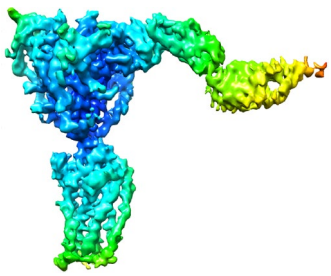
STRUCTURAL BIOLOGY

HIV seals an envelope

Nature **565**, 318–323 (2019)



Credit: Bing Chen

The ability of HIV-1 to infect human T cells requires interactions between the viral envelope (Env) fusion protein and primary receptor CD4 and co-receptors CCR5 and/or CXCR4 of the host. Binding of CD4 to the gp120 fragment of Env leads to conformational changes that allow binding to the co-receptor as well as refolding of the fusogenic gp41 fragment to induce virus–host cell fusion. To better understand how CCR5 functions as an HIV co-receptor, Shaik et al. solved a cryo-EM structure of a CD4–gp120–CCR5 complex. This revealed a CD4-induced gp120 conformation that allows two major contacting interfaces between gp120 and CCR5, one contributing to the high affinity of Env for CCR5, and another interface characterized by at least one cation–π interaction with sulfated CCR5 tyrosines. Though the authors could not identify any allosteric changes propagating from gp120 to gp41, they proposed that gp120 dissociation is critical for initiating gp41 refolding events preceding its insertion into target membranes. These results suggest a model in which CCR5 is responsible for stabilizing CD4-induced gp120 conformational changes bringing gp41 in close proximity to the target membrane to induce fusion. *MB*

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PROTEOSTASIS

To be or not to be?

EMBO J. https://doi.org/10.15252/embj.201798786 (2018)

Proteosomal inhibition results in the accumulation of protein aggregates that can promote proteotoxic effects if not removed properly. However, the redundant pathways for removing these aggregates remain unclear. While studying the cross-talk between mitochondria and the ubiquitin–proteasome system, Li et al. identified an interaction between the mitochondrial outer-membrane protein FUNDC1, which is normally involved in mitochondrial degradation, and the cytosolic chaperone protein HSC70. This interaction enables recruitment of unfolded cytosolic proteins to the mitochondria to be degraded by the mitochondrial protease LONP1 upon proteosomal inhibition. Interestingly, the actions of FUNDC1 were associated with the formation of mitochondrion-association protein aggregates (MAPAs). Loss of FUNDC1 prevented the autophagic degradation of MAPAs. Further studies showed that accumulation of proteasomal clients in mitochondria resulted in mitochondria dysfunction and cellular senescence. Though the mechanism of MAPAs formation remains unclear, these findings reveal the role of mitochondrial quality control as a backup system to properly handle cytosolic proteins under loss of proteasomal activity. *YS*

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CANCER EPIGENETICS

METTLing with translation

Cell **176**, 491–504 (2019)

Nat. Commun. **9**, 3411 (2018)

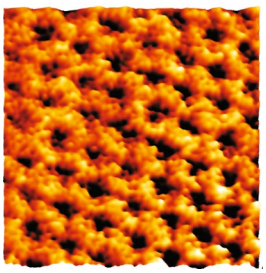
Eukaryotic elongation factor 1A (eEF1A) is a GTPase that regulates protein synthesis as a component of the translational machinery and has been observed to undergo dimethylation at K55 (eEF1AK55me2). However, the functional relevance of this modification and the enzymes that mediate it were not known. Liu et al. screened a CRISPR–Cas9 knockout collection of lysine methyltransferases, whereas Jakobsson et al. utilized a MS-based quantitative interaction peptide pull-down screen to identify METTL13 as a methyltransferase for eIF1A. Liu et al. detected high levels of eEF1AK55me2 in pancreatic and lung cancer tissues, and knockdown of METTL13 or eIF1A2 blocked cancer cell proliferation. In vitro GTPase assays demonstrated increased catalytic activity of methylated eIF1A, while METTL13 knockdown decreased protein synthesis in cancer cells, suggesting that METTL13-mediated methylation of eEF1A may promote oncogenesis through increased protein synthesis. Finally, Liu et al. performed a cell-based screen to identify compounds that were effective against METTL13-deficient pancreatic cancer cells and revealed a synthetic lethality with PI3K-mTOR and MAPK pathway inhibitors, demonstrating that METTL13 may be a targetable node for cancer therapy. *GM*

https://doi.org/10.1038/s41589-019-0237-2

BIOMATERIALS

A super-powered S-layer

ACS Synth. Biol. **8**, 181–190 (2019)



Credit: ACS

Surface-layer (S-layer) proteins form regular lattices on the external surfaces of many cells. In the bacterium *Caulobacter crescentus*, the S-layer protein RsaA forms a hexameric lattice, and previous work has demonstrated that it tolerates insertions of peptides and protein domains. Charrier et al. now demonstrate the use of RsaA as a platform for engineering living biomaterials by employing the SpyTag–SpyCatcher split protein system. Following expression of an RsaA variant with an inserted SpyTag sequence, incubation with a SpyCatcher-tagged protein results in the covalent, irreversible attachment of desired functionalities to the lattice. The SpyTag sequence can be inserted at any of eight positions in RsaA without disrupting the expression and patterning of the S-layer protein; however, this positioning affects the density of SpyCatcher modification, providing versatility in the biomaterial structure. The authors used this system to build ordered biomaterials on the *C. crescentus* surface with elastin-like polypeptide or quantum dots without compromising cellular viability. This approach could potentially be adapted for engineering S-layer proteins in other organisms and be developed further to produce increasingly complex biomaterials. *CD*

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