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The vascular niche and its basement membrane

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Over the past few years, scientists have realized that many cellular and developmental processes, including pancreatic β-cell growth and differentiation, stem cell and progenitor cell proliferation and cancer cell metastasis, occur in what are known as 'vascular niches'. Despite increasing numbers of reports on these niches, few common mechanisms have been identified to explain their various effects. Here, we define the term 'vascular niche' and suggest that a common and conserved feature of this niche is to provide a basement membrane to cells that are unable to form their own. We further propose that these cells require a vascular niche when they retain a high degree of plasticity.

Introduction

The environment of a cell affects its differentiation, survival and proliferation. This environment can be termed a 'niche' and is specific for the cell in question. For example, a stem cell niche enables stem cells to self-renew and to give rise to various different cell types within a given tissue. During the past few years, stem cell research has become popular because of a possible therapy using stem cell-based tissue replacement [1–4]. However, it is still difficult to extract stem cells from any given tissue and maintain these cells in culture, because their *in vivo* niches are difficult to reconstitute *in vitro* [5,6]. The same holds for pancreatic β-cells, which can proliferate *in vivo* to adjust to an increased demand for insulin but are difficult to expand *in vitro* without losing their endocrine function [7,8]. Thus, the therapeutic potential of stem cells and differentiated cells can be fully exploited only if the components of their particular niches and their roles are better understood [6].

In addition to promoting normal growth and tissue homeostasis, a niche can contribute to disease development. For example, metastatic tumors prefer certain tissue locations, or niches, for their growth [9,10]. Knowledge about the tumor niche can therefore be used to make this niche uninhabitable for tumor cells [5]. However, the molecular components of a tumor niche and their specific roles in tumor cell homing and growth must first be identified if we are to succeed in halting spread and growth of tumors.

The term 'vascular niche' has been used for when an important step in cellular development happens in close proximity to blood vessels (Figure 1) [11]. During the past few years, however, the term has mainly been applied to certain stem and progenitor cell niches that are particularly rich in blood vessels [11–16].

Blood vessels are formed by vascular endothelial cells and mural cells (Figure 1a), and they are generally required to provide cells and tissues with oxygen and nutrients. However, the finding that endothelial cells are found in direct contact with certain cell types suggests a special role of vascular cells beyond their role as suppliers of oxygen and nutrients [11]. This notion has been supported by the finding that co-culture with isolated endothelial cells or blood vessels positively affects proliferation and differentiation of many cells and tissues [16–20].

Here, we propose that vascular niches share the ability to provide a basement membrane to cells that are unable to form their own. We discuss the fact that the vascular basement membrane is a conserved feature of vascular niches and is used in combination with tissue-specific components to create cell- and tissue-specific vascular niches. Finally, we discuss the importance of the knowledge of these niches for better understanding complex human diseases, such as cancer and type II diabetes.

What is a vascular niche?

To avoid overuse of the term 'vascular niche' and its application to any blood vessel that happens to be in close proximity to a stem cell or developing cell, it is important to first define what it means. We propose that this term can be used for a microenvironment that is generated by endothelial cells and/or mural cells and that affects the behavior of adjacent cells (Figure 1). The term 'vascular niche' does not exclude an influence of non-vascular cells in the niche.

Experimental evidence for a vascular niche

To provide evidence for the existence of a vascular niche, it is essential to show that it is not only the blood supply that supports the cells in question. This can be achieved by several means. One way would be to reproduce the effects of the vascular niche by co-culturing cells with endothelial cells or mural cells. For example, in co-culture experiments, endothelial cells induce endocrine pancreatic differentiation from embryonic gut epithelium [18]; similar experiments show that endothelial cells stimulate self-renewal and neurogenesis of neural stem cells [19]; and bone marrow-derived sinusoidal endothelial cells support megakaryocyte progenitor maturation [16].

