IL-6, IL-10, and tumor necrosis factor (TNF)-α, which are involved in RA pain, are found throughout pain pathways in the peripheral and central nervous systems. Other cytokines involved in RA pain are found in specific locations within the pain pathway. IL-18, for instance, is found in the periphery close to the joint. Cytokines with a red arrow are pro-nociceptive and increase pain sensation. Cytokines with a green arrow are anti-nociceptive and decrease pain sensation.
CNS: central nervous system; DRG: dorsal root ganglion; GM-CSF: granulocyte-macrophage colony–stimulating factor; IFN: interferon.

Table 1
Cytokine interactions with the Jak/STAT pathway and likely involvement in pain.

Cytokine (ligand/receptor)	Elements of Jak/STAT pathway affected	Association with pain mechanisms
GM-CSF/ GM-CSFR	Jak2 [31, 71] STAT3 [71], STAT5 [11]	Induces hyperalgesia [36, 40, 71] Upregulates sodium channel expression (Nav1.7-Nav1.9) [71]
IFN-γ/IFN-γR	Jak1/Jak2 [9, 11] STAT1 [9, 11] STAT3 [72]	Initiation or maintenance of pain [73, 74] IFN-γ– and IFN-γ receptor–deficient mice demonstrate social dysfunction [75] Can signal through inhibitory (GABAergic-specific) neurons [75]
IL-1β/IL-1R	Indirect via IL-6/STAT3 {Ahmed, 2000 #295}	Initiation of pain [19] Can have detrimental effect on cognitive function [76]
IL-4/IL-4R	Jak1, Jak3 [31] STAT1, STAT3, STAT6 [11, 77]	Overexpression of IL-4 can decrease hyperalgesia [34] IL-4–deficient mice show improved social function, may have mechanical allodynia, and demonstrate cognitive deficits [75, 78, 79]
IL-6/IL-6R, sIL-6R	Jak1, Jak2, TYK2 [9, 80] STAT3 [9, 31]	Pro-nociceptive factor [21] Contributes to development of hyperalgesia/allodynia in rats [81] Can have detrimental effect on cognitive function [82]
IL-10/IL-10R	Jak1 STAT3 [9]	Mitigates pain (anti-nociceptive effects) [19, 21]
IL-12/IL-12R	TYK2 and STAT4 [34]	Leads to release of pro-nociceptive cytokines TNF and IFN-γ [34]
IL-15/IL-15Rα, IL-2Rβ,γ_C	Jak1/Jak3 STAT5 [11]	Associated with severity of pain in osteoarthritis [83] Induces neuropathic pain [84]
IL-17/IL-17RA	Jak2 [38] STAT1, STAT3 [38]	Causes allodynia [85]
IL-18/IL-18R	TYK2 and STAT4 [34]	Pro-nociceptive factor [21]
IL-22/IL-22R	Jak1 [86] STAT3 [86]	Increased expression level is noted in experimental arthritis [87] Inhibiting IL-22 reduces pain [87]

IL-27/gp130	TYK2 [88] STAT1, STAT3, STAT5a/b [32] gp130-signaling subunit [32]	Diminished expression of gp130 can attenuate pain [89]
TNF-α/TNFR1, TNFR2	Indirect via IFN-β–Jak/STAT expression and STAT1 [69]	Can initiate pain and induce pain-receptor sensitization (both mechanical and thermal hyperalgesia) [90] Is associated with neuropathic pain [91, 92] and has detrimental effect on cognitive function [93, 94]

GABA: γ-aminobutyric acid; GM-CSF: granulocyte-macrophage colony-stimulating factor; gp: glycoprotein; IFN: interferon; IL: interleukin; Jak: Janus kinase; R: receptor; STAT: signal transducer and activator of transcription; TNF: tumor necrosis factor; TYK: tyrosine kinase.

