学位の種類	博士（医学）
報告番号	甲第１５７５号
学位記番号	第１１３０号
氏名	小椋　俊太郎
授与年月日	平成 29 年 3 月 24 日
学位論文の題名	Sustained inflammation after pericyte depletion induces irreversible blood-retina barrier breakdown (ペリサイト消失に伴う遷延した炎症による不可逆的な血液網膜関門の破綻) JCI Insight.2017;2:e90905
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Abstract

Endothelial cells (ECs) and pericytes (PCs) in the central nervous system (CNS) cooperatively form a physical and chemical barrier, called the blood-brain barrier, which tightly controls the passage of fluids, molecules, and ions, thereby maintaining the proper environment for neurons and glial cells, and protecting them from toxins and pathogens. In certain CNS disorders, PC deficiency is implicated in barrier disruptions during disease progression. Especially in diabetic retinopathy (DR), the loss of PCs from vessel walls is assumed to cause breakdown of the blood-retina barrier (BRB) and subsequent vision-threatening vascular dysfunctions. However, because hyperglycemic animal models fail to fully recapitulate the pathophysiology of human DR, molecular and cellular mechanisms underlying the barrier dysfunctions in PC-free retinal vessels remains elusive. In this study, we show that transient and partial inhibition of PC recruitment to developing retinal vessels circumvented the retinal collapse, but the EC-PC associations failed to be spontaneously normalized even in adult retinas, thus reproducing various forms of DR, including sustained hyper-permeability, hypo-perfusion, and hypoxia. Notably, PC depletion directly induced inflammatory responses in ECs and perivascular infiltration of macrophages, whereby macrophage-derived VEGF and placental growth factor (PlGF) activated VEGFR1 in macrophages and VEGFR2 in ECs. Moreover, angiopoietin-2 (Angpt2) upregulation and Tie1 downregulation activated FOXO1 in PC-free ECs locally at the leaky aneurysms. This vicious cycle was shut down by simultaneously blocking VEGF, PlGF, and Angpt2, restoring the BRB integrity. Thus, our experimental model facilitates a new means to understand how PC deficiency in retinas initiates the sustained inflammation and irreversible BRB breakdown, and provides a potentially new drug discovery system, not only for DR, but also for neurological disorders and diabetic microvascular complications.