Alternatively, it is possible to show that a factor expressed by endothelial cells or mural cells reproduces

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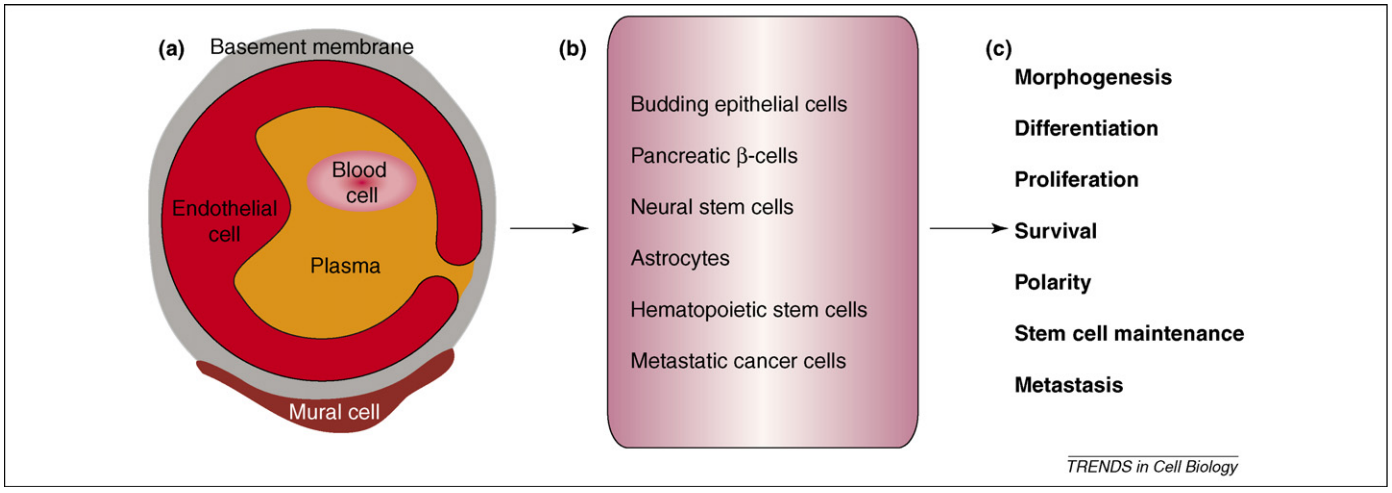

Figure 1. Components of vascular niches and their effects. **(a)** Vascular niches consist of endothelial cells surrounded by a basement membrane and mural cells (pericytes or smooth muscle cells). The endothelial cells enclose blood cells and plasma. Endothelial cells, together with non-vascular cells, create a vascular niche for various cell types [30,35,38]. **(b)** Responding cells are not usually part of a polarized tissue with a stable basement membrane. They are budding epithelial cells [17,18,22,28], pancreatic β-cells [22], neural stem cells and astrocytes [11,19,66], proliferating hematopoietic stem cells and metastatic cancer cells [10,16]. **(c)** The response of cells residing within a vascular niche varies from cell to cell. The niche creates a permissive environment that enables different cell types to pursue their developmental or regenerative programs.

the effects of vascular niches. For example, pigment epithelium-derived factor (PEDF) and brain-derived neurotrophic factor (BDNF) localize to the vascular beds of neurogenic brain regions and support neurogenesis *in vitro* [12,15,21]. Moreover, endothelial cells within pancreatic islets produce laminins and collagen IV, and *in vitro* these factors increase insulin secretion and pancreatic β-cell proliferation [22,23].

Cellular components of vascular niches

Endothelial cells develop from mesoderm and form cell cords surrounded by a vascular basement membrane (Box 1). When a vascular lumen is formed, it connects with the circulatory system, and this enables blood cells and plasma to enter the tissues. Because the resulting blood vessels are initially leaky, the endothelial cells need to attract mural cells, such as pericytes or smooth muscle cells, which stabilize the developing vessel [24]. Thus, a mature blood vessel contains several cell types and components, all of which could contribute to the formation of a vascular niche (Figure 1a) [10,12,14,17–19,22,25–28]. What makes the situation more complex is the fact that blood vessels, especially capillaries, are under the influence of the surrounding tissues and, therefore, have tissue-specific components [29,30].

However, it is likely that there are factors common to all vascular niches that act in concert with tissue-specific factors. Here, we present the hypothesis that the vascular basement membrane (Box 1) is a common factor essential for all vascular niches.

