IN BRIEF

CANCER

Antiapoptotic BCL-2 is required for maintenance of a model leukemia.

Letai, A. *et al. Cancer Cell* **6,** 241–249 (2004)

Resistance to apoptosis, often resulting from the overexpression of anti-apoptotic proteins, is common in cancers, but it remains uncertain whether defects in apoptosis are essential for tumour maintenance. Letai *et al.* investigated this idea using mice that develop leukaemia in which the overexpression of the key anti-apoptotic protein B-cell lymphoma-2 (BCL2) could be conditionally turned off. Eliminating BCL2 rapidly induces apoptosis and leukaemia remission, providing support for the potential of BCL2 as an anticancer drug target, and suggesting that if apoptotic defects are eliminated, inherent death signals would kill cancer cells.

ANTIBACTERIALS

The nisin–lipid II complex reveals a pyrophosphate cage that provides a blueprint for novel antibiotics.

Hsu, D. S. *et al. Nature Struct. Mol. Biol.* **11**, 963–967 (2004)

The family of lanthionine-containing antibiotics, of which nisin is a member, could be promising candidates for alleviating the growing problem of antibiotic resistance. Nisin acts by binding to lipid II, an essential precursor of cell-wall synthesis. Hsu and colleagues report the solution structure of the complex of nisin and lipid II, which indicates possibilities for the structure-based design of novel antibiotics.

CHEMICAL GENETICS

Identification of novel small-molecule inhibitors of severe acute respiratory syndrome-associated coronavirus by chemical genetics.

Kao, R. Y. *et al. Chem. Biol.* **11**, 1293–1299 (2004)

Kao *et al.* screened ~50,000 structurally diverse compounds for their capacity to protect cells from the cytopathic effects induced by the severe acute respiratory syndrome-associated coronavirus (SARS-CoV). Of around 100 compounds that were found to have strong antiviral activity, several were further characterized and found to target specific proteins involved in viral pathogenesis; these compounds represent possible leads for drug development.

DIABETES

Possible novel therapy for diabetes with cell-permeable JNK-inhibitory peptide.

Kaneto, H. *et al. Nature Med.* **10**, 1128–1132 (2004)

The activity of c-Jun N-terminal kinase-1 (JNK1) is known to be abnormally elevated in several tissues in the diabetic state, and activation of the JNK1 pathway interferes with insulin action. Kaneto *et al.* treated diabetic mice with a cell-permeable JNK-inhibitory peptide derived from the JNK-binding domain of JNK-interacting protein-1, and found that it markedly improved insulin resistance and ameliorated glucose tolerance, indicating that the JNK pathway has a key role in diabetes.

STRUCTURAL BIOLOGY

Crystallizing the changes

Integrins — a family of cell-adhesion molecules that mediate the bidirectional transfer of signals across the plasma membrane — have a key role in a wide range of biological processes, including angiogenesis, inflammation and haemostasis. Dysregulation of integrins also underlies the pathogenesis of several diseases, making them attractive drug targets. To understand the mechanism of antagonism by therapeutics, it is necessary to clearly map the structural basis of integrin activation. There has been much speculation about how integrins become active, and, until now, only the crystal structure of an inactive integrin has been available. Writing in *Nature*, Springer and co-workers report in atomic detail the first crystal structure of an integrin in its active form.

Integrins are heterodimers formed from an α- and a β-subunit, with each subunit containing an extracellular domain, a single transmembrane domain and a short cytoplasmic domain. The extracellular domain includes a headpiece that binds to the integrin ligand, and a tailpiece that connects to the transmembrane domain. When integrins are activated, marked structural changes occur to the spatial relationships between integrin domains, which leads to high-affinity ligand binding.

The integrin $\alpha_{IIb}\beta_3$, which resides on the membranes of platelets, is important for activating the clotting process following vascular injuries, but is also involved in pathological thrombosis. Platelet signalling is initiated in response to vascular injury, causing changes in the cytoplasmic domains of $\alpha_{IIb}\beta_3$ that are transmitted into conformational changes in the extracellular domain of $\alpha_{IIb}\beta_3$. This leads to high-affinity binding of fibrinogen, giving rise to platelet aggregation.

Springer and co-workers describe details of these conformational changes in $\alpha_{IIb}\beta_3$ and how they are transferred between domains. They used two antagonists — tirofiban and eptifibatide — designed to mimic fibrinogen, and therefore prevent ligand binding, and which are known to be effective for treating and preventing coronary artery thrombosis. The crystal structures revealed the basis for drug binding and selectivity, which might aid further drug development targeted at $\alpha_{IIb}\beta_3$. Furthermore, the structural changes in the extracellular domain identified in the $\alpha_{IIb}\beta_3$ integrin seem to generalize to all integrins, and so this knowledge could lead to improvements in the design of integrin antagonists for a range of other diseases.

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References and links

ORIGINAL RESEARCH PAPER Xiao, T., Takagi, J., Coller, B. S., Wang, J.-H. & Springer, T. A. Structural basis for allostery in integrins and binding to fibrinogen-mimetic therapeutics. *Nature* 19 Sep 2004 (doi:10.1038/nature02976)

FURTHER READING Shimaoka, M. & Springer, T. A. Therapeutic antagonists and conformational regulation of integrin function. *Nature Rev. Drug Discov.* **2**, 703–716 (2003)