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# Different expression of human GFAP promoter-derived GFP in different subsets of astrocytes in the mouse brain

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Transgenic mice expressing green fluorescent protein (GFP) under the control of human glial fibrillary acidic protein promoter (hGFAP) have been utilized for in vivo labeling of astrocytes. Although it has been considered that virtually all astrocytes express GFP in this transgenic mouse, we found that different subsets of GFAP-expressing astrocytes express considerably different levels of GFP in the adult brain. Astrocytes in the spinal cord, the molecular layer of thecerebellum, meninges, white matter, corpus callosum and blood vessels exhibited strong GFP, whereas subsets of astrocytes associated with granule cells in the cerebellum and dentate gyrus did not or only marginally exhibited GFP. We also found that a small subset of GFP-expressing cells in the periglomeruli of the olfactory bulb did not express GFAP immunoreactivity. Collectively, these results suggest that human GFAP promoter-derived GFP expression does not faithfully recapitulate the endogenous GFAP expression in mice, suggesting that upstream regulatory mechanisms controlling GFAP transcription are different in different populations of astrocytes, and may reflect the functional diversity of astrocytes.

**Keywords:** astrocyte; GFAP expression; GFP; transgenic mice; granule cell

## Introduction

Astrocytes are the most abundant neural populations, and their role is critical for the development and maintenance of the brain (Emsley et al. 2004; Araque and Navarrete 2010). Astrocytes are often characterized by their expression of intermediate filament protein, glial fibrillary acidic protein (GFAP), because most astrocytes are believed to express GFAP. Considering that astrocytes are in fact extremely diverse in terms of their morphology and function, there are increasing demands for the identification of novel markers for selective recognition of subpopulations of astrocytes.

The heterogeneity of astrocytes has been addressed at multiple levels, including their developmental origin (Gressens and Evrard 1993; Zhang 2001; Zerlin et al. 2004), morphology (Bailey and Shipley 1993; Ogata and Kosaka 2002; Kimelberg 2004), expression of receptors and ion channels (Sontheimer 1992; Ruzicka et al. 1995; Bordey and Sontheimer 2000; Matthias et al. 2003; Jabs et al. 2005), and differential activation upon brain injury (Kondo et al. 1995; Hill et al. 1996; Morga et al. 1999). Additionally, transgenic mouse lines which express under the control of 2.2 kb human GFAP promoter have been utilized to identify the heterogeneity of astrocytes (Nolte et al. 2001; Lee et al. 2006). So far, several different transgenic lines have been established and extensively utilized for the in vivo identification of astrocytes (Brenner et al. 1994; Zhuo et al. 1997; Casper and McCarthy 2006; Silbereis et al. 2010).

We serendipitously found that transgenic GFP expression and endogenous GFAP expression are dissociated in several brain regions, especially granule cell layers, of hGFAP-GFP transgenic mice generated by Zhou et al. (1997). Our current observation might reflect the differential regulation of GFAP gene transcription depending on the subtype of astrocytes.

## Materials and methods

### *Animals*

Transgenic mice with a 2.2 kb human GFAP promoter driving expression of GFP were obtained from Jackson Laboratories (Bar Harbor, ME, USA, stock #003257) and maintained as hemizygotes on a FVB/N background. The genotypes of the sibling animals were individually confirmed by polymerase chain reaction (PCR) using primers for the GFP gene forward 5′-AAG TTC ATC TGC ACC ACC G-3′ and reverse 5′-TCC TTG AAG AAG ATG GTG CG-3′ to generate a band of 173 bp. In this experiment, we

