and the two proteins were colocalized in HUVEC nuclei. Therefore, the authors propose that a putative UMLILO–WDR5–MLL1 complex regulates H3K4me3 of chemokine promoters in *cis*. In support of this mechanism, replacing the genomic UMLILO sequence of HeLa cells with the well-characterized WDR5-interacting lncRNA HOTTIP restored TNF-induced chemokine expression.

Finally, Fanucchi et al. showed that the mechanism described for TNF-induced UMLILO is also relevant to β-glucan-mediated epigenetic reprogramming of human monocytes. β-Glucan signalling through dectin 1 triggers calcium-dependent activation of the transcription factor NFAT, and all of the IPLs described in this study contain NFAT-binding motifs in their promoters. Pretreatment of monocytes with tacrolimus (which inhibits NFAT activation) prevented the β-glucan-induced upregulation of expression of UMLILO and other IPLs and, hence, of chemokine gene transcription. This suggests that tacrolimus may block trained immune responses. Interestingly, the mouse CXC-chemokine TAD lacks UMLILO and is resistant to β-glucan-induced training of the chemokine promoters. UMLILO knock-in of a mouse macrophage cell line resulted in accumulation of H3K4me3 at chemokine promoters and enhanced the trained immune response to β-glucan. This observation may partly explain why mice are more resistant to inflammatory stimuli than humans.

This study therefore identifies a mechanism of lncRNA-mediated regulation of H3K4me3 during trained immunity, resulting in robust transcriptional responses. Chromatin looping positions IPLs such as UMLILO proximal to innate immune genes to focus WDR5–MLL1-mediated histone methylation at relevant gene promoters.

Kirsty Minton

ORIGINAL ARTICLE Fanucchi, S. et al. Immune genes are primed for robust transcription by proximal long noncoding RNAs located in nuclear compartments. *Nat. Genet.* https://doi.org/10.1038/s41588-018-0298-2 (2018)

Previous studies have suggested that NLRP3 activation involves its translocation to mitochondria. However, using several different approaches, the authors were unable to detect any colocalization of NLRP3 puncta with mitochondria. Indeed, the TGN was the only cellular organelle to strongly colocalize with NLRP3 activity.

In response to NLRP3 activators, the dTGN formed before NLRP3 puncta, suggesting it promotes the recruitment and aggregation of NLRP3. Indeed, mutation analyses indicated that the conserved polybasic region in the amino-terminal of NLRP3 is crucial for NLRP3 recruitment to the dTGN and its activation. The authors identified phosphatidylinositol-4-phosphate (PtdIns4P) as the negatively charged phospholipid mediating the recruitment of NLRP3 to the dTGN.

Finally, potassium (K^+) efflux is important for NLRP3 activation in response to some stimuli (such as nigericin) but not in response to others (such as imiquimod and CL097). The authors found K^+ efflux was necessary for NLRP3 recruitment to the dTGN following nigericin treatment; they suggest K^+ efflux is likely to promote ionic binding between NLRP3 and PtdIns4P. By contrast, imiquimod and CL097 induced dispersion of the TGN and NLRP3 recruitment and activation independently of K^+ efflux. The authors suggest that NLRP3 activators that do not require K^+ efflux may cause greater dispersion of the TGN and expose PtdIns4P in a more efficient conformation for NLRP3 recruitment.

Based on their findings, the authors propose that NLRP3 activation resembles the 'guard model' seen in plants, in that the immune system is responding to changes in the integrity of self components (in this case the TGN). This model for NLRP3 inflammasome activation has been proposed before, but the authors have now provided the mechanistic basis.

Yvonne Bordon

ORIGINAL ARTICLE Chen, J. & Chen, Z. J. PtdIns4P on dispersed trans-Golgi network mediates NLRP3 inflammasome activation. *Nature* **564**, 71–76 (2018)
FURTHER READING Liston, A. & Masters, S. L. Homeostasis-altering molecular processes as mechanisms of inflammasome activation. *Nat. Rev. Immunol.* **17**, 208–214 (2017)

Journal club

21ST CENTURY NATURAL KILLERS

The introduction of new technologies and their application to biological questions has enhanced our understanding of a range of topics. For example, cytometry by time of flight (CyTOF; also known as mass cytometry) has transformed ideas about the immune system. In a study published in 2013, Horowitz et al. used mass cytometry to investigate the exquisite variety of natural killer (NK) cells, revealing the complexity of expression of activating and inhibitory receptors on their surface. The myriad of phenotypes they describe bring to light new questions regarding NK cell maturation, functionality and memory potential.

At the start of the 21st century, a great deal was still unknown about the regulation and expression of NK cell receptors and the mechanisms underlying NK cell function and tolerance. It had been speculated that any combination of the many germline-encoded activating and inhibitory receptors would function as a rheostat to increase or decrease sensitivity of the NK cell for activation. Horowitz et al. show that the NK cell repertoire is 'anchored' by the expression of a small number of receptors (CD16–CD57 and NKG2A–CD94) that account for the only major subdivision of NK cells, upon which the immense diversity of phenotypes is built through the stochastic expression of all other NK cell receptors.

This paper also shows, for the first time, that the receptor expression of peripheral NK cells is influenced by the environment, providing evidence that these innate cells can adapt. By comparing the phenotypic variation of NK cells between monozygotic twins with the variation between genetically diverse individuals, the authors suggest that whereas inhibitory receptor expression seems to be bound by the genetic code, activating receptor expression may be influenced by environmental cues in the periphery. Viral infection is one way in which the activating receptor expression of NK cells may be altered, and the authors describe the presence of a common receptor expression cluster ($CD57^+NKG2C^+$) on a subset of NK cells in individuals infected with cytomegalovirus. It is thought that this phenotype identifies a subset of memory NK cells; thus, these data provide further support for the existence of innate cell memory (Goodier et al., 2007; Lopez-Vergès et al., 2011).

Overall, this paper highlights how the unbiased collection of high resolution data can refine models and provide a new framework within which investigators can study the mechanisms underlying NK cell functionality.

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ORIGINAL ARTICLE Horowitz, A. et al. Genetic and environmental determinants of human NK cell diversity revealed by mass cytometry. *Sci. Transl Med.* **5**, 208ra145 (2013)
FURTHER READING Goodier, M. R. et al. $NKG2C^+$ NK cells are enriched in AIDS patients with advanced-stage Kaposi's sarcoma. *J. Virol.* **81**, 430–433 (2007) | Lopez-Vergès, S. et al. Expansion of a unique $CD57^+NKG2C^{hi}$ natural killer cell subset during acute human cytomegalovirus infection. *Proc. Natl Acad. Sci. USA* **108**, 14725–14732 (2011)