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Detection of mouse endogenous type B astrocytes migrating towards brain lesions

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Abstract Neuroblasts represent the predominant migrating cell type in the adult mouse brain. There are, however, increasing evidences of migration of other neural precursors. This work aims at identifying *in vivo* endogenous early neural precursors, different from neuroblasts, able to migrate in response to brain injuries. The monoclonal antibody Nilo1, which unequivocally identifies type B astrocytes and embryonic radial glia, was coupled to magnetic glyconanoparticles (mGNPs). Here we show that Nilo1–mGNPs in combination with magnetic resonance imaging in living mice allowed the *in vivo* identification of endogenous type B astrocytes at their niche, as well as their migration to the lesion site in response to glioblastoma, demyelination, cryolesion or mechanical injuries. In addition, Nilo1$^+$ adult radial glia-like structures were identified at the lesion site a few hours after damage. For all damage models used, type B astrocyte migration was fast and orderly. Identification of Nilo1$^+$ cells surrounding an induced glioblastoma was also possible after intraperitoneal injection of the antibody. This opens up the possibility of an early identification of the initial damage site(s) after brain insults, by the migration of type B astrocytes.
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Abbreviations: CC, corpus callosum; LPC, lysophosphatidilcholine; mGNPs, magnetic glyconanoparticles; GBM, human glioblastoma; MRI, magnetic resonance imaging; Nilo1–mGPs, monoclonal antibody coupled to magnetic glyconanoparticles; OB, olfactory bulb; PF, paraformaldehyde; RMS, rostral migratory stream, RG, radial glia; SGZ, subgranular zone; SVZ, subventricular zone.

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Introduction

Neural stem cells in adult rodents are mainly restricted to the niches at the subventricular zone (SVZ) in the lateral ventricles and the subgranular zone (SGZ) in the hippocampal dentate gyrus (Doetsch et al., 1999; Palmer et al., 1997; Reynolds and Weiss, 1992; Richards et al., 1992). In the adult SVZ, type B cells express glial markers, have astrocyte characteristics, bundles of intermediate filaments and multiple processes (Doetsch et al., 1999; Peters et al., 1991), and generate neuroblasts (type A cells, neuronal precursors) through a highly proliferative transit amplifying population (type C cells) (Doetsch et al., 1999; Kriegstein and Alvarez-Buylla, 2009). The cell bodies of type B astrocytes are generally located under the ependymal layer of the lateral ventricles, have short processes that extend through it, with small apical endings on the ventricle, in addition to frequently tangentially oriented long basal processes with specialized end feet on blood vessels (Kriegstein and Alvarez-Buylla, 2009; Mirzadeh et al., 2008). Thus, adult SVZ B cells, similarly to the radial glia (RG) during development, retain an apical—basal polarity and are part of the ventricular epithelium (Kriegstein and Alvarez-Buylla, 2009). In fact, although the radial glia disappears postnatally by transformation into parenchymal astrocytes, some radial glial cells persist within the adult SVZ hidden among astrocytes of the glial tubes. This modified radial glia belongs to the astroglial lineage (type B cells) and maintains self-renewal potential and pluripotency, the two stem cell characteristics (Bonfanti and Peretto, 2007; Gubert et al., 2009; Sundholm-Peters et al., 2004).