FIGURES

Figure 1

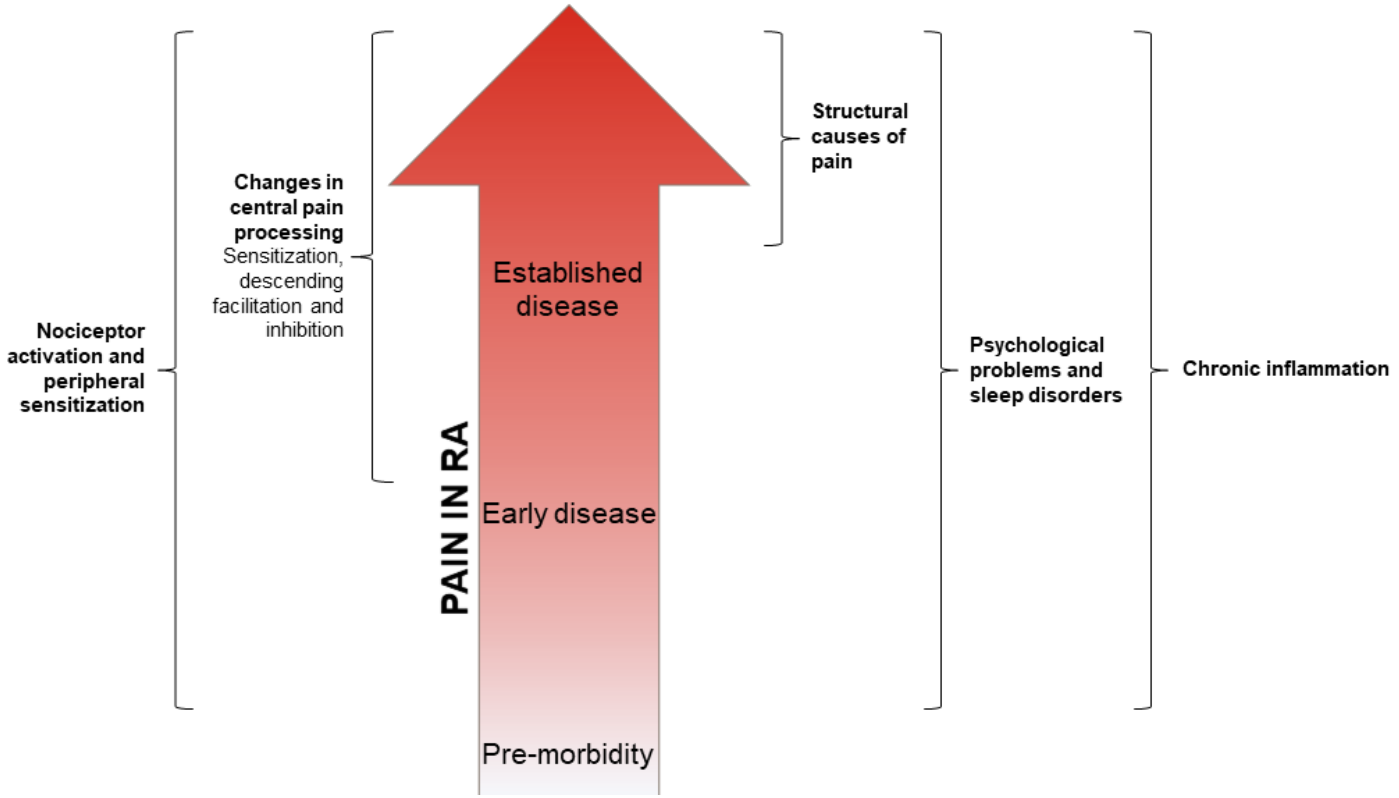
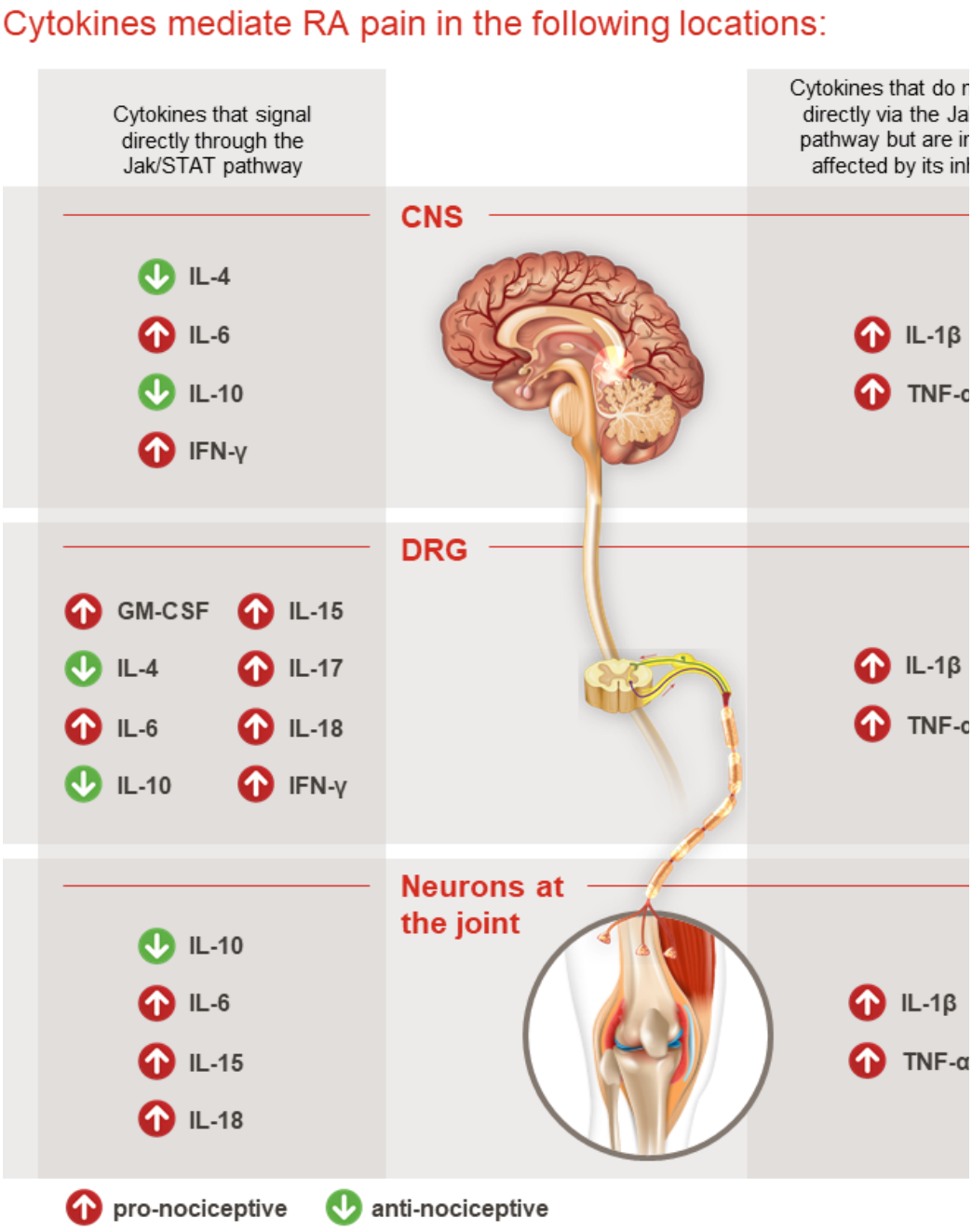


Figure 2


Cytokines mediate RA pain in the following locations:
Cytokines that signal directly through the Jak/STAT pathway
Cytokines that do r directly via the Ja pathway but are ir affected by its inl
CNS
IL-4
IL-6
IL-10
IFN-γ
IL-1β
TNF-α
DRG
GM-CSF
IL-4
IL-6
IL-10
IL-15
IL-17
IL-18
IFN-γ
IL-1β
TNF-α
Neurons at the joint
IL-10
IL-6
IL-15
IL-18
IL-1β
TNF-α
pro-nociceptive
anti-nociceptive