The vascular niche and its basement membrane

The vascular basement membrane is an essential component of the vascular niche in pancreatic islets (Figure 2a) [22]. Islets are mini-organs or aggregates of endocrine cells, most of which are insulin-secreting β-cells. Pancreatic β-cells are extremely plastic in the sense that they can strongly up-regulate their proliferation rate and insulin secretion when the body's demand for insulin increases [31].

Similar to most endocrine organs, islets are highly vascularized (Figure 3a) [32]. They have 5–7 times more capillaries than most other tissues, such as the surrounding exocrine pancreatic tissue (Figure 3c) [32]. This enables every pancreatic β-cell to be directly adjacent to a capillary (Figure 3b). It was initially suggested that this dense capillary network helps secreted insulin to gain access to the blood stream [33]. However, most insulin granules are released towards the islet interstitium rather than directly into the capillaries [34]. It was therefore proposed that one of the main functions of endothelial cells is to provide β-cells with a vascular basement membrane that stimulates their endocrine function and enables them to proliferate (Figure 2a) [22].

Communication between endothelial cells and β-cells is as follows (Figure 2a): pancreatic β-cells secrete vascular endothelial growth factor-A (VEGF-A) to attract endothelial cells. These cells subsequently form capillaries surrounded by a basement membrane. Laminin-411, a protein of the vascular basement membrane, interacts with the α6β1-integrin on β-cells to promote insulin gene expression and β-cell proliferation [22]. In addition, collagen IV enhances insulin secretion by interacting with α1β1-integrin [23].

There are many examples that are consistent with the idea that the vascular basement membrane is a key part of all vascular niches. For example, hematopoietic stem cells shift from a quiescent osteoblastic niche to a vascular niche that supports their proliferation and further differentiation in the bone marrow [35]. This happens on the outside of sinusoidal blood vessels [35], where the vascular basement membrane is localized. Thus, the endothelial cell-derived basement membrane might give structural support for proliferating and differentiating stem and progenitor cells. Because it contains heparan sulfate proteoglycans (HSPGs) (Box 1), the basement membrane might also be able to potentiate signaling by growth factors that are crucial for hematopoietic stem cells, including fibroblast growth factor-4 (FGF4) and stromal cell derived factor-1 (SDF1) [35].

Box 1. The vascular basement membrane

The basement membrane (BM), also known as the basal lamina, is a specialized form of extracellular matrix (ECM) that lies close to the basolateral surface of endothelial cells and epithelial cells, smooth and skeletal muscle cells, peripheral nerve cells and adipocytes [67,68]. The BM provides mechanical stability to cells and also serves as a barrier between different cell types and as a substrate for cellular interactions. The individual components of the BM have important roles in cell proliferation, differentiation, migration, development and repair. All BMs contain laminins, type IV collagen, entactin (also called nidogen) and heparan sulfate proteoglycans (HSPGs). Depending on its specific location and function, the exact composition of the BM in terms of types and isoforms of glycoproteins can vary. The formation of the BM is driven by the intrinsic property of certain laminins (heterotrimeric glycoproteins composed of α, β and γ chains) to polymerize and to form a scaffold. This scaffold is further stabilized by entactin and type IV collagen. Additional glycoproteins, such as HSPGs and growth factors, bind to this structure [69].

In mature blood vessels, the BM is a thin layer located between endothelial cells (ECs) and mural cells. Deposition of single BM components by ECs can be observed as early as during the initial steps of vasculogenesis and angiogenesis [50] (Figure I).

