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Bone morphogenetic protein-4 inhibits adult neurogenesis and is regulated by fractone-associated heparan sulfates in the subventricular zone

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ABSTRACT

Fractones are extracellular matrix structures that display a fractal ultrastructure and that are visualized as puncta after immunolabeling for laminin or heparan sulfate proteoglycans. In the adult brain, fractones are found throughout the subventricular zone (SVZ). The role of fractones is just emerging. We have recently shown that fractones sequester fibroblast growth factor-2 and bone morphogenetic protein-7 from the brain ventricles to regulate cell proliferation in the SVZ of the lateral ventricle, the primary neural stem cell niche and neurogenic zone in adulthood. Here, we have examined in vivo the effect of bone morphogenetic protein-4 (BMP-4) on cell proliferation in the SVZ and we have determined whether BMP-4 interacts with fractones to promote this effect. To examine BMP-4 effect on cell proliferation, BMP-4 was intracerebroventricularly injected, and bromodeoxyuridine immunolabeling was performed on frozen sections of the adult mouse brain. To identify the location of BMP-4 binding, biotinylated-BMP-4 was injected, and its binding localized post-mortem with streptavidin, Texas red conjugate. Injection of heparitinase-1 was used to desulfate fractones and determine whether the binding and the effect of BMP-4 on cell proliferation are heparan sulfate-dependent. BMP-4 inhibited cell proliferation in the SVZ neurogenic zone. Biotinylated-BMP-4 bound to fractones and some adjacent blood vessels. Co-injection of heparitinase-1 and biotinylated-BMP-4 resulted in the absence of signal for biotinylated-BMP-4, indicating that the binding was heparan sulfate dependent. Moreover, preventing the binding of BMP-4 to fractones by heparitinase-1 reinforced the inhibitory effect of BMP-4 on cell proliferation in the SVZ. These results show that BMP-4 inhibits cell proliferation in the SVZ neurogenic zone and that the binding of BMP-4 to fractone-associated heparan sulfates moderates this inhibitory effect. Together with our previous results, these data support the view that fractones capture growth factors and modulate their activity in the neural tissues lining the ventricles.

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1. Introduction

The cerebrospinal fluid (CSF) circulating in the brain ventricles carries ions and numerous signaling molecules including growth factors, cytokines, chemokines and neurohormones. These signaling molecules are produced by the choroid plexus (Chodobski et al., 1997; Redzic et al., 2005; Stopa et al., 2001; Zappaterra and Lehtinen, 2012), circumventricular organs (Frautschy et al., 1991), and by the ependymal lining (ventricular zone or VZ) and subventricular zone (SVZ) (Bain et al., 2013) that together form the ventricle walls. How do the CSF-borne signaling molecules penetrate from the ventricle to the VZ/SVZ? The ependyma does not form a barrier for the passage of growth factors and other molecules injected in the ventricle (Brightman, 1965; Anderson et al., 1995). Biological molecules reach the SVZ by two routes: trans-ependymal diffusion and direct diffusion in the intercellular space between ependymocytes (Brightman, 1965, 2002). Opened tight junctions (fascia adherens) are found in the luminal side of adjacent ependymocytes, lying in direct continuity with the ventricular lumen, allowing for the passage of the CSF and its signaling molecules. The regular "proof"

Abbreviations: BMP-4, bone morphogenetic protein-4; BrdU, bromodeoxyuridine; CSF, cerebrospinal fluid; ECM, extracellular matrix; FGF-2, fibroblast growth factor-2; HSPG, heparan sulfate proteoglycans; ICV, intracerebroventricular; IgM, immunoglobulin M; LRP-2, low-density lipoprotein receptor-related protein-2; NS-HSPG, N-sulfated heparan sulfate proteoglycans; NSPC, neural stem and progenitor cells; SVZ, subventricular zone; VZ, ventricular zone.

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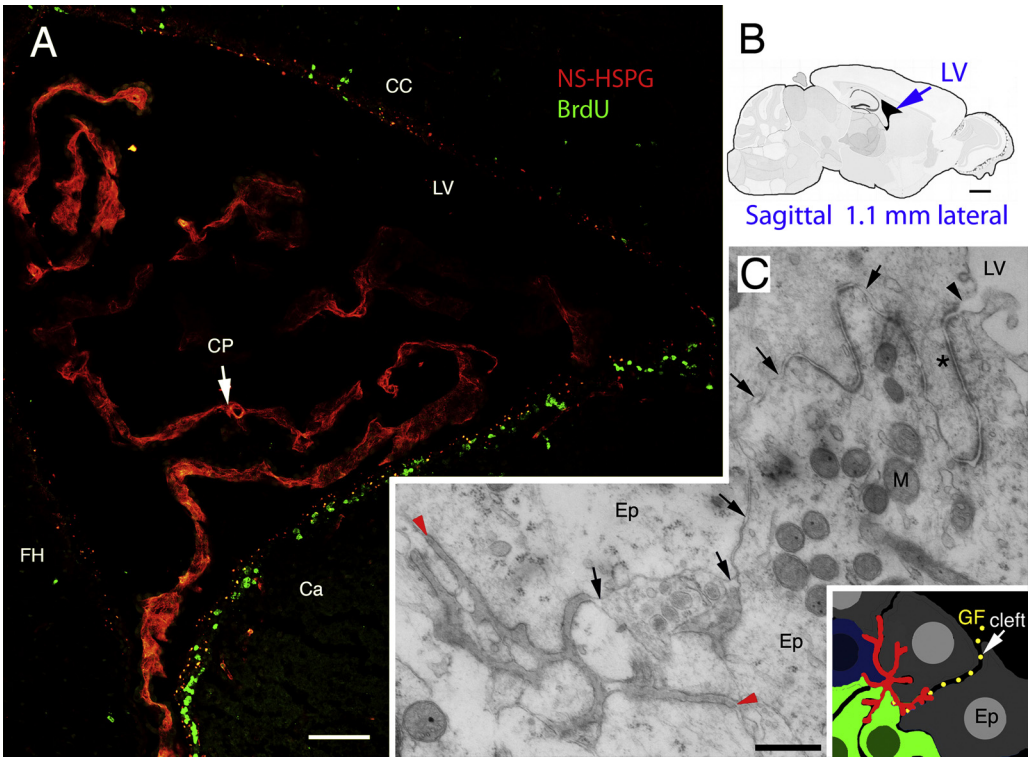

