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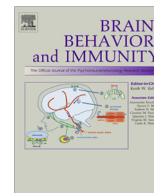

Interleukin-33 treatment reduces secondary injury and improves functional recovery after contusion spinal cord injury

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ABSTRACT

Interleukin-33 (IL-33) is a member of the interleukin-1 cytokine family and highly expressed in the naïve mouse brain and spinal cord. Despite the fact that IL-33 is known to be inducible by various inflammatory stimuli, its cellular localization in the central nervous system and role in pathological conditions is controversial. Administration of recombinant IL-33 has been shown to attenuate experimental autoimmune encephalomyelitis progression in one study, yet contradictory reports also exist.

Here we investigated for the first time the pattern of IL-33 expression in the contused mouse spinal cord and demonstrated that after spinal cord injury (SCI) IL-33 was up-regulated and exhibited a nuclear localization predominantly in astrocytes. Importantly, we found that treatment with recombinant IL-33 alleviated secondary damage by significantly decreasing tissue loss, demyelination and astrogliosis in the contused mouse spinal cord, resulting in dramatically improved functional recovery. We identified both central and peripheral mechanisms of IL-33 action. In spinal cord, IL-33 treatment reduced the expression of pro-inflammatory tumor necrosis factor-alpha and promoted the activation of anti-inflammatory arginase-1 positive M2 microglia/macrophages, which chronically persisted in the injured spinal cord for up to at least 42 days after the treatment. In addition, IL-33 treatment showed a tendency towards reduced T-cell infiltration into the spinal cord. In the periphery, IL-33 treatment induced a shift towards the Th2 type cytokine profile and reduced the percentage and absolute number of cytotoxic, tumor necrosis factor-alpha expressing CD4+ cells in the spleen. Additionally, IL-33 treatment increased expression of T-regulatory cell marker FoxP3 and reduced expression of M1 marker iNOS in the spleen. Taken together, these results provide the first evidence that IL-33 administration is beneficial after CNS trauma. Treatment with IL33 may offer a novel therapeutic strategy for patients with acute contusion SCI.
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1. Introduction

Primary damage after spinal cord injury (SCI) is followed by a wave of secondary inflammatory, apoptotic and degenerative changes that greatly increase neurological deficits and complicate the restoration of spinal cord functions (Tator, 1995; Kwon et al., 2004; Rowland et al., 2008; Oyinbo, 2011; Oudega, 2013). Numerous cell types participate in a highly complex inflammatory response after SCI. Although inflammatory cells are known to promote the secondary damage via generation of reactive oxygen species and release of pro-inflammatory mediators, immune cells residing in or invading the spinal cord also participate in clearance of cellular debris and promote regeneration by secreting growth factors and protective cytokines. Despite the controversial role of inflammation in SCI, it is apparent that uncontrolled immune response can damage healthy tissue and aggravate the injury and, therefore, tight regulation is required to maximize functional recovery (Kwon et al., 2004; Rossignol et al., 2007; Rowland et al., 2008; Donnelly and Popovich, 2008; David et al., 2012). Because a growing amount of evidence indicates the dual role of immune

Abbreviations: BMS, Basso Mouse Scale; BSA, bovine serum albumin; CBA, cytometric bead assay; CNS, central nervous system; dpi, day post injury; EAE, experimental autoimmune encephalomyelitis; FBS, fetal bovine serum; FoxP3, forkhead box P3; GFAP, glial fibrillary acidic protein; HBSS, Hank's balanced salt solution; Iba-1, ionized calcium-binding adapter molecule 1; IL, interleukin; IL-1RAcP, IL-1 receptor accessory protein; IFN-γ, interferon gamma; LFB, Luxol Fast Blue; NF-κB, nuclear factor kappa-B; PFA, paraformaldehyde; SCI, spinal cord injury; Tregs, T regulatory cells; TNF-α, tumor necrosis factor alpha; Th1, type 1 helper T-cell; Th2, type 2 helper T cell.

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response in neurodegenerative disorders, including SCI, novel approaches to modulate the immune system towards an anti-inflammatory and regeneration-supporting mode have been suggested as potential therapies (Amor et al., 2013).

Macrophages are central players in the innate immune response following injury to the central nervous system (CNS) (David and Kroner, 2011). Exposure of macrophages to type 1 helper T cell (Th1) cytokines, such as interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), leads to their polarization to the M1 subpopulation (the classical pro-inflammatory macrophages), which is associated with cytotoxic processes and correlates with the severity of the disease progression and tissue damage in SCI. In contrast, the "alternatively activated" M2 macrophages are induced by type 2 helper T cell (Th2) cytokines such as interleukin (IL)-4, IL-10 and IL-13. M2 cells demonstrate anti-inflammatory activities, scavenge debris, promote angiogenesis and are involved in tissue remodeling and repair (Gordon, 2003; Mantovani et al., 2004; Schwartz and Yoles, 2006; Kigerl et al., 2009; David and Kroner, 2011; Cassetta et al., 2011; Shechter and Schwartz, 2013). Unfortunately, the microenvironment of the injured spinal cord favors M1 polarization and the appearance of M2 cells remains transient (Kigerl et al., 2009; Schwartz, 2010; David and Kroner, 2011; Shin et al., 2013). Therefore, the polarization of microglia/macrophages to the M2 state may be desirable *in situ* in the injured spinal cord (David and Kroner, 2011; Guerrero et al., 2012; Jiang et al., 2012b).

