Correspondence

Stem Cell INVESTIGATION

Response to: Where do you come from and what are you going to become, reactive astrocyte?

Maryam Faiz[1,2,3], Andras Nagy[3], Cindi M. Morshead[1,2]

[1]Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Toronto, Ontario, M5S 3E1, Canada; [2]Department of Surgery, University of Toronto, Toronto, Ontario, M5T 1P5, Canada; [3]Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Ontario, M5G 1X5, Canada

Correspondence to: Cindi M. Morshead. Donnelly Centre for Cellular and Biomolecular Research, University of Toronto, Toronto, ON M5S 3E1, Canada. Email: cindi.morshead@utoronto.ca.

Received: 23 June 2016; Accepted: 14 July 2016; Published: 22 July 2016.
doi: 10.21037/sci.2016.07.04
View this article at: http://dx.doi.org/10.21037/sci.2016.07.04

Reactive astrogliosis is the process by which astrocytes respond to central nervous system injury or disease. The origin of these cells is under debate. Herein, we contribute to comments regarding our recent report and discuss the context of our findings.

One of the main goals in the field of neuroscience is to understand the cellular basis and molecular pathways that underlie injury and disease, with the ultimate endpoint being repair and regeneration. Exciting findings have come from the use of novel tools and elegant approaches and models to achieve this end. Recent studies have made some important advances in understanding the role of astrocytes, including an examination of how different subpopulations of reactive astrocytes contribute to various aspects of the post-injury response. Equally important is the question—what is the origin of reactive astrocytes?

Regarding the function of reactive astrocytes, a number of studies proposed the transformation or "de-differentiation" of a subset of reactive astrocytes into multipotent self-renewing cells, as measured by their ability to form neurospheres *in vitro* (1,2). This led to a consideration of these de-differentiated reactive astrocytes as a local source of multipotent cells and in particular, new neurons for brain repair. While the need for new neurons at the injury site was not established, having a local source of cells with multipotent capacity warranted further attention. In our studies we confirmed the presence of multipotent stem cells at the injury site, again using the *in vitro* neurosphere assay, but in contrast, we reported that these multipotent stem cells migrated from the neurogenic subventricular zone (SVZ) lining the lateral ventricles to the damaged cortex after injury (3). The finding that neural stem cells can actually leave their niche and migrate to sites of injury, similar to what has been described for SVZ progenitor cells (4,5), was striking. As discussed by Bocazzi *et al.* differences in the injury models and cellular responses seemed the most obvious explanation for the different reports (6). That said, we went on to show that SVZ-derived neural stem cells could be isolated from different brain regions and in two distinct injury models with varying degrees of damage. Hence, the migration of SVZ-derived neural stem cells is not limited to a single injury paradigm or brain location. Nonetheless, it will be instructive for future studies to conduct a detailed analysis of injury paradigms and brain regions to determine if neural stem cell activity is due to migratory or resident cells or possibly both. It will be critical to use tools and approaches that will enable this distinction.

Astrocytes for neurorepair?

Most interesting was the question of what neural stem cells do, if anything, once they reach the site of injury? We showed that they contribute to the formation of a subpopulation of reactive astrocytes that comprise the glial scar (3). It is well established that reactive astrocytes play both beneficial and detrimental roles after injury (6,7). Hence our results revealed a novel and important role for the SVZ in post-injury astrogliosis. This is in line with findings in the neonatal brain, after hypoxia/ischemia,

where SVZ-derived reactive astrocytes were shown to be responsible for proper scar formation and reduction of microvascular haemorrhaging (8). While astrocyte scars have traditionally been viewed as barriers to central nervous system (CNS) repair, a recent study suggests scar formation is integral to CNS regeneration (9). Transgenic prevention of scar formation or ablation of scar forming reactive astrocytes diminishes axon regrowth (9). The specific role of scar forming reactive astrocytes originating from SVZ-derived neural stem cells may be fundamental to the brain's regenerative response. If this proves to be correct, strategies aimed at converting reactive astrocytes to neurons in an attempt to promote neural repair and functional recovery should be approached with caution. It seems unlikely that losing reactive astrocytes would create an environment more favourable to CNS function; rather, reprogramming these cells could result in impaired function or a diseased state.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Response to: Boccazzi M, Ceruti S. Where do you come from and what are you going to become, reactive astrocyte? Stem Cell Investig 2016;3:15.

doi: 10.21037/sci.2016.07.04
Cite this article as: Faiz M, Nagy A, Morshead CM. Response to: Where do you come from and what are you going to become, reactive astrocyte? Stem Cell Investig 2016;3:32.

References

1. Buffo A, Rite I, Tripathi P, et al. Origin and progeny of reactive gliosis: A source of multipotent cells in the injured brain. Proc Natl Acad Sci U S A 2008;105:3581-6.
2. Shimada IS, LeComte MD, Granger JC, et al. Self-renewal and differentiation of reactive astrocyte-derived neural stem/progenitor cells isolated from the cortical peri-infarct area after stroke. J Neurosci 2012;32:7926-40.
3. Faiz M, Sachewsky N, Gascón S, et al. Adult neural stem cells from the subventricular zone give rise to reactive astrocytes in the cortex after stroke. Cell Stem Cell 2015;17:624-34.
4. Leong SY, Turnley AM. Regulation of adult neural precursor cell migration. Neurochem Int 2011;59:382-93.
5. Dibajnia P, Morshead CM. Role of neural precursor cells in promoting repair following stroke. Acta Pharmacol Sin 2013;34:78-90.
6. Boccazzi M, Ceruti S. Where do you come from and what are you going to become, reactive astrocyte? Stem Cell Investig 2016;3:15.
7. Pekny M, Pekna M. Astrocyte reactivity and reactive astrogliosis: costs and benefits. Physiol Rev 2014;94:1077-98.
8. Benner EJ, Luciano D, Jo R, et al. Protective astrogenesis from the SVZ niche after injury is controlled by Notch modulator Thbs4. Nature 2013;497:369-73.
9. Anderson MA, Burda JE, Ren Y, et al. Astrocyte scar formation aids central nervous system axon regeneration. Nature 2016;532:195-200.

