Neurochemistry International 78 (2014) 35–42

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

Review

Signaling molecules regulating phenotypic conversions of astrocytes and glial scar formation in damaged nerve tissues

Yutaka Koyama *

Laboratory of Pharmacology, Faculty of Pharmacy, Osaka Ohtani University, 3-11-1 Nishikiori-Kita, Tonda-bayashi, Osaka 584-8540, Japan

ARTICLE INFO

Article history:
Received 25 April 2014
Received in revised form 17 July 2014
Accepted 22 August 2014
Available online 30 August 2014

Keywords:
Astrocytes
Glial scar
Transcription factors
Brain pathology

ABSTRACT

Phenotypic conversion of astrocytes from resting to reactive (i.e., astrocytic activation) occurs in numerous brain disorders. Astrocytic activation in severely damaged brain regions often leads to glial scar formation. Because astrocytic activation and glial scar largely affect the vulnerability and tissue repair of damaged brain, numerous studies have been made to clarify mechanisms regulating the astrocytic phenotype. The phenotypic conversion is accompanied by the increased expression of intermediate filament proteins and the induction of hypertrophy in reactive astrocytes. Severe brain damage results in proliferation and migration of reactive astrocytes, which lead to glial scar formations at the injured areas. Gliogenesis from neural progenitors in the adult brain is also involved in astrocytic activation and glial scar formation. Recent studies have shown that increased expression of connexin 43, aquaporin 4, matrix metalloproteinase 9, and integrins alter the function of astrocytes. The transcription factors: STAT3, OLIG2, SMAD, NF-κB, and Sp1 have been suggested to play regulatory roles in astrocytic activation and glial scar formation. In this review, I discuss the roles of these key molecules regulating the pathophysiological functions of reactive astrocytes.

1. Introduction

Astrocytes play an important role in maintaining the physiological functions of neurons by regulating the turnover of neurotransmitters, maintaining extracellular ionic environments, and providing trophic support. In response to brain injury, astrocytes undergo "activation", which is a phenotypic conversion from a resting to reactive state (Sofroniew, 2009). Astrocytic activation is commonly observed in many brain disorders, such as stroke, traumatic nerve injury, and neurodegenerative diseases. Reactive astrocytes are characterized by hypertrophy, high expression of intermediate filament (IF) proteins, and functional changes. Astrocytic activation is also accompanied by the production of a variety of cytokines, chemokines, growth factors, and neurotrophic factors (Eddleston and Mucke, 1993; Ridet et al., 1997). These factors regulate the pathophysiological effects of the damaged brain, including neuroinflammation, brain edema, neurogenesis, neuronal degeneration, and axonal elongation. During severe brain damage, reactive astrocytes proliferate and undergo migration, which are alterations that underlie glial scar formation at damaged sites (Sofroniew, 2009). Initially, the glial scar was considered to serve as a physical barrier to inhibit axonal elongation and synaptogenesis during repair processes of damaged nerve tissues (Liuzzi and Lasek, 1987; Davies et al., 1997). However, further studies have shown that the glial scar reduces neuroinflammatory responses and protects nerve tissues from secondary damages following insults (Bush et al., 1999; Voskuhl et al., 2009; Li et al., 2008; Liedtke et al., 1998; Herrmann et al., 2008; Wanner et al., 2013). Therefore, astrocytic activation and the glial scar is generally considered to largely affect the vulnerability and recovery of nerve tissues that have been damaged by neuronal disorders (Karimi-Abdolrezaee and Billakanti, 2012). Thus, numerous studies have investigated the signaling mechanisms underlying the phenotypic conversion to reactive astrocytes, revealing several key signaling molecules that play a role in regulating astrocytic functions during this conversion. These molecules include proteins involved in astrocytic reactivity (connexins, integrins, MMP9, and aquaporin 4(AQP4)) and gene transcription factors

Abbreviations: IF, intermediate filament; GFAP, glial fibrillary acidic protein; AxD, Alexander disease; AD, Alzheimer disease; ECM, extracellular matrix; FAK, focal adhesion kinase; FA, focal adhesion; MMP, matrix metalloproteinase; AQP, aquaporin; CX, connexin; IL, interleukin; LIF, leukemia inhibitory factor; CNTF, ciliary neurotrophic factor; ET-1, endothelin-1; FGF2, fibroblast growth factor-2; EGF, epidermal growth factor; TGF-β1, transforming growth factor-β1; BMP, bone morphogenic protein; TNF-α, tumor necrosis factor-α; JAK, Janus kinase; CSPGs, chondroitin sulfate proteoglycans; Pax, paxillin; Vin, vinculin.

* Tel./fax: +81 721 24 9462.
E-mail address: koyamay@osaka-ohtani.ac.jp

http://dx.doi.org/10.1016/j.neuint.2014.08.005
0197-0186/

(STAT3, OLIG2, SMAD, NF-κB, and Sp1). In this article, I review recent studies on some of the key molecules that induce astrocytic activation and glial scar formation.

2. Astrocytic activation and glial scar formation

Astrocytic proliferation, hypertrophy, and migration, and their production of extracellular signal molecules are involved in the conversion of astrocytes to the reactive state (Buffo et al., 2010; Hamby and Sofroniew, 2010). However, changes in these properties during reactivity are not induced by a single stimulus or a common signaling process, rather a coordination of individual signaling mechanisms depending on the severity of the nerve injury (Buffo et al., 2010) (Fig. 1). In mild brain insults or in brain regions in which damage is not severe, reactive astrocytes exhibit hypertrophy of their cell bodies and processes, however, glia scar formation is absent. Glial scar formation occurs at injured sites where nerve tissues are severely damaged. Hypertrophy, proliferation, and migration of reactive astrocytes have been shown to be involved in glial scar formation in a coordinated manner (Sofroniew, 2009). Neural progenitor cells in some areas of the adult brain have been showed to differentiate into reactive astrocytes forming glial scar (Alonso, 2005; Cassiani-Ingoni et al., 2006; Zhao et al., 2009; Meletis et al., 2008; Carlén et al., 2009). In the following sections, the key molecules underlying astrocytic hypertrophy, proliferation, migration, and gliogenesis are described (Fig. 1).

