CANCER IMMUNOEDITING

Scoring presentation

Cell (26 October 2017) doi:10.1016/j.cell.2017.09.050

The major histocompatibility class I (MHCI) genotype determines the sub-peptidome that can be effectively presented. In *Cell*, Carter and colleagues show that a 'presentation score' derived from MHCI's binding affinities to residues of interest can identify mutations with a high likelihood of generating neoantigens, and they use this score to evaluate individual MHCI genotypes as a determinant of the antigenicity of cancer mutations. In 9,176 patients with known HLA alleles, the score identifies individual variation in the presentation of 1,018 mutations in known oncogenes and tumor suppressors. The analysis indicates that patients have a higher probability of acquiring mutations less effectively presented by their MHCI, which indicates that the frequency of a mutation is not determined only by fitness advantage. The MHCI genotype provides predictive information about the mutations likely to occur in a particular person should a tumor arise, but the score cannot predict which patients are at higher risk for a mutation of known probability and is more predictive in some tumor types than other. *IV*

https://doi.org/10.1038/s41590-017-0015-9

INFLAMMATION

Silent clearance

Immunity 47, 913–927(2017)

Apoptotic cell–derived nucleic acids do not initiate inflammation in healthy tissues, although professional phagocytes express nucleic acid–sensing receptors, such as TLR7 and TLR9, in the phagosomal compartment. In *Immunity*, Barton and colleagues use a system that allows the tracking of phagocytic cells *in vivo* to identify Tim-4$^+$ peritoneal macrophages, Tim-4$^+$ pleural cavity macrophages and Tim-4$^-$ lung alveolar macrophages as populations that clear apoptotic cells at steady state. These macrophages lack expression of TLR9 and have high expression of apoptotic-cell receptors and inhibitors of TLR signaling *in vivo* and do not induce an inflammatory response to apoptotic cells *ex vivo*. However, following 3 days of *in vitro* culture, they acquire TLR9 expression and the ability to induce a pro-inflammatory response to apoptotic cells. This *in vitro* 'deprogramming' is associated with downregulation of the transcription factor Klf2, which seems to control a tissue-enforced program for the silent clearance of apoptotic cells. *IV*

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CANCER IMMUNOTHERAPY

Microbiota & cancer response

Science (2 November 2017) doi:10.1126/science.aan4236 & doi:10.1126/science.aan3706

Immunotherapy that uses checkpoint blockade via inhibitors can provide clinical benefit to some but not all patients with cancer. In *Science*, two reports describe the influence of the patient's gut microbiome on the response to checkpoint inhibition with antibody to the immunoinhibitory receptor PD-1 (anti-PD-1). Gopalakrishnan *et al.* report that patients with melanoma who respond to anti-PD-1 have a greater diversity in their gut microbiota, particularly more Clostridiales and Ruminococcaceae but less Bacteroidales, than that of non-responding patients. Routy *et al.* show that patients with epithelial tumors who are treated with antibiotics respond less well to anti-PD-1 immunotherapy. Both studies show that the transfer of fecal microbiota to germ-free or antibiotics-treated tumor-bearing mice influences the response to checkpoint inhibitor blockade. In particular, Routy *et al.* show that monocolonization with *Akkermansia muciniphila* confers a protective anti-tumor response by inducing expression of the cytokine IL-12 and promoting the infiltration of effector T cells in tumors. These findings suggest a role for the gut microbiome in patients' immune responses to tumors. *LAD*

https://doi.org/10.1038/s41590-017-0017-7

DIET AND INFLAMMATORY DISEASE

Assaulting the microbiota

Nature (15 Nov. 2017) doi:10.1038/nature24628

A high-salt diet (HSD) has well-established links to cardiovascular disease and is also increasingly appreciated as driving the differentiation of pathogenic cells in the T_H17 subset of helper T cells. In *Nature*, Müller and colleagues investigate whether an HSD can also perturb gut microbiota and whether this affects, at least in part, pathogenic T_H17 cells. Mice maintained on an HSD show the expected elevation in blood pressure but also a greater frequency of T_H17 cells in the gut. Accordingly, mice fed an HSD exhibit exacerbated experimental autoimmune encephalitis. The HSD does not elicit gross alterations in the microbiome but instead seems to selectively deplete mice of *Lactobacillus murinus*. Administration of *L. murinus* to mice fed an HSD might normalize their otherwise elevated frequency of T_H17 cells and ameliorate experimental autoimmune encephalitis. As with mice, male human volunteers on an HSD show an increased frequency of T_H17 cells in the blood and a generalized reduction in *Lactobacillus* genera. Salt-induced perturbations of the gut microbiota can therefore influence the differentiation of T_H17 cells and subsequent manifestations of autoimmune disease and cardiovascular disease. *ZF*

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T CELL HOMEOSTASIS

STAT5B in RICD

J. Immunol. (29 November 2017) doi:10.4049/jimmunol.1701133

Common γ-chain cytokines such as IL-2 and IL-7 promote the proliferation and survival of T cells but can also trigger the restimulation-induced cell death (RICD) of effector memory T cells (T_{EM} cells) to maintain T cell homeostasis. In *The Journal of Immunology*, Majri *et al.* show that the signal transducer STAT5b uniquely triggers the apoptosis of T_{EM} cells, not that of naive or central memory T cells, via RICD. Mice that lack STAT5b accumulate T_{EM} cells. Additionally, a patient with a heterozygous point mutation in *STAT5B* also exhibited accumulation of CD4$^+$ T_{EM} cells and clinical symptoms of autoimmunity, as did his heterozygous mother. This Q206R substitution in the STAT5B coiled-coil domain yields a dominant-interfering protein in the IL-2–STAT5 signaling pathway that results in a hypomorphic phenotype. The patient's T_{EM} cells were also resistant to apoptosis after stimulation *in vitro*. It is unclear how STAT5b protein–protein interactions trigger RICD, and the identity of those interacting proteins is currently unknown. *LAD*

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