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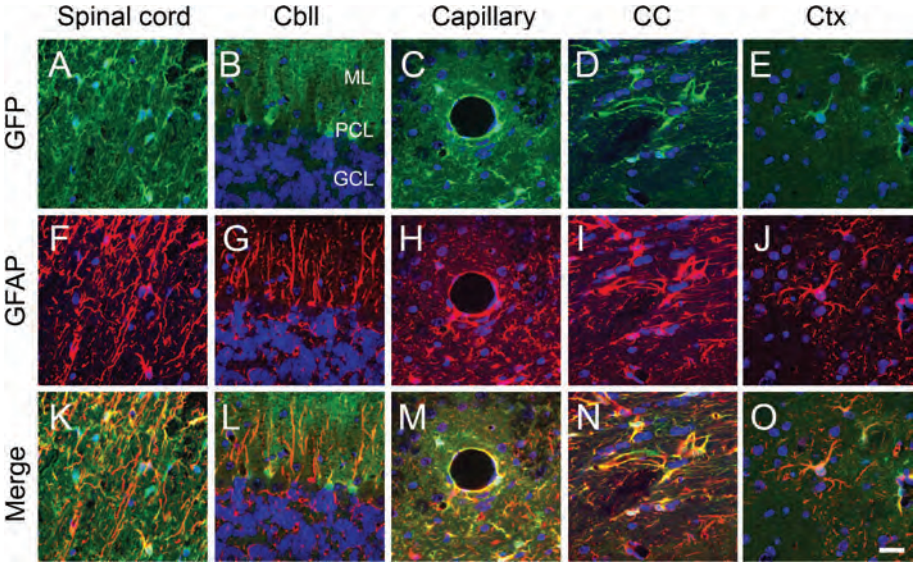


Figure 1. Expression of GFP in GFAP-expressing astrocytes. Most of GFP (A–E, green) labeled cells were co-localized with GFAP-expressing astrocytes (F–J, red) in the spinal cord (A, F, K), cerebellum (B, G, L), capillary (C, H, M), corpus callosum (D, I, N), and cortex (E, J, O). Cbll, cerebellum; CC, corpus callosum; Ctx, cerebral cortex; ML, molecular layer; PCL, Purkinje cell layer; GCL, granule cell layer. Scale bar = 20 μm.

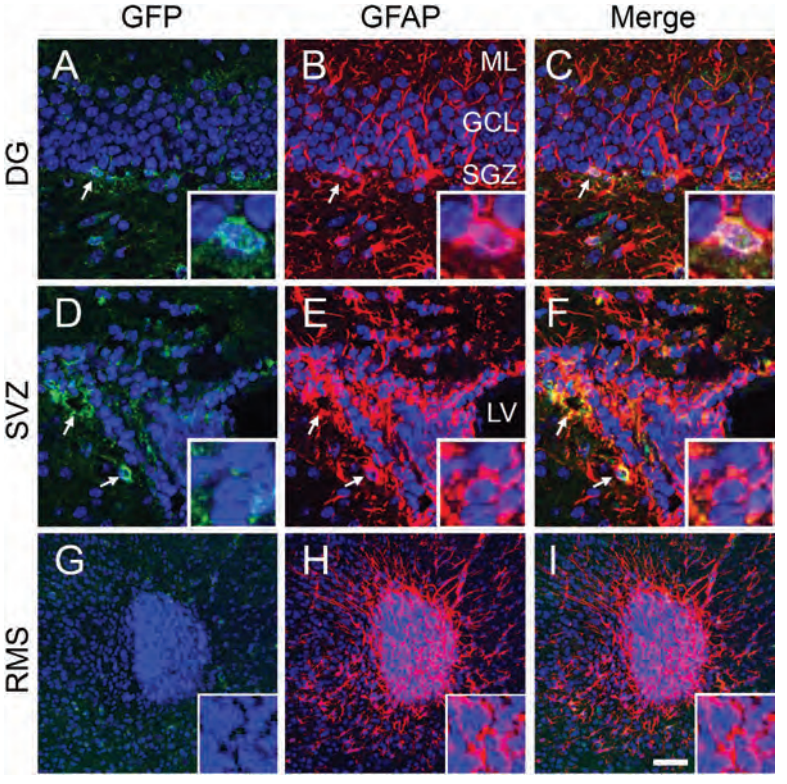


Figure 2. Expression of GFP in neurogenic niches. GFP (A, D, G, green) labeling was found in GFAP-expressing neural stem cells (B and E, red) in neurogenic regions and in GFAP-expressing glial tube in RMS (H, red). Double-labeled cells are indicated by white arrows and displayed in insets. Merged images are shown in C, F, I. DG, dentate gyrus; ML, molecular layer; GCL, granule cell layer; SGZ, subgranular zone; SVZ, subventricular zone; LV, lateral ventricle; RMS, rostral migratory stream. Scale bar = 50 μm.

used 3–5-month-old male mice. All experiments were carried out in accordance with the ethical guidelines of Korea University, and with the approval of the Animal Care and Use Committee of Korea University.

