Biochemistry of Back Pain

Erin L Kaufman[1,*] and Allen Carl[2]

[1]*University of Kentucky, College of Public Health, 121 Washington Ave, Lexington, KY 40506*

[2]*Albany Medical College, Albany, New York, USA*

Abstract: Biochemistry of Spinal Pain

Background Context: Cytokines and neuropeptides are involved in the nervous system response and their role in pain is only beginning to be understood and incorporated into routine care. We present here a review on several cytokines and neuropeptides that might be implicated in spinal pain as well as the future directions of this field of research.

Purpose: A review on the biochemistry of spinal pain.

Study Design: A literature review.

Methods: A literature review of pubmed using studies published in the English language and focusing on studies dealing with the cytokines and/or neuropeptides and pain. We did not restrict the years of publication. All studies were accessed through either the University of Kentucky, Albany Medical College or Emory University's system.

Conclusions: Cytokines such as TNF-α, IL-1α, IL-1ß, IL-6, IL-4 and IL-10 may play a role in the biochemistry of spinal pain.

Keywords: Cytokines, back pain, pro-inflammatory, anti-inflammatory, spinal pain, review.

INTRODUCTION TO PAIN AND CYTOKINES

Pain, especially chronic pain, is one of the most common reasons for seeking medical care in the United States [1]. In the U.S., 88.6% of individuals that experience chronic low back pain and seek treatment are between the ages of 45-64 (80.6% of 65 and older [2]). Despite the high prevalence rates there is still uncertainty as to how a patient will respond to back pain treatment. As our understanding continues to develop we may be able to both expand and target new interventions [3, 4]. Cytokines have been found to be a new direction for back pain and spinal research. This review will look at cytokines as potential avenues for treatment, discussing both salient human and animal studies. This is because some cytokines (e.g., IL-10) are further along than others in the research continuum. We will then look at statistical methods that might be useful to determine thresholds for patient care.

Cytokines are small proteins (molecular weight from 4-80,000 kDa [5]) that make up a part of our immunogenic and pathogenic recognition system. Cytokines are the general name which is then broken down into more specific nomenclature depending on where they are manufactured (e.g., monokines come from monocytes, interleukins are manufactured by a leukocyte and act on another leukocyte) [6]. Cytokines focus on receptor cells which in turn react according to a combination of external stressors, their genetic programming, and their individual structure [7]. When initiated, they can respond in a "cascade" fashion with one cytokine exciting another cytokine [6]. Originally studied with regards to the immune system, cytokines have shown promise both as a potential biomarker, as well as an intervention opportunity, in the treatment of spinal pain. Table **1** shows the specific cytokines that are being studied for back pain.

It should be noted before we begin, throughout this review we will move between "back pain" and "spinal cord injury" (SCI) as we explore the biochemistry literature. Wherever possible "back pain" and SCI are discussed, we will use a definition specific to the research project it is being described in at the time (and defined as acute, subacute or traumatic). If the focus is on the biochemistry and not the illness/injury then "spinal pain" will be used to describe the overall process. In addition, we will discuss both animal and human studies. The reason for including both types of studies is that cytokine research is still rather novel and we feel that it is more helpful to see all aspects to gain a better understanding of the future of cytokines in the treatment of spinal pain.

CYTOKINES

Research using cytokines in other medical conditions has been underway for decades in an attempt to improve patient outcomes. Illnesses such as cancer [30], rheumatoid arthritis [7, 14] and psoriasis [31] all have different cytokine arrays which affect the various treatment protocols. Even so, their

*Address correspondence to this author at the University of Kentucky, College of Public Health, 121 Washington Ave, Lexington, KY 40506; Tel: 248-756-4004; Fax: 859-257-5624; E-mail: ELKaufman@gmail.com

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Table 1. Cytokines Implicated in Spinal Pain in both Human and Animal Studies

