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Necrosis of IL-1 β -containing monocytes may drive NOMID

NOMID (neonatal-onset multisystem inflammatory disease), the most severe of the cryopyrin-associated periodic syndromes, is caused by activating mutations in *NLRP3* that lead to excess production of IL-1 β . However, until now, the cells producing an excess of this proinflammatory cytokine and the fate of these cells in patients with NOMID were unclear. New work by Jehad Edwan and co-workers shows that most of the IL-1 β in peripheral blood samples from these patients comes from monocytes with high CD14 expression, relatively low CD16 expression, and large amounts of intracellular CD83.

As neither ELISA nor immunoblotting can determine which cell populations in a complex mixture generate a given cytokine, Edwan developed an assay utilizing both free anti-IL-1 β antibodies (which can enter permeabilized cells) and anti-IL-1 β antibodies attached to microbeads (which can bind IL-1 β in supernatant). The bead and cell mixtures

were analysed by flow cytometry, giving a more-complete picture of how much IL-1 β was being produced, and by which cells.

“Interestingly, many of these CD14^{hi}CD16^{lo}CD83⁺ cells seemed to die very rapidly at the same time they released IL-1 β ,” notes Robert Colbert, the study’s corresponding author. This cell death was caspase-independent and cathepsin-B-dependent. “These cells were undergoing pyronecrosis,” Colbert deduces. “This is important because necrotic cell death

tends to promote inflammation, while apoptosis is protective,” he explains.

The dying NOMID monocytes also released large amounts of adaptor protein ASC, a potent driver of inflammation that is also involved in conversion of pro-IL-1 β to the active cytokine. “IL-1 β seemed to contribute to a positive feedback loop where it promoted the death of cells after being released, suggesting that one of the proinflammatory effects of this cytokine in NOMID might be to promote the death of cells sensitized by the *NLRP3* mutation,” Colbert notes. The team is conducting further studies of the mechanisms by which *NLRP3* activation induces cell death, which could ultimately lead to improved treatments for NOMID.

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Original article Edwan, J. H. *et al.* Identification of IL-1 β -producing monocytes that are susceptible to pyronecrotic cell death in patients with NOMID. *Arthritis Rheumatol.* doi:10.1002/art.39307