Retinal pigment epithelium (RPE) cell system to uncover the molecular mechanisms of ARSACS-related retinal defects

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Retinal abnormalities are among the clinical hallmarks in ARSACS. In affected patients, myelinated retinal nerve fibers are often detectable at fundoscopy and observation of increased peripapillary retinal nerve fiber layer thickness at optical coherence tomography (OCT) seems to be unique in ARSACS, though other retinal changes have been also described. In ARSACS research, retinal defects represent an unexplored field by a molecular point of view. To investigate the molecular mechanisms underlying retinal abnormalities, we generated a *SACS* knock-out model of ARPE-19 cells, a retinal pigment epithelium (RPE) cell line widely used as model of macular degeneration.

Our model resembled main ARSACS molecular defects, including the presence of vimentin perinuclear bundles, autophagy defects, and altered mitochondrial function. Transcriptomic and proteomic analyses confirmed recent findings about the involvement of inflammation and apoptosis among the biological process underlying the disease, and indicated that crucial pathways for typical RPE functions are dysregulated, including cell adhesion, RPE differentiation, retinoid cycle, and voltage-gated channel activity. Hence, our model exhibited known altered pathways involved in ARSACS, uncovered novel ones essential and specific for proper RPE functions, and generated a reliable model for ARSACS retinal defects studies and suitable for biomarker discovery and pharmacological tests.