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Biology

Microbiology

Stimulation of the SOS response by β-lactam antibiotics can provide temporary protection for bacteria

β-lactam antibiotics inhibit penicillin binding proteins (PBPs) and prevent the synthesis of cell wall peptidoglycan, but they are only active against dividing bacteria. Resistance arises through production of β-lactamases, low-affinity PBPs or decreased uptake and/or increased efflux. Miller *et al.* describe a previously unrecognized pathway that enables *Escherichia coli* to partially escape the bactericidal activity of β-lactams by activating the SOS response and inhibiting cell division [1].

This study began with the unexpected observation that exposure of *E. coli* to ampicillin, cephalexin or piperacillin caused induction of the *dpiB–dpiA* two-component signal-transduction system, whereas several other classes of antibiotics had no effect. Growth of a temperature-sensitive PBP3 mutant at 42°C also induced the *dpiBA* operon. Although the primary function of these genes in *E. coli* is unknown, DpiA can activate the *recA*-dependent SOS response regulon, which includes SfiA, a protein that inhibits formation of the septation ring and blocks cell division.

dpiA, *recA* and *sfiA* mutants were tested to determine whether DpiA-mediated growth inhibition could protect bacteria from β-lactams. All three mutants exhibited a tenfold decrease in viability compared with wild type when cells were incubated in ampicillin for 1–2 hours. These observations suggest that β-lactam inactivation of PBP3 can inhibit cell division through a *dpiA–recA–sfiA* pathway and that this response can provide partial protection from the bactericidal activity of β-lactam antibiotics. Although induction of the *dpiA* pathway provides only temporary protection, it might permit bacteria to buy time while they activate more-potent resistance mechanisms.

1 Miller, C. *et al.* (2004) SOS response induction by β-lactams and bacterial defense against antibiotic lethality. *Science* 305, 1629–1631

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Co-expressed attack and defense by group B streptococci

Group B *Streptococcus* (GBS) is a major cause of serious infections in human newborns. The surface-associated β-hemolysin/cytolysin (βH/C) is thought to contribute to pathogenesis by its ability to form pores in host cells membranes. The gene responsible for βH/C production, *cylE*, is also necessary for a distinguishing feature of GBS, production of a carotenoid pigment. GBS has the ability to persist within phagocytic cells, but the underlying mechanisms are not known.

Liu *et al.* [2] generated isogenic *cylE* mutants with the dual phenotype lack of βH/C and carotenoid. These mutants were tested for virulence and in intracellular-persistence assays. Mice infected with *cylE* mutants had a much higher survival rate. Mutants are cleared more rapidly, both in mice and in whole human blood inoculated with bacteria. *cylE* mutants are more sensitive to exposure to neutrophils or macrophages than wild types, and this is dependent on the cytolytic activity of βH/C. *cylE* mutants have decreased survival within macrophages and neutrophils.

At higher bacterial inoculums, the wild type, but not the *cylE* mutant causes apoptosis of macrophages. *cylE* mutants are more sensitive than wild types to oxidative killing within phagocytes and to oxidants *in vitro*. The mutants could be rescued *in vitro* by addition of carotenoid from wild type, indicating that it contributes to oxidative resistance.

This study clearly demonstrates that the *cylE* gene is important for evasion of phagocytic killing in two ways: expression of the β-hemolysin/cytolysin that attacks the cell by cytolysis and apoptosis induction; and the carotenoid pigment that defends the bacteria from potent reactive oxygen species.

2 Liu, G.Y. *et al.* (2004) Sword and shield: Linked group B streptococcal ß-hemolysin/cytolysin and carotenoid pigment function to subvert host phagocyte defense. *Proc. Natl. Acad. Sci .U. S. A.* 101 14491–14496

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The hexameric structure of a retroviral capsid has implications for HIV assembly

Retroviruses cause a number of human diseases including AIDS. In the final step of the life cycle, the viral capsids are formed from proteolytic cleavage of the Gag polyprotein, but it is still not understood how the mature virions assemble. Mortuza *et al.* have solved the structure of a hexamer of the N-terminal domain of the capsid protein from the murine leukaemia virus, showing how the monomers form hexamers in the mature virus [3].

Electron microscopy has shown that retroviruses are comprised from a network of hexameric rings, and the contacts were thought to be mediated by the N-terminal domains. This structure now shows that the N-terminal domains alone are capable of forming this hexameric structure.

