Nature Reviews Immunology | Published online 22 Dec 2017; doi:10.1038/nri.2017.154

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INFLAMMASOME

Looking death in the eye

Activation of the NLRP3 inflammasome has been widely implicated in age-related macular degeneration (AMD), the leading cause of blindness in elderly people. In human eyes with geographic atrophy (the advanced form of the disease), low levels of the RNase DICER1 lead to accumulation of the endogenous retroelement *Alu* RNA, inflammasome activation and the death of retinal pigmented epithelium (RPE) cells. This study describes an unexpected role for noncanonical inflammasome activation through the DNA sensor cyclic GMP–AMP synthase (cGAS) in this process.

The authors found that levels of caspase 4, which controls noncanonical inflammasome activation, are higher in the RPE of human eyes with geographic atrophy than of normal eyes from aged individuals. Forced expression of *Alu* RNA or knockdown of *DICER1* induced caspase 4 activation in human RPE cells. Furthermore, mice that lacked functional caspase 11 (the mouse homologue of caspase 4) were resistant to *Alu* RNA-induced RPE degeneration, and *Alu* RNA did not induce caspase 1 activation or IL-18 secretion in *Casp11*$^{-/-}$ mice. Thus, caspase 4-mediated noncanonical inflammasome activation functions upstream of caspase 1 activation during RPE degeneration.

Pyroptotic cell death downstream of caspase 11 and caspase 1 activation can be mediated by the pore-forming protein gasdermin D. Indeed, *Gsdmd*$^{-/-}$ mice were resistant to *Alu* RNA-induced RPE degeneration. However, cleavage of gasdermin D to the pore-forming p30 fragment was not required for RPE degeneration and, instead, the RPE toxicity of *Alu* RNA was shown to involve IL-18-dependent apoptosis.

Upstream of caspase 11 activation, the authors focused on a role for type I interferon (IFN) signalling. *Alu* RNA-induced activation of caspase 11 and RPE degeneration were reduced in mice lacking the type I IFN receptor or downstream signalling molecules or after administration of an IFNβ-neutralizing antibody. In mice lacking the innate immune sensor cGAS or its adaptor protein STING, which can activate type I IFN signalling, *Alu* RNA did not induce IFNβ production, caspase 11 activation, IL-18 production or RPE degeneration. Thus, cGAS–STING-pathway-mediated IFN production drives *Alu* RNA-induced noncanonical inflammasome activation and apoptosis of the RPE. As cGAS does not recognize RNA directly, further experiments showed that *Alu* RNA induces opening of the mitochondrial permeability transition pore and the release of mitochondrial DNA into the cytoplasm, which binds cGAS and induces IFNβ production and RPE degeneration.

The authors believe this to be the first reported example of caspase 4-driven activation of the noncanonical inflammasome in a noninfectious human disease. Furthermore, it provides a new mechanism for how endogenous RNAs can activate cGAS through mitochondrial dysfunction and a novel non-pyroptotic function of gasdermin D in promoting IL-18-dependent apoptosis. These results, therefore, have broad relevance to other human diseases, such as type 1 diabetes and certain viral infections, in which accumulation of *Alu* RNA has been observed.

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> “*Alu* RNA induces opening of the mitochondrial permeability transition pore and the release of mitochondrial DNA”

ORIGINAL ARTICLE Kerur, N. *et al.* cGAS drives noncanonical-inflammasome activation in age-related macular degeneration. *Nat. Med.* http://dx.doi.org/10.1038/nm.4450 (2017)