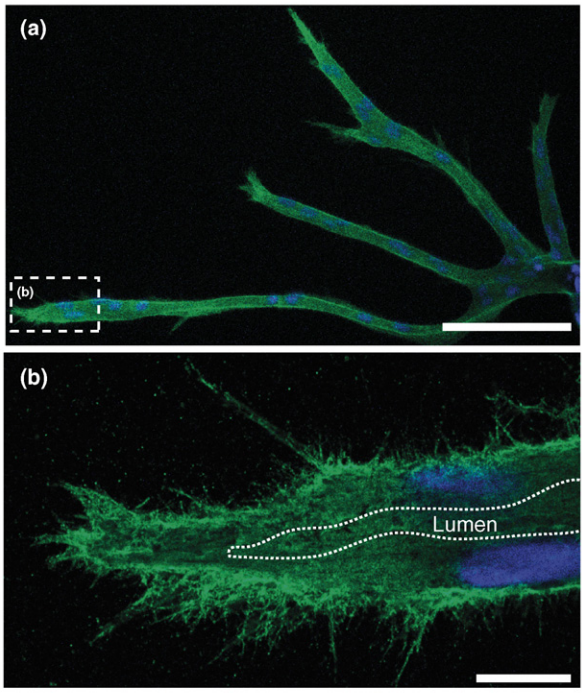

Figure I. Confocal images of vascular sprouts formed by human umbilical vein endothelial cells (HUVECs) according to a previously described method [70]. **(a)** Sprouts including **(b)** sprout tips are covered with laminin. Nuclei are in blue and pan-laminin-1 antibody staining is in green. Scale bars represent (a) 200 μm and (b) 20 μm. The shape of the lumen was detected on the corresponding phase-contrast image and is shown as a dotted line.

Investigations on the vascular niche of the brain also point to the vascular basement membrane as an essential factor [11,36,37]. Two germinal regions persist in the adult brain that generate large numbers of neurons from neural stem cells: the subgranular zone (SGZ) of the hippocampus and the subventricular zone (SVZ) of the lateral ventricle [36]. Interestingly, neural stem cells are found in direct proximity to blood vessels within the SGZ. By contrast, in the SVZ an extracellular matrix seems to extend from blood vessels towards the neural stem cells in form of finger-like processes called 'fractones' [37]. Given that HSPGs of the vascular basement membrane activate several growth factors for neural progenitor cells, including FGF2 and VEGF-A [38], the vascular basement membrane or its fractones might create a local vascular niche in neural tissue by sequestering and potentiating growth factor activity. In addition, neural stem cells express β1-integrins and might therefore respond to the vascular basement membrane in a similar way to pancreatic β-cells (Figure 2a) [39].

Is there an ancestral vascular niche?

The observation that endothelial cells affect tissue development in the mouse embryo before they have formed a circulatory system with a blood flow [17] suggests that vascular niches and their basement membrane components are more conserved than are blood vessels. In many invertebrates, there is no endothelial cell-derived vascular system. Instead, there is an open vascular system containing hemocytes (Figure 2b). Interestingly, hemocytes are motile macrophage-like blood cells that share several features with the endothelial cells of vertebrates [40]. Hemocytes express PDGF/VEGF-like growth factor receptors (PVRs) [41] that bind Pvf2, a PDGF/VEGF-like growth factor. Pvf2 induces the hemocytes to migrate to, proliferate and survive within a tissue (Figure 2b) [41–43]. Thus, hemocytes respond to Pvf2 just as endothelial cells respond to VEGF-A (compare Figure 2b with Figure 2a). Taken with recent genetic evidence for hematopoietic contribution to vascular development [44], these findings suggest that hemocytes are evolutionary ancestors of the hematopoietic–vascular cell lineage of vertebrates.

What makes hemocytes interesting with regard to the formation of vascular niches is the observation that in many tissues these cells are major producers of basement membrane components, including laminin, collagen IV and proteoglycans [45]. Hemocytes secrete these extracellular matrix components towards foreign objects, in particular pathogens, to encapsulate and immobilize them [40,46]. In addition to this immune function, they seem to be involved in tissue development by providing tissues with extracellular matrix and by removal of apoptotic cells [46–48]. Deletion of hemocytes in *Drosophila* leads to several developmental defects, which coincide with a reduced deposition of extracellular matrix. For example, blocking hemocyte migration to the ventral nerve cord inhibits condensation of the central nervous system in *Drosophila* embryos [47]. In addition, this defect coincides with an absence of collagen IV that is normally deposited around the nerve cord [47]. Another role of hemocytes is to promote gut morphogenesis in some invertebrates, possibly by secreting extracellular matrix around the gut tube [46]. Moreover, hemocytes are essential for wing maturation in *Drosophila* [48], and it has been suggested that this might be due to the synthesis of extracellular matrix that bonds the two wing epithelia together, as well as to removal of apoptotic cells [48]. Some *Drosophila* integrins are also required for gut morphogenesis and wing maturation [49], suggesting a possible link between hemocytes, integrins and tissue morphogenesis. Thus, hemocytes might create a vascular niche in invertebrates by

