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CSF makes waves in the neural stem cell niche

Neil Dani[1] and **Maria K. Lehtinen**[1,*]

[1]Department of Pathology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, 02115, USA

Abstract

Adult neural stem cells reside in specialized niches that maintain neurogenesis, but the components of the niche and its secretome are only partially understood. Silva-Vargas et al. (2016) show that the choroid plexus, within the lateral ventricles of the adult brain, secretes signals that regulate adult neurogenesis in an age-dependent manner.

Neural stem cells (NSC) rely on extrinsic cues to optimally guide their identity, proliferation, and maintenance. Extrinsic signals can arise from diffusible morphogen gradients within tissue (e.g. Toyoda et al., 2010), from the blood (e.g. Katsimpardi et al., 2014; Villeda et al., 2011), or from the cerebrospinal fluid (CSF; e.g. Chau et al., 2015; Kokovay et al., 2012; Lehtinen et al., 2011) and regulate NSC function in a complementary manner to well-characterized genetic programs (Kriegstein & Alvarez-Buylla, 2009; Bjornsson et al., 2015). A key challenge in the field has been determining the identities and principal sources of specific fluid-borne signals within the adult stem cell niche. The identification of these cues could have tremendous potential for unlocking brain plasticity for repair and rejuvenation of the aging brain. In this issue of *Cell Stem Cell*, Fiona Doetsch and colleagues provide compelling *in vitro* and *in vivo* evidence supporting the model that the choroid plexus within the lateral ventricle secretes signals into the CSF to instruct adult neurogenesis in an age-dependent manner (Silva-Vargas et al., 2016). The findings suggest that impaired choroid plexus/CSF signaling in aging may contribute to age-associated neurologic diseases.

Silva-Vargas and colleagues focus on the ventricular-subventricular zone (V-SVZ). Quiescent neural stem cells (qNSCs, or type B cells) within this niche produce olfactory interneurons as well as astrocytes and oligodendrocytes. qNSCs extend a single primary cilium into the lateral ventricle while maintaining contact with endothelial cells in the vascular plexus. qNSCs can be activated (aNSCs) and generate transit amplifying cells (TACs, or type C cells), ultimately producing neuroblasts or glia (see Figure 2A in Silva-Vargas et al., this issue). As the V-SVZ niche is adjacent to CSF-filled lateral ventricles, an obvious question is whether, and how, qNSCs and their primary cilia sense and react to signals within the CSF. Periventricular NSCs have previously been shown to sense instructive cues including IGF2 in the CSF during embryonic development (Chau et al., 2015; Lehtinen et al., 2011). Kokovay and colleagues provided evidence for a similar model

*Correspondence: maria.lehtinen@childrens.harvard.edu.

for the adult V-SVZ, showing that interleukin 1β (IL-1β) is secreted by the choroid plexus into CSF and sensed by qNSCs to regulate lineage progression (Kokovay et al., 2012).

The authors provide intriguing evidence for a diverse cast of signals secreted in the CSF by the adult choroid plexus. They find that both choroid plexus-conditioned medium (termed 'LVCP*sec*') collected in culture and CSF collected from native brains promote NSC colony formation and proliferation *in vitro*. LVCP*sec* is sufficient to support colony formation of FACS-purified qNSCs, aNSCs, and TACs. Further, these self-renewing spheres retain the ability to differentiate into neurons, astrocytes, and oligodendrocytes – a hallmark of neural stem cells. Remarkably, intraventricular infusion of concentrated LVCP*sec in vivo* stimulates the proliferation of V-SVZ astrocytes and progenitors, suggesting fluid-based signaling actions on multiple target cell types.

Heterochronic cultures of NSCs grown with CSF from young adults (2 months old), or aged adults (18 months old) reveal that these effects are age-dependent: growing young aNSCs with young LVCP*sec* stimulates more robust proliferation when compared to these same aNSCs cultured with aged LVCP*sec*. LVCP*sec* from young adults is also more effective than LVCP*sec* from aged adults in stimulating aged aNSCs to form clones, and these effects are accompanied by rescue of age-associated decreases in aNSC differentiation. Transcriptome and proteomic analyses of young *vs*. aged lateral ventricle choroid plexus tissue reveal how the choroid plexus secretome changes with advanced age. The authors find changes in many different secreted ligands and molecules, some of which have previously been implicated in NSC regulation. They also identify a number of candidate factors including BMP5 and IGF1, that are enriched in young LVCP*sec* and which, in further experiments show a robust ability to independently stimulate neurogenesis *in vitro.* Other candidates likewise increase clonal NSC growth. Future studies should further test the dose-dependence of these effects. In addition, gene ontology analyses reveal diverse biological pathways including the regulation of neuropeptide and hormone synthesis, extracellular matrix remodeling, and immune modulation that change in the choroid plexus in an age-dependent manner.

These exciting findings extend to the adult and aging brain the notion of age-specificity of CSF-stem cell interactions previously described during embryonic forebrain development (Chau et al., 2015; Lehtinen et al., 2011). Interestingly, many secreted factors identified by Silva-Vargas and colleagues in young adult lateral ventricle choroid plexus (e.g. BMP5 and IGF1) are already prominent in fetal choroid plexus (Lun et al., 2015), providing candidate mechanisms underlying previous findings that embryonic CSF can support adult NSCs *in vitro* (Lehtinen et al., 2011). Further examination of similarities and differences between pre-natal or early post-natal CSF should help identify additional common factors that support neurogenesis across the lifespan.

Together, these findings raise a key question: *What controls factor secretion from the choroid plexus?* Choroid plexus epithelial cells form the blood-CSF barrier and are the workhorse of CSF production. The choroid plexus transcriptome and secretome are regionalized across ventricles (Lun et al., 2015), and the tissue is responsive to a dizzying array of physiological states and challenges. This arrangement raises the intriguing possibility that the choroid plexus-CSF system may serve as a regulator of brain

homeostasis, serving both as sensor of systemic signals and generative source of a plethora of signaling molecules. Given these previous and current findings, it is possible that choroid plexus regulation and secretion of hundreds of signals into the local CSF can tightly control different brain microenvironments in an age, ventricle, and state-dependent manner. In future, it will be important to test if the magnitude of effects observed using younger LVCP*sec* alone are sufficient to influence olfactory (Katsimpardi et al., 2014) and other behaviors.

Silva-Vargas et al. attempt to explain the age-dependent effects of LVCP*sec* on adult neurogenesis by focusing on the favorable effects of signals enriched in younger LVCP*sec*. While these signals are certainly important, it is possible that the suboptimal effects of older LVCP*sec* may also be explained, in part, by increasing concentrations of deleterious factors and/or inappropriate regulation of secretion with age. This could come about, for example, due to maladaptive changes in the choroid plexus itself over the course of aging and age-associated diseases – an important but understudied phenomenon. Defining minimal cocktails of factors that can drive favorable CSF-based active signaling and counteract maladaptive signals should pave the way for future synthetic CSF supplementation therapies in oncogenic diseases like glioblastoma, neurodegenerative diseases like Parkinson's Disease, and in neuroprotective strategies for the aging nervous system.

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