Fig. 1. The specialized ECM structures fractones along the ventricle walls. Intercellular passage of growth factors in between ependymocytes. (A) Immunolabeling for N-sulfated HSPG (red) shows series of puncta along the ventricle walls. Each red punctum along the ventricle walls is a fractone. The choroid plexus (CP) and some blood vessels at the surface of the caudate nucleus (Ca) are also immunoreactive for N-sulfated HSPG (abbreviated NS-HSPG). The most active zone of cell proliferation in the adult brain is located at the surface of the Ca in the SVZ of the lateral ventricle (LV). Proliferating NSPC are visualized by BrdU immunolabeling (green). CC: corpus callosum; FH: fimbria hippocampus. (B) Location of image A (arrow) in a schematic sagittal section of the adult mouse brain. (C) Ultrastructure of a fractone (electron-dense convoluted structure in between the red arrowheads) and an interstitial cleft in the ventricle wall of the LV. The black arrows indicate the trajectory of the interstitial cleft in between the lateral sides of two ependymocytes (Ep); the black arrowhead shows the entrance of the interstitial cleft; a *fascia adherens* (opened tight junction) is indicated by an asterisk. M: mitochondrion. Inset: schematic representation of an interstitial cleft and a fractone in the ventricle wall. Growth factors (GF) diffuse through the interstitial cleft to reach a fractone at the basal side of ependymocyte. NSPC are represented in red. A microglial cell (blue) also contacts the fractone. Scale bars. A: 100 μm; B: 1 mm, C: 1 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

tight junctions, with barrier properties, are located in the portions of the ependyma that cover brain zones containing fenestrated capillaries, such as the median eminence (Mullier et al., 2010) or are found at the level of the choroid plexus epithelium (the stroma of the choroid plexus has fenestrated capillaries, thus a barrier is required in the choroid plexus epithelium). Therefore, in most zones of the brain ventricles, there is no barrier between the ventricles and the brain tissues. Once having gained access to the intercellular space via the fascia adherens, the CSF and its molecules are free to diffuse into "labyrinthine spaces" named interstitial clefts (Brightman, 1965, 2002) (Fig. 1C). The ends of interstitial clefts, on the basal side of ependymocytes, are occupied by specialized extracellular matrix (ECM) materials that display a fractal morphology after observation by transmission electron microscopy (Mercier et al., 2002). Each of these ECM structures is named a fractone (Mercier et al., 2002, 2003). The ultrastructure of a fractone, a fascia adherens and an interstitial cleft are shown in Fig. 1C and are schematized in the inset of Fig. 1C. In the adult mammalian brain, fractones are located all along the walls of the ventricles, including those of the spinal canal (Kerever et al., 2007; Mercier et al., 2002, 2003).

Fractones consist of highly concentrated ECM molecules: collagen IV, laminin, nidogen and heparan sulfate proteoglycans (HSPG) (Kerever et al., 2007). Despite their fractal ultrastructure, fractones are visualized as puncta with the resolution of light microscopy, after immunolabeling for their components (Mercier et al., 2002; Mercier and Arikawa-Hirasawa, 2012). Therefore, fractones are fundamentally different from basement membranes, which define coverings located between the connective tissue, the vasculature and the parenchyma of tissues (Mercier and Hatton, 2004). Fig. 1A shows series of fractones immunolabeled for N-sulfated HSPG and associated proliferating cells immunolabled with BrdU in the SVZ of the lateral ventricle.

The SVZ located at the surface of the caudate nucleus is the most active neurogenic zone throughout adulthood (Fig. 1A) (Das and Altman, 1970; Mercier and Arikawa-Hirasawa, 2012). The proliferating cells are neural stem and progenitors cells (NSPC) (Lois and Alvarez-Buylla, 1993). The SVZ covering the corpus callosum also contains proliferating NSPC, although to a lesser extent (Fig. 1A). SVZ NSPC display processes that directly contact fractones (Mercier et al., 2002). Other zones such as the rostral migratory stream and the hippocampus are also neurogenic in adulthood (Lois et al., 1996; Seki, 2002) but are not located near a ventricle.

It is now established that proliferation and differentiation of neural stem and progenitor cells in the SVZ is regulated by multiple growth factors (Colak et al., 2008; Douet et al., 2012, 2013; Lim et al., 2000; Lai et al., 2003; Liu et al., 2004; Wachs et al., 2006). These growth factors circulate in the ventricular CSF and may originate from the choroid plexus (Redzic et al., 2005; Stopa et al., 2001) although the source of growth factors regulating the stem cell niche remains unknown.

We have recently demonstrated that fibroblast growth factor-2 (FGF-2) and bone morphogenetic protein-7 (BMP-7) enter the SVZ and bind to heparan sulfates proteoglycans (HSPG) located in fractones, and to a lesser extent adjacent vascular basement membranes, after intracerebroventricular (ICV) injection (Douet et al., 2012, 2013). Moreover, the binding of FGF-2 and BMP-7 is

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