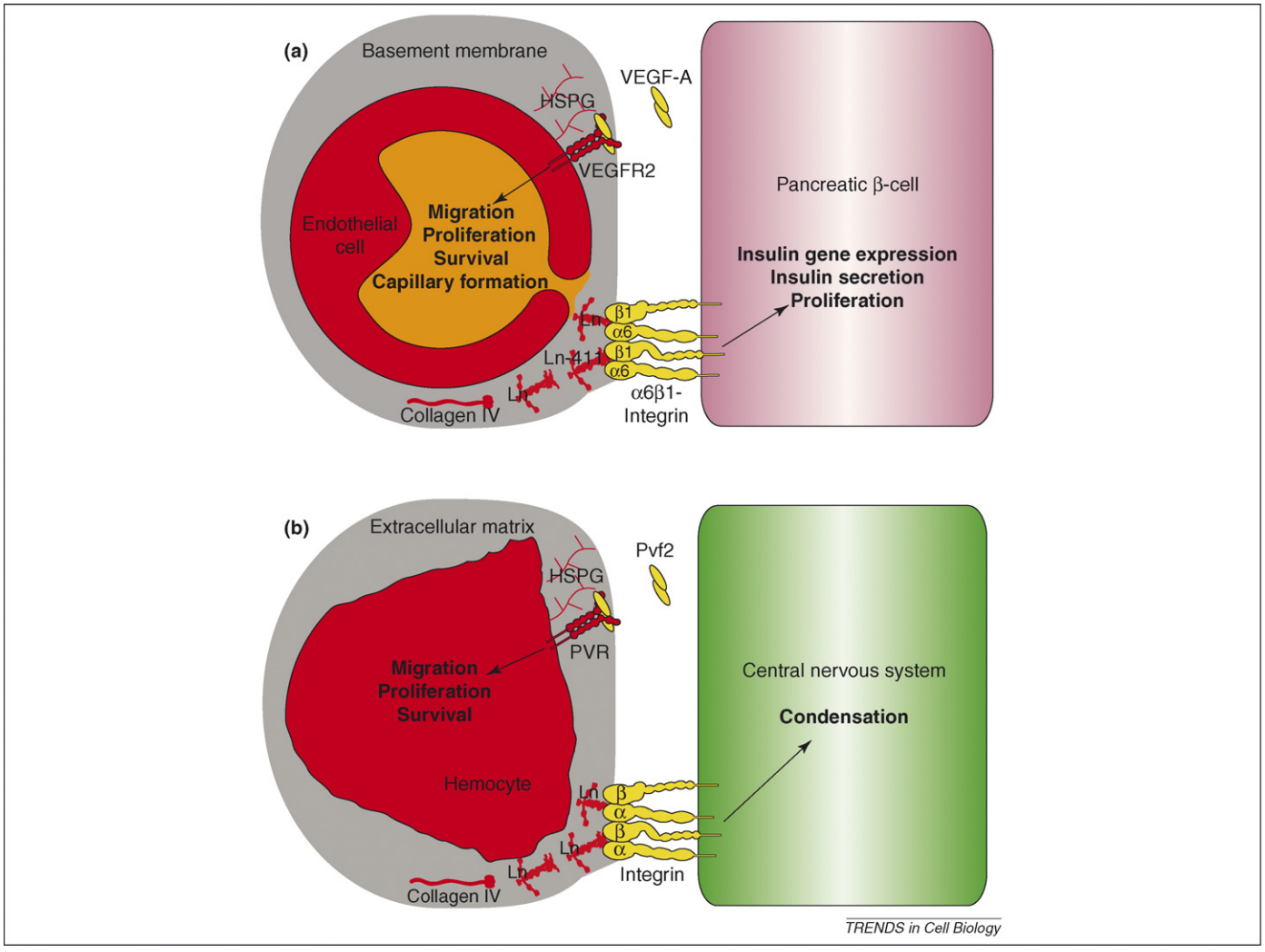

Figure 2. Conserved interactions within vascular niches. **(a)** The vascular niche of pancreatic islets [22]. When VEGF-A binds to VEGFR2 on endothelial cells, these cells migrate towards the β-cells, proliferate and form capillaries [33,53]. Endothelial cells secrete various extracellular matrix components, such as laminins and collagen IV. The laminins bind to α6β1-integrin expressed on pancreatic β-cells to support insulin expression and β-cell proliferation [22], and collagen IV binds to α1β1-integrin to stimulate insulin secretion [23]. **(b)** A putative ancestral vascular niche can be generated by hemocytes. These migratory macrophage-like blood cells are part of the open vascular system in invertebrates such as arthropods, annelids and mollusks. When Pvf2 binds to PVR, hemocytes respond like endothelial cells that are exposed to VEGF-A: they migrate to the source of growth factor, proliferate and survive within the Pvf2-expressing tissue [41–43]. Hemocytes secrete various extracellular matrix components, including laminins, collagen IV and proteoglycans [45], and also facilitate tissue development, such as condensation of the central nervous system in *Drosophila* [47]. Abbreviations: HSPG, Heparan sulfate proteoglycans; Ln, Laminin; Pvf2, PDGF/VEGF-like growth factor-2; PVR, PDGF/VEGF-like growth factor receptor; VEGF-A, Vascular endothelial growth factor-A; VEGFR2, VEGF-A receptor-2.

depositing extracellular matrix within certain tissues (Figure 2b).

Why do certain cell types require a vascular niche?

