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Toll-Like Receptors: At the Intersection of Osteoarthritis Pathology and Pain

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1. Introduction

Osteoarthritis (OA) is a common chronic joint disease projected to affect an astounding 18% of the population in the western world by the year 2020 (Lawrence et al., 1998). In addition, it has a cost of \$15.5 billion per year in the US alone, taking into account the accompanying disability and social consequences (Yelin and Callahan, 1995). Current hypotheses of OA pathology and OA pain tend to be exclusive to either. Here we present a hypothesis that is an attempt to identify a common aetiology for both.

2. OA pathology

The features of OA constitute a group of conditions that are diagnosed upon common pathological and radiological characteristics (Felson et al., 1997) and are believed to be caused by material failure of the cartilage network leading to tissue breakdown (Poole, 1999) or by injury of chondrocytes with increased degradative responses (Aigner and Kim, 2002).

3. OA pain

Pain has been defined as the primary symptom of OA (Creamer, 2000). Physicians typically rely on scores of pain and measures of joint function to make treatment decisions for OA (Swagerty, Jr. and Hellinger, 2001), as pain rather than joint pathology is more pronounced in this disorder.

4. Immunologic mechanisms in OA

OA has been considered to primarily affect cartilage and bone. However, there is increasing awareness that all tissues of the synovial joint, including synovium, ligaments and nerve terminals, are likely affected by this complex disease. Moreover, OA has been described as a non-inflammatory degenerative condition that is characterized by the imbalance of articular cartilage degradation and repair. Traumatic injury of the joint, either acute sport injuries or chronic aging accumulation is the leading cause of this imbalance. But genetic factors also play a role in some OA. Surprisingly, C-reactive protein (CRP), a systemic marker of inflammation, is increased in serum in OA patients at early phases (Saxne et al.,

2003b;Sowers et al., 2002) although it has been suggested that inflammation is actually related to complication by crystalline arthritis (Rothschild and Martin, 2006). This suggests the presence of low-grade inflammation at early stages of the disease process.

Recently, the research of the genetic linkages and the innate immune activation in OA further supports a possible pathogenic role of inflammation and a “chronic wound repair” type of immunologic mechanisms in OA (Kato et al., 2004;Scanzello et al., 2008). There have been reports about linkages between HLA haplotypes and OA, including the linkages of HLA-Cw1, 4, 10 (Wakitani et al., 2001), HLA B35-DQ1, B40-DQ1, DR2-DQ1 (Merlotti et al., 2003), HLA DR2, DR4 (Riyazi et al., 2003). These HLAs are polymorphologic molecules presenting antigens to T cells, which supports a role of immune activation at the onset of OA.

Synovial inflammation is milder than in rheumatoid arthritis (RA). Despite this, cellular infiltration of activated lymphocytes and neo-vascularisation are documented in many advanced OA, as well as patients at early stages (Walsh et al., 2007;Pearle et al., 2007;Saito et al., 2002;Saxne et al., 2003a). The severity of synovial inflammation defined by MRI is correlated with pain intensities in OA patients (Hill et al., 2007). Synovitis seen under arthroscopy is associated with cartilage degradation (Ayril et al., 2005).

Increased levels of immunoglobulins have been reported in OA. Jasin reported IgM and IgG levels in OA cartilage tissue are three times more than in normal cartilage tissue (Jasin, 1985). This suggests that antibodies are synthesized within the affected joint by infiltrating immune cells or that the cartilage is more permeable to immunoglobulins.

5. Toll-like receptors (TLRs)

TLRs are a group of pattern recognition receptors (Barton and Medzhitov, 2002), which gate the immune response. Up to now, a total of 13 TLRs have been identified -TLR1 to TLR10 in human; TLR1 to TLR13 (except TLR10) in murine (Beutler, 2005). A highly specific pattern governs the TLR recognition of various microbial ligands. Each of these TLRs responds only to a limited number of microbial ligands summarized in Table 1 of Akira and Takeda (2004).

TLRs adopt either the myeloid differentiation primary response gene 88 (MyD88)-dependent or MyD88-independent pathway following activation. TLR signalling pathways lead to the production of several critical transcription factors, including NF- κ B, interferon regulatory factor (IRF) and activator protein-1 (AP-1). Three most common TLR-mediated signalling pathways are the MyD88-dependent and MyD88-independent release of NF- κ B, and the MyD88-independent production of IRF. Each of TLRs seems to recruit different subsequent signalling pathways (Akira and Takeda, 2004). But detailed information remains unclear to us. Mollen et al. (2006) proposed the theory of “TLRs and danger signalling”: During tissue stress or injury, a variety of damage-associated molecules are actively secreted by stressed cells, passively released from necrotic cells, or originally from the degradation of the extracellular matrix. These damage-associated molecular patterns are recognized by TLRs in a similar manner as that of exogenous pathogen-associated molecular patterns.

A long list of damage-associated molecules have been proposed as putative endogenous TLR ligands (Beg, 2002), including hyaluronan, heparin sulphate, fibrinogen, high-mobility group protein (HMGB1), HSP 60, host mRNA, host chromatin and small ribonucleoprotein particles as well. Therefore, TLRs seem to be critical players in determining the nature of tissue injury, and initiating corresponding signalling pathways that result in distinct forms of pain.

Increasing evidence supports TLR4 as the main TLR sensing tissue damage in that it responds to a couple of endogenous ligands, such as HSP 60, fibrinogen, heparin sulphate and hyaluronan (Johnson et al., 2002; Ohashi et al., 2000; Smiley et al., 2001; Taylor et al., 2004a; Termeer et al., 2002). TLR4-dependent signalling pathway has been linked to sterile inflammation resulted from various neural and non-neural tissue injuries. Studies reveal that the production of inflammatory cytokines is compromised during tissue injuries in C3H/HeJ strain mice featured with TLR4 mutation - reduced TNF level in wound incision (Bettinger et al., 1994); low circulating IL-6 in hemorrhagic shock (Prince et al., 2006); and decreased IL-1 β expression at the nerve stump in sciatic nerve lesion (Boivin et al., 2007). As a consequence, the overall inflammatory response in TLR4-deficient animals is attenuated. Evidence includes reduced accumulation and activation of macrophages in injured nerve tissue (Boivin et al., 2007); less severe systemic inflammatory response (e.g. lower hepatic IL-6 level, less liver injury) after bilateral femur fracture with soft tissue crush injury (Levy et al., 2006).