Cytokine	Spinal Disease/Injury where Cytokine has been Studied
Pro-inflammatory	
TNF-a	Chronic pain patients [8], SCI [9-11], sciatic [12], rheumatoid arthritis [5, 7, 13-16], intervertebral disc degeneration [17-20], chronic constriction injury [21], complex regional pain syndrome [22], herniated cervical intervertebral discs [23]
IL-1 (general)	Rheumatoid arthritis [5]
IL-1a	SCI, rheumatoid arthritis [10], rheumatoid arthritis [24], herniated cervical intervertebral discs [23]
IL-1ß	Chronic pain patients [8], spinal cord injury [9, 10, 25], rheumatoid arthritis [15], gouty arthritis [26], intervertebral disc degeneration [18], neuropathic and CNS pain [26], herniated cervical intervertebral discs [23]
TGF-ß	Complex regional pain syndrome [27]
Anti-inflammatory	
IL-11	Inflammatory arthritis [28]
IL-13	Rheumatoid arthritis [15]
IL-4	SCI(9), rheumatoid arthritis [15]
IL-6	SCI(9), rheumatoid arthritis [15], intervertebral disc degeneration [19], herniated cervical intervertebral disc [23]
IL-10	Chronic pain patients [8], SCI [9, 11], excitotoxic spinal cord injury [29], rheumatoid arthritis [15], intervertebral disc degeneration [19], complex regional pain syndrome [27]

use is often limited by our understanding of how to target and maintain therapeutic interventions. In a study by Milligan, *et al.* (2005) [32], using rats as a model, they were able to show that treatments such as IL-10 may be a potential therapeutic intervention for pain, even with its short half-life of 2-hours.

Table **2** illustrates the breakdown of cytokines that have been studied for pain in PubMed using the search criteria of "back pain cytokines" and "back pain neuropeptides". This table was constructed using the following limits in the search criteria: Items with links to full text, Humans, English, items found under the topics of Bioethics, Complementary Medicine, Core clinical journals, History of Medicine, MEDLINE, Nursing journals, and Systematic Reviews. Of the 61 articles that were found 44 articles were discarded (17 articles included in the table). This was due to 15 articles not being related to back pain, 20 articles not associated with the topic (10 being associated with neuropeptides) and 9 articles for miscellaneous reasons.

Overall, cytokines are a unique opportunity to create targeted, individualized treatment protocols for spinal pain patients. There are several types of cytokines that are described below that may offer potential opportunities for future patient care. They are typically broken down into pro- and anti-inflammatory cytokines.

PRO-INFLAMMATORY CYTOKINES

Pro-inflammatory cytokines can cause an immune response when triggered. The main cytokines implicated in this reaction are TNF-α, IL-1α and IL-1ß. For patients with injuries such as a SCI there are differences in the amount of pro-inflammatory cytokines between those who have SCI with and without complications [9]. Those patients who have more complications have higher levels for pro-inflammatory cytokines. Complications include "neuropathic pain, UTI and pressure ulcers" [9]. The regulatory environment that cytokines are responsible for can be maintained by medication and therefore understanding which cytokines are triggered by which injuries/conditions may help patients in the future.

TNF-α

Tumor necrosis factor alpha (TNF-α) is a pro-inflammatory cytokine involved in the acute stages of an immune reaction. This is because TNF-α tends to both be released earlier than other pro-inflammatory cytokines and stored on the surface of cells [7]. As TNF-α is typically undetectable it is often it's receptor, sTNFr, that is monitored to detect the presence of TNF-α from both blood and CSF [8]. By monitoring the receptor it is assumed that the presence of the receptor indicates TNF-α activity is occurring as the body rapidly takes in TNF-α, making monitoring of the cytokine directly nearly impossible. Backonja MM, *et al.* (2008) [8] and colleagues found that in both blood and CSF, sTNFr levels were significantly elevated in chronic pain patients.

