The three faces of pericytes

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Perivascular cells (pericytes), which wrap around the endothelium, are morphologically and functionally distinct depending on their location and the type of microvasculature they surround. In recent years, pericyte physiology and its dysfunction in conditions such as diabetes, epilepsy and Alzheimer's disease have been eagerly investigated, but the precise definition and characteristics of pericytes in different parts of the microvasculature is still debated.

According to classification by Zimmerman, pericytes can be divided into precapillary (arteriolar), capillary and postcapillary (venular) pericytes, based on their location and histological features. However, specific markers for each subtype are lacking. Precapillary pericytes are located at the distal end of precapillary arterioles next to arteriolar smooth muscle cells (SMCs). Precapillary pericytes have oval cell bodies giving several asymmetrical circumferentially-arranged finger-like processes tightly wrapping around the endothelium. Precapillary pericytes can be distinguished from arteriolar SMCs by their morphological appearance, as the width of each pericyte is greater (~10μm) than individual SMC (~7μm). On the other hand, each precapillary SMC wraps up to 3 times around the endothelium and occupies a longer segment than individual precapillary pericytes, clearly shown using 3D imaging. Capillary pericytes have elongated cell bodies with two slender processes on each side running parallel to the long axis of the capillary. Postcapillary pericytes are spider-like (stellate) and they form a complicated and dense meshwork. In this issue of *J Physiol*, Hashitani *et al* beautifully illustrate 3 different phenotypes of pericytes comprised within the suburothelial microvasculature of mouse bladder, confirming previous reports in the rat ureter microvasculature (Borysova *et al* 2013).

The capillary network is denser and more branched in tissues such as the heart, retina and brain than in visceral tissues, corresponding to their metabolic demand. Microvascular studies in these tissues rely on a slicing technique, making identification of the various pericyte phenotypes more challenging as the network dives into tissue in a 3D arrangement. As a consequence, some studies have omitted a clear definition of precapillary and postcapillary pericytes and have instead grouped pericytes of various morphologies under the same umbrella

term (Atwell *et al* 2016) (herein termed ‘capillary’ pericytes) causing debate regarding the contractility of true capillary pericytes (Hill *et al* 2015, Vates GE *et al* 2010).

The contractile ability of precapillary pericytes is well accepted (Hashitani *et al* 2018, Borysova *et al* 2013). They exhibit a cytoskeleton similar to vascular SMCs and contain a number of proteins associated with the contractile phenotype including actin microfilaments, tropomyosin, cGMP dependent protein kinase and α-smooth muscle actin (α-SMA) Contraction of a single pericyte is sufficient to completely occlude a precapillary arteriole and arrest blood supply into a capillary bed (Borysova *et al* 2013).

Recent data suggest that both cerebral and myocardial ischaemia can lead to constriction of ‘capillary’ pericytes, resulting in the no-reflow phenomenon (Attwell *et al* 2016). In contrast, Hashitani *et al* (2018) convincingly demonstrate that NG2 positive capillary pericytes in the suburothelial vasculature do not express α-SMA and are not contractile. These data are in agreement with earlier publications in both visceral (Borysova *et all* 2013) and neuronal (Hill *et al* 2015) microvasculature. Taken together, the literature supports the notion that the contractility of pericytes is rather dependent on their branching order within the capillary network than the vascular bed.

What is the role of capillary pericytes if they do not directly control vascular diameter? In this issue Hashitani *et al* (2018) report that mouse bladder suburothelial capillary pericytes are not influenced by perivascular nerves, based on electrical field stimulation experiments. Instead, the pericytes may respond to the metabolic state of capillary-fed tissues (e.g. tissue oxygen concentration) and conduct corresponding locally generated membrane potential changes to upstream precapillary arterioles and downstream postcapillary venules, in this case depolarization.

Hashitani *et al* (2018) demonstrate that capillary pericytes in the mouse bladder suburothelial microvasculature exhibit temporally correlated spontaneous Ca^{2+} oscillations, triggered by Ca^{2+} release from the sarco-endoplasmic reticulum. Activation of Ca^{2+} - dependent Cl^{-} channels causes depolarisation of capillary pericytes, which propagates via gap junctions to adjacent capillary pericytes and appears to be effective enough for maintaining almost synchronised spontaneous activity amongst them. Notably, regenerative opening of L-type Ca^{2+} channels is absolutely critical for signal conduction from non-contractile capillary pericytes to upstream and downstream contractile precapillary and postcapillary pericytes, respectively. Functional implication of propagated Ca^{2+} signals in precapillary and

postcapillary pericytes is vasoconstriction of precapillary and postcapillary microvessels, mediated by contractile pericytes. It is possible that this synchronised vasoconstriction of upstream and downstream microvessels encircled by precapillary and postcapillary pericytes may lead to hydrostatic pressure changes in capillaries and facilitation of capillary perfusion.

To summarise, Hashitani *et al* elegantly show capillary pericytes in the mouse bladder are electrically coupled (either directly and/or indirectly via the endothelium) to pericytes of upstream precapillary arterioles and downstream postcapillary venules. Capillary pericytes constitute a functional unit, and their activation can transmit currents bi-directionally via gap junctions to help regulate blood flow within the microcirculation. What these capillary pericytes sense (e.g. excessive tissue oxygenation, pH, metabolic factors) and how they sense it remains elusive but could be a fundamental mechanism leading to matched tissue nutrient supply and demand.

References

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