TLR2 was implicated in the pathogenesis of arthritis (Cho et al., 2007). TLR2, IL-8, and vascular endothelial growth factor (VEGF) were upregulated in arthritic joints in human synovial tissue culture, which was blocked by anti-TLR2 antibodies. Interestingly, HMGB1 was up-regulated at the same time frame in arthritic joints in human (Kokkola et al., 2002; Taniguchi et al., 2003). HMGB1 has been proposed as the primary putative endogenous TLR2 ligand (Park et al., 2004; van Beijnum et al., 2008; Yu et al., 2006). Although there is no direct evidence for the involvement of HMGB1-TLR2-mediated pathway in arthritis, some results favour the notion. Park et al. (2006) showed the protein-protein interaction between HMGB1 and TLR2 was functional in terms of initiating intracellular signal transductions. Yu et al. (2006) demonstrated that anti-TLR2 antibody blocked HMGB1-induced TLR2-dependent IL-8 release in HEK cells. TLR3 and TLR9 are known to recognize microbial nucleic acids. However, host nucleic acids are also capable of initiating immune response via TLR activation - chromatin can induce the production of anti-DNA antibodies via a TLR9-dependent mechanism (Leadbetter et al., 2002). In Alzheimer's patients, TLR3 expression was identified in brains without previous viral infection (Jackson et al., 2006). The up-regulation of TLR3 expression might partly be explained by the finding that RNA is a constituent in senile plaques (Marcinkiewicz, 2002). The inflammatory nature of the disease may result from TLR3 activation by host RNA. Necrotic cells resulted from various processes including tissue injuries release host nucleic acids. Kariko et al. (2004) demonstrated that it was RNA released from necrotic cells that led to TLR3-dependent release of TNF- α . Necrotic cell lysates lost the capability to stimulate TNF- α release once they were pretreated with Benzonase, a potent and nonspecific nuclease that degrades all RNA into oligomers of 2-5 nucleotides in length.

6. TLR pathways in OA pathology

Age and joint trauma are two risk factors for the development and progression of OA. Endogenous damage-associated molecules, including hyaluronan, fibronectin, have been identified in OA in response to initial tissue injury. Hyaluronan is highly viscous polysaccharide found in the extracellular matrix, and is a major component of synovial fluid and cartilage, which plays an important role in the lubrication and shock absorption for the joint tissue. Its molecular weight/length is reduced in exercise and joint injury (Brown et al., 2007). In OA, both of the concentration and molecular weight of hyaluronan are reduced (Dahl et al., 1985). Hyaluronan fragments of specific sizes have been shown to promote

angiogenesis and have immune regulatory effects mediated by the TLR-4 receptor (Taylor et al., 2004b). However, TLR-4 responses initiated by bacterial product lipopolysaccharide (LPS) and endogenous product hyaluronan are different, due to the recruitment of different accessory molecules, CD14 for the LPS-TLR-4 response and CD44 for the hyaluronan-TLR-4 response (Taylor et al., 2007). Fibronectin is another extracellular matrix component affected by both age and tissue injury, and the presence of fibronectin and a specific isoform containing the B sequence, Ed-B fibronectin, in osteoarthritic cartilage but not in normal cartilage has led to the suggestion that the isoform might play a role in extracellular matrix remodelling (Chevalier et al., 1996). In addition to the traditional integrin-mediated pathways, certain splice variants of fibronectin are also capable of activating a TLR-4 dependant pathway (Lasarte et al., 2007; Gondokaryono et al., 2007; Okamura et al., 2001).

Although TLRs are constitutively expressed on immune cells, the expression of TLR can be induced on other cell types as a result of IL-1 stimulation or TLR-4 activation (Matsumura et al., 2003; Kim et al., 2006; Ojaniemi et al., 2006). Radstake et al. (2004) reported the expression of TLR-2 and TLR-4 in osteoarthritic synovial membrane. Moreover, cultured synovial cells and chondrocytes from OA subjects show responsiveness to TLR-4 agonist LPS and TLR-2 agonist peptidoglycan (Kim et al., 2006; Kyburz et al., 2003; Ozawa et al., 2007). TLR-4 deficiency rescues cartilage and bone erosion in arthritis, while TLR-2 deficiency promotes the disease severity (Abdollahi-Roodsaz et al., 2008).

Activation of TLR-2 and TLR-4 recruits downstream adaptors such as MyD88 and Toll-interleukin 1 receptor domain containing adaptor protein (TIRAP), and ultimately leads to the activation of various transcription factors including IRFs, AP-1, and NF- κ B. All TLR pathways are capable of activating NF- κ B, and recent evidence suggests a role of NF- κ B in OA. The activation of NF- κ B requires the degradation of I κ B bounding to it. Amos et al. (2006) showed that inhibiting NF- κ B via over-expressing I κ B α inhibited the production of many inflammatory and destructive mediators in OA, including TNF- α , IL-6, IL-8, oncostatin M, and metalloproteinase (MMP)-1, 3, 9, 13. The Bondeson group further showed that several MMPs and aggrecanases such as a disintegrin and metalloprotease with thrombospondin motifs 4 and 5 (ADAMTS 4, 5) are NF- κ B dependent (Bondeson et al., 2007). MMP-1 and MMP-13 are capable of cleaving collagen type II, and MMP-3 cleaves other components of extracellular matrix, such as fibronectin and laminin (Yoshihara et al., 2000). ADAMTS4 and ADAMTS5 work together to cleave aggregating proteoglycan aggrecan in cartilage (Song et al., 2007; Lohmander et al., 1993). Chen et al. (2008) reported the suppression of early surgically induced OA, such as minimized synovitis and articular cartilage damage, by intra-articular delivery of NF- κ Bp65 specific siRNA NF- κ B.

Several autoantibodies against degradative products of cartilage tissues have been identified in OA, in both humans and other animal species. These include antibodies against collagen 2 (Jasin, 1985; Niebauer et al., 1987; Osborne et al., 1995), cartilage link protein (Guerassimov et al., 1998), G1 domain proteoglycan aggrecan (Niebauer et al., 1987), cartilage intermediate layer protein (Tsuruha et al., 2001), human chondrocyte gp-39 homologous, YKL-39 (Tsuruha et al., 2002), and osteopontin (Sakata et al., 2001). Collagen II has been indentified as one of the major autoantigens in human and other animal models of RA, but much remains to be known about the autoantigen(s) driving the synovitis in OA. MyD88 dependent TLR signalling is critical for the induction of adaptive immune responses, including B-cell activation and antibody production (for review see Pasare and Medzhitov, 2005). Stimulating TLRs on B cells can result in polyclonal activation and production of low-

affinity immunoglobulin M (IgM) antibodies, which may be one of mechanisms producing autoreactive antibodies (Iwasaki and Medzhitov, 2004).

7. TLR bridges traumatic injury and OA pain

Chronic pain can arise from a wide variety of causes - arthritis pain, low back pain, migraine, cancer pain, post-herpetic neuralgia, diabetic neuropathy, and others. Currently, chronic pain is explained more or less on the basis of structural abnormalities, such as osteoarthritis or herniated disk (Omoigui, 2007a). Chronic pain has not been able to be classified into well mechanism-based entities. To distinguish inflammatory pain from neuropathic pain is the best attempt so far. Hawker et al. (2008) revealed two distinct types of OA pain: an early predictable dull, aching, throbbing “background” pain and an unpredictable short episode of intense pain that develops later (Hawker et al., 2008). During the progression of OA, pain evolves from the “background” pain that is use-related in early OA (Kidd, 2006), to unpredictable short episodes of intense pain on top of the “background” pain in advanced OA (Hawker et al., 2008). However, the nature of the pain in OA still remains unclear (Hunter et al., 2008; Kidd, 2006; McDougall, 2006; Wu and Henry, 2010). Our poor understanding of chronic pain results in poor mechanism-based treatments, particularly for neuropathic pain (Gordon and Dahl, 2004; Colombo et al., 2006; Jackson, 2006; Rice and Hill, 2006; Dworkin et al., 2007).