As each type of condition is different, it is important to look at each treatment with regard to each suspected source of spinal pain. In a study by Tobinick EL, *et al.* (2003) [17] they were able to show that anti-TNF-α therapy might be useful for additional types of spinal pain patients, specifically discogenic pain patients. In their retrospective review of etanercept in discogenic pain, they looked at 20 patient's charts of individuals who where injected with 25mg of etanercept at baseline. Using baseline as time 1, they then looked at the Oswestry Disability Index (ODI) at time 2 (an average of 24 days after baseline) and at time 3 (an average of 230 days after baseline). In this study they found that there was statistical significance between time periods 1 and

Table 2. Back Pain and Human Studies

Back Pain	Cytokine Significant in Human Studies	Cytokine Not Significant in Human Studies	Study
Ankylosing spondylitis	TNF-α		Elewaut D and Matucci-Cerinic M (2009)[33]
Ankylosing spondylitis	TNF-α		Maksymowych WP (2004)[34]
Ankylosing spondylitis	TNF-α, IL-10, INF-γ		Sieper J, *et al* (2002)[35]
Rheumatoid arthritis	TNF-α		Dougados M, *et al* (2011)[36]
Chronic low back pain	TNF-α		Wang H, *et al* (2010)[37]
Chronic low back pain	TNF-α		Wang H, *et al* (2010)[38]
Degenerate intervertebral disc	IL-1, TNF-α, IL-1r, TNF-αr		Le Maitre CL, *et al* (2007)[18]
Discogenic low back pain (patients undergoing fusion)	IL-6, IL-8		Burke JG, *et al* (2002)[39]
Herniated disc	TNF-α, IL-6	IL-1, sTNF-r	Kraychete DC, *et al* (2010)[40]
Herniated intervertebral disc	IL-1, TNF-α, TNF-αr	IL-1r	Le Maitre CL, *et al* (2007)[18]
Modic changes	IL-1 gene locus polymorphisms		Karppinen J, *et al* (2009)[41]
Neuropathic pain	TNF-α, IL-6		Omoigui S (2007)[42]
Schmorl's nodes	TNF-α		Sakellariou GT, *et al* (2005)[43]
Sciatica	TNF-α		Genevay S (2004)[12]
Sciatica caused by lumbosacral radiculopathy	TNF-α		Cohen SP, *et al* (2009)[44]
Sciatica in patients undergoing discectomy	IL-6, IL-8		Burke JG, *et al* (2002)[39]
Spondyloarthropathies	IL-1		Tan AL, *et al* (2004)[45]

2 ($p<0.003$) and time periods 1 and 3 ($p=0.003$) but not time periods 2 and 3 ($p=0.10$).

More recently Sainoh *et al.* (2013) [46] have presented a paper at the 40th ISSLS on intradiscal injection of anti TNF-α in a randomized study of 30 patients that echoed the finding of Tobinick *et al.* This study was able to look at the effects of etanercept (as compared to bupivacaine) on low back pain patients following an injection at 1, 2 and 4 weeks using a visual analog scale and ODI. At the 4-week time point it was shown that TNF-α provided patients with a statistically significant relief of pain ($p<0.005$) according to the ODI.

These two studies combined have been able to demonstrate that TNF-α is effective in certain types of spine pain. The Study by Tobinick *et al.* suggests that the effect of an anti-TNF-α therapy such as etanercept for discogenic pain is effective in the long term but levels out after approximately one month [17]. This was confirmed by the Sainoh study. Therefore, this may be an effective early treatment for discogenic pain that can have sustained but not continuously improving results over time.

For systemic administration of anti TNF- α there are several significant issues related to widespread adoption of anti-TNF-α treatments. These include cost (treatments can run approximately $16,000.00 for rheumatoid arthritis [7]), side effects and the fact that early treatment will have a better effect on an individual's chance of recovery then starting treatment later in the disease process. Even so, the ability of anti-TNF-α treatments to enhance patient outcomes is a promising area of research. However, the recent use of intradiscal injection of Etanercept may pave the road for a widespread use of anti TNF- α while eliminating the majority of the side effects that are related to the systemic high dose of the anti TNF- α.

IL-1α AND IL-1β

IL-1α and IL-1ß are pleiotropic cytokines that are often elevated in inflammatory responses such as nerve injury and inflammatory disorders such as gouty arthritis [26]. Although the two interleukins have only about 26% of their amino acid sequence in common, the receptors that they bind to in the immune system, and subsequently the way they act on the nervous system, are thought to be the same [47]. It has been proposed that further understanding of IL-1 subtypes can lead to therapeutic treatments for conditions such as low back pain caused by radiculopathy [48] and other chronic spinal pain patients (e.g., neuropathic pain) [26].

