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Characterization of a new animal model for retinal vasoregression

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Retinal vasoregression characterized by the formation of acellular capillaries, is the hallmark of vascular eye diseases, such as diabetic retinopathy. Vasoregression is a complex processes entailing activation of neuroglia and vascular damage. There is emerging evidence indicating that neuroglial changes can precede vascular alterations. Recently, we described a new transgenic rat (PKD TGR) that contains a c-terminal truncated human polycystin-2 cDNA under control of CMV promoter and develops extensive retinal vasoregression. Our data suggest that PKD TGR retinas exhibit primary neuronal degeneration and secondary vasoregression. These data suggest some similarities between this model and the changes found in DR. However, little is known about the molecular mechanisms of retinal vasoregression. In order to identify genes and pathway involved in the transition from neurodegeneration to vasoregression, we performed gene microarray analysis, TaqMan real-time PCR, western blot analysis and immunofluorescence staining of 1 month- and 3 month-old PKD TGR and SD retinas, i.e. before and after the initiation of vasoregression. Our study demonstrated that predominantly genes involved in immune/inflammatory pathways were strongly upregulated, CD74 being the strongest upregulated one. Glial cells including astrocytes and Müller cells became activated prior to vasoregression. CD74 was predominantly expressed in microglial cells in proximity of the deep capillary layers in which vasoregression ensues. HSP27 was upregulated in glial cells around degenerating vessels in PKD rats. Up-regulated expression of FGF2 and CNTF prior to vasoregression likely reflects a response to photoreceptor damage, while NGF upregulated after the onset of vasoregression may have an association to vascular degeneration. Our findings indicate that genes involved in immune/inflammatory pathways may act as predominant regulators in the development of vasoregression in the degenerating retina and a marked activation of glia cells may closely link to the vasoregression in the PKD retina.

Taken this together, the mechanisms underlying vasoregression in PKD TGR seem to be a sequential cascade starting from neuronal damage. Defects in cilia of the photoreceptor cells lead to apoptotic changes in these cells, releasing molecules and cell debris that can contribute to activation of glial and microglial cells. Glial cells produce, among many others, small heat shock proteins and neurotrophins to protection the retina from further injury, and phagocytotic microglia may eliminate harmful molecules, but also release inflammatory cytokines, which may cause or aggravate blood vessel damage. Vasoregression may occur when pericytes and endothelial cells are exposed to glial activation and lose their function in maintaining vascular integrity.

Our study suggests that CD74 and immune/inflammatory pathways together with activated glia cells can cause retinal vasoregression as exemplified in this animal model. Further analysis addressing functional modification may provide insights of the relative importance of the genetic alterations identified herein.