One critical fact about chronic pain is that its nature is determined shortly after the initial insult. For example, nerve section induces neuropathic pain only, but never inflammatory pain, no matter how complicated the subsequent cytokine cascade is. Different types of tissue injury are associated with distinct forms of chronic pain. TLRs likely play an important role in the “judgment of pain” in various tissue injuries, as they are the most important interface initiating the release of cytokines following cellular response to distinct pathogen- or damage-associated molecular patterns, and they have limited yet highly specific subtypes associated with distinct intracellular signalling pathways.

The notion that inflammatory mechanisms are underlying all pain syndromes was recently proposed in two review papers (Moalem et al., 2005; Omoigui, 2007b). Alteration of the chemical environment surrounding sensory neurons changes nociception (Clatworthy et al., 1995) demonstrated that the development of the thermal hyperalgesia was tightly governed by peri-axonal inflammation. These findings lead to a re-examination of the significance of the accumulation of immune cells and inflammatory factors in nerve injuries. Cytokines likely play critical roles in the above processes. TNF- α , IL-1 and IL-6 have been shown to induced hyperalgesia if injected peripherally into the paw (Cunha et al., 1992; Ferreira et al., 1988), which can be blocked by the application of antibodies against each of these cytokines (Cunha et al., 1992; Schafers et al., 2001; Sommer et al., 1999). A second line of evidence is from inflammatory models of neuropathic pain. Those models are able to mimic neuropathic type of pain by means that are unlikely to injure sensory axons. Neuropathic pain can be induced by placing chromic gut thread next to sciatic nerve (Maves et al., 1993), by cutting ventral roots of spinal nerves which are motor efferents (Li et al., 2002; Sheth et al., 2002), by applying complete Freund’s adjuvant (CFA) (Eliav et al., 1999) or zymosan (Chacur et al., 2001) around the intact sciatic nerve. Third line of evidence is from neurology clinics. Neurologists surprisingly found that pain is a common comorbidity in autoimmune diseases of nervous system: 65% of multiple sclerosis patients reported pain during the

course of their disease (Kerns et al., 2002); 70-90% of Guillain-Barre syndrome patients complained pain (Pentland and Donald, 1994; Moulin et al., 1997).

A sundry of signalling pathways – such as PKA, PKC, PKG, ERK, P38 MAPK, NF- κ B and JAK/STAT have been implicated to be involved in the development of chronic pain (Hanada and Yoshimura, 2002; Ji and Woolf, 2001; Obata and Noguchi, 2004). Among them, NF- κ B, JAK/STAT and MAPK pathways are of particular importance in chronic pain: NF- κ B pathway is the most important cellular pathway responsible for the production of inflammatory cytokines (Nguyen et al., 2002); JAK/STAT pathway is the primary pathway responsible for cytokine receptor signalling (Ihle, 1995); and MAPKs play a pivotal role in transducing extracellular stimuli into intracellular posttranslational and transcriptional responses, and are hot topics in recent pain mechanism studies, particularly ERK and P38 (Ji and Suter, 2007; Ma and Quirion, 2005; Obata and Noguchi, 2004). TLR signalling pathways have intensive crosstalk with the above mentioned pain-related pathways.

TLR and NF- κ B pathway - Different adaptor molecules recruited by different TLRs result in differences in NF- κ B activation. TLR signalling via the MyD88-dependent pathway leads to the early phase release of NF- κ B. During TLR2 or TLR4 signalling, TIRAP/MAL is recruited to TIR domain, and then MyD88, whereas during TLR5, TLR7 or TLR9 signalling, MyD88 is recruited to TIR domain. Activation of MyD88-independent pathway downstream of TLR3 or TLR4 accounts for the late phase release of NF- κ B, where TRIF is the key adaptor recruited.

TLR and IFN-JAK-STAT pathway - Type I IFNs previously were found mainly due to the activation of the MyD88-independent pathway which triggers the expression of IFN- β and chemokine genes (Sakaguchi et al., 2003). Recruitment of MyD88 by TLR7, TLR8 or TLR9 also results in the release of different set of type I IFNs, including both IFN- α and IFN- β species. (Honda et al., 2004; Takaoka and Yanai, 2006). The activation of IFN-receptors by Type I IFNs is an important mechanism linking TLR pathway and the JAK-STAT pathway (Akira and Takeda, 2004; Kawai and Akira, 2005), as the JAK-STAT pathway is one of the best characterized IFN-signalling pathways (Stark et al., 1998).

TLR and MAPK pathway - TGF- β -activated protein kinase 1 (TAK1) is a member of the MAP3K family, which is a key regulator of MAP kinase activity (Yamaguchi et al., 1995). TAK1 can be activated by TLR3 or TLR4 signalling via the MyD88-independent pathway. Moreover, another MAP3K, MEKK3 could be activated via the MyD88-dependent pathway. TLR4 but not TLR9 signalling via MEKK3 induced the activation of JNK/P38 but not ERK, suggesting differential activation of MAPKs during TLR signalling (Huang et al., 2004).

Accumulating evidence shows that TLRs are involved in chronic pain determination, likely at the level of primary sensory neurons. Dorsal root ganglion (DRG) neurons are located at the first stop of the sensory pathway. Different types of pain seem to affect different subgroups of DRG neurons. TLRs are constitutively expressed in immune cells. However, TLR expression is also found in CNS and PNS - in microglia, astrocytes (Bsibsi et al., 2002) and sensory ganglia neurons (Wadachi and Hargreaves, 2006). In polyarthritis models induced by CFA injection (Djouhri and Lawson, 1999; Xu et al., 2000), only A δ neurons and C neurons were significantly altered in electrophysiological properties, with C neurons the more severely altered. In complete sciatic nerve transection model (Abdulla and Smith, 2001), partial sciatic nerve transection model (Liu and Eisenach, 2005), or lumbar spinal nerve transection models (Kim et al., 1998; Liu et al., 2000; Ma et al., 2003; Sapunar et al., 2005; Stebbing et al., 1999), changes in A type neurons were common, even in the large size

neurons. In some studies (Abdulla and Smith, 2001; Kim et al., 1998; Ma et al., 2003), changes in C neurons were also reported, but are less prominent than those in A neurons. Therefore, it seems that there are distinct changes in subgroups of DRG neurons in various chronic pain models resulted from different mechanisms, which can be regarded as pain manifestation at the neuronal level. Several TLRs have clearly established their correlation with hyperalgesia or allodynia. Compared with wild type mice, TLR2 knock-out mice showed reduced mechanical allodynia and thermal hyperalgesia after spinal nerve axotomy (Kim et al., 2007). Intrathecal administration of TLR3 antisense oligodeoxynucleotide (ODN) suppressed the spinal nerve ligation-induced tactile allodynia, whereas intrathecal injection of TLR3 agonist induced behavioural changes similar to the nerve-injury induced sensory hypersensitivity (Obata et al., 2008). TLR4 knock-out mice and the rats treated with TLR4 antisense ODN both showed significantly attenuated mechanical allodynia and thermal hyperalgesia in L5 spinal nerve transection (Tanga et al., 2005). TLR activation in microglia in spinal cord was proven to play a critical role in spinal nerve axotomy-induced sensory hypersensitivity (Kim et al., 2007; Tanga et al., 2005; Obata et al., 2008).

