Recent evidence suggests that vascular dysfunction is a critical component of AD pathology, and potentially a necessary predisposing feature (REF). Further, vascular dysfunction has been shown to be necessary for the development of Alzheimer’s-like phenotypes in a mouse model of amyloid pathology (Soto et al., 2016). We have localized PDGFA and PRKAR1B to specific components of vascular anatomy. Our immunofluorescence shows PDGFA expression between the collagen-rich tunica externa and the endothelium of the tunica intima, supporting the presence of PDGFA in vascular smooth muscle cells (VSMCs). Previous studies have shown PDGF to effect VSMC proliferation by inducing a phenotypic switch from a contractile state to a proliferative one (Owens et al., 2004). Insufficient PDGFA expression, then, would likely impair vascular regeneration following plaque-related insults, thereby exacerbating AD. PRKAR1B was seen in a punctate fashion suggesting the presence of cytoplasmic clusters of the protein, and we hypothesize that the PRKAR1B puncta represent accumulation of protein kinase A (PKA) at either the endoplasmic reticulum or the insulin receptor. Calcium release from the endoplasmic reticulum is typically suppressed by phospholamban (PLN), however such suppression is lifted following PLN phosphorylation by PKA. Changes in the regulation of calcium release due to altered PRKAR1B expression may very well have important consequences for AD, including but not limited to changes in vascular smooth muscle contraction that limit circulation to plaque-burdened brain regions. In addition to its calcium-related role, PKA is essential for signal transduction following activation of the insulin receptor, a process that has been shown to be the mechanism by which PDGF induces phenotypic switching in VSMCs (Zhao et al, 2011). In this way, changes in PRKAR1B may yield corresponding changes in circulation through suppressed arterial muscle contractility or through a direct influence on vascular growth and maintenance.

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