IL-1 is an essential component in the body's ability to signal the presence of pain. The pain sensitivity to IL-1 is thought to be genetic and was illustrated in a study by Wolf G and *et al.* (2003) [49]. In this study, mice treated with IL-1ra (IL-1 receptor antagonist) in utero had lower basal pain sensitivity to the hot-plate test ($p<0.05$) and the paw-flick test ($p<0.01$) [49]. In that same study it is hypothesized that, IL-1 has a role in neural functions in the hippocampus, and is already known to regulate sleep [50] and body temperature [50]. It can affect electrical synaptic potential, where a change in the synaptic plasticity may account for the change in pain perception when IL-1 is reduced. Consequently, if IL-1 can be decreased then potentially sensation of pain from neuropathic pain or low back pain caused by radiculopathy can be decreased. This can be accomplished in several ways,

with the most straightforward being the injection of an anti-inflammatory cytokine such as IL-10, which will temper the effect of IL-1.

In a study by Le Maitre, *et al* (2007) [18] they were able to demonstrate that IL-1 was implicated in disc degeneration and disc herniation. In addition, it was to a greater degree than TNF-α while examining both cytokines simultaneously. This was done using tissues which were collected during surgery or post-mortem and examined using protein and gene expression for IL-1ß and TNF-α and their receptors [18]. This was to better understand if both cytokines existed simultaneously in disc degeneration and/ or disc herniation. Due to the complexity of intervention choices it is critical to understand which cytokines are prominent in which diseases entities and therefore this information is important.

SUMMARY OF PRO-INFLAMMATORY CYTOKINES AND SPINAL PAIN

There are many types of pro-inflammatory cytokines beyond the ones mentioned above (e.g., IL-4 [28], IL-6 [28], and TGF-ß(28)) and their role in spinal pain is only beginning to be understood. There are several reasons for this problem.

There are most likely different cytokine profiles for different conditions (e.g., different profiles for human herniated discs [18] vs. discogenic pain [17]) and the methods for data comparison are inconsistent (mainly because this is a new area of research). As each diagnosis has it's own specific treatment protocol, each diagnosis may have its own cytokine profile. For instance, there may be different cytokine profiles of pain from human herniated discs [18], human degenerated discs [17], human painful and painless neuropathies [22]. Later, in this review we will discuss some future directions to address this issue.

In conclusion, the ability to stop the cascade of the pro-inflammatory cytokine response, and return to homeostasis, is critical for successful patient outcomes. One possibility is to increase anti-inflammatory cytokines as a "buffer" to help keep the immune system in balance. This next section is a review of the literature that discusses how one particular anti-inflammatory cytokine, IL-10, plays a significant role in exitotoxic and traumatic SCI as well as traumatic brain injury patients.

ANTI-INFLAMMATORY CYTOKINES

Anti-inflammatory cytokines can also cause an immune response when triggered. The main cytokines implicated in this reaction are IL-10, IL-6, IL-4, IL-11 and IL-13 [28]. This review will focus on IL-10, IL-6 and IL-4 as the main contributors to spinal pain. IL-10 is a potent anti-inflammatory cytokine that has been shown to play an important role in both severe illness in human studies [51] and injury in both human and rat studies [29, 52]. IL-6 has been studied in IVD degeneration in a porcine model [19] and IL-4 is also an anti-inflammatory cytokine that has been looked at in SCI in humans [9], although neither IL-4 nor IL-6 has been looked at to the extent as IL-10. Therefore, we will look at IL-10 first and then give a review of IL-6 and IL-4.

IL-10

IL-10 is one of the most powerful anti-inflammatory cytokines that can result in systemic changes when injected into the body. Simplified, typically IL-10 is used to mediate the pro-inflammatory responses by activating B lymphocytes [5]. IL-10 has been successfully used in exitotoxic and traumatic SCI [29, 52] and traumatic brain injury [53] rat models as a way to modulate the pain response, reduce neuronal loss, and improve motor function.

