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The role of primary cilia in human cerebral cortex development and vascularization

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Primary cilia are present in the developing brain, implicated in transduction of several signaling pathways essential during cerebral cortex development. Primary cilia have been described on the apical membrane of ventricular progenitor cells, bathed in the cerebrospinal fluid rich in morphogens and growth factors. At this site, primary cilia sense and transduce a variety of signals which control cell precursor proliferation, as well as migration of differentiating neurons and glial cells. Moreover, during brain vascularization, also endothelial cells (ECs) are characterized by apical cilia specialized in mechanosensing and seem to be involved in stabilization of the neo-formed vessels, which is a critical phase associated to pre-term intraventricular hemorrhage (IVH). Interestingly, previous studies on endothelial cilia in zebrafish and mouse brain have unexpectedly revealed endothelial cilia not only on the apical, but also on the basolateral endothelial surfaces. These results have been confirmed with ciliary markers that co-localize with PDGF-BB ligand in primary human brain microvascular ECs (hBMECs) and the visualization of cilia on both luminal and abluminal side. In the present study we have investigated the presence and subcellular localization of EC primary cilia during brain development in a 22-week-old human fetus, using cell-specific markers of ECs and pericytes and ARL13B as a ciliary marker, by immunofluorescence confocal microscopy. The results show ARL13B-stained primary cilia of radial progenitor cells at the ventricular surface, together with cilia of intermediate progenitors in the ventricular zone (VZ) and subventricular zones (SVZ). The periventricular vascular plexus that lies at the VZ/SVZ border, is revealed by endothelial CD31 and helps in the identification of the endothelial luminal and abluminal sides. On double CD31/ARL13B immunostainings, EC primary cilia are detected on both apical and basal endothelial surfaces. During differentiation of the blood-brain barrier (BBB) endothelial phenotype and assembly of neurovascular unit (NVU) cells, the abluminal EC cilium-associated PDGF-BB ligand fulfills autocrine and juxtacrine (endothelium-pericyte) roles and promotes vascular BBB function and NVU stability.

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