8. Conclusion

We propose a novel concept regarding the mechanism underlying the pain in OA induced by traumatic injuries. Following an initial trauma to the joint, two distinct yet interacting processes are initiated. One is neural injury of joint afferents and ensuing maladaptive changes of the nervous system, which results in pain in OA. The other is the cartilage degradation and bony changes in the joint, which generates characteristic pathology in OA. These two processes are likely initiated by damage-associated molecules produced during the initial joint injury, such as hyaluronan, fibronectin and proteoglycan aggrecan, mediated by pattern-recognition receptors like the TLRs. The TLR-dependent pathways lead to the activation of NF- κ B and downstream transcription factors to produce various inflammatory and destructive mediators and autoantibodies. Thus, various downstream pathways, such as the MMP-mediated, ADAMTS-mediated, MAPK-mediated, are activated to generate a spectrum of osteoarthritic changes, both functional (pain) and structural (deficit in cartilage and bone deformity). TLRs, maybe other pattern-recognition receptors, are at the intersection of OA pathology and pain.

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10. List of abbreviations

AP-1, Activator Protein-1; **CFA**, Complete Freund's Adjuvant; **CRP**, C-Reactive Protein; **DRG**, Dorsal Root Ganglion; **HMGB**, High-Mobility Group Protein; **IRF**, Interferon Regulatory Factor; **LPS**, Lipopolysaccharide; **MyD88**, Myeloid Differentiation Primary Response Gene 88; **OA**, Osteoarthritis; **ODN**, Oligodeoxynucleotide; **RA**, Rheumatoid Arthritis; **TAK1**, Transforming Growth Factor (TGF)- β -Activated Protein Kinase 1; **TIRAP**,

Toll-Interleukin 1 Receptor (TIR) Domain Containing Adaptor Protein; TLR, Toll-like Receptor ; VEGF, Vascular Endothelial Growth Factor

11. References

- [1] Abdollahi-Roodsaz S, Joosten LA, Koenders MI, Devesa I, Roelofs MF, Radstake TR, Heuvelmans-Jacobs M, Akira S, Nicklin MJ, Ribeiro-Dias F, van den Berg WB (2008) Stimulation of TLR2 and TLR4 differentially skews the balance of T cells in a mouse model of arthritis. *J Clin Invest* 118:205-216.
- [2] Abdulla FA, Smith PA (2001) Axotomy- and autotomy-induced changes in the excitability of rat dorsal root ganglion neurons. *J Neurophysiol* 85:630-643.
- [3] Aigner T, Kim HA (2002) Apoptosis and cellular vitality: issues in osteoarthritic cartilage degeneration. *Arthritis Rheum* 46:1986-1996.
- [4] Akira S, Takeda K (2004) Toll-like receptor signalling. *Nat Rev Immunol* 4:499-511.
- [5] Amos N, Lauder S, Evans A, Feldmann M, Bondeson J (2006) Adenoviral gene transfer into osteoarthritis synovial cells using the endogenous inhibitor IkappaBalpha reveals that most, but not all, inflammatory and destructive mediators are NFkappaB dependent. *Rheumatology (Oxford)* 45:1201-1209.
- [6] Ayral X, Pickering EH, Woodworth TG, Mackillop N, Dougados M (2005) Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis -- results of a 1 year longitudinal arthroscopic study in 422 patients. *Osteoarthritis Cartilage* 13:361-367.
- [7] Barton GM, Medzhitov R (2002) Toll-like receptors and their ligands. *Curr Top Microbiol Immunol* 270:81-92.
- [8] Beg AA (2002) Endogenous ligands of Toll-like receptors: implications for regulating inflammatory and immune responses. *Trends Immunol* 23:509-512.
- [9] Bettinger DA, Pellicane JV, Tarry WC, Yager DR, Diegelmann RF, Lee R, Cohen IK, DeMaria EJ (1994) The role of inflammatory cytokines in wound healing: accelerated healing in endotoxin-resistant mice. *J Trauma* 36:810-813.
- [10] Beutler B (2005) The Toll-like receptors: analysis by forward genetic methods. *Immunogenetics* 57:385-392.
- [11] Boivin A, Pineau I, Barrette B, Filali M, Vallieres N, Rivest S, Lacroix S (2007) Toll-like receptor signaling is critical for Wallerian degeneration and functional recovery after peripheral nerve injury. *J Neurosci* 27:12565-12576.
- [12] Bondeson J, Lauder S, Wainwright S, Amos N, Evans A, Hughes C, Feldmann M, Caterson B (2007) Adenoviral gene transfer of the endogenous inhibitor IkappaBalpha into human osteoarthritis synovial fibroblasts demonstrates that several matrix metalloproteinases and aggrecanases are nuclear factor-kappaB-dependent. *J Rheumatol* 34:523-533.
- [13] Brown MP, Trumble TN, Plaas AH, Sandy JD, Romano M, Hernandez J, Merritt KA (2007) Exercise and injury increase chondroitin sulfate chain length and decrease hyaluronan chain length in synovial fluid. *Osteoarthritis Cartilage* 15:1318-1325.
- [14] Bsibsi M, Ravid R, Gveric D, van Noort JM (2002) Broad expression of Toll-like receptors in the human central nervous system. *J Neuropathol Exp Neurol* 61:1013-1021.

