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 system composed 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). Inflammasomes promote the maturation of certain pro-inflammatory cytokines including interleukin (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 increase in 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 mitochondrial degeneration, 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; and higher 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 to aberrant expression of IL-17A and IL-17-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.

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