It is well documented the migration of adult neuroblasts in a pathway known as rostral migratory stream (RMS), in longitudinal clusters from their SVZ niche towards the olfactory bulb (OB), where dying neurons should be replaced (Doetsch et al., 1999; Doetsch and Alvarez-Buylla, 1996; Lois and Alvarez-Buylla, 1994; Lois et al., 1996). In addition, migration of cells from SVZ towards non-olfactory bulb regions in the adult has been reported on several disease or injury models (Arvidsson et al., 2002; Cantarella et al., 2008; Nakatomi et al., 2002; Thored et al., 2006). Surgical RMS disruption led to migration of BdrU$^+$PSA-NCAM$^+$ cells from the SVZ into the anterior olfactory nucleus, the frontal cortex and the *striatum* (Alonso et al., 1999; Jankovski et al., 1998). In addition, in response to an induced brain tumor, the migration of endogenous neuroblasts towards the lesion site could be followed *in vivo* by MRI (Elvira et al., 2012). Although DCX$^+$ neuroblasts are thought to be the major migratory SVZ cells, type C cells might migrate as well (Aguirre and Gallo, 2004). Many of the migration experiments have been done using BrdU-labeled cells, where some, but not all the labeled cells were neuroblasts (Arvidsson et al., 2002; Cantarella et al., 2008; Nakatomi et al., 2002; Thored et al., 2006; Gotts and Chesselet, 2005; Sundholm-Peters et al., 2005). Indeed, several reports suggest that other precursor cells from the SVZ are able to migrate towards a brain lesion site. For instance, on transgenic mice expressing a nestin driven green fluorescent protein (GFP), in response to a glioblastoma, the GFP$^+$ cells surrounding the brain tumor were actively dividing (Ki67$^+$), mushashi$^+$, glial precursors (NG2$^+$), GFAP$^+$, PSA-NCAM$^+$ or DCX$^+$. These phenotypes at the lesion site are compatible with the migration of committed and non-committed precursors (Glass et al., 2005). Time-lapse experiments showed that among the nestin-eGFP$^+$ cells in the SVZ, there were type C cells, GFAP$^+$ cells, neuroblasts, ependymal cells and microglia, where a high percentage of motile nestin-eGFP$^+$ cells were DCX$^-$ (Nam et al., 2007). Taken together, these data suggest that DCX$^+$ neuroblasts do not represent the only motile SVZ-derived cells in the postnatal mouse brain. In cortical injuries, NG2$^+$ cells, Nestin$^+$ GFAP$^+$ cells or SVZ cells able to differentiate into glia were identified in the vicinity of the lesion site at different time points (Glass et al., 2005; Goings et al., 2004; Picard-Riera et al., 2002; Holmin et al., 1997).

We hypothesized that type B astrocytes might be among the other SVZ-derived cell types able to migrate in response to a damage insult. In this study we used Nilo1, a previously characterized mAb that identifies early neural progenitors in the SVZ niche (Del Valle et al., 2010), demonstrating that Nilo1$^+$ cells showed an immunophenotype and subependymal localization compatible with B astrocytes. After coupling Nilo1 mAb to magnetic nanoparticles, we followed by MRI and confirmed by immunohistochemistry the fast mobilization of B astrocytes towards the lesion site, as a trait shared by different brain injuries in adult mice.

Materials and methods

Animals

Experiments involving animals were performed in compliance with the European Union and Spanish laws (Council Directive 86/609/EEC) and approved by the CSIC Committee of Animal Experimentation. For these experiments, 6—8 week old C57Bl/6J mice (males), bred and housed in our animal facility under standard conditions were used. Surgery was performed under anesthesia, and efforts were made to minimize suffering of the animals.

Antibodies

Nilo1 and Nilo2 mAbs were generated by the fusion of hamster B cells and the mouse myeloma X63Ag8, as described (Del Valle et al., 2010). Purification of Nilo1 and Nilo2, biotinylation and Cy5 labeling was from ProteinTools (CNB-CSIC, Madrid, Spain). Commercial antibodies and other reagents are described in Supplementary material Table S1.

Characterization of the protein G-magnetic glyconanoparticles (mGNPs) and coupling to Nilo1

Water-soluble magnetic glyconanoparticles, consisting on a magnetic core (4 nm of diameter) covered with a 1 nm gold shell and coated with carbohydrates and an amphiphilic linker ended in a carboxyl group, were prepared and characterized as previously described (Gallo et al., 2010). Recombinant protein G was covalently immobilized to these particles, which enabled the subsequent capture of IgG antibodies (Gallo et al., 2011; García et al., 2011). Characterization of protein G-glyconanoparticles (mGNPs)

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