- [15] Chacur M, Milligan ED, Gazda LS, Armstrong C, Wang H, Tracey KJ, Maier SF, Watkins LR (2001) A new model of sciatic inflammatory neuritis (SIN): induction of unilateral and bilateral mechanical allodynia following acute unilateral peri-sciatic immune activation in rats. *Pain* 94:231-244.
- [16] Chen LX, Lin L, Wang HJ, Wei XL, Fu X, Zhang JY, Yu CL (2008) Suppression of early experimental osteoarthritis by in vivo delivery of the adenoviral vector-mediated NF-kappaBp65-specific siRNA. *Osteoarthritis Cartilage* 16:174-184.
- [17] Chevalier X, Groult N, Hornebeck W (1996) Increased expression of the Ed-B-containing fibronectin (an embryonic isoform of fibronectin) in human osteoarthritic cartilage. *Br J Rheumatol* 35:407-415.
- [18] Cho ML, Ju JH, Kim HR, Oh HJ, Kang CM, Jhun JY, Lee SY, Park MK, Min JK, Park SH, Lee SH, Kim HY (2007) Toll-like receptor 2 ligand mediates the upregulation of angiogenic factor, vascular endothelial growth factor and interleukin-8/CXCL8 in human rheumatoid synovial fibroblasts. *Immunol Lett* 108:121-128.
- [19] Clatworthy AL, Illich PA, Castro GA, Walters ET (1995) Role of peri-axonal inflammation in the development of thermal hyperalgesia and guarding behavior in a rat model of neuropathic pain. *Neurosci Lett* 184:5-8.
- [20] Colombo B, Annovazzi PO, Comi G (2006) Medications for neuropathic pain: current trends. *Neurol Sci* 27 Suppl 2:S183-S189.
- [21] Creamer P (2000) Osteoarthritis pain and its treatment. *Curr Opin Rheumatol* 12:450-455.
- [22] Cunha FQ, Poole S, Lorenzetti BB, Ferreira SH (1992) The pivotal role of tumour necrosis factor alpha in the development of inflammatory hyperalgesia. *Br J Pharmacol* 107:660-664.
- [23] Dahl LB, Dahl IM, Engstrom-Laurent A, Granath K (1985) Concentration and molecular weight of sodium hyaluronate in synovial fluid from patients with rheumatoid arthritis and other arthropathies. *Ann Rheum Dis* 44:817-822.
- [24] Djouhri L, Lawson SN (1999) Changes in somatic action potential shape in guinea-pig nociceptive primary afferent neurones during inflammation in vivo. *J Physiol* 520:565-576.
- [25] Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, Kalso EA, Loeser JD, Miaskowski C, Nurmikko TJ, Portenoy RK, Rice AS, Stacey BR, Treede RD, Turk DC, Wallace MS (2007) Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain* 132:237-251.
- [26] Eliav E, Herzberg U, Ruda MA, Bennett GJ (1999) Neuropathic pain from an experimental neuritis of the rat sciatic nerve. *Pain* 83:169-182.
- [27] Felson DT, McAlindon TE, Anderson JJ, Naimark A, Weissman BW, Aliabadi P, Evans S, Levy D, LaValley MP (1997) Defining radiographic osteoarthritis for the whole knee. *Osteoarthritis Cartilage* 5:241-250.
- [28] Ferreira SH, Lorenzetti BB, Bristow AF, Poole S (1988) Interleukin-1 beta as a potent hyperalgesic agent antagonized by a tripeptide analogue. *Nature* 334:698-700.
- [29] Gondokaryono SP, Ushio H, Niyonsaba F, Hara M, Takenaka H, Jayawardana ST, Ikeda S, Okumura K, Ogawa H (2007) The extra domain A of fibronectin stimulates murine mast cells via toll-like receptor 4. *J Leukoc Biol* 82:657-665.
- [30] Gordon DB, Dahl JL (2004) Quality improvement challenges in pain management. *Pain* 107:1-4.

- [31] Guerassimov A, Zhang Y, Banerjee S, Cartman A, Webber C, Esdaile J, Fitzcharles MA, Poole AR (1998) Autoimmunity to cartilage link protein in patients with rheumatoid arthritis and ankylosing spondylitis. *J Rheumatol* 25:1480-1484.
- [32] Hanada T, Yoshimura A (2002) Regulation of cytokine signaling and inflammation. *Cytokine Growth Factor Rev* 13:413-421.
- [33] Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L, Suarez-Almazor M, Gooberman-Hill R (2008) Understanding the pain experience in hip and knee osteoarthritis--an OARSI/OMERACT initiative. *Osteoarthritis Cartilage* 16:415-422.
- [34] Hill CL, Hunter DJ, Niu J, Clancy M, Guermazi A, Genant H, Gale D, Grainger A, Conaghan P, Felson DT (2007) Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. *Ann Rheum Dis* 66:1599-1603.
- [35] Honda K, Yanai H, Mizutani T, Negishi H, Shimada N, Suzuki N, Ohba Y, Takaoka A, Yeh WC, Taniguchi T (2004) Role of a transductional-transcriptional processor complex involving MyD88 and IRF-7 in Toll-like receptor signaling. *Proc Natl Acad Sci U S A* 101:15416-15421.
- [36] Huang Q, Yang J, Lin Y, Walker C, Cheng J, Liu ZG, Su B (2004) Differential regulation of interleukin 1 receptor and Toll-like receptor signaling by MEKK3. *Nat Immunol* 5:98-103.
- [37] Hunter DJ, McDougall JJ, Keefe FJ (2008) The symptoms of osteoarthritis and the genesis of pain. *Rheum Dis Clin North Am* 34:623-643.
- [38] Ihle JN (1995) Cytokine receptor signalling. *Nature* 377:591-594.
- [39] Iwasaki A, Medzhitov R (2004) Toll-like receptor control of the adaptive immune responses. *Nat Immunol* 5:987-995.
- [40] Jackson AC, Rossiter JP, Lafon M (2006) Expression of Toll-like receptor 3 in the human cerebellar cortex in rabies, herpes simplex encephalitis, and other neurological diseases. *J Neurovirol* 12:229-234.
- [41] Jackson KC (2006) Pharmacotherapy for neuropathic pain. *Pain Pract* 6:27-33.
- [42] Jasin HE (1985) Autoantibody specificities of immune complexes sequestered in articular cartilage of patients with rheumatoid arthritis and osteoarthritis. *Arthritis Rheum* 28:241-248.
- [43] Ji RR, Suter MR (2007) p38 MAPK, microglial signaling, and neuropathic pain. *Mol Pain* 3:33.
- [44] Ji RR, Woolf CJ (2001) Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. *Neurobiol Dis* 8:1-10.
- [45] Johnson GB, Brunn GJ, Kodaira Y, Platt JL (2002) Receptor-mediated monitoring of tissue well-being via detection of soluble heparan sulfate by Toll-like receptor 4. *J Immunol* 168:5233-5239.
- [46] Kariko K, Ni H, Capodici J, Lamphier M, Weissman D (2004) mRNA is an endogenous ligand for Toll-like receptor 3. *J Biol Chem* 279:12542-12550.
- [47] Kato T, Xiang Y, Nakamura H, Nishioka K (2004) Neoantigens in osteoarthritic cartilage. *Curr Opin Rheumatol* 16:604-608.
- [48] Kawai T, Akira S (2005) Toll-like receptor downstream signaling. *Arthritis Res Ther* 7:12-19.

