Chi-Chao Chan, J Clin Exp Ophthalmol 2014, 5:3
http://dx.doi.org/10.4172/2155-9570.S1.015

OMICS Group Conferences
Accelerating Scientific Discovery

4th International Conference on
Clinical & Experimental Ophthalmology
July 14-16, 2014 DoubleTree by Hilton Baltimore-BWI Airport, USA

Chi-Chao Chan
National Institutes of Health, USA

A potential link between inflammasomes and cytokines in age-related macular degeneration

Inflammation and oxidative stress are closely involved in age-related macular degeneration (AMD). Inflammasomes are multimeric components of the innate immune systemcomposed of caspase-1, nod-like receptors (NLRs), and an apoptosis-associated speck-like protein containing a C-terminal caspase-recruitment domain (CARD) and N-terminal PYRIN-PAAD-DAPIN domain (PYD). Inflammasomespromote the maturation of certain pro-inflammatory cytokines includinginterleukin (IL)-1β and IL-18.Activation of the NLRP3 inflammasome, a key mediator of neuroinflammation, is linked to AMD. Others and we have detected an increasein NLRP3, IL-1β, and IL-18 expression in human geography atrophic (dry) and neovascular (wet) AMD lesions compared to the peripheral retina and normal macula. We have measured higher levels of NLRP3, caspase-1, IL-1β, and IL-18 human adult retinal pigment epithelium (ARPE)-19 cells under oxidative stress, inflammation, or both stimuli. Ultrastructure illustrates mitochondrialdegeneration, cytoplasmic vacuoles, and autophagosomes in ARPE-19 cells under these stimuli. Knockdown of NLRP3 expression in ARPE-19 cells resulted in lower expression of caspase-1, IL-1β, and IL-18. Moreover, in the retina of *Ccl2-/-/Cx3cr1-/-* mice on *rd8* background (DKO/*rd8*), which develop focal retinal lesions mimicking AMD, we found greater expression of NLRP3, IL-1β, and IL-18.The DKO/*rd8*RPE cells depicted a greater number of damaged mitochondria, autophagosomes, and glycogen granules; andhigher accumulation of cytoplasmic vacuoles when compared to control mouse. Interestingly, IL-1β and IL-18 can induce IL-17 production through other inflammatory cells, such as Th17, γδ T cells, and macrophage. There are elevated serum IL-17A and hypomethylation of the receptor *IL17-RC*promoter in AMD patients, in addition toaberrant expression of IL-17A and IL17-RC in the AMD macula. *In vitro*, IL-17A induces ARPE-19 cell death characterized by the accumulation of cytoplasmic lipids and autophagosomes with subsequent activation of pro-apoptotic Caspase-3 and Caspase-9, which is reduced by siRNA knockdown of *IL17-RC*. IL17-dependent retinal degeneration in DKO/rd8 can be prevented by gene therapy with adeno-associated virus vector encoding soluble IL-17 receptor. This intervention rescues RPE and photoreceptors in a MAPK-dependent process. The above data suggest that NLRP3 inflammasome activation and IL-17 pathway play an important role in AMD pathogenesis and could be considered potential therapeutic targets.

Biography

Chi-Chao Chan earned her M.D. from Johns Hopkins University and ophthalmology residency from Stanford University School of Medicine. She has completed two post-doctoral fellowships: ophthalmic pathology at Wilmer Institute, Johns Hopkins and clinical ocular immunology at National Eye Institute, National Institutes of Health. Chan is the Chief of Immunopathology Section, Laboratory of Immunology and Head of Histopathology Core, National Eye Institute, the federal government medical research institute in the US. She has published more than 600 papers in peer-reviewed journals and one textbook. She also serves as an editorial board member for 20 medical journals.

ChanC@NEI.NIH.GOV