Rat models are often the preferred model for investigating IL-10 properties in a laboratory setting. In a study by Brewer KL, *et al.* (1999) [29] they injected rats with quisqualic acid (QUIS) and IL-10 and calculated the time for reducing damage to the neuronal system. They found that there was a small increase in the acute phase but over the long term there was a significant decrease in the amount of gray matter damage if IL-10 injections were given 30 minutes, maximum, post-injury. A similar study was carried out by Plunkett JA, *et al.* (2001) [52] that looked at whether injections of IL-10 can cause a reduction of mRNA levels and cell death that lead to less inflammatory responses (and ultimately less pain) for patients. Similar results were also found in this study where continuous administration of IL-10 was more effective in the long-term than in the acute phase.

The rationale behind the need for injections in the first 30-60 minutes is that rat models have shown that a spinal injury can produce pro-inflammatory mRNAs as early as 15 minutes after the injury(10). To limit a potential cytokine cascade, early intervention is critical and therefore the first hour may be the most important.

IL-6

IL-6 is an anti-inflammatory cytokine that has been studied in a wide variety of illnesses ranging from arthritis [15] to temporomandibular disorders [54] to neuromyelitis optica [55] and post-operative pain for transabdominal hysterectomy [56] in humans. IL-6 is unique as it is a pleiotropic cytokine [57] which means that it can present as either a pro- or anti-inflammatory cytokine depending on if it's upregulated or downregulated. It is for this reason that in the literature it has been referred to as a pro-inflammatory cytokine [54], an anti-inflammatory cytokine [28], or both [58] depending on the study.

IL-6 has been considered as a mediator for intervertebral disc degeneration (IVD) degeneration. In a study by Holm S, *et al.* (2009) [19] they took 6 domestic pigs and looked at the balance between pro- and anti-inflammatory mediators, specifically IL-6, TNF-α and IL-10 to determine which types of cytokines have a role in the late stages of IVD degeneration. After 3 months, they were able to show that, although, IL-6 does not differ between the experimental and control groups, IL-10 and TNF-α do have a significant role towards the end of IVD disease [19].

IL-6 is a complex, pleiotropic cytokine [57] with many potential avenues for investigation. Like all cytokines, its regulation is controlled by other cytokines [19] as well as potentially by a person's life experience. Its unique ability may make it a potentially useful, early intervention target for the future.

IL-4

IL-4, and its receptor, are anti-inflammatory cytokines that have been studied in diseases ranging from cancer [59] and asthma [60] in mice, to HIV susceptibility [61] and inflammatory arthritis [15] in humans. In the field of spinal pain, IL-4 is only starting to be studied and has not yet been shown to have statistically significant results as a potential biomarker for certain spinal issues. In a study by Scuderi GJ, *et al* (2006) [62] they performed a panel of tests for over 25 pro- and anti-inflammatory cytokines and neuropeptides including IL-4 on 50 consecutive patients with "acute radiculopathy secondary to a symptomatic herniated lumbar disc and spinal stenosis and who were indicated for epidural steroid injection." In their study they found, using lavage techniques in the epidural space, that there was no correlation for the inflammatory mediators and the patient symptoms, including IL-4. This is an important finding and highlights the need for greater sensitivity in using cytokine panels for identifying specific spinal issues.

In 2007, Davies AL, *et al*. (2007)(9) conducted another study that showed similar results. In their study they looked at patients with SCIs (acute and chronic) and found that levels of IL-4 did not statistically increase as compared to controls ($p>0.05$). Their sample population was composed of twenty-two individuals in the post-acute stage (2-52 weeks post-injury), 34 individuals with chronic SCIs (>52 weeks) and 35 healthy, able-bodied volunteers [9]. Even though IL-4 was not significant, other cytokines such as IL-6 were found to be significant in the collective SCI group compared to the control group ($p<0.05$). This was emphasized even more when stratifying for IL-6 in SCI subjects with complications as compared to controls and subjects without complications ($p<0.01$) [9]. This shows that there are increased levels of pro-inflammatory cytokines in SCI patients (both acute and chronic), although IL-4 may not be the best cytokine to target for these patients.

It is plausible that different diagnoses have different cytokine profiles and IL-4 may not the best target for such interventions. Alternatively, as we are still learning, these are only two diagnoses and we might find that it has a significant role in another illness/injury that has yet to be uncovered.