- [49] Kerns RD, Kassirer M, Otis J (2002) Pain in multiple sclerosis: a biopsychosocial perspective. *J Rehabil Res Dev* 39:225-232.
- [50] Kidd BL (2006) Osteoarthritis and joint pain. *Pain* 123:6-9.
- [51] Kim D, Kim MA, Cho IH, Kim MS, Lee S, Jo EK, Choi SY, Park K, Kim JS, Akira S, Na HS, Oh SB, Lee SJ (2007) A critical role of toll-like receptor 2 in nerve injury-induced spinal cord glial cell activation and pain hypersensitivity. *J Biol Chem* 282:14975-14983.
- [52] Kim HA, Cho ML, Choi HY, Yoon CS, Jhun JY, Oh HJ, Kim HY (2006) The catabolic pathway mediated by Toll-like receptors in human osteoarthritic chondrocytes. *Arthritis Rheum* 54:2152-2163.
- [53] Kim YI, Na HS, Kim SH, Han HC, Yoon YW, Sung B, Nam HJ, Shin SL, Hong SK (1998) Cell type-specific changes of the membrane properties of peripherally-axotomized dorsal root ganglion neurons in a rat model of neuropathic pain. *Neuroscience* 86:301-309.
- [54] Kokkola R, Sundberg E, Ulfgren AK, Palmblad K, Li J, Wang H, Ulloa L, Yang H, Yan XJ, Furie R, Chiorazzi N, Tracey KJ, Andersson U, Harris HE (2002) High mobility group box chromosomal protein 1: a novel proinflammatory mediator in synovitis. *Arthritis Rheum* 46:2598-2603.
- [55] Kyburz D, Rethage J, Seibl R, Lauener R, Gay RE, Carson DA, Gay S (2003) Bacterial peptidoglycans but not CpG oligodeoxynucleotides activate synovial fibroblasts by toll-like receptor signaling. *Arthritis Rheum* 48:642-650.
- [56] Lasarte JJ, Casares N, Gorraiz M, Hervás-Stubbs S, Arribillaga L, Mansilla C, Durantez M, Llopiz D, Sarobe P, Borrás-Cuesta F, Prieto J, Leclerc C (2007) The extra domain A from fibronectin targets antigens to TLR4-expressing cells and induces cytotoxic T cell responses in vivo. *J Immunol* 178:748-756.
- [57] Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, Heyse SP, Hirsch R, Hochberg MC, Hunder GG, Liang MH, Pillemer SR, Steen VD, Wolfe F (1998) Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 41:778-799.
- [58] Leadbetter EA, Rifkin IR, Hohlbaum AM, Beaudette BC, Shlomchik MJ, Marshak-Rothstein A (2002) Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. *Nature* 416:603-607.
- [59] Levy RM, Prince JM, Yang R, Mollen KP, Liao H, Watson GA, Fink MP, Vodovotz Y, Billiar TR (2006) Systemic inflammation and remote organ damage following bilateral femur fracture requires Toll-like receptor 4. *Am J Physiol Regul Integr Comp Physiol* 291:R970-R976.
- [60] Li L, Xian CJ, Zhong JH, Zhou XF (2002) Effect of lumbar 5 ventral root transection on pain behaviors: a novel rat model for neuropathic pain without axotomy of primary sensory neurons. *Exp Neurol* 175:23-34.
- [61] Liu B, Eisenach JC (2005) Hyperexcitability of axotomized and neighboring unaxotomized sensory neurons is reduced days after perineural clonidine at the site of injury. *J Neurophysiol* 94:3159-3167.
- [62] Liu CN, Wall PD, Ben-Dor E, Michaelis M, Amir R, Devor M (2000) Tactile allodynia in the absence of C-fiber activation: altered firing properties of DRG neurons following spinal nerve injury. *Pain* 85:503-521.

- [63] Lohmander LS, Neame PJ, Sandy JD (1993) The structure of aggrecan fragments in human synovial fluid. Evidence that aggrecanase mediates cartilage degradation in inflammatory joint disease, joint injury, and osteoarthritis. *Arthritis Rheum* 36:1214-1222.
- [64] Ma C, Shu Y, Zheng Z, Chen Y, Yao H, Greenquist KW, White FA, LaMotte RH (2003) Similar electrophysiological changes in axotomized and neighboring intact dorsal root ganglion neurons. *J Neurophysiol* 89:1588-1602.
- [65] Ma W, Quirion R (2005) The ERK/MAPK pathway, as a target for the treatment of neuropathic pain. *Expert Opin Ther Targets* 9:699-713.
- [66] Marcinkiewicz M (2002) BetaAPP and furin mRNA concentrates in immature senile plaques in the brain of Alzheimer patients. *J Neuropathol Exp Neurol* 61:815-829.
- [67] Matsumura T, Degawa T, Takii T, Hayashi H, Okamoto T, Inoue J, Onozaki K (2003) TRAF6-NF-kappaB pathway is essential for interleukin-1-induced TLR2 expression and its functional response to TLR2 ligand in murine hepatocytes. *Immunology* 109:127-136.
- [68] Maves TJ, Pechman PS, Gebhart GF, Meller ST (1993) Possible chemical contribution from chronic gut sutures produces disorders of pain sensation like those seen in man. *Pain* 54:57-69.
- [69] McDougall JJ (2006) Pain and OA. *J Musculoskelet Neuronal Interact* 6:385-386.
- [70] Merlotti D, Santacroce C, Gennari L, Geraci S, Acquafredda V, Conti T, Bargagli G, Canto ND, Biagi F, Gennari C, Giordano N (2003) HLA antigens and primary osteoarthritis of the hand. *J Rheumatol* 30:1298-1304.
- [71] Moalem G, Grafe P, Tracey DJ (2005) Chemical mediators enhance the excitability of unmyelinated sensory axons in normal and injured peripheral nerve of the rat. *Neuroscience* 134:1399-1411.
- [72] Mollen KP, Anand RJ, Tsung A, Prince JM, Levy RM, Billiar TR (2006) Emerging paradigm: toll-like receptor 4-sentinel for the detection of tissue damage. *Shock* 26:430-437.
- [73] Moulin DE, Hagen N, Feasby TE, Amireh R, Hahn A (1997) Pain in Guillain-Barre syndrome. *Neurology* 48:328-331.
- [74] Nguyen MD, Julien JP, Rivest S (2002) Innate immunity: the missing link in neuroprotection and neurodegeneration? *Nat Rev Neurosci* 3:216-227.
- [75] Niebauer GW, Wolf B, Bashey RI, Newton CD (1987) Antibodies to canine collagen types I and II in dogs with spontaneous cruciate ligament rupture and osteoarthritis. *Arthritis Rheum* 30:319-327.
- [76] Obata K, Katsura H, Miyoshi K, Kondo T, Yamanaka H, Kobayashi K, Dai Y, Fukuoka T, Akira S, Noguchi K (2008) Toll-like receptor 3 contributes to spinal glial activation and tactile allodynia after nerve injury. *J Neurochem*.
- [77] Obata K, Noguchi K (2004) MAPK activation in nociceptive neurons and pain hypersensitivity. *Life Sci* 74:2643-2653.
- [78] Ohashi K, Burkart V, Flohe S, Kolb H (2000) Cutting edge: heat shock protein 60 is a putative endogenous ligand of the toll-like receptor-4 complex. *J Immunol* 164:558-561.
- [79] Ojaniemi M, Liljeroos M, Harju K, Sormunen R, Vuolteenaho R, Hallman M (2006) TLR-2 is upregulated and mobilized to the hepatocyte plasma membrane in the space of