### *Immunohistochemistry*

Immunohistochemical analyses were performed as previously reported (Kim et al. 2007, Kim et al. 2010). Briefly, mice were deeply anesthetized, and perfused with 4% paraformaldehyde. Following post-fixation in the same fixative overnight, isolated brains were cryoprotected in 30% sucrose, sectioned serially (40 μm) and stored in 50% glycerol/50% PBS solution at −20°C until use. GFAP (1:1000, Cell Signaling Technology, Danvers, MA, USA) antibody was applied overnight. After several washes with PBS, Cy3-conjugated donkey anti-mouse IgG (1:500, Jackson ImmunoResearch Laboratories, West Grove, PA, USA) was applied for 30 min. Subsequently, sections were washed, mounted and observed with a confocal microscope (Zeiss LSM510, Goettingen, Germany).

## Results

### *Expression of GFP in GFAP-expressing astrocytes*

GFP was observed in most GFAP-expressing astrocytes (Figure 1), as previously reported (Zhuo et al. 1997). GFAP-expressing cells in the white matter of spinal cord (Figure 1A, F, K) and Bergmann glia cells in the cerebellum (Figure 1B, G, L) exhibited strong GFP. However, astrocytes in the granule cell layer (GCL) of the cerebellum exhibited virtually no GFP. Astrocytes surrounding blood capillaries also exhibited strong GFP (Figure 1C, H, M). The intensity of GFP in the GFAP-expressing astrocytes in the corpus callosum was highly heterogeneous and about 50% of GFAP-expressing astrocytes exhibited strong GFP (Figure 1D, I, N). Overall intensity of GFP in the grey matter of cerebral cortex (Figure 1E, J, O) was weak but significant in most astrocytes.

### *Expression of GFP in neurogenic niches*

In the adult brain, neural stem/progenitor cells localized in the subgranular zone of the hippocampal dentate gyrus (DG) (Figure 2A–C) and the subventricular zone of the anterior lateral ventricle (Figure 2D–F) also express GFAP. Double labeling of GFP and GFAP revealed that both populations of neural stem/progenitor cells appeared to exhibit GFP (Figure 2A, D, inset), which is in consistent with previous reports (Ganat et al. 2006; Liu et al. 2006; Platel et al. 2009). On the other hand, most GFAP-expressing astrocytes in the GCL of DG did not exhibit GFP (Figure 2B). Neuroblasts are produced from neural stem/progenitor cells in the subventricular zone then migrate toward the olfactory bulb (OB) via the rostral migratory stream (RMS). Within the RMS, these migrating neuroblasts do not express GFAP, but surrounding glial cells strongly express GFAP (Kim et al. 2007). In the hGFAP-GFP transgenic mice, RMS did not exhibit significant GFP (Figure 2G–I), indicating that RMS glial cells did not exhibit GFP.

