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CAVEOLIN-1 REGULATES SMOOTH MUSCLE CONTRACTILITY IN AGING AND RETINAL INJURY

COMMITTEE IN CHARGE: MICHAEL H. ELLIOTT, PHD; MICHELLE CALLEGAN, PHD; DAVID SHERRY, PHD; SCOTT PLAFKER, PHD; FERENC DEAK, PHD; MARK LANG, PHD

ABSTRACT: Caveolin-1, (Cav-1) the principal scaffolding protein of caveolae membrane domains, is essential for caveolae formation and functions including transcytosis, mechanosensing and cell signaling. Cav-1 is expressed in numerous cells in the retina, and plays important roles in vascular function, and neuroprotection.

Risk variants near the CAV1 locus have been associated with high intraocular pressure (IOP) and primary open angle glaucoma (POAG). A subset of POAG that strongly associates with CAV1 has been reported to demonstrate abnormal vascular tone, autoregulation and blood flow. The present study examines the effect of Cav-1 deficiency on retinal and vascular responses to acute intraocular pressure elevation induced by ischemia-reperfusion (I/R).

Another risk factor for POAG is age, but physiological aging is not well understood. In vivo measurements of healthy aged humans have shown significant heterogeneity in retinal arterial diameter as a function of length compared to young controls, but a cellular/molecular mechanism for these observations has not been identified. Physiological vascular aging could prime certain populations for later pathology. As a result, the central **hypothesis** is that Cav-1 regulates retinal vascular tone under physiological conditions, but demonstrates reduced function following injury and with age.

Vascular morphology was assessed in retinal wholemounts from aged animals and after ischemic injury using immunohistochemistry. Cav-1 KO retinal arteries show significant reduction in the contractile protein alpha smooth muscle actin (αSMA) immunoreactivity after I/R when compared to controls, demonstrating that loss of Cav-1 influences the arterial response to pressure. Experiments were repeated in endothelial-specific KO mice, as well as in smooth muscle-specific KO mice and similar reduction in αSMA coverage was observed. Untreated aged animals present with an identical vascular phenotype, demonstrating a correlation between pressure, aging and smooth muscle cell coverage. Additionally, the segmental loss of contractile αSMA in normal healthy aged mice provides a cellular explanation for the in vivo aging human studies.

We identify a novel role for Cav-1 as a regulator of vessel contractile properties in the post-ischemic retina, which may have further implications in retinal aging. Specifically, endothelial and smooth muscle Cav-1 expression is required independently to maintain VSMC coverage both basally and following injury.