- Disse and to the Kupffer cells TLR-4 dependently during acute endotoxemia in mice. *Immunol Lett* 102:158-168.
- [80] Okamura Y, Watari M, Jerud ES, Young DW, Ishizaka ST, Rose J, Chow JC, Strauss JF, III (2001) The extra domain A of fibronectin activates Toll-like receptor 4. *J Biol Chem* 276:10229-10233.
- [81] Omoigui S (2007b) The biochemical origin of pain: the origin of all pain is inflammation and the inflammatory response. Part 2 of 3 - inflammatory profile of pain syndromes. *Med Hypotheses* 69:1169-1178.
- [82] Omoigui S (2007a) The biochemical origin of pain--proposing a new law of pain: the origin of all pain is inflammation and the inflammatory response. Part 1 of 3--a unifying law of pain. *Med Hypotheses* 69:70-82.
- [83] Osborne AC, Carter SD, May SA, Bennett D (1995) Anti-collagen antibodies and immune complexes in equine joint diseases. *Vet Immunol Immunopathol* 45:19-30.
- [84] Ozawa T, Koyama K, Ando T, Ohnuma Y, Hatsushika K, Ohba T, Sugiyama H, Hamada Y, Ogawa H, Okumura K, Nakao A (2007) Thymic stromal lymphopoietin secretion of synovial fibroblasts is positively and negatively regulated by Toll-like receptors/nuclear factor-kappaB pathway and interferon-gamma/dexamethasone. *Mod Rheumatol* 17:459-463.
- [86] Park JS, Svetkauskaite D, He Q, Kim JY, Strassheim D, Ishizaka A, Abraham E (2004) Involvement of toll-like receptors 2 and 4 in cellular activation by high mobility group box 1 protein. *J Biol Chem* 279:7370-7377.
- [87] Pasare C, Medzhitov R (2005) Control of B-cell responses by Toll-like receptors. *Nature* 438:364-368.
- [88] Pearle AD, Scanzello CR, George S, Mandl LA, DiCarlo EF, Peterson M, Sculco TP, Crow MK (2007) Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. *Osteoarthritis Cartilage* 15:516-523.
- [89] Pentland B, Donald SM (1994) Pain in the Guillain-Barre syndrome: a clinical review. *Pain* 59:159-164.
- [90] Poole AR (1999) An introduction to the pathophysiology of osteoarthritis. *Front Biosci* 4:D662-D670.
- [91] Prince JM, Levy RM, Yang R, Mollen KP, Fink MP, Vodovotz Y, Billiar TR (2006) Toll-like receptor-4 signaling mediates hepatic injury and systemic inflammation in hemorrhagic shock. *J Am Coll Surg* 202:407-417.
- [92] Radstake TR, Roelofs MF, Jenniskens YM, Oppers-Walgreen B, van Riel PL, Barrera P, Joosten LA, van den Berg WB (2004) Expression of toll-like receptors 2 and 4 in rheumatoid synovial tissue and regulation by proinflammatory cytokines interleukin-12 and interleukin-18 via interferon-gamma. *Arthritis Rheum* 50:3856-3865.
- [93] Rice AS, Hill RG (2006) New treatments for neuropathic pain. *Annu Rev Med* 57:535-551.
- [94] Riyazi N, Spee J, Huizinga TW, Schreuder GM, de Vries RR, Dekker FW, Kloppenburg M (2003) HLA class II is associated with distal interphalangeal osteoarthritis. *Ann Rheum Dis* 62:227-230.
- [95] Rothschild BM, Martin LD. *Skeletal Impact of Disease*. Albuquerque: New Mexico Museum of Natural History Press, 2006.

- [96] Saito I, Koshino T, Nakashima K, Uesugi M, Saito T (2002) Increased cellular infiltrate in inflammatory synovia of osteoarthritic knees. *Osteoarthritis Cartilage* 10:156-162.
- [97] Sakaguchi S, Negishi H, Asagiri M, Nakajima C, Mizutani T, Takaoka A, Honda K, Taniguchi T (2003) Essential role of IRF-3 in lipopolysaccharide-induced interferon-beta gene expression and endotoxin shock. *Biochem Biophys Res Commun* 306:860-866.
- [98] Sakata M, Tsuruha JI, Masuko-Hongo K, Nakamura H, Matsui T, Sudo A, Nishioka K, Kato T (2001) Autoantibodies to osteopontin in patients with osteoarthritis and rheumatoid arthritis. *J Rheumatol* 28:1492-1495.
- [99] Sapunar D, Ljubkovic M, Lirk P, McCallum JB, Hogan QH (2005) Distinct membrane effects of spinal nerve ligation on injured and adjacent dorsal root ganglion neurons in rats. *Anesthesiology* 103:360-376.
- [100] Saxne T, Lindell M, Mansson B, Petersson IF, Heinegard D (2003a) Inflammation is a feature of the disease process in early knee joint osteoarthritis. *Rheumatology (Oxford)* 42:903-904.
- [101] Saxne T, Lindell M, Mansson B, Petersson IF, Heinegard D (2003b) Inflammation is a feature of the disease process in early knee joint osteoarthritis. *Rheumatology (Oxford)* 42:903-904.
- [102] Scanzello CR, Plaas A, Crow MK (2008) Innate immune system activation in osteoarthritis: is osteoarthritis a chronic wound? *Curr Opin Rheumatol* 20:565-572.
- [103] Schafers M, Brinkhoff J, Neukirchen S, Marziniak M, Sommer C (2001) Combined epineurial therapy with neutralizing antibodies to tumor necrosis factor-alpha and interleukin-1 receptor has an additive effect in reducing neuropathic pain in mice. *Neurosci Lett* 310:113-116.
- [104] Sheth RN, Dorsi MJ, Li Y, Murinson BB, Belzberg AJ, Griffin JW, Meyer RA (2002) Mechanical hyperalgesia after an L5 ventral rhizotomy or an L5 ganglionectomy in the rat. *Pain* 96:63-72.
- [105] Smiley ST, King JA, Hancock WW (2001) Fibrinogen stimulates macrophage chemokine secretion through toll-like receptor 4. *J Immunol* 167:2887-2894.
- [106] Sommer C, Petrusch S, Lindenlaub T, Toyka KV (1999) Neutralizing antibodies to interleukin 1-receptor reduce pain associated behavior in mice with experimental neuropathy. *Neurosci Lett* 270:25-28.
- [107] Song RH, Tortorella MD, Malfait AM, Alston JT, Yang Z, Arner EC, Griggs DW (2007) Aggrecan degradation in human articular cartilage explants is mediated by both ADAMTS-4 and ADAMTS-5. *Arthritis Rheum* 56:575-585.
- [108] Sowers M, Jannausch M, Stein E, Jamadar D, Hochberg M, Lachance L (2002) C-reactive protein as a biomarker of emergent osteoarthritis. *Osteoarthritis Cartilage* 10:595-601.
- [109] Stark GR, Kerr IM, Williams BR, Silverman RH, Schreiber RD (1998) How cells respond to interferons. *Annu Rev Biochem* 67:227-264.
- [110] Stebbing MJ, Eschenfelder S, Habler HJ, Acosta MC, Janig W, McLachlan EM (1999) Changes in the action potential in sensory neurones after peripheral axotomy in vivo. *Neuroreport* 10:201-206.

