Journal Club

THE INFLAMMASOME STARTS ROLLING

The cloning of IL-1 β in 1984 and characterization of its myriad immunological activities spanned decades of research and heralded extensive studies on cytokine biology and inflammation in general. However, the mechanisms leading to the processing and release of IL-1 β remained elusive even after caspase 1 was identified as the IL-1-converting enzyme in 1992. This all changed in 2002, when Jürg Tschopp and colleagues reported the identification of a caspase-activating complex, which they named 'the inflammasome', that drives the maturation and secretion of IL-1 β .

They showed that a multiprotein complex comprising ASC (also known as PYCARD) and the NOD-like receptor (NLR) family, pyrin domain-containing 1 (NLRP1) protein recruits and activates caspase 1 and caspase 5, which subsequently process pro-IL-1 β . This study set the ball rolling for the era of the inflammasome, sparking intense research to further understand inflammasome activation and cytokine production, as well as its implications in health and disease.

Studies by many investigators around the globe led to the discovery of several additional inflammasome complexes that assemble in response to distinct stimuli. A unique form of cell death known as pyroptosis was shown to facilitate the release of inflammasome-dependent cytokines, and gasdermin D was identified recently as a caspase substrate that executes membrane pore formation during pyroptosis.

Although inflammasomes mostly protect against infectious diseases, we now know that dysregulated inflammasome activation may underpin immunopathology during acute infections and is an important driver of chronic inflammatory, metabolic and neurodegenerative diseases and cancer. Indeed, speculation by Tschopp and colleagues regarding the possible role of inflammasomes in hereditary periodic fever syndromes was soon proved right, and pharmacological targeting of inflammasomes is being pursued as a strategy for the treatment of autoinflammatory diseases and cancer.

I was fortunate to be part of this exciting new field of inflammasome research from its infancy. Future studies will no doubt bring additional insights regarding the regulation of inflammasomes and might guide the development of novel therapeutic approaches for patients with high unmet need.

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ORIGINAL ARTICLE Martinon, F., Burns, K. & Tschopp, J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-1 β . *Mol. Cell* **10**, 417–426 (2002)

leak during respiration, which is indicative of mitochondrial damage. Experiments with an eATP analogue suggested that P2RX7-induced calcium flux enhances mitochondrial function in memory-like CD8⁺ T cells.

As well as being released in infected and injured tissues, ATP is exported by T cells through Pannexin 1 (PANX1) channels; the authors showed that a PANX1 inhibitor caused similar metabolic defects to P2RX7 deficiency in memory-like CD8⁺ T cells, suggesting that these molecules regulate the same metabolic pathways. Further experiments suggested that elevated intracellular ATP concentrations and defects in calcium flux in the absence of P2RX7 impaired the activation of the key metabolic enzyme AMPK, which is important for the transition from an effector to memory T cell phenotype. In keeping with this, pharmacological activation of AMPK in P2rx7^{-/-} T cells partially reversed their metabolic defects and enhanced the generation of T_{CM} and T_{RM} cell populations.

As inhibitors of P2RX7 are being developed for neuropathic pain, the authors examined whether these therapies affect CD8⁺ T cell memory. In a model of spared nerve injury combined with LCMV infection, treatment with the P2RX7 inhibitor A-438079 reduced both nerve injury-induced hypersensitivity and the formation of T_{CM} cells. Of note, this drug also caused a loss of pre-existing memory CD8⁺ T cells, which suggests that P2RX7 is required for the long-term maintenance of memory CD8⁺ T cells.

These findings reveal a previously unappreciated role for the eATP sensor P2RX7 in supporting long-lived memory CD8⁺ T cell responses. Moreover, this study cautions that the therapeutic blockade of P2RX7 to treat neuropathic pain may inadvertently compromise the memory CD8⁺ T cell compartment.

Yvonne Bordon

ORIGINAL ARTICLE Borges da Silva, H. et al. The purinergic receptor P2RX7 directs metabolic fitness of long-lived memory CD8⁺ T cells. *Nature*. <https://doi.org/10.1038/s41586-018-0282-0> (2018)

Notably, the presence of high levels of IL-15 was able to rescue the NK cell defect, allowing survival of Vav Rfx7^{fl/fl} NK cells to levels equal or greater than their wild-type counterparts.

Next, the authors performed global RNA-sequencing analyses to better understand the pathways affected by Rfx7 deletion. 1,636 genes were differentially expressed in the presence and absence of RFX7, with a majority of genes related to cellular and metabolic processes. By cloning some of the top differentially expressed genes, the authors identified direct targets of RFX7 transcription. In particular, *Rec8*, *Mxd4* and *Ddit4* were identified as having regions that are bound by RFX7. Consistent with an effect on metabolism, RFX7-deficient NK cells were more active, were larger in size and had greater granularity than control cells. They also showed increased proliferation and metabolic rate (as assessed by oxygen consumption and extracellular acidification rate), together suggesting a heightened energetic state of NK cells lacking RFX7.

Notably, when Vav Rfx7^{fl/fl} mice were crossed with mice heterozygous for

mechanistic target of rapamycin complex 1 (mTORC1), NK cell defects were partially rescued, suggesting that RFX7 regulates NK cell metabolism in part by limiting mTORC1 signalling. High levels of IL-15 rescued the survival of RFX7-deficient NK cells by restoring harmonized activation of both the mTORC1 and Janus kinase (JAK)–signal transducer and activator of transcription 5 (STAT5) pathways.

Finally, the authors showed that RFX7 is required for optimal NK cell-mediated immunity. Compared with control mice, Vav Rfx7^{fl/fl} mice showed a decreased ability to reject MHC class I-deficient target cells, and *Ncr1* Rfx7^{fl/fl} mice showed defective early responses against infection with murine cytomegalovirus.

So, this study identifies RFX7 as a new regulator of NK cell homeostasis and metabolic quiescence.

Lucy Bird

ORIGINAL ARTICLE Castro, W. et al. The transcription factor Rfx7 limits metabolism of NK cells and promotes their maintenance and immunity. *Nat. Immunol.* <https://doi.org/10.1038/s41590-018-0144-9> (2018)