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## **Molecular mechanisms of NLRP3 and AIM2 inflammasome activation**

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Innate immunity evolved to recognize microbial infection and to respond to danger signals that appear under disease conditions. The most recently described innate immune receptor family is the Nod-like receptor (NLR) family. The NLR member NLRP3 and the adapter protein ASC form a multi-molecular complex termed the NLRP3 inflammasome. Inflammasomes control the activity of caspase-1, which cleaves and activates the pro-form of the inflammatory cytokines IL-1 $\beta$  and IL-18. The NLRP3 inflammasome can be activated by various membrane active bacterial toxins (e.g. nigericin, maitotoxin or gramicidin) or after phagocytosis of crystalline materials (e.g. silica, asbestos, monosodium urate or alum). The mechanisms by which the NLRP3 inflammasome is activated by physico-chemical diverse activators are not well understood.

We demonstrate that crystals activate the NLRP3 inflammasome in a process that requires phagocytosis and we found that crystal uptake leads to lysosomal damage and rupture. Furthermore, sterile lysosomal damage is also sufficient to induce NLRP3 activation and inhibition of phagosomal acidification or inhibition or lack of cathepsins impairs NLRP3 activation. These results indicate that the NLRP3 inflammasome can sense lysosomal damage as an endogenous danger signal. Our results demonstrate a novel strategy of immune cells to recognize different classes of stimuli by a common, indirect mechanism.

Cytosolic DNA can also induce caspase-1 activation and release of IL-1 $\beta$  cytokine family members. DNA delivered into the cytoplasm can activate a NLRP3-independent yet ASC dependent inflammasome. AIM2, a member of the PYHIN protein family, has a pyrin domain and a HIN200 DNA binding domain. We found that AIM2 binds to dsDNA and forms an inflammasome together with ASC leading to caspase-1 activation. These pathways are promising new targets for pharmacological inhibitors with broad clinical significance.

### **Recent publications:**

Bauernfeind, F. G., Horvath, G., Stutz, A., Alnemri, E. S., MacDonald, K., Speert, D., Fernandes-Alnemri, T., Wu, J., Monks, B. G., Fitzgerald, K. A., Hornung, V. & Latz, E. (2009 Jul 15) Cutting edge: NF-kappaB activating pattern recognition and cytokine receptors license NLRP3 inflammasome activation by regulating NLRP3 expression, *J Immunol.* 183:787-791.

Hornung, V., Ablasser, A., Charrel-Dennis, M., Bauernfeind, F., Horvath, G., Caffrey, D. R., Latz, E\*. & Fitzgerald, K\*. A. (2009 Mar 26) AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC, *Nature.* 458:514-518 \* equal contribution.

Hornung, V., Bauernfeind, F., Halle, A., Samstad, E. O., Kono, H., Rock, K. L., Fitzgerald, K. A. & Latz, E. (2008 Aug) Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization, *Nat Immunol.* 9:847-856.

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