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INNATE IMMUNITY

Inflammasome triggered by cell swelling

> These data support the use of hypertonic solutions to treat inflammatory diseases

Changes in extracellular osmolarity alter cell volume, thereby activating a volume-regulatory response that involves the activity of multiple ion channels. Compan *et al.* now report an evolutionarily conserved role for ion channels that sense cell swelling in the activation of the NLRP3 (NOD-, LRR- and pyrin domain-containing 3) inflammasome.

Several stress-associated stimuli induce the oligomerization of NLRP3 molecules and the formation of active inflammasomes, which cleave pro-caspase 1 and thereby promote caspase 1-mediated maturation of the pro-inflammatory cytokines interleukin-1β (IL-1β) and IL-18. Cell swelling in the presence of a hypotonic solution, or as a result of water influx following the intracellular accumulation of uric acid crystals, has been previously shown to induce the maturation of IL-1β in macrophages. So, Compan *et al.* set out to characterize the molecular events that lead to cell volume-dependent IL-1β processing.

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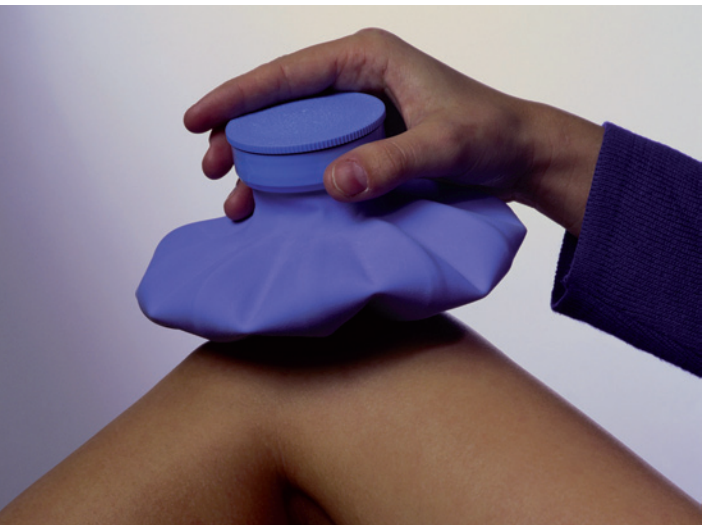

Treatment of macrophages with a hypotonic solution and the resulting cell swelling were associated with caspase 1 activation, pro-IL-1β processing and increased secretion of IL-1β in an NLRP3-dependent manner. Interestingly, hypo-osmotic stress promoted caspase 1 activation in both mouse- and fish-derived macrophages, indicating an evolutionarily conserved link between osmotic stress and inflammasome activation.

Next, NLRP3 was shown to oligomerize into inactive complexes in the steady state (and not following stimulation as previously thought), and a hypo-osmotic environment promoted inflammasome activation by inducing a conformational change in the pre-assembled NLRP3 complexes that depended on a decrease in intracellular K^+ levels. A decrease in K^+ concentration has been previously implicated in inflammasome activation, and, indeed, inhibition of K^+ efflux during hypo-osmotic shock was sufficient to block both regulatory volume decrease (RVD) and IL-1β processing. However, the RVD response involves the efflux of both K^+ and Cl^- through cell swelling-sensing K^+ and Cl^- channels, and inhibition of Cl^- channels also prevented IL-1β processing, although K^+ efflux was unaffected. Thus, the molecular components that promote both the RVD response and IL-1β processing in response to cell swelling lie downstream of K^+ and Cl^- efflux.

Transient receptor potential (TRP) channels are non-selective cation channels, and membrane stretch (which occurs following changes in the cell volume) can activate some TRP channels (including TRPV2). Macrophages were found to express two RVD-associated TRP channels, TRPV2 and TRPM7, and blocking of either of these TRP channels reduced the release of IL-1β in the presence of a hypotonic solution. Moreover, hypotonicity-dependent TRP channel activation induced changes in intracellular Ca^{2+} levels and promoted TGFβ-activated kinase 1 (TAK1) phosphorylation, which in turn was required for caspase 1 activation and IL-1β processing in response to cell swelling. Thus, cell swelling in response to hypo-osmotic stress promotes inflammasome activation through a pathway that involves K^+ and Cl^- efflux, TRP channel activation and TAK1 phosphorylation.

Interestingly, all known inflammasome activators induce changes in cell volume, so the authors propose that mechanosensitive ion channels may be general regulators of inflammasome activation. In accordance with this hypothesis, application of hypertonic solutions blocked the release of IL-1β in response to all the known NLRP3 activators *in vitro* and reduced inflammasome activity in a rat model of brain inflammation. Furthermore, application of a TRP channel inhibitor in a mouse model of ear inflammation reversed inflammation and reduced the size of lesion-infiltrating macrophages (which are larger than macrophages that infiltrate healthy tissues). These data support the use of hypertonic solutions to treat inflammatory diseases.

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ORIGINAL RESEARCH PAPER Compan, V. *et al.* Cell volume regulation modulates NLRP3 inflammasome activation. *Immunity* **37**, 487–500 (2012)