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Mitochondrial DNA oxidation induces imbalanced activity of NLRP3/NLRP6 inflammasome by activation of caspase-8 and BRCC36 in dry eye

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The concept of innate immunity has been expanded to recognize environmental pathogens other than microbial components. However, whether and how the innate immunity is initiated by epithelium in response to environmental physical challenges such as low humidity and high osmolarity in an autoimmune disease, dry eye, is still largely unknown. Using two experimental dry eye models, primary human corneal epithelial cultures exposed to hyperosmolarity and mouse ocular surface facing desiccating stress, we uncovered novel innate immunity pathway by ocular surface epithelium, where oxidized mitochondrial DNA induces imbalanced activation of NLRP3/NLRP6 inflammasome via stimulation of caspase-8 and BRCC36 in response to environmental stress. Activated NLRP3 with suppressed NLRP6 stimulates caspase-1 activation that leads to IL-1β and IL-18 maturation and secretion. NLRP3-independent caspase-8 noncanonically activates caspase-1 via reciprocal regulation of NLRP3/NLRP6-mediated inflammasome. Reactive oxygen species-induced mitochondrial DNA oxidative damage and BRCC36 deubiquitinating activity provide a missing link and mechanism by which innate immunity responds to environmental stress via caspase-8-involved NLRP3/NLRP6 inflammasome.

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