ANTIVIRAL RESPONSES

STING-ing insights

Nature https://doi.org/10.1038/s41586-019-0998-5, https://doi.org/10.1038/s41586-019-1000-2 & https://doi.org/10.1038/s41586-019-1006-9 (2019)

STING is a dimeric endoplasmic reticulum–resident adaptor that is activated by the recognition of cytosolic DNA and the generation of cyclic GMP-AMP (cGAMP), which ultimately results in the production of type I interferons. In *Nature*, Chen and colleagues present three studies that reveal how binding of cGAMP alters the conformation of STING to trigger its oligomerization and translocation to the Golgi and interactions with the kinase TBK1. Cryo–electron microscopy reveals that cGAMP induces allosteric conformational changes in STING to form tetramers. While apo-STING can bind to dimeric TBK1, the STING-phosphorylation site is not accessible to either kinase domain of TBK1. Instead, cGAMP-induced tetramerization of STING is needed to position tandem TBK1 kinases for trans-phosphorylation of one STING dimer by the TBK1 dimer bound to an adjacent STING dimer. Such oligomerization then facilitates recruitment and activation of the transcription factor IRF3. A separate study identifies a cGAS–STING-dependent non-canonical autophagy pathway activated by cytosolic DNA and DNA viruses. Neither TBK1 nor IRF3 is required for this process, suggestive of a primordial anti-viral function of STING that is independent of interferons. *LAD*

https://doi.org/10.1038/s41590-019-0370-9

ANTI-MICROBIAL PEPTIDES

Digest to diverge

Proc. Natl Acad. Sci USA https://doi.org/10.1073/pnas.1817376116 (2019)

Immunohomeostasis in the gut relies on the maintenance of a diversified microbiota. In the *Proceedings of the National Academy of Sciences USA*, Wehkamp and colleagues investigate how the environment of the small intestine can alter the activity of the Paneth cell–produced antimicrobial peptides HD-5 and HD-6. The duodenum is mainly a reducing environment and is flooded with duodenal proteases. Reduced HD-6 is resistant to these proteases, but reduced HD-5 is cleaved into a large number (hundreds) of different fragments. These HD-5 fragments retain variable degrees of antimicrobial activity depending on the microbial species to which they are exposed. Cleavage of HD-5 by the duodenal environment thereby, in a combinatorial way, increases the range of antimicrobial activity and can help enforce a diverse microbiome. *ZF*

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HIV IMMUNOEVASION

Vpu broadens its effects

eLife https://doi.org/10.7554/eLife.41930 (5 Feb. 2019)

Vpu is an accessory protein of human immunodeficiency virus type 1 that serves well-described immunomodulatory functions mainly via its antagonism of the host cell–expressed restriction factor tetherin. In *eLife*, Sauter and colleagues compare wild-type and mutant versions of Vpu to investigate other potential immunomodulatory effects. Functional Vpu imposes considerable suppression of $CD4^+$ T cell transcription, and this is independent of any effects on tetherin. In particular, many genes controlled by the transcription factor NF-κB — including those encoding the proinflammatory cytokines IL-6 and type 1 interferons and chemokines such as CXCL10 — are selectively suppressed. Although the mechanistic details of how Vpu impairs NF-κB activity remain to be determined, these findings demonstrate that Vpu has a much wider range of immunomodulatory effects than previously appreciated. *ZF*

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MUCOSAL IMMUNOLOGY

Inflammation-induced remodeling

Cell https://doi.org/10.1016/j.cell.2018.12.039 (2019)

Mouse γδ T cells seed the intestine early in life and persist as intra-epithelial lymphocytes (IELs). In *Cell*, Jabri and colleagues show that a population of $NKp46^-IFN\text{-}\gamma^+V_\gamma1^+$ IELs accumulates in the small intestine of patients with celiac disease (CeD), but not those on a gluten-free diet, at the expense of the innate-like, cytotoxic $NKp46^+NKp44^+V_\gamma1^+$ IELs found in healthy control subjects. $NKp46^-V_\gamma1^+$ IELs from patients with CeD have a transcriptional program distinct from that of $NKp46^+V_\gamma1^+$ IELs from healthy subjects, irrespective of adherence to a gluten-free diet. $V_\gamma1^+$ IELs from healthy subjects show enrichment for transcripts encoding the TCR γ-chain variable region 4, express genes encoding molecules associated with tissue repair and are reactive to the butyrophilin-like molecules BTNL3 and BTNL8, while $NKp46^-V_\gamma1^+$ IELs from patients with CeD lack all those characteristics, even after restauration of expression of BTNL3 and BTNL8 in patients on a gluten-free diet. Thus, gluten-induced inflammation remodels the $V_\gamma1^+$ IEL compartment, with consequences for tissue pathology. *IV*

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Laurie A. Dempsey, Zoltan Fehervari and Ioana Visan

IMMUNOMETABOLISM

Tumor adaptations

Science **363**, 644–649 (2019)

The metastatic potential of primary tumor cells greatly increases after they migrate to draining lymph nodes (LNs). In *Science,* Lee et al. report that tumor cells adapt to this fatty-acid-rich environment by altering their cellular metabolism to fatty-acid oxidation. The transcription factor YAP is activated and translocates to the nucleus in LN-resident tumor cells but not primary tumors or distal sites of metastasis. Bile acids produced as cholesterol metabolites within the LN environment promote this response. Inhibition of fatty-acid oxidation or small interfering RNA–mediated knockdown of YAP or the bile-converting enzyme CYP7A1 in tumor cells diminishes their metastatic potential in LNs. Notably, in a small cohort of patients with tumors, the nuclear localization of YAP in tumors that have metastasized to the LNs also correlates with reduced survival. These findings show that tumor cells can adapt their metabolism to their local environment. *LAD*

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