- [111] Swagerty DL, Jr., Hellinger D (2001) Radiographic assessment of osteoarthritis. *Am Fam Physician* 64:279-286.
- [112] Takaoka A, Yanai H (2006) Interferon signalling network in innate defence. *Cell Microbiol* 8:907-922.
- [113] Tanga FY, Natile-McMenemy N, DeLeo JA (2005) The CNS role of Toll-like receptor 4 in innate neuroimmunity and painful neuropathy. *Proc Natl Acad Sci U S A* 102:5856-5861.
- [114] Taniguchi N, Kawahara K, Yone K, Hashiguchi T, Yamakuchi M, Goto M, Inoue K, Yamada S, Ijiri K, Matsunaga S, Nakajima T, Komiya S, Maruyama I (2003) High mobility group box chromosomal protein 1 plays a role in the pathogenesis of rheumatoid arthritis as a novel cytokine. *Arthritis Rheum* 48:971-981.
- [115] Taylor KR, Trowbridge JM, Rudisill JA, Termeer CC, Simon JC, Gallo RL (2004a) Hyaluronan fragments stimulate endothelial recognition of injury through TLR4. *J Biol Chem* 279:17079-17084.
- [116] Taylor KR, Trowbridge JM, Rudisill JA, Termeer CC, Simon JC, Gallo RL (2004b) Hyaluronan fragments stimulate endothelial recognition of injury through TLR4. *J Biol Chem* 279:17079-17084.
- [117] Taylor KR, Yamasaki K, Radek KA, Di NA, Goodarzi H, Golenbock D, Beutler B, Gallo RL (2007) Recognition of hyaluronan released in sterile injury involves a unique receptor complex dependent on Toll-like receptor 4, CD44, and MD-2. *J Biol Chem* 282:18265-18275.
- [118] Termeer C, Benedix F, Sleeman J, Fieber C, Voith U, Ahrens T, Miyake K, Freudenberg M, Galanos C, Simon JC (2002) Oligosaccharides of Hyaluronan activate dendritic cells via toll-like receptor 4. *J Exp Med* 195:99-111.
- [119] Tsuruha J, Masuko-Hongo K, Kato T, Sakata M, Nakamura H, Nishioka K (2001) Implication of cartilage intermediate layer protein in cartilage destruction in subsets of patients with osteoarthritis and rheumatoid arthritis. *Arthritis Rheum* 44:838-845.
- [120] Tsuruha J, Masuko-Hongo K, Kato T, Sakata M, Nakamura H, Sekine T, Takigawa M, Nishioka K (2002) Autoimmunity against YKL-39, a human cartilage derived protein, in patients with osteoarthritis. *J Rheumatol* 29:1459-1466.
- [121] van Beijnum JR, Buurman WA, Griffioen AW (2008) Convergence and amplification of toll-like receptor (TLR) and receptor for advanced glycation end products (RAGE) signaling pathways via high mobility group B1 (HMGB1). *Angiogenesis* 11:91-99.
- [122] Wadachi R, Hargreaves KM (2006) Trigeminal nociceptors express TLR-4 and CD14: a mechanism for pain due to infection. *J Dent Res* 85:49-53.
- [123] Wakitani S, Imoto K, Mazuka T, Kim S, Murata N, Yoneda M (2001) Japanese generalised osteoarthritis was associated with HLA class I--a study of HLA-A, B, Cw, DQ, DR in 72 patients. *Clin Rheumatol* 20:417-419.
- [124] Walsh DA, Bonnet CS, Turner EL, Wilson D, Situ M, McWilliams DF (2007) Angiogenesis in the synovium and at the osteochondral junction in osteoarthritis. *Osteoarthritis Cartilage* 15:743-751.
- [125] Wu Q, Henry JL (2010) Changes in A β non-nociceptive primary sensory neurons in a rat model of osteoarthritis pain. *Mol Pain* 6:37.

- [126] Xu GY, Huang LY, Zhao ZQ (2000) Activation of silent mechanoreceptive cat C and Adelta sensory neurons and their substance P expression following peripheral inflammation. *J Physiol* 528:339-348.
- [127] Yamaguchi K, Shirakabe K, Shibuya H, Irie K, Oishi I, Ueno N, Taniguchi T, Nishida E, Matsumoto K (1995) Identification of a member of the MAPKKK family as a potential mediator of TGF-beta signal transduction. *Science* 270:2008-2011.
- [128] Yelin E, Callahan LF (1995) The economic cost and social and psychological impact of musculoskeletal conditions. National Arthritis Data Work Groups. *Arthritis Rheum* 38:1351-1362.
- [129] Yoshihara Y, Nakamura H, Obata K, Yamada H, Hayakawa T, Fujikawa K, Okada Y (2000) Matrix metalloproteinases and tissue inhibitors of metalloproteinases in synovial fluids from patients with rheumatoid arthritis or osteoarthritis. *Ann Rheum Dis* 59:455-461.
- [130] Yu M, Wang H, Ding A, Golenbock DT, Latz E, Czura CJ, Fenton MJ, Tracey KJ, Yang H (2006) HMGB1 signals through toll-like receptor (TLR) 4 and TLR2. *Shock* 26:174-179.

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This volume addresses the nature of the most common form of arthritis in humans. If osteoarthritis is inevitable (only premature death prevents all of us from being afflicted), it seems essential to facilitate its recognition, prevention, options, and indications for treatment. Progress in understanding this disease has occurred with recognition that it is not simply a degenerative joint disease. Causative factors, such as joint malalignment, ligamentous abnormalities, overuse, and biomechanical and metabolic factors have been recognized as amenable to intervention; genetic factors, less so; with metabolic diseases, intermediate. Its diagnosis is based on recognition of overgrowth of bone at joint margins. This contrasts with overgrowth of bone at vertebral margins, which is not a symptomatic phenomenon and has been renamed spondylosis deformans. Osteoarthritis describes an abnormality of joints, but the severity does not necessarily produce pain. The patient and his/her symptoms need to be treated, not the x-ray.

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