When looking at all cell types described as requiring a vascular niche, it turns out that most of these cells are unable to form a basement membrane. This limitation might be caused by the plasticity of these cells, which interferes with formation of a stable basement membrane. For example, stem cells can proliferate, migrate and give rise to different cell types as tissues grow and regenerate; and pancreatic β-cells can start to proliferate and up-regulate insulin production [8] when there is an increased demand for insulin secretion.

Importantly, endothelial cells (and hemocytes) are exceptional in that they can migrate into every tissue, change their morphology tremendously and, simultaneously produce various basement membrane components (Box 1) [45]. These components are found on endothelial cells during angiogenesis and vasculogenesis (Box 1) [50]. In mouse embryonic skin, collagen IV is found on filopodia of tip cells (Ralph Adams, pers. commun.), which are the first endothelial cell body extensions that enter many tissues during angiogenesis [51]. Conversely, during vascular regression, endothelial cells were shown to leave their basement membranes behind them in form of empty sleeves [52,53]. These examples indicate that basement membrane components are among the first molecules to which many tissues are exposed (Box 1), when endothelial cells arrive, and that parts of the vascular basement membrane still remain within the tissue, when endothelial cells leave [52,53].

Based on the production of basement membranes by endothelial cells and hemocytes, we propose that a conserved function of endothelial cells is to provide tissues with an extracellular matrix, which serves as a permissive

