

PERSPECTIVE

ENDOTHELIAL CELLS MAINTAIN NEURAL STEM CELLS QUIESCENT IN THEIR NICHE

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Abstract—Niches are specialized microenvironments that regulate stem cells' activity. The neural stem cell (NSC) niche defines a zone in which NSCs are retained and produce new cells of the nervous system throughout life. Understanding the signaling mechanisms by which the niche controls the NSC fate is crucial for the success of clinical applications. In a recent study, Sato and colleagues, by using state-of-the-art techniques, including sophisticated *in vivo* lineage-tracing technologies, provide evidence that endothelial amyloid precursor protein (APP) is an important component of the NSC niche. Strikingly, depletion of APP increased NSC proliferation in the subventricular zone, indicating that endothelial cells negatively regulate NSCs' growth. The emerging knowledge from this research will be important for the treatment of several neurological diseases. © 2017 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: neural stem cells, vascular niche, microenvironment, endothelial cells.

INTRODUCTION

Tremendous advances have been made in our understanding of the signals that promote stem cell

quiescence in various tissues (Birbrair and Frenette, 2016; Borges et al., 2017). Nevertheless, deciphering the complex mechanisms involved in this process may be very challenging in the brain. In a recent article in *Development*, Sato and colleagues revealed an important component of the neural stem cell (NSC) niche: an endothelial cell-derived molecule that keeps NSCs' quiescence in the subventricular zone *in vivo* (Sato et al., 2017). The authors identified by *in vitro* assays soluble amyloid precursor protein (APP) as an extrinsic cue that suppresses NSCs' growth, and enhances neurosphere-forming ability, while retaining their multipotency. Furthermore, Sato and colleagues investigated the role of APPs on NSCs *in vivo* by using APP-null mouse model. The authors discovered that, in the absence of APP, NSCs' proliferation in the subventricular zone increases, suggesting that APP is important for NSCs' quiescence in their niche (Sato et al., 2017).

Additionally, using state-of-the-art lineage-tracing Cre/loxP-mediated technologies, the authors deleted APP specifically in endothelial cells, or in NSCs and astrocytes. These experiments revealed that endothelial cells, but not astrocytes, regulate NSCs' proliferation in the subventricular zone via APP (Sato et al., 2017). This study uncovers an important molecular component of the NSC microenvironment: APP derived from endothelial cells.

The main findings from this study are based on the data obtained from Tie2-Cre/APP-floxed mice (Sato et al., 2017). It is known that Tie2-Cre mice exhibit Cre recombinase activity in both hematopoietic and endothelial cells (Tang et al., 2010). Thus, it is possible that the effect on NSCs could be due to a specific hematopoietic cell in which APP was deleted in Tie2-Cre/APP-floxed mice. To perform endothelial-specific gene targeting, a more specific mouse model should be used in future studies, i.e. VE-Cadherin-CreERT2 mice (Park et al., 2017). In VE-Cadherin-CreERT2/APP-floxed mice will be possible to temporally control APP expression in the endothelium. Interestingly, endothelial cells are heterogeneous in their distribution and function. Thus, endothelial cells may vary between different segments of the vasculature within the same organ (Aird, 2007; Paiva et al., 2017). It remains unknown, for instance, whether all endothelial cells are important as a niche for NSCs or a specific subtype (arteriolar, venular, or capillary). Deciphering the molecular

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Abbreviations: APP, amyloid precursor protein; NSC, neural stem cell.

