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Astrocyte roles in traumatic brain injury

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ABSTRACT

Astrocytes sense changes in neural activity and extracellular space composition. In response, they exert homeostatic mechanisms critical for maintaining neural circuit function, such as buffering neurotransmitters, modulating extracellular osmolarity and calibrating neurovascular coupling. In addition to upholding normal brain activities, astrocytes respond to diverse forms of brain injury with heterogeneous and progressive changes of gene expression, morphology, proliferative capacity and function that are collectively referred to as reactive astrogliosis. Traumatic brain injury (TBI) sets in motion complex events in which noxious mechanical forces cause tissue damage and disrupt central nervous system (CNS) homeostasis, which in turn trigger diverse multi-cellular responses that evolve over time and can lead either to neural repair or secondary cellular injury. In response to TBI, astrocytes in different cellular microenvironments tune their reactivity to varying degrees of axonal injury, vascular disruption, ischemia and inflammation. Here we review different forms of TBI-induced astrocyte reactivity and the functional consequences of these responses for TBI pathobiology. Evidence regarding astrocyte contribution to post-traumatic tissue repair and synaptic remodeling is examined, and the potential for targeting specific aspects of astrogliosis to ameliorate TBI sequelae is considered.

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Introduction

Responses to injury and disease in the central nervous system (CNS) involve multiple neural and non-neural cell types that interact over time in an effort to maintain homeostasis, protect viable cells, clear debris and preserve function (Burda and Sofroniew, 2014). Astrocytes are pivotal responders to all forms of CNS insults through diverse potential changes commonly referred to as reactive astrogliosis. In the healthy CNS, astrocytes play critical roles in maintaining the homeostasis of ions, transmitters, water and blood flow that are critical for neural circuit function. Many aspects of astrocyte responses to CNS damage and disease have been reviewed (Pekny and Pekna, 2014; Sofroniew, 2014b; Sofroniew and Vinters, 2010). In this article we will focus on astrocyte responses to, and roles in, traumatic brain injury (TBI).

Multiple forms and severities of TBI and tissue damage

Traumatic brain injury (TBI) can be caused by a wide variety of stimuli and encompasses a large range of severities (Graham et al., 2000). There is increasing recognition that TBI can not only have direct and immediately recognizable consequences, but also has the potential for long-term and gradually evolving sequelae, such as increased susceptibility for behavioral disturbances, seizure disorders or neurodegenerative disease (Kovacs et al., 2014; Sharp et al., 2014). It is also becoming clear that clinically mild forms of TBI that initially do not cause overt symptoms or easily detectable tissue damage can have long-term consequences, particularly if repetitive. To understand and address the consequences of TBI, there is a need for a better understanding of the cell biological consequences of different forms and severities of TBI and how they evolve over time and give rise to different forms and severities of tissue damage. The potentially beneficial or sometimes harmful effects of cellular responses to TBI such as reactive astrogliosis, are determined by a multitude of potential specific signaling events that can vary considerably with different forms and severities of CNS insults (Burda and Sofroniew, 2014; Sofroniew, 2009, 2014b). Thus it is important to understand how different triggering events can lead to different cellular responses and different forms of pathology.

Tissue pathology and its functional consequences resulting from TBI are heterogeneous and determined largely by (i) the mechanical properties of the injury, (ii) the degree of injury severity and (iii) the anatomical location of the injury. For analytical purposes it is useful to differentiate the features and origins of focal and diffuse tissue damage, which are associated with different types of astrocyte responses (Fig. 1). It deserves emphasis that clinically mild, moderate or severe TBI have the potential exhibit all of these forms of tissue damage to varying degrees and across varying expanses of tissue.

