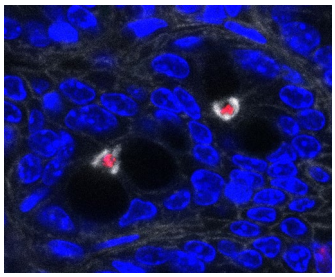
GUT MICROBIOTA

Tricks for taking up residence

Nature **557**, 434–438 (2018)



Credit: Nature

The human gut microbiome plays a key role in maintaining the health of its host, with certain compositions being implicated in diseases such as diabetes and autism. The composition of the gut microbiome is stable over time, which can prevent newly introduced bacterial strains from successfully colonizing. To better understand how new bacterial strains can be stably and predictably integrated into a pre-existing microbiota, Shepherd et al. performed experiments where they introduced a rare strain of the commensal species *Bacteroides ovatus*, NB001, into mice colonized with different complex microbiotas, some of which were donated from humans. NB001 is able to utilize the polysaccharide porphyran, which is abundant in seaweed, so that when NB001 was introduced into any of the mice, even those with the most resistant microbiota, there was a predictable increase in the levels of NB001 if the mice were fed seaweed. This effect was dependent on the NB001 genes required for porphyran metabolism and was observed in the specialized microhabitat of the colonic crypts. NB001 abundance upon engraftment could be tuned by varying the amount of porphyran fed to the mice. These results highlight the powerful influence of nutrient availability in shaping microbiota membership and have implications for treating disease by manipulating microbiota composition. *MB*

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DNA REPAIR

Stabilizing synapsis

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Nonhomologous end joining (NHEJ) mediates repair of double-strand DNA (dsDNA) breaks through formation of a multimeric complex. The Ku heterodimer binds DNA ends and recruits the catalytic subunit DNA-PKcs to form the DNA-PK holoenzyme, which bridges two DNA ends. DNA-PK recruits additional factors such as PAXX, XRCC4, XLF and ligase IV to mediate DNA synapsis. To determine the contribution of each component to synapsis stability, Wang et al. utilized a single-molecule forceps approach on a dsDNA construct with two overhanging blunt ends facing each other combined with a dsDNA linker. By modulating force on one end of the DNA construct, DNA synapsis formation could be characterized by observing the change in length of the construct. Using the complete NHEJ complex, the authors observed synaptic junctions with 66-second lifetimes. Loss of a single protein such as PAXX or one of the XRCC4, XLF or ligase IV components reduced synapsis lifetime; however, loss of two proteins nearly abolished synapsis entirely. This suggests that NHEJ complexes progressively assemble and stabilize through the summation of weak yet additive interactions between components. This study provides unique insights into the NHEJ machinery and ushers in a detailed chemomechanical understanding of DNA repair complexes. *YS*

https://doi.org/10.1038/s41589-018-0095-3

CANCER IMMUNOTHERAPY

ZIPing around CARs

Cell **173**, 1426–1438 (2018)

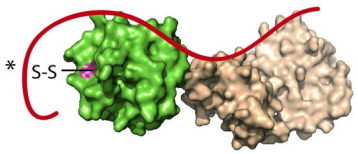
A promising approach in cancer immunotherapy is the use of T cells expressing chimeric antigen receptors (CARs), which consist of an antigen-specific single-chain fragment (scFv) linked to an intracellular signaling domain. Interaction of the CAR-expressing T cell with an antigen-specific tumor cell results in T-cell activation. However, the limited flexibility, specificity, and modularity of existing CARs require constant re-engineering of the T cells for new applications. To address some of these limitations, Cho et al. developed a split, universal and programmable (SUPRA) CAR system, zipCAR, composed of an extracellular leucine zipper fused to the intracellular signaling domain, while a zipFv component contained the complementary leucine zipper linked to the scFv. The level of SUPRA-mediated T-cell activation is determined on the basis of the affinity of the leucine zipper pairs, the expression levels of the zipCAR and zipFv, and the interaction between the T cell and the antigen-presenting cell. SUPRA also enables CAR inhibition by using a competitive zipFv containing a high-affinity leucine zipper, preventing zipFv–zipCAR interaction as well as combinatorial targeting of multiple antigens by adding different antigen-specific zipFv constructs. Overall, SUPRA offers improved utility and modality for cancer immunotherapy strategies. *GM*

https://doi.org/10.1038/s41589-018-0093-5

PROTEIN FOLDING

Please hold for chaperones

Mol. Cell **70**, 614–627 (2018)



Credit: Cell Press

Hypochlorous acid (HOCl) exerts its bactericidal activity through oxidation or chlorination of various residues, leading to protein unfolding and aggregation. To protect itself during HOCl stress, *Escherichia coli* employs holdases, which bind to unfolded proteins and prevent their aggregation. When the cell is no longer under stress, these holdases transfer their substrates to the DnaK/J/GrpE chaperone system for refolding. Goemans et al. have now identified a new player in the *E. coli* response to HOCl, CnoX, which is upregulated upon HOCl exposure. CnoX is activated by chlorination of several residues in its tetratricopeptide (TPR) domain, which increases the hydrophobicity of its surface and endows it with holdase activity for a broad range of substrates. Like other holdases, CnoX can cooperate with DnaK/J/GrpE to refold proteins, but, unlike other known holdases, it can also cooperate with GroEL/ES. In addition to the holdase function of the TPR domain, CnoX contains a thioredoxin (Trx) domain that can form mixed disulfide complexes with other proteins, protecting them from oxidation by HOCl. These dual protective functions of CnoX led the researchers to name it a "chaperedoxin," thus defining a new protein family. *CD*

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