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Title: Single-cell dynamics of inflammasome activation and cell death in *M. tuberculosis* infected macrophages

Abstract: Virulent mycobacteria, such as *Mycobacterium tuberculosis* (Mtb), can induce necrotic cell death of their host cells. Pyroptosis is one necrotic pathway that can be induced following inflammasome activation, but the importance of pyroptosis and the mechanisms of inflammasome induction by Mtb are unclear. We are performing live-cell imaging and correlative light and electron microscopy (CLEM) studies of Mtb-infected macrophage cell cultures. We find that virulent Mtb can trigger phagosome rupture followed by canonical NLRP3 inflammasome activation and pyroptosis with release of IL-1b. Pyroptosis is enhanced by increasing bacterial burdens and is the main form of necrosis at early time-points of infection. Correlative imaging reveals inflammasome complexes as fibrillar bundles in pyroptotic macrophages. This approach provides temporal and ultrastructural insight into the sequence of events leading from Mtb uptake to inflammasome activation and pyroptosis in single cells.

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