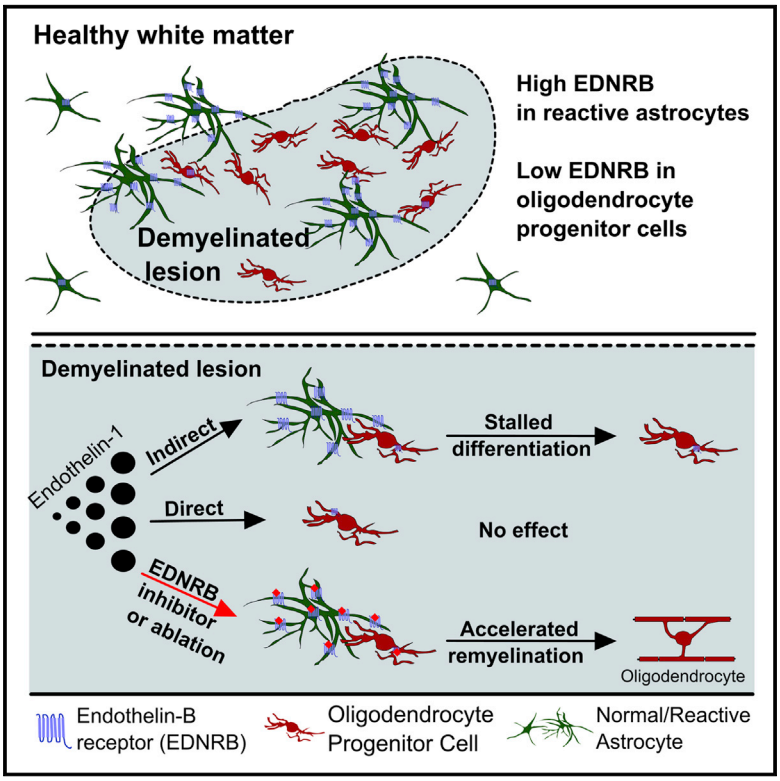
Cell Reports

Endothelin-B Receptor Activation in Astrocytes Regulates the Rate of Oligodendrocyte Regeneration during Remyelination

Graphical Abstract



Highlights

- EDNRA and EDNRB are upregulated after demyelination in reactive astrocytes
- Pharmacological inhibition of EDNRB, but not EDNRA, accelerates remyelination
- EDNRB loss in astrocytes, but not in OPCs, accelerates remyelination
- Endothelin indirectly inhibits OPC differentiation through astrocytes

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In Brief

Astrocyte-derived endothelin-1 (ET-1) inhibits remyelination through unknown mechanisms. Using pharmacological and genetic approaches, Hammond et al. demonstrate that ET-1 signals through endothelin receptor-B in reactive astrocytes, indirectly inhibiting oligodendrocyte progenitor cell (OPC) differentiation and remyelination. Inhibiting this pathway could provide an exciting therapeutic strategy to promote remyelination in MS.

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Endothelin-B Receptor Activation in Astrocytes Regulates the Rate of Oligodendrocyte Regeneration during Remyelination

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SUMMARY

Reactive astrogliosis is an essential and ubiquitous response to CNS injury, but in some cases, aberrant activation of astrocytes and their release of inhibitory signaling molecules can impair endogenous neural repair processes. Our lab previously identified a secreted intercellular signaling molecule, called endothelin-1 (ET-1), which is expressed at high levels by reactive astrocytes in multiple sclerosis (MS) lesions and limits repair by delaying oligodendrocyte progenitor cell (OPC) maturation. However, as ET receptors are widely expressed on neural cells, the cell- and receptor-specific mechanisms of OPC inhibition by ET-1 action remain undefined. Using pharmacological approaches and cell-specific endothelin receptor (EDNR) ablation, we show that ET-1 acts selectively through EDNRB on astrocytes—and not OPCs—to indirectly inhibit remyelination. These results demonstrate that targeting specific pathways in reactive astrocytes represents a promising therapeutic target in diseases with extensive reactive astrogliosis, including MS.

INTRODUCTION

Reactive astrogliosis is the cellular and biochemical transformation of astrocytes in response to brain injury, and it significantly impacts—both positively and negatively—neural regeneration (Sofroniew and Vinters, 2010; Williams et al., 2007). Reactive astrogliosis was once thought to be an all-or-nothing transformation, but emerging evidence suggests that reactive astrocytes (RAs) are highly dynamic and tailor their transcriptional response to the type of injury and the region in which it occurs (Zamanian et al., 2012). This response includes production of growth factors, cytokines, and other intercellular signaling molecules that influence the ability of progenitor cell populations to repair damaged tissue. Therefore, it is essential to understand how specific signals produced by RAs impact neural regeneration so that we can develop targeted approaches to enhance the beneficial aspects of the astrocyte response while preventing the deleterious ones.

Endothelin-1 (ET-1) is upregulated by astrocytes in a number of brain pathologies, including stroke, traumatic brain injury, Alzheimer's disease, cancer, and multiple sclerosis (MS) (D'haeseleer et al., 2013; Hammond et al., 2014; Palmer et al., 2012; Petrov et al., 2002; Schinelli, 2006; Stiles et al., 1997; Torbidoni et al., 2005). While ET-1 has been well characterized for its role as a secreted signaling peptide in the cardiovascular system, its role in the normal and pathological brain is not well defined (Rubanyi and Botelho, 1991). Both neurons and glia, including astrocytes, express endothelin receptors (EDNRs), and ET-1 has been shown to promote reactive astrogliosis in vitro and in vivo (Gadea et al., 2008; Schinelli, 2006). Interestingly, EDNR inhibition improves recovery in several animal models of brain injury (Guo et al., 2014a; Hammond et al., 2014; Moldes et al., 2012), suggesting that ET-1 plays a deleterious role in the pathological lesion environment. However, given the widespread expression of EDNRs, the mechanisms by which ET-1 signaling impacts the regenerative response, including its effect on specific cellular targets, are not well understood.

MS is a disease characterized by oligodendrocyte (OL) death, focal demyelinated CNS lesions, and extensive RA scar formation (Compston and Coles, 2008; Williams et al., 2007). In response to demyelination, OL progenitor cells (OPCs) can replace lost OLs by maturing into new myelin-producing cells in a process called remyelination (Franklin and Ffrench-Constant, 2008). However, stalled OPC differentiation is frequently found in patients with progressive MS (Chang et al., 2002; Wolswijk, 1998), possibly due to the aberrant expression of signals within the demyelinated lesions (Franklin and Ffrench-Constant, 2008). These signals could derive, at least in part, from permanent astrocytic scars that are common in MS brain tissue.

ET-1 is highly upregulated in RAs in human chronic active MS lesions and in experimentally induced demyelinated lesions in mice (D'haeseleer et al., 2013; Hammond et al., 2014). We recently showed that ET-1 contributes to stalled OPC differentiation by promoting inhibitory astrocyte-OPC signaling (Hammond et al., 2014). This led to delayed remyelination, an effect that was reversed using EDNR antagonists during the repair phase. Consistent with these findings, others demonstrated that overexpression of ET-1 by astrocytes exacerbates experimental autoimmune encephalomyelitis (EAE), a mouse model