IL-33 is a member of the IL-1 cytokine family (Schmitz et al., 2005). It is described as a cytokine with two different functions: it acts as an intracellular regulator of gene expression (Carriere et al., 2007; Ali et al., 2011) and as an alarm mediator when released from damaged cells (Cayrol and Girard, 2009; Lamkanfi and Dixit, 2009; Lüthi et al., 2009). Nuclear IL-33 can interact with the transcription factor nuclear factor kappa-B (NF-κB) and dampen its activity in non–IL-33 receptor mediated fashion (Carriere et al., 2007; Ali et al., 2011), whereas extracellular IL-33 binds to its receptor consisting of a heterodimer between ST2 and IL-1 receptor accessory protein (IL-1RAcP) (Ali et al., 2007; Chackerian et al., 2007; Liew et al., 2010; Liu et al., 2013). The IL-33 receptor is expressed on a broad range of immune cells, including Th2 cells and macrophages, and can promote Th2 cell expansion and shift the macrophage polarization from M1 to M2 (Xu et al., 1998; Schmitz et al., 2005; Kurowska-Stolarska et al., 2009; Miller et al., 2010). Therefore, increased systemic levels of IL-33 may have a dual function, as its intracellular form can suppress NF-κB-mediated inflammation and its extracellular form stimulates adaptive and innate immune cells in order to clear the initial trigger and repair damaged tissues (Sattler et al., 2013).

IL-33 has been reported to be highly expressed in the naïve mouse brain and spinal cord (Schmitz et al., 2005), and to be up-regulated by inflammatory stimuli (Hudson et al., 2008; Yasuoka et al., 2011; Christophi et al., 2012; Jiang et al., 2012a; Li et al., 2012; Zhao et al., 2013). However, in pathological conditions, the cellular localization of IL-33 in the CNS remains controversial and has been studied only in experimental autoimmune encephalomyelitis (EAE) (Yasuoka et al., 2011) and bone cancer-induced pain (Zhao et al., 2013) models.

Here we show that following SCI, IL-33 is up-regulated and expressed predominantly in spinal cord astrocytes. Administration of recombinant IL-33 in the acute phase of SCI modulated both local and systemic inflammation, resulting in long-term existence of anti-inflammatory M2 microglia/macrophages in the injured spinal cord and leading to reduction of secondary damage and improvement of functional recovery. Therefore, administration of IL-33 may serve as a treatment of patients with acute contusion SCI.

2. Materials and methods

2.1. Animals and surgical procedure

Female 10–12 week old C57BL/6J mice were obtained from the National Laboratory Animal Centre, University of Eastern Finland. The mice were housed in groups of three in cages under 12-h light/dark cycle with water and standard rodent chow provided *ad libitum*. Additional water and powdered food was made available for the first 7 days after SCI. The experimental procedures were approved by the Animal Experiment Committee in State Provincial Office of Southern Finland and conducted according to the national regulation of the usage and welfare of laboratory animals.

The mice were anesthetized with 5% isoflurane in 30% O_2/70% N_2O and maintained in surgical depth anesthesia with 1–1.5% isoflurane delivered through a nose mask during the operation. For the surgery the mice were placed on a controlled heating blanket to maintain body temperature at a constant level of 37 ± 1 °C. A clinically relevant moderate contusion SCI (60 kDynes force) was performed at T10 level using an Infinite Horizons Impactor (Precision Scientific Instrumentation, Lexington, KY) as described in Pomeshchik et al. (2014). The model was chosen as it results in bilateral injury and paralysis, and is also optimal for conclusive evaluation of therapeutic treatments. The mice were kept on 37 °C heating pads for three days after surgery. Analgesia was provided with buprenorfine (Temgesic®, Schering-Plough, Belgium) 0.1 mg/kg injected subcutaneously 30 min before surgery and then same dosage every 12 h for 3 days. The bladder was manually expressed two times daily for approximately 2 weeks until mice were able to regain normal bladder function. Mice that underwent laminectomy without impact served as sham controls.

2.2. IL-33 treatment

Before intraperitoneal administration, recombinant mouse IL-33 (Mouse IL-33 protein, Biorbyt, San Francisco, CA) was diluted in 0.0025% bovine serum albumin (BSA) in sterile PBS to 5 μg/ml concentration. The mice were randomly divided into IL-33 and vehicle groups. In IL-33 treatment group mice received 1 μg of IL-33 immediately after wound closing, followed by 1 μg at 3 days post injury (dpi) and 0.5 μg at 7 and 10 dpi. The dosing was based on a previous mouse study of atherosclerosis (Miller et al., 2008). Control and sham mice were injected similarly with 0.0025% BSA in PBS.

2.3. Functional assessment

Hindlimb motor function recovery was assessed using the Basso Mouse Scale (BMS) (Basso et al., 2006) by two raters blinded to the experimental groups. Each mouse was observed separately for 4 min per session and BMS scores for the right and left hindlimbs were recorded. For further data processing averages of the BMS scores for right and left hindlimbs were used. The BMS is a sensitive, valid and reliable scale allowing assessing the degree of hind-limb functional recovery after SCI. The scale ranges from 0 (no ankle movement) to 9 (complete functional recovery) points and includes the assessment of ankle movement, plantar placement, weight support, stepping, coordination, paw position and trunk stability. Motor function was assessed 24 h after injury, and then weekly for 42 days. The mice with a BMS score higher than one at 24 h after injury were excluded from future evaluation.

2.4. Blood collection and processing

Blood was collected from the heart and tail vein 24 h after SCI and mixed with 3.8% trisodium citrate (1:10) as anticoagulant.

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