Pericytes

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Pericytes are increasingly recognized as being important in the control of blood–brain barrier permeability and vascular flow. Research on this important cell type has been hindered by widespread confusion regarding the phenotypic identity and nomenclature of pericytes and other perivascular cell types. In addition, pericyte heterogeneity and mouse–human species differences have contributed to confusion.

Alzheimer's disease | blood–brain barrier | endothelial cell | laminin | multiple sclerosis | pericyte | perivascular macrophage | sonic hedgehog | vascular smooth muscle cell

1. Introduction

Pericyte biology is a growing field which focuses on the role of pericytes (PCs) in vascular homeostasis and disease. While PCs can be found surrounding microvasculature throughout the body, they are of particular importance to the blood–brain barrier (BBB) where they surround endothelial cells (ECs) and, in conjunction with astrocytes, help to establish a selectively permeable cellular system. A majority of research on PCs and the BBB uses mice and mouse models of diseases, and relatively little neurovascular research is conducted in humans. Mice may be a more accessible model; however, studies suggest that differences within the vascular anatomy of mice when compared to humans, or even other strains of mice, may make it difficult to make side-by-side comparisons [1][2]. It is becoming increasingly important to consider new and meaningful ways to investigate the role of vascular elements, such as microvascular PCs, in human tissue. Some of the roles that PCs play in BBB homeostasis and brain pathology are already known and can be further defined through closer investigations.

Under physiological conditions, PCs produce extracellular matrix and other proteins which contribute to the formation of basement membranes and regulate BBB homeostasis [3][4]. Additionally, PCs play an important role in promoting production of tight junction proteins (TJPs), which are essential for creating the tight seams found between ECs of the BBB [5][6]. While PCs affect endothelial tight junction formation via several pathways including transforming growth factor-β1/SMAD signaling [7], it was recently shown that the Sonic Hedgehog (Shh) signaling pathway in PCs may mediate the effect of PCs on TJP production by ECs [8].

The Shh pathway supports the selective permeability of the BBB by promoting the upregulation of TJP production by activating the transcription factor GLI1 [9]. Shh is secreted in a soluble form from astrocytic endfeet into the BBB, where it then binds to patched-1 receptors on the EC surface, releasing smoothened to activate GLI1-induced TJP transcription, but recently other contributors, produced in PCs, to this pathway have been discovered [10][11][12].

Developing a deeper understanding of how PCs work to regulate BBB homeostasis could ultimately lead to therapeutic advances in maintaining the ideal homeostatic conditions of the neurovasculature, thus preventing or reducing the pathological effects of BBB breakdown.

In addition to their role in maintaining BBB homeostasis, PCs have been implicated in pathological processes leading to many neurological disorders. The normal production of pericytic laminin-211 is involved in oligodendrocyte progenitor cell maturation during remyelination, and a lack of PCs or an inability for PCs to produce laminin-211 can result in myelin defects [13][14]. Based on these data, PCs are currently being considered as a new therapeutic target for treatment of demyelinating diseases such as multiple sclerosis (MS). Similarly, like ECs, PCs have been shown to express low density lipoprotein receptor-related protein 1 (LRP1), which, in conjunction with apolipoprotein E (apoE), can transport amyloid beta (Aβ) across the BBB as an export mechanism to remove it from the brain parenchyma [15]. This could indicate a role for PCs in Alzheimer's disease. While PCs are being found in association with these and other diseases and disorders of the brain, it is still unclear whether specific PC subsets may play different roles in vivo, or whether PCs can change their phenotype or function under pathological conditions.

2. Pathological PC Subsets in the Human Brain

In addition to the complexities of identifying PC from other vascular and perivascular cell types, a pathological subset of neurovascular PCs has recently been identified [8][16]. Following nomenclature set by the cancer field, physiological capillary PCs were termed Type-1 Pericytes (PC1), while the pathological subset of these capillary PCs were termed Type-2 Pericytes (PC2) [16][17]. Both subsets can be found on brain capillary vessels of less than 10 µm in luminal diameter and of the same branching order, but whether these correspond to mesh PCs or thin-strand PCs is unclear [16].