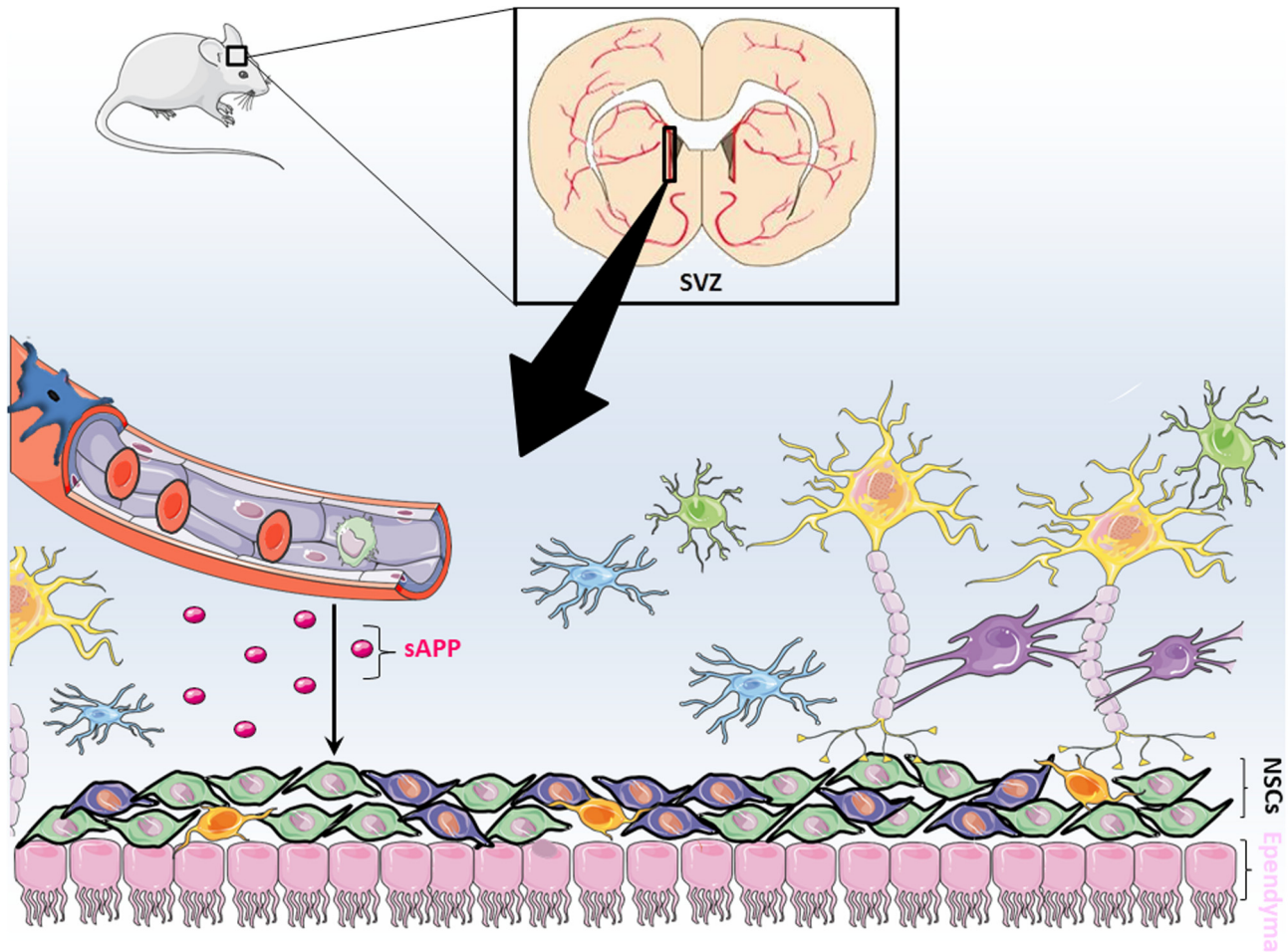


Fig. 1. Endothelial cells create a stem cell niche in the subventricular zone. Neural stem cell (NSC) niche is a specialized microenvironment that regulates NSCs' activity. Sato and colleagues now suggest that endothelial cells present in the subventricular zone secrete soluble amyloid precursor protein (sAPP) which inhibits NSC proliferation (Sato et al., 2017).

differences of endothelial cells in the brain may bring novel concepts about their role as NSC niche cells.

As the molecular functions of proteins may depend on the specific area of the tissue in analysis in which they are produced, restricting gene manipulation to specific brain regions and time will be very useful in understanding the function of specific genes in complex microenvironments, such as the brain. In this scenario, the use of viral vectors to deliver transgenes, such as APP floxed, into CreER-bearing mice comes as a powerful tool. Viral vectors may integrate into both post-mitotic and dividing cells, generating little or no immune response, and expressing stably these transgenes over several months (Lai and Brady, 2002).

In the adult brain, an arterial network covers its surface, and terminates in capillary beds; blood vessels supply the brain with oxygen and glucose, and assure that metabolic end products are removed to maintain tissue homeostasis (Anstrom et al., 2002). The subventricular zone is extensively vascularized by a rich plexus of blood vessels (Ihrle and Alvarez-Buylla, 2011). Vascular niches play important roles supporting stem cells in different organs (Kunisaki et al., 2013; Birbrair and Frenette,

2016; Khan et al., 2016; Asada et al., 2017; Borges et al., 2017; Lousado et al., 2017), including the brain (Goldberg and Hirschi, 2009). The vascular niches themselves are heterogeneous and contain distinct cell populations besides endothelial cells (Sena et al., 2017a,b), including vascular smooth muscle cells (Wanjare et al., 2013), perivascular microglia (Guillemin and Brew, 2004), perivascular adventitial cells (Crisan et al., 2012), perivascular fibroblasts (Soderblom et al., 2013), perivascular macrophages (Bechmann et al., 2001; Prazeres et al., 2017; Birbrair et al., 2017a,b, 2011, 2014a,b,c, 2013a,b, c,d, 2015; Birbrair and Delbono, 2015; Dias Moura Prazeres et al., 2017; Coatti et al., 2017; Santos et al., 2017). Interestingly, possibly perivascular macrophages were also targeted in Tie2-Cre/APP-floxed mice. Future studies will elucidate what is the relationship between distinct components of the vascular NSC niche. It remains unknown whether those other vascular cells also produce APP. Notice that APP is also produced in large quantities in neurons (Lee et al., 2008), and hypothalamic neurons are a key component of the SVZ NSC niche (Andreotti et al., 2017). Future studies should analyze the influence

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