

NUCLEIC ACID SENSING

Receptor oligomerization

Cell <https://doi.org/10.1016/j.cell.2019.03.017> (2019)

The E3 ligase RIPLET is required for activation of the viral dsRNA receptor RIG-I. In *Cell*, Hur and colleagues show that RIPLET uses its dimeric structure to recognize and ubiquitinate pre-oligomerized RIG-I bound to dsRNA and promotes antiviral signaling in a manner dependent on the length of the RNA. RIPLET binds and conjugates K63 ubiquitin on RIG-I–dsRNA complexes but not on free RIG-I. RIPLET needs to be a dimer to bind RIG-I, requires dsRNAs long enough to accommodate two RIG-I molecules (at least 21 bp) and induces maximum ubiquitination of RIG-I on 30- to 40-bp dsRNAs. On long dsRNA (160 or 512 bp), RIPLET bridges multiple RIG-I filaments through inter-filament binding and induces filamentation of the adaptor MAVS independently of the ubiquitination of RIG-I. The filament-bridging activity and ubiquitination activity of RIPLET are synergistic in amplifying RIG-I signaling. IV

<https://doi.org/10.1038/s41590-019-0409-y>

TUMOR IMMUNOLOGY

Death by iron

Nature <https://doi.org/10.1038/s41586-019-1170-y> (2019)

Ferroptosis is an iron-dependent form of programmed cell death that results

from inefficient glutathione redox activity and the accumulation of lipid peroxides. In *Nature*, Wang et al. show that interferon- γ (IFN- γ) produced by CD8⁺ T cells acts in synergy with immunoreceptor checkpoint inhibition to enhance tumor-cell death by ferroptosis. IFN- γ signaling leads to lower tumor-cell expression of the glutamate–cystine antiporter complex proteins SLC3A2 and SLC7A11, which results in decreased cystine uptake, loss of glutathione and increases in oxidized membrane lipids, including phosphatidylethanolamine and phosphatidylcholine. Inhibition or ablation of the ferroptosis pathway negates the synergistic effects of IFN- γ on tumor-cell death, in both in vitro and in vivo mouse tumor models. Notably, retrospective analysis shows that the responses of tumor-bearing patients to checkpoint-blockade therapy and survival are correlated with high *IFNG* expression by CD8⁺ T cells and low tumor-cell expression of *SLC3A2*. These findings point to synergies that might prove advantageous for cancer immunotherapy. LAD

<https://doi.org/10.1038/s41590-019-0411-4>

INHIBITORY RECEPTORS

Controlling PD-L1 in cis

Science <https://doi.org/10.1126/science.aav7062> (2019)

The co-inhibitory receptor PD-1 is important for restraining T cell responses; however, as it is rapidly upregulated

on T cells (hours after activation), it is unclear how its effects are curtailed to allow a productive response. In *Science*, Okazaki and colleagues find that the PD-1 ligand PD-L1 and the co-stimulatory molecule CD80 interact in *cis* on the surface of antigen-presenting cells. This *cis* interaction prevents PD-L1 from binding to its receptor PD-1 on T cells and therefore mitigates its inhibitory effects. Interestingly, the functionally closely related molecule CD86 does not demonstrate this interaction with PD-L1. Mutations in the gene encoding PD-L1 or CD80 that prevent their interaction dampen T cell activation both in vitro and in vivo in the context of cancer and autoimmune responses. ZF

<https://doi.org/10.1038/s41590-019-0412-3>

OPTOGENETICS

Proving kinetic proof-reading

eLife <https://doi.org/10.7554/eLife.42475> & <https://doi.org/10.7554/eLife.42498> (2019)

How T cell antigen receptors (TCRs) distinguish rare stimulatory ligands among a vast excess of non-stimulatory self peptides is a fundamental question of immunology. In *eLife*, Yousefi et al. and Tischer and Weiner investigate this question by complementary optogenetic approaches. The kinetic proofreading model is a useful framework with which to understand TCR ligand discrimination and states that the half-life of TCR–ligand interactions dictates signaling. However, investigating half-life without affecting other biophysical parameters has been technically very challenging. The studies in *eLife* use engineered receptors (either TCRs or chimeric antigen receptors) for which interactions with stimulatory ligand can be finely controlled in isolation by exposure to blue or red light. Through the use of either calcium flux or diacylglycerol accumulation as a ‘readout’ of T cell activation, these studies demonstrate that the kinetic proofreading mode provides the most accurate description of TCR ligand discrimination. ZF

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MUCOSAL IMMUNOLOGY

Triggers of inflammation

Sci. Immunol. <https://doi.org/10.1126/sciimmunol.aaw4341> (2019)

Variants of the pattern-recognition receptor NOD2 are associated with Crohn’s disease. In *Science Immunology*, Nunez and colleagues show that combined deficiency in NOD2 and the oxidase CYBB causes spontaneous intestinal inflammation in mice that is triggered by *Mucispirillum schaeferi*, a Gram-negative mucus-dwelling bacteria. *Nod2*^{-/-}*Cybb*^{-/-} mice from Taconic Bioscience, but not those from Jackson Laboratories, develop T_H1-type inflammation with the pathological hallmarks of Crohn’s disease at 4 weeks of age. *M. schaeferi*, which is detected only in Taconic mice, accumulates more in *Nod2*^{-/-}*Cybb*^{-/-} mice than in *Nod2*^{-/-}, *Cybb*^{-/-} or wild-type Taconic mice. Maternally derived immunoglobulins IgA and IgG directed against *Mucispirillum* protect *Nod2*^{-/-}*Cybb*^{-/-} mice before they are weaned. Colonization of Jackson *Nod2*^{-/-}*Cybb*^{-/-} mice with *Mucispirillum* induces inflammation, which suggests that the development of intestinal inflammation requires multiple genetic hits and specific disease-causing microbes. IV

<https://doi.org/10.1038/s41590-019-0410-5>