11. Invest Ophthalmol Vis Sci. 2020 Sep 1;61(11):21. doi: 10.1167/iovs.61.11.21.

Caveolin-1 Promotes Cellular Senescence in Exchange for Blocking Subretinal Fibrosis in Age-Related Macular Degeneration.

Shimizu H(1), Yamada K(1), Suzumura A(1), Kataoka K(1), Takayama K(2), Sugimoto M(3), Terasaki H(1)(4), Kaneko H(1).

Author information: (1)Department of Ophthalmology, Nagoya University Graduate School of Medicine, Nagoya, Japan. (2)Department of Ophthalmology, National Defense Medical College, Japan. (3)Department of Mechanism of Aging, National Center for Geriatrics and Gerontology, Obu, Aichi, Japan. (4)Institutes of Innovation for Future Society, Nagoya University, Nagoya, Japan.

PURPOSE: To determine whether caveolin-1 (i) prevents epithelial-mesenchymal transition in the RPE and laser-induced subretinal fibrosis and (ii) promotes or inhibits cellular senescence in the RPE. METHODS: We examined laser-induced subretinal fibrosis and RPE cell contraction in wild-type and Caveolin-1 knockout (Cav-1-/-) mice treated with or without cavtratin, a cell-permeable peptide of caveolin-1. The senescence marker p16INK4a was measured in RPE tissues from patients with geographic atrophy and aged mice, laser-induced subretinal fibrosis, and primary human RPE cells. Human RPE was examined by TUNEL staining, reactive oxygen species generation, cell viability, and senescence-associated β-galactosidase staining. RESULTS: The volume of subretinal fibrosis was significantly smaller in cavtratin-injected eyes from wild-type mice than in control eyes from wild-type, P = 0.0062, and Cav-1-/- mice, P = 0.0095. Cavtratin treatment produced significant improvements in primary RPE cell contraction in wild-type, P = 0.04, and Cav-1-/- mice, P = 0.01. p16INK4a expression in the RPE was higher in patients with than without geographic atrophy. p16INK4a was expressed in 18-month-old but not 2-month-old wild-type mouse eyes. p16INK4a and collagen type I antibodies showed co-localization in subretinal fibrosis. Cavtratin did not affect RPE cell apoptosis or reactive oxygen species generation, but decreased cell viability and increased senescence-associated β-galactosidase-positive cells. CONCLUSIONS: Enhanced expression of caveolin-1 successfully blocked epithelial-mesenchymal transition of RPE and the reduction of subretinal fibrosis in mice. Nevertheless, in exchange for blocking subretinal fibrosis, caveolin-1 promotes RPE cellular senescence and might affect the progression of geographic atrophy in AMD.

DOI: 10.1167/iovs.61.11.21 PMCID: PMC7490224 PMID: 32926104 [Indexed for MEDLINE]

Conflict of interest statement: Disclosure: H. Shimizu, None; K. Yamada, None; A. Suzumura, None; K. Kataoka, None; K. Takayama, None; M. Sugimoto, None; H. Terasaki, Otsuka Pharmaceutical Co., Ltd., Japan (F); NIDEK Co., Ltd., Japan (F); Kowa Pharmaceutical Company Ltd., Japan (F); Santen Pharmaceutical Co., Ltd, Japan (F); Senju Pharmaceutical Co., Ltd., Japan (F); Alcon Japan Ltd., Japan (F); Novartis Pharma K.K., Japan (F); Bayer Health Care, Japan (F); Pfizer Japan Inc., Japan (F); ROHTO Pharmaceutical Co., Ltd., Japan (C); WAKAMOTO Co., Ltd., Japan (F); Carl Zeiss Meditec Co., Ltd., Japan (F); Nitten Pharmaceutical Co., Ltd., Japan (S, F); Tomey Corporation Ltd., Japan (F); AMO Japan K.K., Japan (F); Eisai Co., Ltd., Japan (F); Mitsubishi Tanabe Pharma Corporation Ltd., Japan (F); AbbVie GK, Japan (F); DAIICHI SANKYO Co., Ltd., Japan (C); CHUO SANGIO Co., Ltd., Japan (F); Sanofi K.K., Japan (F); Alcon Pharmaceuticals Ltd., Japan (F); HOYA Corporation Ltd., Japan (F); H. Kaneko, Senju Pharmaceutical Co., Ltd., Japan (F); AMO Japan K.K., Japan (F); HOYA Corporation Ltd., Japan (F)