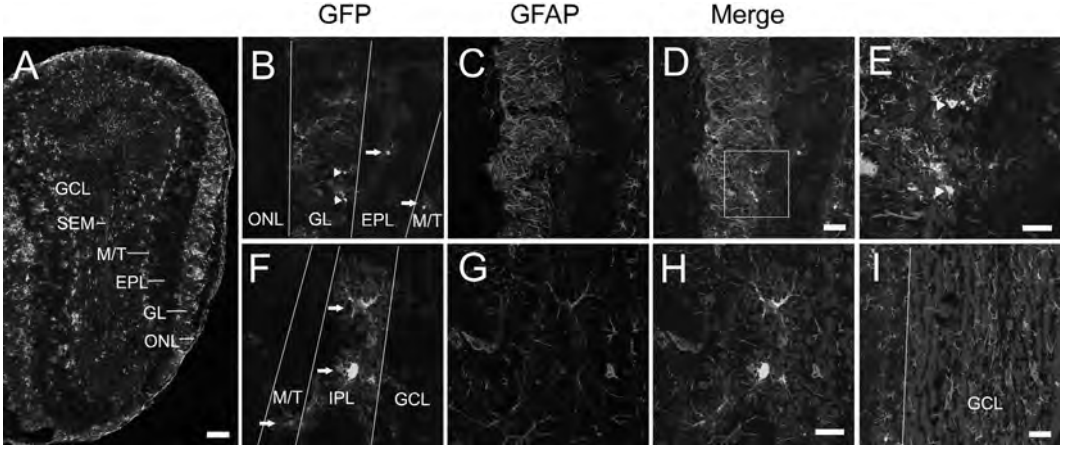


Figure 3. Expression of GFP in the olfactory bulb. Many GFP (B and F, green) labeled cells (arrow) are shown in the glomerular layer (B–E), mitral/tufted cell layer (F–H) and inner plexiform layer (F–H), but not many in the granule cell layer (I). Moreover, some GFP only expressing cells without GFAP were found in the glomerular layer (B, E, yellow arrowheads). GCL, granule cell layer; SEM, subependyma layer; IPL, inner plexiform layer: M/T, mitral and tufted cell layer; EPL, external plexiform layer; GL, glomerular layer; ONL, olfactory nerve layer. Scale bar = 200 μm in A, 50 μm in D, I, 20 μm in E, H.

***Expression of GFP in the olfactory bulb***

Next, we examined the GFP expression in the OB (Figure 3). In the subependymal layer, the terminal inlet of the RMS in the OB, GFAP-expressing astrocytes did not exhibit GFP (Figure 3A). GFP expression was most profound in the inner plexiform layer, mitral/tufted cell layer, and glomerular layer of the OB. Large magnification views of the glomerular layer (Figure 3B–E), inner plexiform layer and mitral/tufted cell layer (Figure 3F–H) show considerable heterogeneity of GFP expression levels among GFAP-expressing astrocytes. For instance, in the inner plexiform layer between the olfactory GCL and the mitral/tufted cell layer, many GFAP-expressing astrocytes exhibited very strong GFP. On the other hand, only small subsets of GFAP-expressing astrocytes exhibited GFP in the GCL and the external plexiform layer between the mitral/tufted cell layer and glomeruli (Figure 3B–D, I). Interestingly, we found that some GFP-expressing cells in the glomeruli exhibited virtually no GFAP immunoreactivity (arrowhead, Figure 3B–D). This may be the first identification of cells exhibiting GFP without GFAP expression in the adult brain.

## Discussion

Transgenic hGFAP-GFP mice have provided useful tools to study the properties of GFAP-expressing cells such as astrocytes and neural stem cells in the brain (Zhuo et al. 1997; Nolte et al. 2001; Su et al. 2004; Liu et al. 2006; Lee et al. 2008). In this study, we confirmed that transgenic GFP was expressed in the astrocytes and neural stem cells in the subventricular zone and the subgranular zone. However, GFP expression levels did not faithfully represent endogenous GFAP expression levels in many brain regions and it appeared that GFP expression was affected by astrocyte subtypes and also by individual differences. Although GFP and GFAP proteins may have different protein stability half-lives, these vast discrepancies in the GFP vs. GFAP expressions cannot be explained solely by their differential protein stabilities. Bac-transgenic mice with sufficiently long hGFAP promoter regions or mice with GFP knock-in into the GFAP locus might be required to clarify this and related issues.

We found that GFP was absent or considerably weak in subsets of GFAP-expressing astrocytes, especially in the GCLs in the cerebellum, DG and OB. In the cerebellum and DG, most GFAP-expressing astrocytes did not exhibit noticeable levels of GFP. On the other hand, a subset ($>50\%$) of GFAP-expressing astrocytes in the olfactory GCL did not express GFP, whereas the rest of the GFAP-expressing cells also exhibited GFP. Astrocytes associated with migrating neuroblasts in the RMS, which will become olfactory granule cells, also did not exhibit GFP. Taken together, most astrocytes associated with granule cell populations appeared to fail to express hGFAP promoter-derived GFP. On the other hand, GFAP-expressing neural stem cells in the subgranular zone of DG expressed detectable levels of GFP, as well as their endogenous GFAP expression. These results indicate that the 2.2 kb upstream regulatory sequence of human GFAP promoter is not sufficient for the expression of downstream genes in these subsets of astrocytes. Similar dissociation of GFAP and GFP expression was also reported in a different line of hGFAP-GFP transgenic mice generated by other researchers (Nolte et al. 2001), suggesting that the differential expression of GFP and GFAP was not due to the transgenic integration site, but related to the differences in the endogenous GFAP promoter vs. 2.2 kb hGFAP promoter. However, Nolte et al. did not examine the GFP expression in the GCLs, and our current report for the first time reveals the striking dissociation of GFAP and GFP expressions in the GCLs. Currently it is yet to be clarified why granule cell-associated astrocytes failed to express hGFAP promoter-derived GFP. However, this obvious correlation raised the possibility that these astrocytes are different from astrocytes in other brain regions in terms of their developmental origin and/or biological function.

