Neuroscience Letters 565 (2014) 23–29

Contents lists available at ScienceDirect

Neuroscience Letters

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

Mini review

# Heterogeneity of reactive astrocytes

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## HIGHLIGHTS

- Astrocyte reactivity is not a single stereotypic program.
- Reactive astrocytes exhibit substantial heterogeneity at multiple levels.
- Heterogeneity includes gene expression, cell morphology and cell function.
- Astrocyte reactivity varies in a context specific manner.
- Astrocyte reactivity occurs in response to many different specific signaling events.

## ARTICLE INFO

*Article history:*
Received 2 September 2013
Received in revised form 1 December 2013
Accepted 12 December 2013

*Keywords:*
Reactive astrogliosis
Glial scar
Trauma
Inflammation
Autoimmune disease
Heterogeneity

## ABSTRACT

Astrocytes respond to injury and disease in the central nervous system (CNS) with a process referred to as reactive astrogliosis. Recent progress demonstrates that reactive astrogliosis is not a simple all-or-none phenomenon, but is a finely gradated continuum of changes that range from reversible alterations in gene expression and cell hypertrophy, to scar formation with permanent tissue rearrangement. There is now compelling evidence that reactive astrocytes exhibit a substantial potential for heterogeneity at multiple levels, including gene expression, cell morphology, topography (distance from lesions), CNS regions, local (among neighboring cells), cell signaling and cell function. Structural and functional changes are regulated in reactive astrocytes by many different potential signaling events that occur in a context dependent manner. It is noteworthy that different stimuli of astrocyte reactivity can lead to similar degrees of GFAP upregulation while causing substantially different changes in transcriptome profiles and cell function. Thus, it is not possible to equate simple and uniform measures such as cell hypertrophy and upregulation of GFAP expression with a single, uniform concept of astrocyte reactivity. Instead, it is necessary to recognize the considerable potential for heterogeneity and determine the functional implications of astrocyte reactivity in a context specific manner as regulated by specific signaling events.



**Contents**

1. Introduction ..... 23
2. Diversity of astrocyte responses to CNS insults ..... 24
   2.1. Terminology ..... 24
   2.2. Mild to moderate reactive astrogliosis ..... 24
   2.3. Severe diffuse reactive astrogliosis ..... 24
   2.4. Compact astroglial scar formation ..... 24

## 1. Introduction

Astrocytes respond to all forms of injury and disease in the central nervous system (CNS) through a process referred to as astrogliosis [47]. Studies over the past twenty years provide compelling evidence that reactive astrogliosis is not a simple all-or-none phenomenon, but is a finely gradated continuum of changes that range from reversible alterations in gene expression and cell hypertrophy, to scar formation with permanent tissue rearrangement. It has also become clear that the structural and functional changes associated with reactive astrogliosis occur in context dependent manners as regulated by many different potential signaling events [45,47]. Observations such as these have

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http://dx.doi.org/10.1016/j.neulet.2013.12.030

3. Multiple levels of reactive astrocyte heterogeneity ..... 24
3.1. Gene expression ..... 25
3.2. Morphology: hypertrophy with domain preservation or process interdigitation ..... 25
3.3. Proliferation ..... 25
3.4. Topography (with respect to distance from insults) ..... 26
3.5. Local (among neighboring cells) ..... 26
3.6. CNS region and precursor lineage ..... 26
3.7. Signaling and regulation ..... 26
3.8. Physiology ..... 27
4. Functional implications ..... 28
5. Conclusions ..... 28
Conflict of interest ..... 28
Acknowledgements ..... 28
References ..... 28

gradually revealed various levels of heterogeneity among reactive astrocytes. This article summarizes the increasing evidence for diversity and heterogeneity of reactive astrogliosis and reactive astrocytes.