ANTI-INFLAMMATORY CYTOKINES SUMMARY

Overall, anti-inflammatory cytokines can help balance the effects of pro-inflammatory cytokines, especially during times of injury. Timing can be critical and their use, especially as it relates to timing, is still being explored. Although IL-4 and IL-6 may contribute to spinal pain it is really IL-10 that has been studied the most in the literature, especially in rat models. Even so, we have only begun to understand the role anti-inflammatory cytokines play in spinal disease and injury and over time we will continue to advance our knowledge in this arena.

FUTURE DIRECTIONS

Cytokines present a potential direction for a unique contribution to the field that may make a significant impact on patient outcomes. There is a vast array of knowledge and "bench to bedside" science that is already occurring in the field of immunology. [7, 12, 16, 17, 63] Overall, the imbalance of cytokines has shown to cause chronic pain [8]. In a study by Backonja, *et al.* (2008) they sampled CSF due to the inconsistency of peripheral blood. They were able to demonstrate that sTNF in blood and CSF with IL-1 ß were consistent with non-diabetic polyneuropathy and post-traumatic neuralgia while sTNF in both was strongly associated with an inverse correlation in pain symptoms [8]. This study demonstrates the structure and function that cytokines have on the pain response.

In order to incorporate translational science into the clinic setting we need to better elucidate cytokine properties and the sequence of events of the immunologic response in order to create protocols based on patient needs. At present we have no "gold standard" for measuring cytokines in a clinic setting. This is exemplified in an study by Wang CX, *et al.* (1997) [25] where he was able to illustrate that, in a SCI rat model, the IL-1ß mRNAs were significantly higher in the spinal cord as compared to the cerebral spinal fluid and/or blood levels. Understanding what structure or substance to test, and where, for specific cytokines is an important step in moving forward.

In addition to providing secondary and tertiary spine care, there may be a future role for cytokines in primary care for newly diagnosed spinal pain patients. As inflammation is felt to be a treatment target, so may cytokines. In other fields, such as cardiac surgery, the predictive value of cytokines profiles is being met with success. In a study by Furtado MV, *et al.* (2009) [64] they found that IL-18 had a significant predictive power of identifying cardiac patients who would ultimately have another cardiac event in the following 6 months. This finding was then further substantiated in several other studies [65, 66] with one study finding that it was the ratio of pro-inflammatory to anti-inflammatory cytokines (IL-18/IL-10) that may be the predictor of future cardiac events. This can potentially be applied to spinal care.

One possible step in that direction is to develop a set of receiver operating curves (ROC) to be used to help guide treatment methods. Building on the work in cardiology [64-66] if we take cytokine levels at baseline as a categorical variable (e.g. immediately following surgery for acute SCI patients) along with their associated patient measurements of pain, SCI degree or even amount of mechanical degeneration or deconditioning (taken as a dichotomous variable with a cut-off that we can create and change as our knowledge increases) then we can track the patients outcomes and learn which cytokines we need to focus on, what measures to focus on and where we need to take our samples from (e.g., CSF, blood), in order maximize our effectiveness. In this way we can work as a team with immunology, biostatistics and epidemiologists to use ROC curves to improve patient outcomes.

SUMMARY

Spinal pain is often difficult to characterize and can accompany a wide variety of pain symptoms, diagnoses, biomechanical effects and biochemical profiles. Cytokine profiles such as IL-1α, IL-1β, TNF-α, IL-4, IL-6, and IL-10 all can have an impact on both the disease process and possibly the subsequent recovery of spinal patients. At

present much of the work has focused on the biomechanical contributions to the field rather than biochemical associations. This seems to be slowly changing as studies such as Sainosh, *et al.* (2013) [46] demonstrate the model is working in humans and this is a significant, understudied avenue where we can proceed. Even for clear pathologies the various ways in which it can occur may cause the body to produce different immunological responses, varying even at different stages in the disease process. We are in our infancy in our understanding of how to identify a cytokine footprint and create a treatment protocol based on that information. Collaboration with a broader range of disciplines can help draw more knowledge to both the research and treatment teams as well as help to provide better overall care for the patient.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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