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Mini-Review

Neuropathic Pain: MIRNA-547-5p-Mediated IL-33/ST2 Signaling and Bone Marrow Stromal Cell Therapy

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ABSTRACT

We have recently identified that the depression of MicroRNA (miRNA)-547-5p, which can be induced by a Chronic Constriction Nerve Injury (CCI), is an upstream event causing the enhancement of interleukin-33 (IL-33)/ Suppressor Tumorigenicity 2 (ST2) signaling and leading to pain hypersensitivity in rats. Moreover, the application of Bone Marrow Stromal Cells (BMSCs) reduces CCI-induced pain hypersensitivity by blocking the depression of miRNA-547-5p or its downstream molecules IL-33 and ST2. The roles of the miRNA-547-5p/IL-33/ST2 signaling pathway in the genesis of neuropathic pain and the analgesic effects of treatment with BMSCs are further discussed in this mini-review.

Keywords: MicroRNA; IL-33/ST2; Neuropathic pain; Stem cells; Bone marrow; Stromal cells

INTRODUCTION

Despite extensive research starting over a century ago and including a growing number of recent studies revealing novel molecular mechanisms underlying neuropathic pain, the understanding of the initiation, development, and treatment of neuropathic pain has remained a challenge for both scientists and clinicians [1]. A key question that remains unclear is how pain hypersensitivity associated with nerve injury is induced. Recent studies have shown that following nerve injury, the release of cytokines may be activated in glial cells [2-4]. Interleukin-33 (IL-33) is an interleukin-1-like cytokine that signals via the protein, Suppressor Tumorigenicity 2 (ST2) [5,6]. Multiple downstream mechanisms regulated by IL-33/ST2 signaling and involved in the development of inflammation and chronic pain have been found. For example, IL-33 may induce the proliferation of microglia and enhance the production of cytokines such as interleukin-1β and tumor necrosis factor-α (TNFα) [7]. Furthermore, IL-33/ST2 signaling promotes inflammation via the Extracellular Regulated Kinase (ERK), p38 MAPK, c-Jun N-terminal Kinase (JNK), and Nuclear Factor-kappa B (NF-κB) and is also involved in the induction and maintainers of neuropathic pain via neuronal CaMKII/CREB, NMDA receptors, and astroglial JAK2-STAT3 cascades [5-11]. We recently have investigated the potential upstream mechanism(s) which may enhance IL-33/ST2 signaling in a rodent model of neuropathic pain induced by a Chronic Constriction Nerve Injury (CCI) as well as the possible therapeutic effect of administration of Bone Marrow Stromal Cells (BMSCs).

LITERATURE REVIEW

Resistant and provocative reactions happening in the spinal line assume a vital part in the movement of radicular torment brought about by intervertebral circle herniation. IL-33 arranges fiery reactions in a wide scope of provocative and immune system problems of the sensory system. Along these lines, the motivation behind this review is to explore the outflow of IL-33 and its receptor ST2 in the dorsal spinal rope and to clarify whether the hindrance of spinal IL-33 articulation fundamentally constricts torment related practices in rodent models of noncompressive lumbar plate herniation. The application of Nucleus Pulposus (NP) to the Dorsal Root Ganglion (DRG) induced an increase in IL-33 and ST2 expression in the spinal cord, mainly in the dorsal horn neurons, astrocytes, and oligodendrocytes. Spinally delivered LV-shIL-33 knocked down the expression of IL-33 and markedly attenuated mechanical allodynia. In addition, spinal administration of LV-shIL-33 reduced the overexpression of spina, and COX-2 and attenuated the activation of JNK and ERK. Significant barricade in understanding the capacity of ST2

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was the absence of a useful endogenous ligand. Notwithstanding, in 2005, a β-trefoil overlap protein grouping inferred by superposition of IL-1 and Fibroblast Development Factor (FGF) protein structures was utilized to mine the public genomic information base, which lead to the revelation of a clever individual from the family.

The mouse and human arrangements of this competitor quality were reasoned by communicated grouping label arrangement, which planned to human chromosome and mouse chromosome. By succession investigation, the protein was found to contain a favorable to space with a full-length mass determined and interpretation of this protein and treatment with. This protein, which was named IL-33 (otherwise called IL-1F11), has now been delegated an individual from the IL-1 interleukin family, whose individuals are described by a variety of 12 β-strands and the shortfall of an old style secretory N-end peptide arrangement. Curiously, the IL-33 protein had recently been segregated in a quest for the ST2 ligand, where Kumar and associates distinguished two proteins created by peaceful 3T3 cells that were accelerated by a ST2-Fc combination protein. Antibodies raised against this peptide arrangement accelerated a 30 kD protein37. The arrangement of this protein was subsequently affirmed to be indistinguishable from that recognized by computational techniques in 2005 by Schmitz and associates.

DISCUSSION

MIRNA-547-5p depression is an upstream event causing the enhancement of IL-33/ST2 signaling in CCI animals

Previous studies have shown that IL-33/ST2 signaling can be regulated by miRNAs. For example, an increase in miRNA-487b inhibits the expressions of both IL-33 and ST2 and enhances heart function [12]. By using the TargetScan (http://www.targetscan.org/) [13]. We found that miRNA-547-5p is paired with the RNAs by binding the 3' Untranslated Regions (UTRs) of both IL-33 and ST2. Furthermore, miRNA-547-5p may directly bind to the DNAs of IL-33 and ST2 and regulate their expressions in HEK293T cells [14]. More importantly, we found that the expressions of miRNA-547-5p in both the DRG and Spinal Dorsal Horn (SDH) between the Lumbar 4 (L4) and L6 ipsilateral to the site of CCI on the common peroneal and tibial nerves are significantly reduced [14].