There is little sequence conservation between retroviral capsids but the tertiary structures of mature retroviral capsids are very similar, indicating that the hexameric assembly is also applicable to other viruses, including HIV. The monomers form a planar ring structure with a large central hole of about 15 Å and the contacts between monomers occur through α helices 1, 2 and 3. The monomers contain a two-stranded β hairpin, which is processed by proteolytic cleavage to form the mature capsid. This hairpin lines the central hole of the hexamer and orients many of the residues involved in intersubunit contacts, suggesting that this processing initiates capsid assembly.

The majority of the inter-subunit contacts are polar, including several hydrogen bonds and water-mediated contacts. The lack of hydrophobic contacts suggests that the interactions are weak and might be transient. More research will be required to fully understand the factors that initiate assembly and disassembly.

3 Mortuza, G.B. *et al.* (2004) High-resolution structure of a retroviral capsid hexameric amino-terminal domain. *Nature* 431, 481–485

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Disease mechanisms

Obesity and insulin resistance: S6K1 a new key player

It has been recognized that obesity can cause insulin resistance, the fundamental etiology of type 2 diabetes. However, many details of mechanisms by which the increased adipose tissue mass cause insulin resistance remain unknown. The most notably insulin-induced metabolic responses, such as protein synthesis, are dependent on nutritional state. Sequentially, an increase in protein synthesis relies on S6 kinase 1 (S6K1) activation, which regulates the translation of messenger RNAs encoding components of the protein synthetic apparatus.

Intriguingly, recent studies have shown that mice deficient for S6K1 (S6K1$^{-/-}$) are viable and fertile, but exhibit a conspicuous reduction in body size during embryogenesis, an effect mostly overcome by adulthood. Moreover, such mice were shown to be hypoinsulinemic, glucose intolerant and have reduced beta-cell mass. S6K1-deficient mice maintain normal glucose levels during fasting, suggesting hypersensitivity to insulin.

Using the same S6K1-deficient mice, Ulm *et al.* have recently shown a reduction of weight, specific to adipose tissue, observing a reduction in adipocytes size compared with those of the wild-type mice and an increase in the rates of lipolysis [4]. The authors also identify multi-locular adipocytes with mitochondria of increased size and number compared with the wild type in electron micrographs. The levels of mRNA of proteins involved in oxidative phosphorylation were found to be increased in S6K1$^{-/-}$ mice, suggesting protection against obesity through an enhanced β-oxidation. When the S6K1$^{-/-}$ mice were placed on a high-fat diet, weight accumulation was reduced by 20% compared with wild-type mice, whereas S6K1$^{-/-}$ mice consumed 44% more food.

The authors found that nutritionally or genetically driven obesity leads to the upregulation of S6K1, which acts to suppress insulin signaling through modulating the PI3K–Akt signaling pathway, contributing to insulin resistance. As was expected, the authors found that the absence of S6K1 maintains working the PI3K/Akt pathway, protecting against insulin resistance. Due to the fact that obesity and type 2 diabetes are two widely distributed diseases, the development of specific pharmacological inhibitors of S6K1 could have very important therapeutic potential.

Cancer biology

A helping hand for Gleevec

Imatinib, or Gleevec, has become the standard first-line therapeutic for the treatment of chronic myeloid leukaemia (CML). In many patients it leads to complete remission of the disease by inhibiting the BCR–ABL tyrosine kinase domain. Resistance to Gleevec caused by mutations in the binding site of the drug has become an increasing problem.

Structural studies have led to the development of a new class of dual inhibitors of ABL and the closely related SRC kinase. For two compounds of this pyrido[2,3-d]pyrimidine class of SRC–ABL inhibitors, PD166326 and PD180970, promising *in vitro* data have been reported previously.

In a recent article, Shah *et al.* report on BMS-354825, a novel small-molecule SRC-kinase inhibitor [6]. Based on structural insights from other dual SRC-ABL inhibitors, its activity against imanitib-resistant BCR–ABL mutants was assessed. Cell culture experiments revealed a strong potential to inhibit 14 out of 15 clinically relevant BCR–ABL isoforms. Remarkable differences in the sensitivity of certain mutants were detected, which could be helpful to determine optimal treatment conditions to provide therapeutic benefit in patients.

The therapeutic potential of BMS-354825 was also tested in a CML mouse model. Animals were injected with Ba/F3 cells harbouring wild-type BRC-ABL or the common mutation M351T. In contrast to placebo-treated mice, animals treated with BMS-354825 appeared healthy, with no evidence of side effects. Additionally, BMS-354825 showed no inhibition on the growth of human bone marrow progenitors from healthy volunteers, but inhibited by 60–80% those of CML patients with either imatinib-sensitive or resistant disease.