Granule cells are small and round neuronal cell populations which are generated during postnatal development (Kuhn et al. 1996; Suhonen et al. 1996; Bahjaoui-Bouhaddi et al. 1997). In the DG, the first granule cells migrate from a primary proliferative zone in the suprapyramidal blade of DG along the primordial radial glial scaffold. In this period, radial glia, a subset of astrocytes, guide granule cells to the target, playing a similar role in neocortex development. However, after birth, migrated stem cells form a secondary proliferative zone in the hilar region as the subgranular zone. It becomes a major source of ongoing postnatal neurogenesis (Eckenhoff and Rakic 1984; Frotscher et al. 2007). Although granule cells migrate a very short distance after this stage, some of the radial glia remain in the hilar region until 2 weeks after birth. Interestingly, most of them transform into normal astrocytes in the DG and hilar region, but a few remaining radial glia start to co-express neuronal precursor markers by turning into adult neural stem cells (Kriegstein and Gotz 2003; Rakic 2003; Garcia et al. 2004; Seri et al. 2004; Brunne et al. 2010). Considering that neural stem cells expressing GFP produce astrocytes in the DG, these results suggest that GFP expression is dependent on the fate of cells from the same lineage. Bergman glia cells in the cerebellum also undergo a similar developmental process with the

DG and transform precursor-like astrocytes for development of the GCLs (Hatten 1999). In contrast to these granule cell-associated astrocytes, most astrocytes are continually derived from neuroepithelial cells in the subventricular zone during early postnatal development (Tramontin et al. 2003; Bonfanti and Peretto 2007). Although it is yet premature to reach a conclusion, these results suggest that different lineages of astrocytes may have different ability to express 2.2 kb hGFAP promoter-derived GFP expression. Alternatively, it is also possible that hGFAP promoter activity is modulated by environmental signals. Astrocytes in the GCLs are surrounded by densely packed granule cell bodies. It is known that reciprocal interaction of astrocytes and surrounding granule cells may play a central role in the development of cerebellum (Lafarga et al. 1993; Yamada et al. 1997). Therefore, interactions between granule cells and glial cells could affect the hGFAP promoter activity.

Another interesting observation in this study is the unique distribution of GFP-expressing cells in the glomerular layer and the plexiform layer of the OB. While GFAP-expressing astrocytes are evenly distributed in the entire OB, GFP expression was more preferentially observed in the inner and outer plexiform layer and glomerular layer. It is known that the morphology of OB astrocytes is highly diverse and closely linked to their function (Reyher et al. 1991; Bailey and Shipley 1993). However, we failed to identify a significant correlation between the morphological classification of astrocytes and GFP expression. On the other hand, a subset of GFP-expressing cells in the periglomerular layer did not express endogenous GFAP protein. Although we do not completely rule out the possibility that there was a leaky expression of GFP in non-astrocytes, the morphology of these small subsets of GFP-expressing cells was indistinguishable from nearby GFAP-expressing astrocytes. Furthermore, we failed to observe any $GFP^+$ neurons in the OB (data not shown). Considering that immature astrocytes do not express GFAP (Pixley and de Vellis 1984; Eng et al. 2000; Chu et al. 2001), these GFP-only cells may be immature or de-differentiated astrocytes in the adult OB, and we are currently examining this idea.

In summary, our current observations suggest that human GFAP promoter-derived GFP expression does not faithfully recapitulate the endogenous GFAP expression in mice, implying the heterogeneity of astrocytes depending on region of the adult brain.

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