PNAS Plus Significance Statements

Functional architecture of MFS D-glucose transporters

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The crystallographic model (pp. E719–E727) of the Major Facilitator Superfamily (MFS) member, D-xylose permease XylE from *Escherichia coli*, a homologue of human D-glucose transporters, the GLUTs (SLC2), provides a structural framework for the identification and physical localization of crucial residues in transporters with medical relevance (i.e. the GLUTs). The mechanism and substrate specificity of human and prokaryotic sugar transporters are discussed by using homology modeling, molecular docking, and experimentation. Substrate-specificity determinants for XylE, GLUT1, and GLUT5 are proposed. Furthermore, concepts derived from other bacterial MFS transporters are examined for their relevance to the GLUTs by comparing conservation of critical residues. XylE mutants that mimic the characteristics of GLUT1 are tested, revealing that uniport and symport are mechanistically related.

PARP1-dependent recruitment of KDM4D histone demethylase to DNA damage sites promotes double-strand break repair

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Sophisticated DNA damage repair mechanisms are required to fix DNA lesions and preserve the integrity of the genome. This manuscript provides characterization of KDM4D role in promoting the repair of double-strand breaks (DSBs). Our findings show (pp. E728–E737) that KDM4D lysine demethylase is swiftly recruited to DNA breakage sites via its C-terminal region in a PARP1-dependent manner. Further, we have uncovered an exciting function of KDM4D in regulating the association of the DNA damage response master kinase, ATM, with chromatin, thus explaining the defective phosphorylation of ATM substrates found in KDM4D-depleted cells. Altogether, this study advances our understanding of the molecular mechanisms that regulate the repair of DSBs, a critical pathway that is essential for maintaining genome integrity.

Vaccine-elicited primate antibodies use a distinct approach to the HIV-1 primary receptor binding site informing vaccine redesign

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The development of broadly neutralizing antibodies (bNAbs) to HIV-1 is often thought to be a key component of a successful vaccine. A common target of bNAbs is the conserved CD4 binding site (CD4bs) on the HIV envelope glycoprotein (Env) trimeric spike. Although CD4bs-directed bNAbs have been isolated from infected individuals, elicitation of such bNAbs by Env vaccination has proven difficult. To help understand the limitations of current immunogens, we structurally characterized two vaccine-elicited, CD4bs-directed non-bNAbs from primates. We demonstrate (pp. E738–E747) that these vaccine-elicited Abs attempt a vertical approach to the CD4bs, thereby clashing with the variable region of the trimeric spike cap, whereas CD4bs-directed bNAbs adopt angles of approach that avoid such clashes. This analysis can inform future vaccine redesign.

Mapping the molecular determinants of BRAF oncogene dependence in human lung cancer

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Oncogenic mutations in the BRAF kinase occur in 6–8% of nonsmall cell lung cancers (NSCLCs), but the biological and clinical relevance of these mutations is unclear. We uncovered mechanisms of resistance to BRAF inhibition in NSCLC using an integrated functional chemical genetics approach in human BRAF-mutant NSCLC cells and clinical specimens. Our results (pp. E748–E757) provide biological insights into the regulation of BRAF oncogene dependence and identify strategies to optimize outcomes in BRAF-mutant NSCLC patients.

Secretion of a pneumococcal type II secretion system pilus correlates with DNA uptake during transformation

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Streptococcus pneumoniae is a naturally competent organism, which can take up extracellular DNA by natural transformation. However, the mechanism by which DNA traverses the capsule and cell well layer is not understood. Here (pp. E758–E765) we describe a pilus structure in *S. pneumoniae* that is initially assembled on the bacterial surface when competence is induced, but subsequently secreted into the medium. We propose a mechanism for DNA uptake whereby the assembling pilus locally disrupts the rigid cell wall, creating a channel upon its release, creating an entry port for exogenous DNA. As DNA uptake coincides with pilus secretion, we suggest that, rather than acting as a retractile apparatus dragging DNA inside, the pilus acts as a cell-wall channel "drilling device."

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