Commentary

Stem Cell INVESTIGATION

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

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Received: 17 April 2016; Accepted: 27 April 2016; Published: 12 May 2016.

doi: 10.21037/sci.2016.05.02

View this article at: http://dx.doi.org/10.21037/sci.2016.05.02

Astrocytes are fascinating resident cells of the central nervous system (CNS). They overcome neurons in number, and they were long believed to play a mere structural and homeostatic function in the healthy brain and spinal cord. This shortsighted view has now profoundly changed and astrocytes are universally recognized as one of the major players in the response of brain tissue to pathological conditions. In particular, following an acute brain injury (such as stroke or stab wound) but also in chronic degenerative pathologies, astrocytes leave their quiescent state and become activated (1). Reactive astrocytes undergo significant and substantial changes, in fact they: (I) become hypertrophic; (II) up-regulate intermediate filaments [composed of nestin, vimentin and glial fibrillary acidic protein (GFAP)]; (III) activate cell proliferation; and (IV) migrate to the site of injury to form the so-called "glial scar" (1). Reactive astrocytes contribute in a substantial way to the outcome of the lesion by releasing a plethora of different factors and molecules, and whether their reaction is beneficial or detrimental has been (and still is) long debated. In fact, reactive astrogliosis is undoubtedly important for the functional recovery of damaged tissues due to their release of beneficial cytokines and growth factors and thanks to other trophic actions favoring tissue remodeling and repair. Conversely, reactive astrocytes also contribute to the inflammatory process that can become overtly maladaptive when exacerbated and prolonged over time, like in chronic pathologies (2). Moreover, also the glial scar has double-edged sword characteristics: in fact, it physically separates the damaged tissue from the surviving one, thus impeding the spread of damage, but also inhibiting axonal regeneration (1).

A significant advance in our comprehension of the properties and functions of reactive astrocytes came from the demonstration that they can re-acquire stem cell properties and generate multipotent and self-renewing neurospheres when grown *in vitro* (3). Neurospheres are clonal floating aggregates of cells that are normally generated by brain neural stem cells dissected from the more extended neurogenic area in the adult mammalian brain, the ventricular-subventricular zone (V-SVZ), and grown in culture (4). The stem cells that generate neurospheres have the ability to differentiate into the three main brain cell types, namely neurons, astrocytes and oligodendrocytes. Under physiological conditions *in vivo* they predominantly give rise to neuroblasts, which migrate to the olfactory bulb and generate new neurons (5). However, traumatic and ischemic events profoundly affect the fate of these cells, not only by dramatically modifying their environment, but also by recruiting them outside their "natural" migratory pathway towards the injury site, in an often-unsuccessful attempt of regeneration (6). In fact, newborn neuroblasts do not functionally integrate in the damaged tissue, and undergo cell death very quickly.

The paper by Faiz and coworkers (7) unveils a new and unexpected link between reactive astrocytes and V-SVZ neural stem cells, by elegantly showing that in the injured rodent cortex only a subpopulation of reactive astrocytes is endowed with the stem cell-like ability to generate neurosphere: this subpopulation of cells was not already resident in the brain parenchyma, but rather migrated from the V-SVZ after injury. Once reached the damage

site, the majority of V-SVZ-derived cells generates reactive astrocytes and contributes to the formation of the glial scar, as previously suggested by (8). Interestingly, authors also demonstrated that Ascl-1, a transcription factor already known to convert parenchymal astrocytes to neurons (9), is also able to convert V-SVZ-derived reactive astrocytes in neurons expressing the typical neuronal markers doublecortin and NeuN both *in vitro* and *in vivo*, thus highlighting a possible new cellular conversion strategy aimed at enhancing neurogenesis.

Results presented in this article add diversity to the current knowledge on the stem cell potential of reactive astrocytes, and seem to contradict previous papers demonstrating the generation of neurospheres and new neurons from resident parenchymal cells after injury (1,3). As authors correctly state, they have employed different, and less severe, models of stroke with respect to already published data, which affect different brain areas (i.e., only cortex compared to both cortex and subcortical regions). These differences might be responsible of the opposite conclusions raised from data, and this is not surprising. While waiting for a generalization of the observed effects in more standard protocols of acute damage or even in chronic degenerative pathologies, we believe that the paper by Faiz *et al.* has the merit to have unveiled neural stem cells from the V-SVZ as a previously unforeseen source of reactive astrocytes still endowed with a neurogenic potential, which might have important clinical implications. Cells composing the V-SVZ are, in fact, in direct contact with the cerebrospinal fluid, and could therefore be reached more easily by possible pharmacological treatments aimed at boosting their neurogenic activity with respect to cells residing in the brain parenchyma. It has been recently demonstrated that human astrocytes can be reprogrammed to functional neurons by the *in vitro* administration of a cocktail of small molecules acting on epigenetic pathways (10). One could therefore envisage adopting a similar strategy targeting V-SVZ cells *in vivo*. Moreover, the transition through a more "reactive" state in the path to a final neuronal destiny could be fundamental for their correct integration and survival within the damages tissue, since it is driven by the local milieu. It is worth mentioning that, in one of the first published neurogenic protocols *in vitro*, the ability of glial precursor cells to generate new neurons was unveiled thanks to their "de-differentation" to an intermediate reactive astrocytes state (11), thus suggesting the acquisition of a genetic/epigenetic program which favors neurogenesis.

Taken together, a growing amount of literature data is helping us to understand that reactive astrocytes are actually a family of cells with different origins and, possibly, different functions and destiny. Our challenge is now to understand how to promote and foster their intrinsic beneficial traits and to reduce in parallel their detrimental functions, with the final aim of designing an efficient neuroreparative strategy for acute and chronic CNS disorders.

Acknowledgements

M Boccazzi is recipient of a fellowship of the Umberto Veronesi Foundation.

Footnote

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

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doi: 10.21037/sci.2016.05.02
Cite this article as: Boccazzi M, Ceruti S. Where do you come from and what are you going to become, reactive astrocyte? Stem Cell Investig 2016;3:15.