2.1. Origin of PC2

In our recent study examining PCs in the brains of humans and nonhuman primates, it was found that uninfected infant rhesus macaques demonstrated few to no PC2 in cortical tissue, which contains almost exclusively capillary PC1 [16]. While PC populations shift during aging or simian immunodeficiency virus infection from PC1 to PC2-dominant populations, the total number of PCs remains largely unchanged except in the most advanced stages of disease where PC loss is observed [8][16]. One proposal which would explain this phenomenon is that PC1 are transitioning to a PC2 phenotype under pathological conditions in vivo. This phenomenon was demonstrated in vitro when SMA-negative primary human PCs became SMA-positive after treatment with TGF-β1 [18][19]. While it is tempting to speculate this change will increase the contractility of microvascular PCs and affect cerebral blood flow, it is yet unclear whether SMA expression leads to or reflects further permanent change in PC phenotype. Visualizing this transition in vivo in human tissue is not practically possible, but future studies in animal models may be able to confirm PC1-to-PC2 transition in vivo.

A PC1-to-PC2 transition is consistent with the environmental sensitivity attributed to PCs and their role in maintaining BBB homeostasis, but, thus far, appears to be limited in vivo to transitioning from one PC subset to another. Some studies have suggested that PCs may demonstrate multipotent or pluripotent capabilities acting as an adult stem cell in the CNS, but recent in vivo studies have had difficulty initiating these stem cell-like activities from PCs under standard physiological or pathological conditions [20][21]. While ability of PC1 to switch to PC2 in vivo has yet to be confirmed, it seems more likely than the alternative, which would be a replacement of PC1 by new PC2 originated from precursors.

2.2. Identifying PC2

Early studies of PCs were often limited by the lack of specific markers, due in part to the existence of PC subsets [22][23][17]. An early study looking at PCs in tumorigenesis introduced the idea of a pathological PC subset after noting different cellular markers for PCs associated with normal vasculature, and PCs associated with tumor vasculature [17]. In this study, the authors demonstrated that tumorigenic PCs, termed PC2, express SMA, but this is neither the first nor the last study to show the presence of SMA on capillary PCs [17].

Studies dating back to 1985 have shown the presence of SMA on a subset of capillary PCs, calling into question the traditional view that PCs were SMA-negative and VSMCs were SMA-positive [24][25]. One explanation for a series of conflicting reports in literature on the presence of SMA in capillary PCs would be the presence of a SMA+ pathogenic PC subtype [24][25]. More recent studies have elucidated more information on the differences between these two PC subtypes [26][16][27]. One study identified two distinct but unnamed PC subsets, one which is CD90-positive with limited expression of SMA, and one being CD90-negative with higher expression of SMA and PDGFRB [27]. Another study used mesenchymal angioblasts to induce the development of PC1, PC2, and VSMC from progenitors and found that PC1 express PDGFRB, but not SMA, while PC2 express SMA and PDGFRB. Both lacked a VSMC marker MYH11 [26]. This same study found that PC1 expressing VCAM1 and CD274 could distinguish PC1 from the DLK1-expressing PC2 [26]. The use of SMA and MYH11 in combination as distinguishing markers was recently confirmed in vivo when a PDGFRB+/SMA−/MYH11− phenotype was successfully used to identify PC1, PDGFRB+/SMA+/MYH11− for PC2, and PDGFRB+/SMA+/MYH11+ marked only VSMCs in the brains of rhesus macaques and humans [16]. While other markers, including nestin, are shown to be expressed in a subpopulation of PCs in the mouse brain [28], further research is needed to determine their expression profiles in PC1 versus PC2.

Not only do PC1 and PC2 have different markers, but data suggest that they likely also have different functions. Numerous studies have described morphological differences between PCs particularly in aging or diseased individuals [26][17][29]. When identifying the two distinct PC subsets, PC1 have the traditional thin bump on a log morphology with a small amount of extracellular matrix, while PC2 are hypertrophied with a greater amount of extracellular matrix and may contain dark granules [8][27][29][30]. These morphological differences may speak to differences in their function and help to elucidate their role in BBB homeostasis and disease.

3. Conclusions

PCs are an important and complex player in maintaining BBB microvasculature in both health and disease, but the identification of PCs within the neurovascular niche has had a convoluted history further complicated by an oversimplified view of pericytic hierarchy and architectural complexity. Many of the early discrepancies in PC literature may be explained by either misidentification of other cellular populations, or differences between PC subsets and their ability to transition from one subset to another under changing environmental conditions. With this novel insight comes new implications for the role of PCs in neurological diseases and disorders and a new framework within which we can study their impact on BBB homeostatic regulation and deterioration. Future research aiming to understand the role of PCs in brain physiology and pathology would benefit from novel techniques to investigate and differentiate them, as there is a substantial pool of novel information yet to be gained by investigating the role of PCs and PC subsets in human disease.

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