2.1. Up-regulation of IF proteins and hypertrophy

IF proteins form part of the cytoskeletal structure and their organization determines cell morphology and mortality. The upregulation of IF proteins in reactive astrocytes induces the re-organization of the astrocytic cytoskeleton causing hypertrophy of these cells (Pekny and Pekna, 2004). In the adult brain, expression of the astrocytic-specific IF protein, glial fibrillary astrocytic protein (GFAP), is up-regulated in reactive astrocytes compared with resting astrocytes. Furthermore, the up-regulation of other IF proteins, vimentin and nestin, has also been shown to occur during the phenotypic conversion to reactive astrocytes (Calvo et al., 1991; Cho et al., 2013). The roles and functions of these IF proteins in the induction of astrocytic activation have been examined in genetically modified mice (Pekny and Pekna, 2004). A null mutation of either GFAP or vimentin does not result in growth and brain morphology abnormalities in mice (Pekny et al., 1995, 1999). Moreover, impairment of astrocytic activation and glial scar formation is not observed after nerve injury in these knockout mice, suggesting that both IF proteins compensate the function of each other. However, the simultaneous knockout of GFAP and vimentin reduces nerve injury-mediated glial scar formation (Pekny et al., 1999). These observations indicate that the re-organization of increased GFAP and vimentin is required for glial scar formation after nerve injury.

Exogenous human GFAP has been shown to induce hypertrophy and up-regulate the expression of vimentin and nestin in astrocytes of human GFAP knockin mice (Sosunov et al., 2013). Furthermore, the application of human GFAP in these mice causes the formation of astrocytic inclusion bodies composed of IF proteins and resembling Rosenthal fibers in Alexander disease (AxD) (Messing et al., 1998). AxD is a neurological disease primarily caused by the abnormal accumulation of GFAP (Messing et al., 2012). Genetic analysis of AxD patients has revealed mutations of the GFAP gene (Brenner et al., 2001). Therefore, GFAP transgenic mice are suggested to be a useful animal model of AxD (Messing et al., 1998).

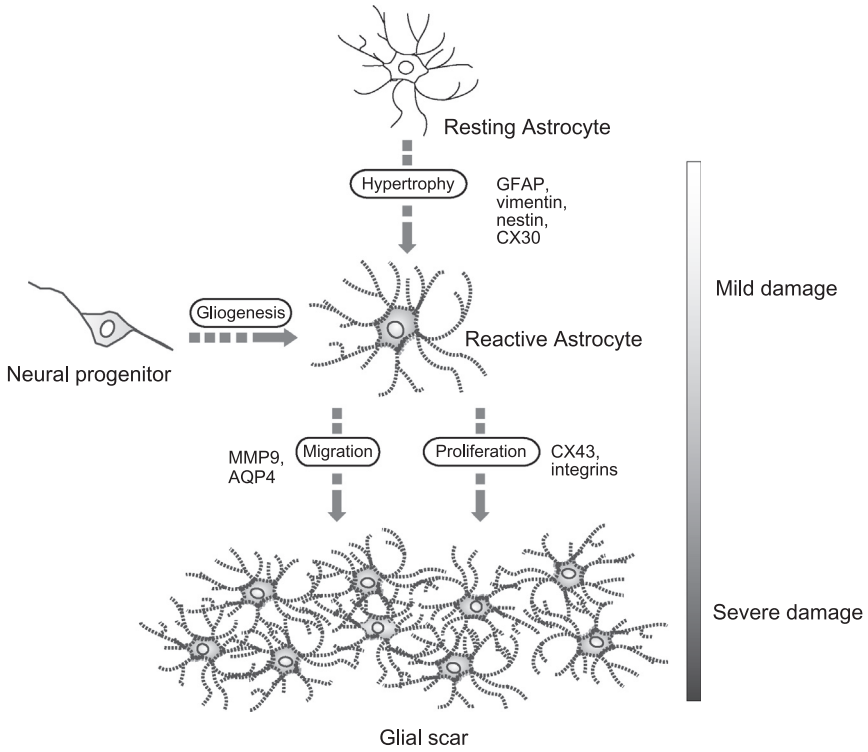

Fig. 1. Functional alterations of reactive astrocytes leading to glial scar formation. Reactive astrocytes are observed in many brain pathologies, and their induction to this phenotype is owed to the gradual alterations of their properties. In mild brain injury, cell bodies and processes of reactive astrocytes show hypertrophy, but glial scar formation is absent. The expression of intermediate filament proteins (GFAP, vimentin, and nestin) is increased in hypertrophied astrocytes. The glial scar is formed by reactive astrocytes at the injured sites in severely damaged nerve tissues. Proliferation, migration, and astrocytic activation are involved in glial scar formation in a coordinating manner. As for induction of reactive astrocytes leading to glial scar formation, several studies showed that gliogenesis from neural progenitors promoted this process in the limited brain regions (see text). These phenotypic alterations are regulated by individual signaling mechanisms. Recent studies have shown key molecules (CX30, CX43, integrins, MMP9, and AQP) that induce glial scar formation. GFAP, glial fibrillary acidic protein; CX, connexin; MMP, matrix metalloproteinase; APQ, aquaporin.