## 2. Diversity of astrocyte responses to CNS insults

Based on a large body of observations in experimental animals and human pathological specimens, we have recently proposed a definition of reactive astrogliosis that includes several grades of severity that may be commonly encountered in experimental and clinical histopathological examinations [45,47]. This definition encompasses four key features: (i) reactive astrogliosis is a spectrum of potential molecular, cellular and functional changes in astrocytes that occur in response to all forms and severities of CNS injury and disease; (ii) the changes undergone by reactive astrocytes vary with severity of the insult along a graded continuum, (iii) the changes of reactive astrogliosis are regulated in a context-specific manner by inter- and intra-cellular signaling molecules; (iv) the changes undergone during reactive astrogliosis have the potential to alter astrocyte activities both through gain and loss of functions [45,47]. Although the increasing severities of reactive astrogliosis transition seamlessly along a continuum, it is convenient to recognize several broad categories.

### 2.1. Terminology

Use of certain terms can vary considerably among authors. We will use “reactive astrogliosis” and “reactive astrocytes” as general all-inclusive descriptors of all forms of astrocyte responses associated with injury or disease. As discussed below, these terms encompass astrocyte responses of considerable diversity and heterogeneity. We will not use “activation” or “activated astrocytes” as terms that solely denote astrocyte responses to injury or disease. Astrocytes in healthy tissue continually exhibit physiological activation in the form of transient, ligand-evoked elevations in intracellular calcium ($[Ca^{2+}]_i$) that represent a type of astrocyte excitability, involved in mediating many critical dynamic astrocyte functions, including interactions with synapses and regulation of blood flow [3,20,49,51]. Astrocyte activation can thus range from physiological contexts in healthy to pathophysiologic contexts involved in mediating or modulating responses to injury and disease. Lastly, we will use the terms ‘glial scar’, ‘astroglial scar’ and ‘scar-forming astrocytes’ only in specific contexts where astrocytes form borders between healthy and necrotic tissue.

### 2.2. Mild to moderate reactive astrogliosis

Mild to moderate reactive astrogliosis consists of changes (up or down) in gene expression that occur together with variable degrees of hypertrophy of cell body and stem processes, without substantive loss of individual astrocyte domains and without astrocyte proliferation [45,47]. There is increased expression of various astrocyte structural proteins such as glial fibrillary acid protein (GFAP) that is somewhat proportional to the degree of reactivity. Mild to moderate reactive astrogliosis is generally associated with mild non-penetrating and non-contusive trauma, or with diffuse innate immune activation (viral infections, system bacterial infections), or with areas that are some distance to focal CNS lesions. In healthy gray matter, individual astrocytes occupy contiguous, essentially non-overlapping domains [11] that are more or less preserved in mild to moderate reactive astrogliosis [54].

### 2.3. Severe diffuse reactive astrogliosis

Severe diffuse reactive astrogliosis included changes (up or down) in gene expression with pronounced upregulation of GFAP, cellular hypertrophy, dispersed astrocyte proliferation and some loss of individual astrocyte domains with overlapping of neighboring astrocyte processes [45,47]. These changes can extend diffusely over substantive areas, and generally occur in response to certain types of infection, or in areas responding to chronic neurodegenerative triggers or multiple areas of small local ischemia. Because there can be considerable tissue reorganization, the potential for resolution and return to normal structure is reduced [47].

### 2.4. Compact astroglial scar formation

Compact astroglial scars derive almost entirely from newly proliferated astrocytes with elongated shapes [53], whose cell processes overlap and intertwine extensively to form compact borders that surround and demarcate areas of severe tissue damage, necrosis, infection or autoimmune-triggered inflammatory infiltration [10,14,17,52,53]. Astrocyte scar borders directly interface with and surround a variety of non-neural cell types in the central core of tissue lesions, including perivascular derived fibroblasts, fibrocytes, pericytes and other glial cells [1,9,24,40,45,47]. The large composite of multicellular lesion core also contains a rich deposit of collagenous extracellular matrix that contains many molecular cues that inhibit axonal and cellular migration [43]. It is noteworthy that glial scar formation is associated with substantive tissue reorganization and structural changes that are essentially permanent and persist even when triggering insults may have resolved.

## 3. Multiple levels of reactive astrocyte heterogeneity

There is a growing awareness of heterogeneity among astrocytes in healthy CNS [50,56]. This awareness, plus observations of different forms of astrogliosis as just discussed, are leading to an