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Invited Review

Therapeutic implications of toll-like receptors in peripheral neuropathic pain

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ABSTRACT

Neuropathic pain is a state of chronic pain arising after peripheral or central nerve injury. These injuries can be mediated through the activation of various cells (astrocytes, microglia and Schwann cells), as well as the dissolution of distal axons. Recent studies have suggested that after nerve injury, Toll-like receptors (TLRs) involved in Wallerian degeneration and generation of neuropathic pain. Furthermore, these TLRs are responsible for the stimulation of astrocytes and microglia that can cause induction of the proinflammatory mediators and cytokines in the spinal cord, thereby leading to the generation and maintenance of neuropathic pain. Indeed considering the prevalence of neuropathic pain and suffering of the affected patients, insights into the diverse mechanism(s) of activation of TLR signaling cascades may open novel avenues for the management of this chronic condition. Moreover, existing therapies like antidepressants, anticonvulsants, opiates and other analgesic are not sufficiently effective in reducing the pain. In this review, we present substantial evidences highlighting the diverse roles of TLRs and their signaling pathways involved in the progression of neuropathic pain. Furthermore, an elaborate discussion on various existing treatment regimens and future targets involving TLRs has also been included.

Contents

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1. Introduction

Neuropathic pain may be defined as the pain arising after peripheral or central nerve injury/dysfunction in the nervous system, which can significantly worsen the quality of life [1–4]. These injuries can be due to systemic diseases like cancer, trauma (phantom limb, spinal cord injury), ischaemic injury (central pain, painful diabetic neuropathic pain), infection/inflammation (HIV, postherpetic neuralgia), neurotoxic chemicals, alcoholism, trigeminal neuralgia, and involve complex pathophysiological changes in peripheral nervous system (PNS) as well in central nervous system (CNS) [5–12]. The major symptoms of neuropathic pain include unexplainable widespread pain, acute pain without noxious stimuli, pain caused by light touch (allodynia), as well as an increased response to mechanical and thermal stimuli (hyperalgesia), an unusual sense of touch (dysaesthesia), a sensation of pricking (paresthesia) and spontaneous burning sensation [1,10,13,14]. The mechanical damage of the nerve stimulates immune cells, inflammation and ischemia, which are responsible for the nerve fibers injury and can lead to the neuropathic pain. Moreover, oxidative stress appears to play a vital job in the pathogenesis of pain. This results into two consequences, as an excessive production of free radicals (due to oxygen reduction) and an ischemia that can decrease the delivery of nutrients to the nerve cells with necrosis of Schwann cells [15]. The proposed mechanism for this pain is central sensitization which is often caused by increased inflammatory/pain-inducing mediator expression by the activated glial cells [7,16]. The activated microglia emerges in the early stage, whereas activated astrocytes appear later and remain functional longer than the activated microglia [17]. The activated Schwann cells secrete various inflammatory mediators such as proinflammatory cytokines (IL-1β, IL-6, IL-17, IL10, IL-15, IL-18, TNF-α, TGF-β and IFN-γ), chemokines, and inducible nitric oxide synthase (iNOS) [10,18–21].

Recent studies have shown that stimulation of Schwann cell leads to the expression of Toll-like receptors (TLRs) [13,18,22]. TLRs, originally discovered in *Drosophila melanogaster* have been found to be associated with development of embryonic dorsal-ventral pattern [8,23–25]. Later it was revealed that TLRs can induce innate immune response by recognizing various pathogen-associated molecular patterns (PAMPs) and the receptors that recognize these molecular structures were named as pattern recognition receptors (PRRs) [20,26]. Overall 14 TLRs have been identified till now which are involved in innate immunity, while ligands for few of these receptors still remain to be identified. TLRs are also expressed in the CNS cells, and being coupled with the activation of various non-neuronal cells (microglia, Schwann cells, oligodendrocytes, and astrocytes) and neurons, thus causing the release of pro-inflammatory cytokines [1,2,13,18,24,27–32].

Till now there is no promising therapy available for the treatment of neuropathic pain. Current regimens for treatment includes the use of tricyclic antidepressants, ion channel modulating drugs (gabapentin, pregabalin, carbamazepine, lidocaine), and certain anticonvulsants, which concentrate on reducing the symptoms, but often lack desired efficacy and produce undesirable side effects [2,12,33]. Opioids and other analgesics are generally considered to be less efficient in neuropathic pain [3,12]. Hence, it is necessary to understand the pathogenesis of neuropathic pain for better diagnosis and more efficient targeted treatment than the existing ones. The possible involvement of the glial cells and immune cells in the development and maintenance of neuropathic pain following nerve injury have provided new insights to the disease modifying therapeutic targets rather than previous attempts aimed at just reducing the symptoms [33]. In this review, pivotal role of different TLRs and signaling pathways through which they contribute to the progression and maintenance of neuropathic pain has been briefly discussed. The possible therapies and natural compounds, which are currently in different phases of clinical trials for neuropathic pain, have been also highlighted.

