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Distinct changes in endosomal composition promote NLRP3 inflammasome activation

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Inflammasome complexes are pivotal in the innate immune response to pathogens and other danger signals. The NLRP3 inflammasome is activated in response to a broad variety of cellular stressors. Most of the stimuli act in a potassium efflux-dependent manner but a primary and converging sensing mechanism by the NLRP3 receptor initiating inflammasome assembly remains ill-defined. In this study, through cell biological and genetic approaches, we have demonstrated that NLRP3 inflammasome activators primarily converge on disruption of ER-endosome membrane contact sites (EECS). This defect causes endosomal accumulation of PI4P and a consequent impairment of endosome-to-TGN trafficking (ETT), necessary steps for binding of NLRP3 to endosomes and subsequent inflammasome activation. Lowering endosomal PI4P levels prevents endosomal recruitment of NLRP3 and inhibits inflammasome activation. Disruption of EECS or ETT is sufficient to enhance endosomal PI4P levels, to recruit NLRP3 to endosomes and to potentiate NLRP3 inflammasome activation. Mice with defects in ETT in the myeloid compartment are more susceptible to LPS-induced sepsis in a NLRP3-dependent manner. Our study thus identifies a distinct cellular mechanism leading to endosomal NLRP3 recruitment and inflammasome activation.