Focal tissue damage

Focal tissue damage after TBI can arise in several ways, for example from direct impact that produces brain contusion with intra- and/or extra-axial hemorrhage, or from penetrating injuries that cause direct parenchymal laceration and hemorrhage. As a result, focal TBI lesions

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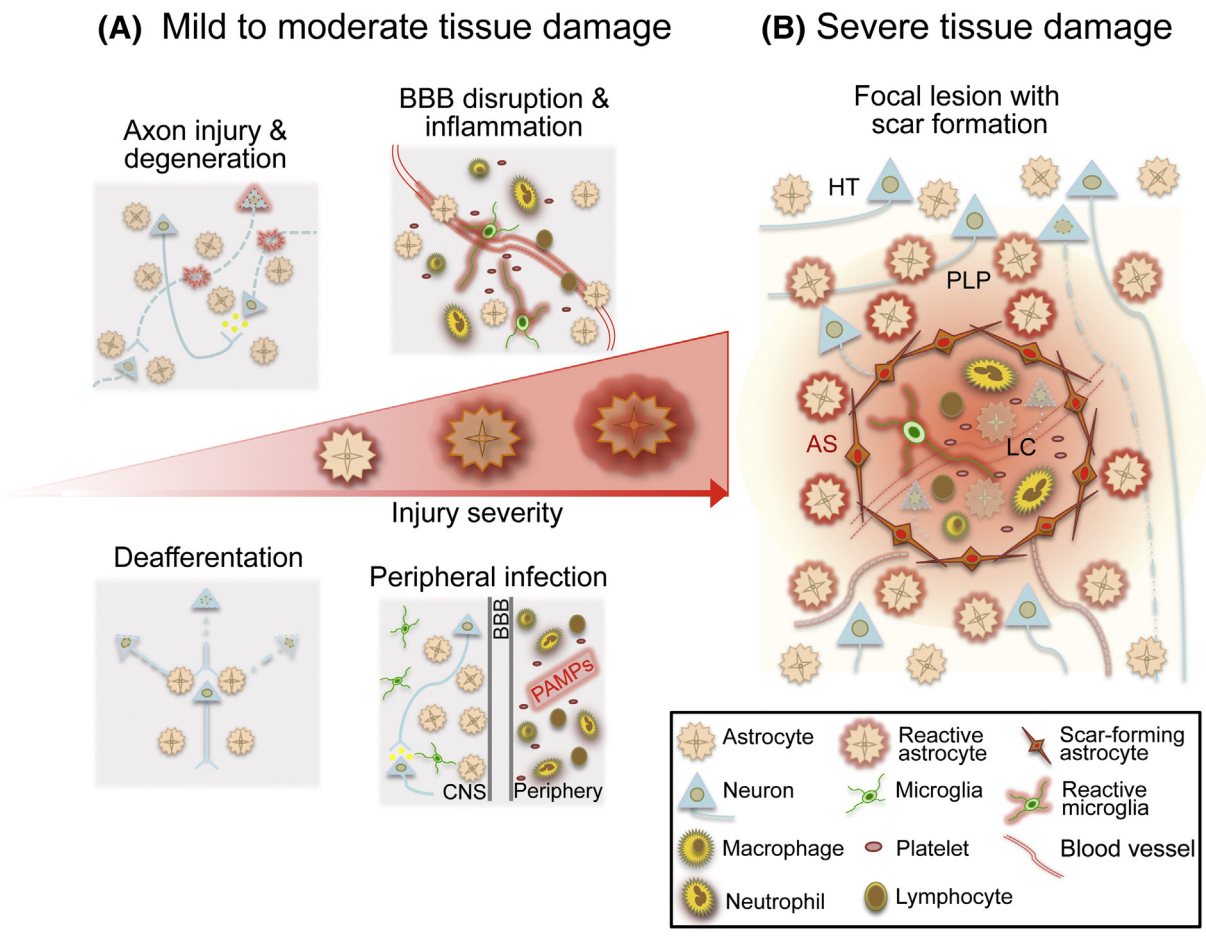

