Laminin beta 2 is localized at the sites of Blood-Brain-Barrier and its disruption is associated with increased vascular permeability; histochemical and transcriptomic study

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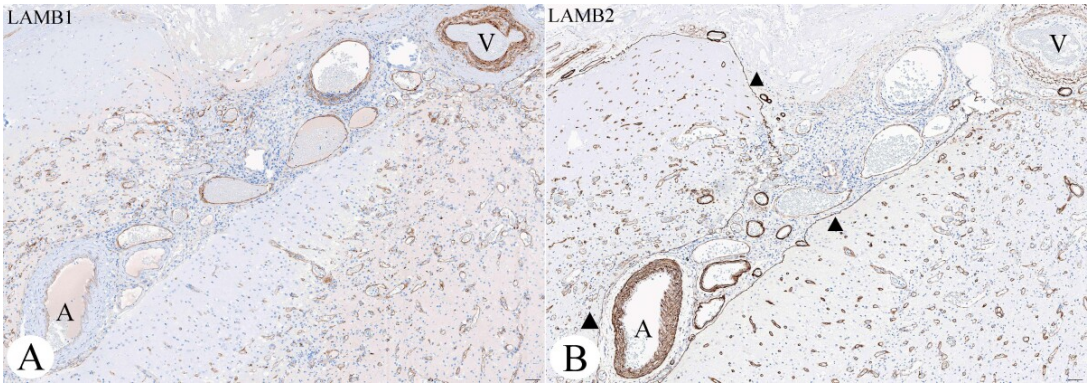
Abstract

Heterotrimeric extracellular matrix proteins laminins are mostly deposited at basal membranes and are important in repair and neoplasia. Here we localize laminin beta 2 (LAMB2) at the sites of blood-brain barrier (BBB). Microvasculature (MV) of normal brain is endowed with complete LAMB2 coverage. In contrast, its cognate protein laminin beta 1 (LAMB1) is absent in microvasculature (MV) of normal brain but emerges at the sprouting tip of a growing vessels. Similarly, vascular proliferation in high grade gliomas (HGG) is accompanied by marked overexpression of LAMB1, whereas LAMB2 shows deficient deposition. We find that many brain pathologies with presence of post-gadolinium enhancement (PGE) on Magnetic Resonance Imaging (MRI) show disruption of LAMB2 vascular ensheathment. Inhibition of vascular endothelial growth factor signaling in HGG blocks angiogenesis, suppresses PGE in HGG, prevents expression of LAMB1 and restores LAMB2 vascular coverage. Analysis of single cell RNA sequencing (scRNA□seq) databases shows that in quiescent brain LAMB2 is predominantly expressed by BBB-associated pericytes (PC) and endothelial cells (EC), whereas neither cell types produce LAMB1. In contrast, in HGG both LAMB1 and 2 are over-expressed by endothelial precursor cells, a phenotypically unique immature group, specific to proliferating hyperplastic MV.



Consecutive sections of neocortex and leptomeninges (subacute infarct). Note predominance of LAMB1 (A) in leptomeningeal veins (V) and LAMB2 (B) in arteries (A). Glia limitans expresses LAMB2 only (triangles). Activated microvessels show weak expression of LAMB1 and strong of LAMB2. Bar: 100 m.