CCI-26

A point mutation in *Semaphorin 4A*, associated with defective endosomal sorting for chronic oxidative stress, causes retinal degenerative diseases

Satoshi Nojima[1,2], Toshihiko Toyofuku[1], Atsushi Kumanogoh[1,3]

1) Department of Immunopathology, WPI Immunology Frontier Research Center, Osaka University
2) Department of Pathology, Osaka University Graduate School of Medicine
3) Department of Respiratory Medicine, Allergy and Rheumatic Disease, Graduate School of Medicine, Osaka University

Abstract

Semaphorin 4A (Sema4A) plays an essential role in photoreceptor survival. In humans, mutations in *Sema4A* are thought to contribute to retinal degenerative diseases. Here, we generated a series of knock-in mouse lines with corresponding mutations (D345H, F350C, or R713Q) in the *Sema4A* gene and found that Sema4A^{F350C} caused retinal degeneration phenotypes. The F350C mutation resulted in abnormal localization of the Sema4A protein, leading to impaired endosomal sorting of molecules indispensable for photoreceptor survival under chronic oxidative stress. Additionally, protein structural modeling revealed that the side chain of the 350th amino acid is critical to retain the proper protein conformation. Furthermore, *Sema4A* gene transfer successfully prevented photoreceptor degeneration in *Sema4A*$^{F350C/F350C}$ and *Sema4A*$^{-/-}$ mice. Thus, our findings not only indicate the importance of the Sema4A protein conformation in human and mouse retina homeostasis but also identify a novel therapeutic target for retinal degenerative diseases.