2. TLRs expression in neuropathic pain

Tanga et al. first demonstrated a preclinical model of neuropathic pain for the verification of the role of TLRs. It was found that TLR4 mRNA can be up-regulated in spinal cord cells upon lumber 5 (L5) nerve transactions in rats [34,35]. Later, they observed that TLR4 expression was essential for nerve injury induced thermal hypersensitivity and spinal cord glial activation [36]. The same group demonstrated that TLR4 knockout mouse model exhibited significantly reduced pain. This study advocates that TLR4 may lead to microglia activation after nerve damage [11]. Numerous findings have also demonstrated that TLR4 is important for the development and maintenance of neuropathic pain [11,37,38]. Moreover, DeLeo et al. established TLR4 dependent nerve injury model in which the lipopolysaccharides (LPS)-TLR4 signaling pathway as well as accessory molecule cluster of differentiation 14 (CD14) protein, generally act in conjunction to contribute to the neuropathic pain [39,40]. Following early findings related to the pivotal function of TLR4, TLRs association in preclinical neuropathic pain models have now also been investigated in relation to the extracellular (TLR2) [27,41] and intracellular (TLR3) in neuropathic pain [42]. Kim et al. demonstrated that nerve injury induced thermal hyperalgesia and mechanical allodynia were decreased in TLR2 knockout mice as compared to wild-type mice, which specify that damaged sensory neurons activate glial cells through TLR2 [27]. Apart from TLR2, TLR3, and TLR4, astrocytes and microglia also express TLR7 and TLR9, which are present intracellularly [34]. Lee et al. demonstrated the expression of TLRs in rats Schwann cells, and found that TLR2, 3 and 4 are largely expressed at the mRNA and protein levels [20]. In addition, studies have reported that a few TLRs are also expressed in sensory and cortical neurons [11]. Moreover, recent findings have also demonstrated that mouse dorsal root ganglion (DRG) neurons express numerous TLRs (TLR1–, 9). Several TLRs which are expressed and activated in microglia, DRG, and astrocytes neurons are summarized in Table 1. Furthermore, this table also depicts that numerus ligands that have been found to activate certain TLRs in these specific cell types and their exact locations [34]. Several TLRs (TLR 2–, 5, 7, and 9) are expressed and activated in glial cells [43]. TLR2 recognizes a broad array of PAMPs resulting from a variety of pathogens, ranging from fungi, bacteria, viruses, and parasites. These ligands include zymosan (fungi), triacylated lipoproteins ((Ac3LP) bacteria and mycobacteria), diacyl lipoproteins (mycoplasma), and hemagglutinin protein (measles virus). In addition, it recognizes HMGB1 and HSPs (HSP60, HSP70). After recognition, these endogenous ligands stimulated generation of monocyte chemotactic protein-1 (MCP-1), reactive oxygen species (ROS), IL-8 or chemokine (C-X-C motif) ligand 8 (CXCL8), nitric oxide (NO), interleukin (IL) 6, and IL-12p40 by astrocytes, and tumor necrosis factor-alpha (TNF-α), IL-1β, NO, iNOS, CXCL2, chemokine (C-C motif) ligand 2 (CCL2), and cyclooxygenase (COX)-2 by microglia [26,34,43–48]. TLR3 recognizes a polyinosinic-polycytidylic acid (poly IC), double-stranded (ds) RNA viruses such as reovirus and respiratory syncytial virus (RSV), encephalomyocarditis virus (EMCV) and murine cytomegalovirus (MCMV). These ligands stimulate generation of MCP-1, NO, TNF-α, IL-6, CCL3, ROS, IL-1α, IL-1β by astrocytes, IL-1β, IL-6, NO, TNF-α, IL-12 by microglia, prostaglandin E2 (PGE2), IL-1α, IL-1β, CXCL10, regulated on activation normal T cell expressed and secreted (RANTES) by DRG [26,43,49–51]. LPS, hyaluronate, envprost, F-prost, vesicular stomatitis virus (VSV), heparin, and taxol can also activate TLR4. Upon activation, these ligands trigger production of