Report

Neuron

The Glia-Derived Alarmin IL-33 Orchestrates the Immune Response and Promotes Recovery following CNS Injury

Highlights

- IL-33 is expressed in mature oligodendrocytes and gray matter astrocytes
- IL-33 is released from injured CNS tissue
- Mice lacking IL-33 have impaired recovery after CNS injury
- IL-33 drives chemokine production critical for monocyte recruitment after SCI

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In Brief

Gadani et al. characterized the cellular localization of interleukin (IL)-33 to oligodendrocytes and gray matter astrocytes in the healthy CNS. Using IL-$33^{-/-}$ mice, the authors show that IL-33 is critical to normal monocyte recruitment and recovery after CNS injury.

Gadani et al., 2015, Neuron *85*, 703–709
February 18, 2015
http://dx.doi.org/10.1016/j.neuron.2015.01.013

CellPress

Neuron
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The Glia-Derived Alarmin IL-33 Orchestrates the Immune Response and Promotes Recovery following CNS Injury

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http://dx.doi.org/10.1016/j.neuron.2015.01.013

SUMMARY

Inflammation is a prominent feature of CNS injury that heavily influences neuronal survival, yet the signals that initiate and control it remain poorly understood. Here we identify the nuclear alarmin, interleukin (IL)-33, as an important regulator of the innate immune response after CNS injury. IL-33 is expressed widely throughout the healthy brain and is concentrated in white mater due to predominant expression in post-mitotic oligodendrocytes. IL-33 is released immediately after CNS injury from damaged oligodendrocytes, acting on local astrocytes and microglia to induce chemokines critical for monocyte recruitment. Mice lacking IL-33 have impaired recovery after CNS injury, which is associated with reduced myeloid cell infiltrates and decreased induction of M2 genes at the injury site. These results demonstrate a novel molecular mediator contributing to immune cell recruitment to the injured CNS and may lead to new therapeutic insights in CNS injury and neurodegenerative diseases.

INTRODUCTION

CNS injury is devastating for those afflicted, frequently resulting in permanent impairment due to limited prospects for normal regeneration. Neurons and glia directly damaged by the initial insult die, both necrotically and apoptotically (Grossman et al., 2001; Liu et al., 1997; Lytle and Wrathall, 2007), followed by secondary degeneration—a spread of damage through apoptotic death of initially uninjured neurons (Dusart and Schwab, 1994). The immune system detects and rapidly responds to injury with a cascade of peripheral effectors and soluble molecules (Trivedi et al., 2006). The overall impact of this immune response remains debated, as it has potential to drive both beneficial (Shechter et al., 2013; Walsh et al., 2015; Walsh et al., 2014) and detrimental (Evans et al., 2014; Kroner et al., 2014) effects on recovery. A potential explanation of these dual aspects is macrophage phenotype, with the alternative (M2) and classical (M1) polarization correlating with beneficial or detrimental responses, respectively (Kigerl et al., 2009; Kroner et al., 2014; Schmitz et al., 2005; Shechter et al., 2009, 2013).

Interleukin (IL)-33 is a nuclear alarmin of the IL-1 cytokine family released by cell damage and is well characterized as an immune activator in conditions such as asthma (Liew et al., 2010), allergy (Oboki et al., 2010), and sepsis (Alves-Filho et al., 2010). Upon release from necrotically dying cells (Lüthi et al., 2009), IL-33 binds IL-33R, a heterodimer of IL-1RAcP and ST2, and initiates an intracellular cascade involving MyD88 and NFκB (Liew et al., 2010). In addition to barrier tissues such as lung and skin, IL-33 is highly expressed in the CNS (Schmitz et al., 2005), though its endogenous location and function remains understudied there. Astrocytes have been suggested as the cellular source of IL-33 (Yasuoka et al., 2011), but this remains poorly characterized in vivo. Furthermore, the cellular targets within the CNS and the potential role of expressed IL-33 in regulating the immune response following trauma remains unknown.

Here we provide evidence that in the healthy brain IL-33 is expressed mainly by post-mitotic oligodendrocytes and gray matter astrocytes. It is released immediately after CNS injury and acts upon astrocytes (and microglia) to induce production of chemokines critical for monocyte recruitment. IL-33 also acts on monocytes to augment their M2 skew, previously shown to be beneficial after CNS injury. Lack of IL-33 results in diminished numbers of infiltrating neuroprotective M2-skewed macrophages and, therefore, leads to impaired recovery after CNS injury.

RESULTS

We first examined the expression levels of IL-33 in different regions of the healthy periphery and CNS. There is high variability of IL-33 expression among CNS areas, with a trend toward tissues with higher myelin content exhibiting higher IL-33 expression (Figure 1A; Figure S1A). Given the high expression levels