Fig. 1. Reactive astrogliosis following TBI is a graded and heterogeneous response that reflects the severity of CNS tissue damage. A, In response to mild or moderate tissue damage, astrocytes undergo hypertrophic reactive astrogliosis that includes molecular, structural and functional changes. Different forms of tissue pathology, such as local axonal injury and degeneration, blood–brain barrier (BBB) disruption with inflammatory cell extravasation, deafferentation and synapse degeneration due to distal axon injury, or exposure to PAMPs associated with peripheral bacterial or viral infection, can all uniquely influence astrocyte function and in different combinations can drive specific forms of astrogliosis. These hypertrophic reactive astrocytes are intermingled among viable neural cells in areas of injured, but surviving and functioning neural tissue. B, Severe tissue damage elicits neural and glial cell degeneration, vascular breakdown and a robust innate and adaptive immune response, leading to the formation of tissue compartments with distinct forms of reactive astrogliosis. Immediately adjacent to the injury, astrocytes proliferate and intertwine to form an astroglial scar (AS) that surrounds and restricts the spread of the intense inflammatory response in the lesion core. These scar forming astrocytes are present in areas that contain few if any surviving neural cells, and their main interactions are with non-neural cells in tissue lesions. Adjacent to the astrocyte scar, features characteristic of mild or moderate brain trauma are present and taper with distance from the lesion core (LC). In these areas reactive astrocytes undergo changes in morphology and function characteristic of hypertrophic reactive astrogliosis as described in A, and these reactive astrocytes interact with injured but surviving cells in the perilesion perimeter (PLP). Astrocyte reactivity in the PLP may also influence neurons and glia in the healthy tissue (HT) distal to the injury.

form due to abrupt and indiscriminate cell death of a majority of neural cells in circumscribed regions (Fig. 1B). Such focal lesions can vary considerably in size, and can encompass large areas or can be restricted to small clusters of cells (Myer et al., 2006; Villapol et al., 2014).

Diffuse tissue damage

The initial insult leading to diffuse tissue damage after TBI results from tissue strain due to inertial forces, such as occurs with rapid head acceleration/deceleration in an automotive crash or in blast injuries (Gennarelli et al., 1982). Unlike the easily detectable gross tissue disruption produced by focal TBI lesions, primary diffuse TBI pathology is difficult to detect by current neuroimaging methods, particularly in its acute stages. Rather, tissue deformation produces sub-lethal damage to neurons, glia and vascular cells, which leads to chronic progressive cellular injury due to oxidative damage, osmotic imbalance, ischemia and inflammation (Fig. 1A). As such, diffuse TBI is often only diagnosed conclusively at the microscopic level during postmortem evaluation, by vascular breakdown and hallmark diffuse axonal injury that manifests as axonal swellings, plasmalemmal disruption, disconnection and Wallerian degeneration (Johnson et al., 2013). The extent of diffuse axonal injury correlates with injury severity and the plane of mechanical loading (Smith et al., 2000), with regions of white–grey matter interface or enriched white matter (e.g. cortical gyri, corpus callosum, brain stem) being particularly susceptible to strain injury (Gennarelli et al., 1982; Meythaler et al., 2001).

In this regard, it is important to realize that tissue damage after TBI is seldom purely focal or diffuse, with a single case often involving a multiplicity of focal and diffuse lesions (Graham et al., 2000; Skandsen et al., 2010). Areas of focal tissue damage are invariably surrounded by tapering perimeters of diffuse tissue damage and its associated cellular changes and responses (Fig. 1B). For example, an acute contusive TBI may produce a gross focal lesion at the site of impact, while generating rapid head acceleration that evokes more diffuse damage by way of compressive countercoup injury and rotational tissue shearing (Ommaya and Gennarelli, 1974). Indeed, animal models of focal contusive and percussive TBI demonstrate diffuse cellular perturbations in regions distal to the epicenter of focal damage (Singleton and Povlishock, 2004; Vlodavsky et al., 2005). Conversely, after a diffuse TBI caused by severe acceleration–deceleration, the coalescence of multiple small vascular deficits created by diffuse multiple small shear injuries may lead to tissue lesions similar in nature to focal lesions (Shih

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