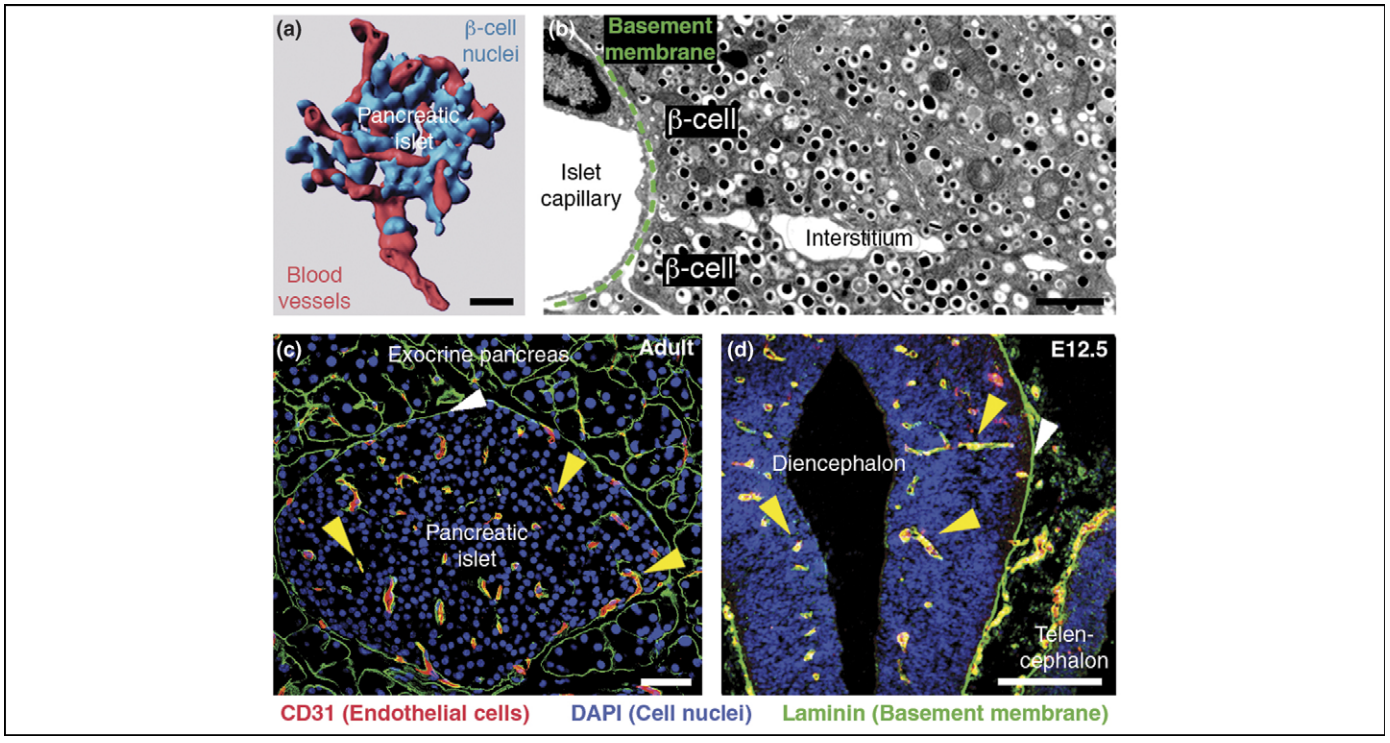

Figure 3. The vascular basement membrane in adult pancreatic islets and embryonic diencephalon. **(a)** A 3D model illustrates the dense capillary network (red) within a pancreatic islet. Most cell nuclei (blue) belong to pancreatic β-cells. The scale bar represents 10 μm. **(b)** An electron microscopic image of a pancreatic islet shows that β-cells form a rosette around an islet capillary. Two labelled β-cells are next to the vascular basement membrane (dotted green line) formed by a capillary endothelial cell (left). The scale bar represents 2 μm. **(c)** A confocal image shows an adult mouse pancreatic islet surrounded by exocrine pancreatic tissue. Within the pancreatic islet, capillaries (red) are the main sites of basement membranes (green; yellow arrowheads). The islet capsule is an alternative location (white arrowhead). Nuclei, blue. The scale bar represents 50 μm. **(d)** A confocal image of an E12.5 mouse embryonic brain. Within the diencephalon, capillaries (red) are surrounded by a basement membrane (green; yellow arrowheads). A white arrowhead indicates the pial basement membrane. Nuclei are in blue. The scale bar represents 200 μm. The basement membranes were stained with a pan-laminin-1 antibody that cross-reacts with most laminins.

environment for tissue development and homeostasis. First, basement membrane proteins bind to integrins, which on the one hand signal on their own and on the other hand amplify the cell response to various growth factors [54]. Second, HSPGs directly activate growth factors such as FGFs and VEGFs [55–57]. Third, basement membranes can polarize cells, thus enabling symmetric and asymmetric cell divisions that depend on the mitotic cleavage plane [2,6]. Finally, basement membranes provide cells with structural support and facilitate their homing and migration [58].

Importantly, endothelial cells are the main sites where basement membrane is formed within the adult mouse pancreatic islet and early embryonic mouse diencephalon (Figure 3c,d). Alternative locations of extracellular matrix exist, but they are not accessible for most cells within these tissues. For example, the non-vascular extracellular matrix of the islet capsule is found only at the margin of the islet (Figure 3c), and the pial basement membrane is found mainly outside the neuroepithelium (Figure 3d) [59]. Thus, cells could require vascular basement membrane when they cannot form their own. Because cells in tissues influence endothelial cells [30], their vascular basement membrane composition and growth factors could vary significantly from tissue to tissue.

