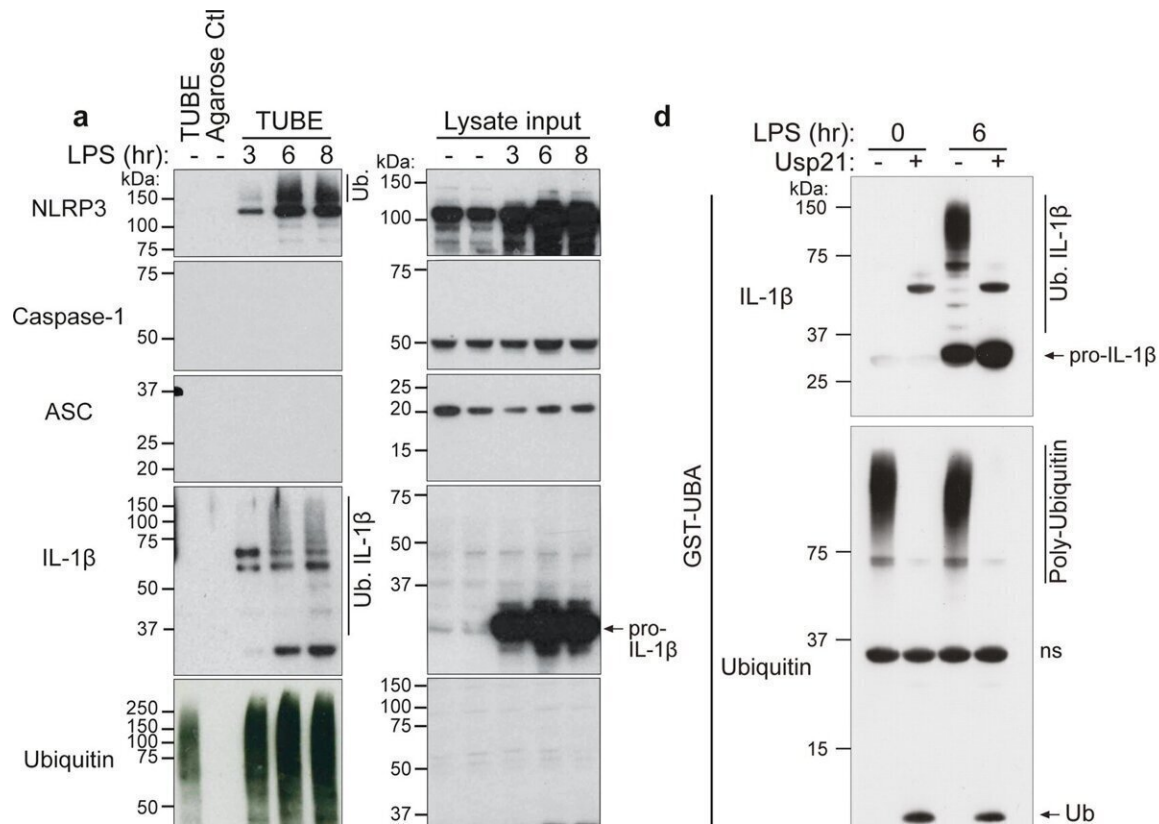


Finding the triggers of inflammation

July 12 2022



TLR-induced inflammasome priming triggers IL-1 β and NLRP3 ubiquitylation. **a** BMDMs were primed with Lipopolysaccharide (LPS, 50 ng/ml) for up to 8 h (hr) and ubiquitylated (Ub.) proteins were isolated from cell lysates by Tandem Ubiquitin Binding Entity (TUBE) purification. Immunoblots were performed on cell lysates (input) and purified ubiquitylated proteins (TUBEs) for the indicated proteins. Agarose control (ctl) shows the specificity of ubiquitylated protein purification. One of two experiments. **b** Immortalized BMDMs (iBMDMs) were treated with LPS (50 ng/ml) for up to 24 h and ubiquitylated proteins were purified from cell lysates using TUBE purification. Immunoblots were performed on cell lysates (input) and purified ubiquitylated proteins (TUBEs)

for the indicated proteins. One of three experiments. **c** IL-1 β deficient iBMDMs were infected with a retroviral *Il1b* cDNA vector containing an internal ribosome entry site (IRES) upstream of Green Florescent Protein (GFP). The complemented cells were sorted for GFP expression and stable cell lines established. Parental *Il1b*^{-/-} or complemented (*Il1b*^{-/-} + *Il1b*) iBMDMs were treated with LPS (100 ng/ml) for the indicated times and IL-1 β and NLRP3 modification examined by TUBE purification and immunoblotting. One of two independent experiments. **d** iBMDMs were treated with LPS (50 ng/ml) for 0 or 6 h and ubiquitylated proteins immunopurified from cell lysates using a Glutathione S-transferase-Ubiquitin Associated domain (GST-UBA) fusion protein. Samples were treated with the ubiquitin specific peptidase USP21 to cleave ubiquitin from isolated proteins. Immunoblots were performed and probed for indicated proteins. One of three experiments. **e** FLAG-IL-1 β was incubated, as indicated, with recombinant E1 ubiquitin activating enzyme, E2 conjugating enzyme UbcH5a and E3 ubiquitin ligase cellular IAP1 (cIAP1), and the conjugation of ubiquitin onto FLAG-IL-1 β analyzed by immunoblot. One of three experiments. ns, non-specific band. Credit: *Nature Communications* (2021). DOI: 10.1038/s41467-021-22979-3

Chronic or acute inflammation can contribute to a range of ailments—some potentially deadly—including stroke, respiratory and heart disease, cancer, arthritis, asthma, dementia, multiple sclerosis, and diabetes. In May, a study by Dr. Kate Lawlor and collaborator Professor Vince James (WEHI) published in *Nature Communications* shed light on the potential triggers of inflammation.

The research focused on the cytokine, interleukin-1 β (IL-1 β), which is critical to clearing infections but is also associated with sepsis and driving autoinflammatory and [inflammatory diseases](#) including rheumatoid arthritis, type 2 diabetes, and atherosclerosis.

Previous IL-1 β research had focused on understanding how it is triggered and how inhibiting this process or neutralizing IL-1 β could

reduce inflammation. However, little was known about how the precursor IL-1 β protein is regulated.

The team discovered a key event that contributes to the depletion of inactive IL-1 β and limits access to the enzyme that activates IL-1 β . The potential trigger of inflammation discovery is a major step in understanding how IL-1 β levels could be manipulated to limit inflammatory responses and developing treatments for diseases associated with excessive inflammation.

More information: Swarna L. Vijayaraj et al, The ubiquitylation of IL-1 β limits its cleavage by caspase-1 and targets it for proteasomal degradation, *Nature Communications* (2021). [DOI: 10.1038/s41467-021-22979-3](https://doi.org/10.1038/s41467-021-22979-3)

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