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INFLAMMASOMES

Polymeric assembly

> prion-like polymerization nucleated by pattern recognition receptors may be a conserved mechanism of signal transduction

Inflammasomes are multi-component signalling complexes that assemble in response to cellular infection or stress and that activate inflammatory cascades and cell death. Although much is known about the composition and function of inflammasomes, the details of inflammasome assembly remain poorly understood. Two studies published in *Cell* now show that the activation of inflammasome sensors nucleates the prion-like polymerization of the adaptor molecule ASC. The resulting filaments function as a platform for caspase activation and inflammatory cytokine maturation.

At the basic level, most inflammasomes are composed of a sensor protein, ASC and a caspase. Interferon-inducible protein AIM2 and NLRP3 (NOD-, LRR- and pyrin domain-containing 3) are two structurally distinct sensor proteins: AIM2 is composed of a pyrin domain (PYD) and a HIN domain, whereas NLRP3 consists of a PYD, a nucleotide-binding domain (NBD) and leucine-rich repeats (LRRs). ASC contains a PYD and a caspase activation and recruitment domain (CARD). Inflammasome assembly occurs following the activation and release of AIM2 or NLRP3 from autoinhibition. This allows their PYDs to interact with the PYD of ASC. In turn, ASC recruits pro-caspase 1 through CARD–CARD interactions, which results in the assembly of a higher-order signalosome, caspase activation and pro-interleukin-1β (pro-IL-1β) processing.

Lu *et al.* found that, following activation of AIM2 or NLRP3, their PYD nucleated the polymerization of ASC PYD (ASC^{PYD}). The formation of ASC^{PYD} filaments was shown to result in the clustering of the flexibly linked CARD of ASC and these clusters, in turn, act as a platform for pro-caspase 1 CARD to form filaments. This brings the caspase domains of pro-caspase 1 into proximity for dimerization, cleavage and caspase 1 activation. These protein aggregates form micron-sized, dense structures that have a star-shaped, branched filamentous morphology. Importantly, structure-based mutations in AIM2 that affect PYD–PYD interactions resulted in defective IL-1β processing, which indicates that polymerization of ASC^{PYD} is necessary for signal transduction. PYD and CARD are members of the death domain superfamily that have a conserved α-helical bundle fold. Their cryoelectron microscopy structure revealed the spiral-like assembly of ASC^{PYD} subunits into a filament.

Similarly, Cai *et al.* showed that AIM2 and NLRP3 nucleate the polymerization of ASC^{PYD}. Preformed ASC^{PYD} filaments were shown to convert native ASC into an active, self-perpetuating and high-molecular-weight polymer that is capable of downstream signalling, which suggests that ASC^{PYD} functions as a prion. The authors tested this possibility using well-established prion assays in budding yeast, the results of which led them to conclude that ASC did indeed form a bona fide prion that perpetuates itself indefinitely in response to upstream signals. They also found that mutations of ASC that disrupt the prion activity of ASC^{PYD} cannot activate caspase 1 and IL-1β.

In addition, activation of the adaptor molecule MAVS (mitochondrial antiviral signalling protein) by its upstream intracellular sensor RIG-I (retinoic acid-inducible gene I) induces the prion conversion of $MAVS^{CARD}$ and, similarly to ASC^{PYD}, $MAVS^{CARD}$ polymerization is required for downstream signalling.

Finally, the authors showed that a conserved pattern recognition receptor and a bona fide prion from a filamentous fungus can functionally replace $NLRP3^{PYD}$ and ASC^{PYD}, respectively, in inflammasome signalling. This indicates that prion-like polymerization nucleated by pattern recognition receptors may be a conserved mechanism of signal transduction from fungi to mammals.

Together, these studies describe a model of inflammasome assembly that involves polymerization of the adaptor molecule ASC. Despite having an α-helical fold that is distinct from the cross-β sheet fold of classical prions, many proteins in the death domain superfamily possess prion-like properties. This form of self-perpetuating signal amplification produces a highly sensitive and robust response to noxious stimuli, and may be conserved across species.

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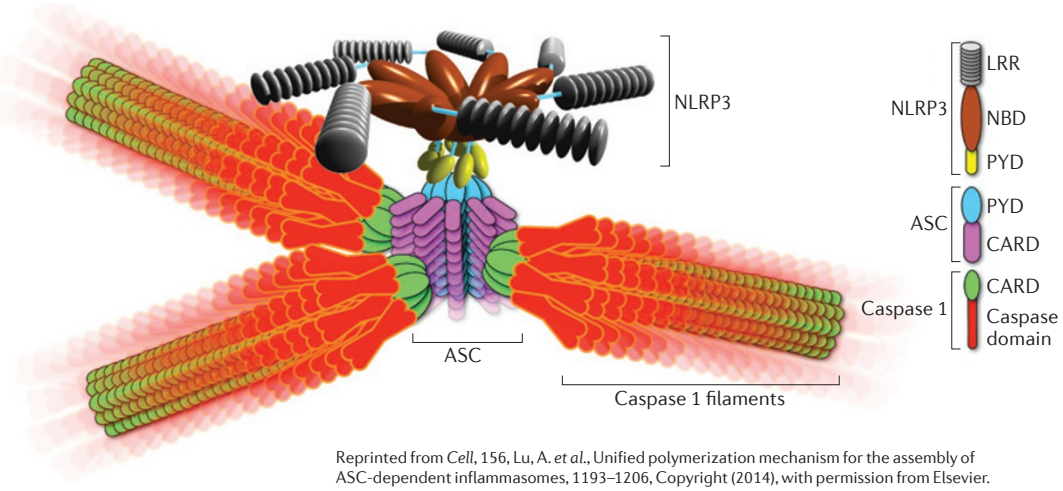

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ORIGINAL RESEARCH PAPERS Lu, A. *et al.* Unified polymerization mechanism for the assembly of ASC-dependent inflammasomes. *Cell* **156**, 1193–1206 (2014) | Cai, X. *et al.* Prion-like polymerization underlies signal transduction in antiviral immune defense and inflammasome activation. *Cell* **156**, 1207–1222 (2014)
FURTHER READING Latz, E. *et al.* Activation and regulation of the inflammasomes. *Nature Rev. Immunol.* **13**, 397–411 (2013)