Vascular niches and diseases

In general, most diseases that affect people in industrialized countries are complex multigenic diseases (i.e. cancer, artherosclerosis, neurodegeneration and diabetes). The role of blood vessels in neurodegenerative diseases has been reviewed recently [38]. Here we highlight some recent reports on vascular niches and their possible roles in cancer cell metastasis and type II diabetes.

Hematopoietic stem cells were recently shown to home to specialized regions within the bone marrow endothelium [10]. Of relevance for cancer research was the finding that several leukemic cell lines home to the same vascular niches to initiate their metastatic growth [10]. In addition, hematopoietic bone marrow progenitor cells expressing VEGF receptor-1 (VEGFR1) initiate so-called 'pre-metastatic sites' that create local niches for tumor metastasis [9]. These two reports suggest that cancer cells either hijack existing vascular niches and/or create their own vascular niches by using several different cell types [9,10]. A significant task for future research will be to identify molecular differences between how cancer cells and stem cells interact with their vascular niches. In the case of stem cells, vascular niches tightly couple cell proliferation to the body's demand for more cells, whereas in the case of cancer cells, vascular niches support excessive cell proliferation. Because most tumors start to grow on the side of blood vessels away from the lumen, the vascular basement membrane is likely to be involved, and the finding that fibroblasts contribute fibronectin to the pre-metastatic niche is in line with the notion that extracellular matrix is a crucial factor [9].

In type II diabetes, recent findings also point to a possible role of the vascular niche in this epidemic disease, which currently affects almost 200 million people worldwide [60]. As mentioned before, pancreatic β-cells lie on the vascular basement membrane, which contributes to the plasticity of β-cells [22]. Obesity is one of the main risk factors for type II diabetes because it can result in peripheral insulin resistance, leading to a strongly elevated demand for insulin. When β-cells cannot adjust to this situation by increasing their proliferation rate and insulin production, type II diabetes develops. Given that deletion of VEGF-A in pancreatic islets impairs both β-cell proliferation and insulin expression [22,33], we speculate that a defect in the vascular niche and its basement membrane is involved in the onset of type II diabetes. Two recent findings on genetic changes associated with type II diabetes are relevant for this hypothesis [31,61].

A genetic study with mice led to the identification of *Sorcs1* (Sorting receptor related Consensus Sequence 1) as a gene associated with onset of type II diabetes [31]. The function of SorCS1 is poorly understood; however, it binds PDGF, which is crucial for pericyte recruitment to the microvasculature [62]. As pericytes are associated with islet capillaries, the authors speculate that genetic changes in *Sorcs1* promote β-cell failure by affecting their islet capillary network [31,63]. Pericytes also contribute components to the vascular basement membrane [62], so it will be interesting if a causal link between SorCS1, the islet vascular basement membrane and onset of type II diabetes is found.

In a study of human type II diabetics, expression of the hypoxia-inducible factor HIF-1β was shown to be strongly down-regulated in their pancreatic islets [61]. HIF-1β is a transcription factor for several important genes involved in β-cell function [64]. However, HIF-1β is also a transcription factor required for VEGF-A gene expression [65]. Thus, it is likely that, during type II diabetes, VEGF-A expression in pancreatic β-cells and maintenance of the islet capillary bed with its basement membrane are disturbed and might contribute to the disease.

Concluding remarks

Here, we have presented recent data on vascular niches, as they are important in various physiological and pathological conditions that are relevant for human medicine. We propose that vascular niches generally provide basement membranes to cells with high plasticity, which cannot form an own basement membrane. In addition, vascular basement membranes act together with tissue-specific factors that enable formation of tissue-specific vascular niches. Finally, we predict that molecular dissection of vascular niches and their basement membranes will be essential for understanding and eventual treatment of complex human diseases.

Acknowledgements

We apologize that we could not refer to several important research findings relevant for the topic of this article because of its limited scope. We thank Glenis Wiebe, Jan Eglinger, Normund Jabs and Tomas Kucera for critical comments and the Deutsche Forschungsgemeinschaft DFG (La1216/2–2 and SFB655) for funding this work.

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