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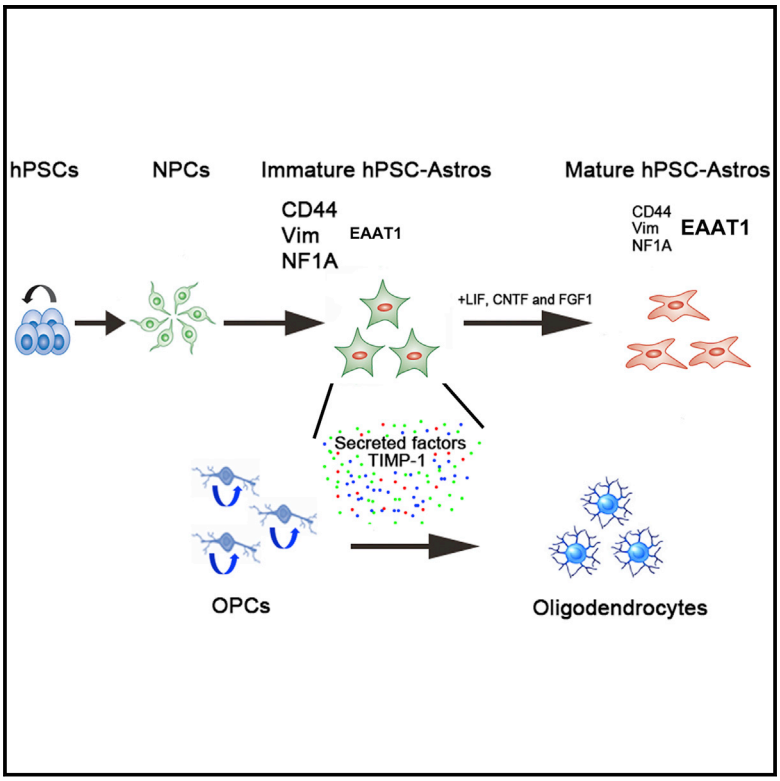
Cell Reports

Human iPSC-Derived Immature Astroglia Promote Oligodendrogenesis by Increasing TIMP-1 Secretion

Graphical Abstract



Highlights

- Immature hiPSC-derived astroglia promote proliferation and differentiation of OPCs
- TIMP-1 mediates, in part, the effects of immature hiPSC-Astros on OPC differentiation
- Transplantation of immature hiPSC-Astros promotes recovery after neonatal brain injury
- Intranasal administration of hiPSC-Astro conditioned medium rescues brain injury

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In Brief

Jiang et al. report that immature human astroglia derived from induced pluripotent stem cells (hiPSC-Astros) promote oligodendrocyte lineage progression, in part by upregulating and increasing the secretion of TMIP-1. In animal models of neonatal brain injury, mimicking cerebral palsy in humans, they also demonstrate that transplanted hiPSC-Astros or their conditioned medium promote myelinogenesis as well as behavioral outcome. The findings provide insights into astroglial regulation of oligodendrogenesis and have important implications for astroglia-based cell therapy.

Jiang et al., 2016, Cell Reports *15*, 1303–1315
May 10, 2016
http://dx.doi.org/10.1016/j.celrep.2016.04.011

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Human iPSC-Derived Immature Astroglia Promote Oligodendrogenesis by Increasing TIMP-1 Secretion

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SUMMARY

Astrocytes, once considered passive support cells, are increasingly appreciated as dynamic regulators of neuronal development and function, in part via secreted factors. The extent to which they similarly regulate oligodendrocytes or proliferation and differentiation of oligodendrocyte progenitor cells (OPCs) is less understood. Here, we generated astrocytes from human pluripotent stem cells (hiPSC-Astros) and demonstrated that immature astrocytes, as opposed to mature ones, promote oligodendrogenesis in vitro. In the PVL mouse model of neonatal hypoxic/ischemic encephalopathy, associated with cerebral palsy in humans, transplanted immature hiPSC-Astros promoted myelinogenesis and behavioral outcome. We further identified TIMP-1 as a selectively upregulated component secreted from immature hiPSC-Astros. Accordingly, in the rat PVL model, intranasal administration of conditioned medium from immature hiPSC-Astros promoted oligodendrocyte maturation in a TIMP-1-dependent manner. Our findings suggest stage-specific developmental interactions between astroglia and oligodendroglia and have important therapeutic implications for promoting myelinogenesis.

INTRODUCTION

Astrocytes play important roles in organizing and maintaining brain structure and function (Barres, 2008). Astrocytes go through prenatal and protracted postnatal maturation during development and can undergo a spectrum of functional changes associated with development (Molofsky et al., 2012; Pekny and Pekna, 2014), serving stage-specific roles in assisting neuronal development, such as synapse stabilization and elimination (Chung et al., 2013; Molofsky et al., 2012). However, it is unclear how astrocytes, at specific immature and mature stages, may differently regulate the development of oligodendrocytes, myelin-producing cells in the CNS.

Human pluripotent stem cells (hPSCs), including human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs), have been efficiently differentiated to astrocytes (Emdad et al., 2012; Jiang et al., 2013b; Krencik et al., 2011; Roybon et al., 2013; Shaltouki et al., 2013). The progenies differentiated from hPSCs are reflective of very early human development (<6 weeks) (Patterson et al., 2012). Particularly, hPSC-derived astrocytes differentiated by using chemically defined, xeno-free protocols can be maintained at an immature stage in culture (Chen et al., 2014a; Emdad et al., 2012; Jiang et al., 2013b; Krencik et al., 2011; Shaltouki et al., 2013). Moreover, hPSC-derived immature astrocytes can be further differentiated to astrocytes with defined mature phenotypes (Krencik et al., 2011; Roybon et al., 2013). Thus, astroglia derived from hPSCs provide an unprecedented opportunity to investigate the interaction between oligodendroglia and human astrocytes that are at defined immature and mature stages.

Astrocytes are implicated in influencing myelination in myelin loss disorders. Prior studies demonstrate that oligodendrocytes preferentially remyelinate axons in areas containing astrocytes (Franklin et al., 1991; Talbott et al., 2005). However, astroglia-based therapy for myelin loss disorders is less studied (Chen et al., 2015) because most of the disorders are associated with profound astrocyte activation and formation of glial scars (Pekny and Pekna, 2014). Scarring astrocytes are regarded as a barrier to regeneration, partly because of the secretion of factors that halt survival and differentiation of oligodendroglia progenitor cells (OPCs) (Back et al., 2005; Nash et al., 2011). Recent studies also suggest that, in the acute phase of injuries, astrogliosis is a defensive reaction. Reactive astrocytes recapitulate numerous processes involved in the early development of immature astroglia and exhibit positive effects in the acute phase of injuries (Pekny and Pekna, 2014), but reactivated processes often go awry later, turning on the detrimental effects of the astrocytes on regeneration (Gallo and Deneen, 2014). Recent studies (Jiang et al., 2013b; Noble et al., 2011) demonstrate that transplanted immature astrocytes do not become reactive after CNS injury. Immature but not mature astrocytes are neuroprotective and suppress the activation of endogenous astrocytes and glial