Immunohistochemical studies have shown that IL-33 is mainly localized in glial cells [7,10,14] in both the DRG and SDH while ST2 is found mainly in neurons in the DRG and in both neurons and glial cells in the SDH [14]. Following CCI the expressions of IL-33 and ST2 RNAs and proteins in the ipsilateral DRG and SDH are significantly increased [4,6,7,10,11,14].

Intrathecal (i.t.) infusion of the agomir or antagomir of miRNA-547-5p (20 μM, once daily for consecutive 4 days) into the region between the L4 and L6 of the spinal cord may significantly increase or decrease the expression of miRNA-547-5p in both the DRG and SDH [14]. Although the i.t. application of agomir-547-5p into naïve rats with no CCI produces no change in the expression of IL-33 and ST2 in the DRG and SDH, the agomir application does block the increases in the expressions of IL-33 and ST2 induced by CCI and also diminishes pain hypersensitivity in CCI animals as reflected in significant reductions of their Mechanical Withdraw Threshold (MWT) and Thermal Withdraw Latency (TWL) associated with hindpaw mechanical and heat stimulations. No effect on the MWT and TWL is produced by the agomir application in naïve animals [14].

In contrast to the effects of the application of the agomir, it was found that application of the antagomir-547-5p induces significant increases in the IL-33 and ST2 expressions and decreases in MWT and TWL in naïve animals [14]. Of particular interest was the finding that increasing IL-33 via the i.t. infusion of recombinant IL-33 (Novus Biologicals, Littleton, CO; http://www.novusbio.com) [10,14] into the L4-L6 region of the spinal cord induces a dose-dependent pain hypersensitivity in animals with no CCI, but does not produce any significant change in the expression of miRNA-547-5p [14]. Conversely, decreasing IL-33 via genetically knocking down IL-33 in the L4 - L6 region significantly reduces the pain hypersensitivity induced by CCI. However, in the animals with IL-33 knockdown, the CCI still induces a significant reduction in miRNA-547-5p expression. Thus, these findings have documented that CCI induces miRNA-547-5p depression, which acts as an upstream signal causing the enhancement of IL-33/ST2 signaling [14].

BMSCs reduce CCI-induced pain hypersensitivity via blocking miRNA-547-5p-mediated IL33/ST2 signaling

It has been well documented that delivering BMSCs locally, intrathecally, or systematically may relieve neuropathic pain induced by nerve injury in both animal models or humans (see reviews) [15,16]. We found that the intravenous infusion of BMSCs (1×10^6 cells in 0.3 ml of phosphate-buffered saline, i.v.) significantly reverses the effects induced by either CCI or the delivering of antagomir-547-5p on pain hypersensitivity and the expressions of miRNA-547-5p, IL-33, and ST2 in both the DRG and SDH. However, no significant change in pain sensitivity and miRNA-547-5p, IL-33, and ST2 expressions were found in naïve animals following the administration of BMSCs [14].

It is also notable that the analgesic effect of BMSC application is significantly reduced in CCI animals pre-administered with agomir-547-5p, whereas no analgesic effect of agomir-547-5p application is found in CCI animals pre-administered with BMSCs. It was further found that IL-33 knockdown also significantly reduces the analgesic effect of BMSCs in the CCI animals. Taken together, these various findings strongly suggest that agomir-547-5p administration or IL-33 knockdown may occlude the effects of BMSCs and that miRNA-547-5p-mediated IL-33/ST2 signaling may play a critical role in the treatment of neuropathic pain with BMSCs [14].

Unanswered questions and future studies

Many recent studies have shown that miRNAs may play important roles in the modulation of neuropathic pain (see reviews [17,18]). We found that increasing miRNA-547-5p expression may significantly reverse the CCI-induced increases in IL-33 and ST2 expressions, and pain sensitivity. Consistently, reducing miRNA-547-5p expression leads to increases in IL-33 and ST2 expressions and pain sensitivity [14]. These findings demonstrate that the miRNA-547-5p/IL-33/ST2 pathway is involved in the genesis and maintenance of neuropathic pain. Furthermore, it has been documented that CCI induces enhancement of IL-33/ST2 signaling in the DRG and SDH via depression of miRNA-547-5p [14]. However, the detailed mechanisms underlying how CCI induces the depression of miRNA-547-5p expression and how IL-33 and ST2 expressions are increased by the depression of miRNA-547-5p remain unclear.

Recent studies have strongly suggested that BMSCs can produce a long-lasting analgesic effect on neuropathic pain through biological agents (e.g., miRNAs) released from the BMSCs [15,16,19,20]. Although we have demonstrated that BMSCs may produce analgesic effects through targeting the miRNA-547-5p depression-IL-33/ST2 signaling pathway [14], further studies addressing the mechanisms underlying the action of BMSCs on this pathway in neuropathic pain and why BMSCs appear not to produce any effect on these molecules in naïve animals are essential to clarify the roles of the miRNA-547-5p/IL-33/ST2 pathway in neuropathic pain and the potential utility of BMSCs.

CONCLUSION

The miRNA-547-5p depression- mediated IL-33/ST2 signaling, which is targeted by BMSCs, may play a critical role in the initiation and maintainers of neuropathic pain. These findings may provide a new scientific basis for developing novel therapeutic approaches to treat neuropathic pain.

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