In all tests, the T351I BCR–ABL isoform remained completely resistant. As this mutation accounts only for 15–20% of imatinib-resistant cases, a large majority of CML patients could benefit from BMS-354825, which is currently being tested in a phase I clinical trial.

6 Shah, N.P. *et al.* (2004) Overriding imatinib resistance with a novel ABL kinase inhibitor. *Science* 305, 399–401

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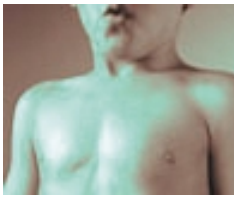
Potential role of vitamin D in asthma



The active metabolite of vitamin D [1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$)] is a recognized modulator of Th1-driven immune disease in experimental models which is thought to be the net result of a shift towards an upregulated Th2 response. However, the role of vitamin D in Th2-driven immune disease has only recently become a subject of investigation.

In a series of novel experiments, Wittke *et al.* have investigated the role of the vitamin D receptor in a Th2-driven model of allergic asthma by using vitamin D receptor knock-out mice (VDR KO) [5]. Following a prime and challenge with ovalbumin (OVA), wild-type mice developed severe symptoms of asthma, including elevated airway hyperresponsiveness (AHR) plus increased mucous secretion and influx of eosinophils and inflammatory T-cells in the lungs. In direct contrast, priming and challenge with OVA in VDR KO mice had relatively few eosinophils and inflammatory T-cells in their lungs, did not produce mucous and only developed an AHR similar to unprimed wild-type mice.

The failure of VDR KO mice to develop experimental asthma did not appear to be related to an inability to generate a Th2 response, as levels of serum IgE were increased and splenocytes from these mice released Th2 cytokines IL-5 and IL-13 following OVA stimulation. The authors discussion postulates that the vitamin D receptor might, therefore, have some role in the trafficking of inflammatory cells to the lung in this model of allergic asthma, although there is limited data to support this. This article suggests that the vitamin D receptor does have some role in the development of experimental asthma but the precise mechanism by which this occurs has yet to be fully elucidated.

5 Wittke, A. *et al.* (2004) Vitamin D receptor-deficient mice fail to develop experimental allergic asthma. *J. Immunol.* 173, 3432–3436

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Business

Announcements

PediaMed Pharmaceuticals acquires Protein Therapeutics

PediaMed Pharmaceuticals Inc. (http://www.pediamedpharma.com/) has recently announced the acquisition of Protein Therapeutics (http://www.protein-therapeutics.com), a company that specializes in the development of novel therapies against immunological diseases. This acquisition also incorporates Protein Therapeutic's current investigational immunoglobulin drug that has demonstrated promising results for treating gastrointestinal (GI) dysfunction in autistic children and will be entering Phase II clinical trials shortly.

Cameron Durrant, President of PediaMed Pharmaceuticals, explained the significance of this drug and the company's latest acquisition, 'Gastrointestinal symptoms associated with autism are debilitating physically, emotionally and socially. Our acquisition is an important step in building our capacity to conduct clinical research in this significant therapeutic area, one with a very important unmet medical need'. The President and CEO of Protein Therapeutics, Leon Barstow, replied that 'This transaction will enable our technologies and products to thrive in a fast-growing pediatric market'.

PediaMed, The Pediatrics Company, focuses on providing safe and effective medicine to pediatric patients, parents and associated healthcare professionals. In particular, PediaMed is investigating opportunities in areas that are currently poorly served by therapies, such as anti-infectives and treatments for respiratory and allergy complications.

Collaborations

New partnership established between SGX and Roche

SGX (Structural GenomiX; http://www.stromix.com), a biotech company specializing in the discovery and development of innovative therapeutics, has announced its new alliance with Roche to initiate an antiviral therapeutics programme.

As part of the collaborative partnership, SGX's leading high-throughput structural biology technology, FAST™ technology, will be used to generate new lead candidates for Roche to develop and commercialize globally.

'We seek partners that will help build our pipeline in areas of strategic focus,' said Peter Hug, the Global Head of Pharma Partnering at Roche. 'SGX will be generating new antiviral leads for Roche, further strengthening our commitment to developing novel medicines in virology' Hug added. The Chief Scientific Officer at SGX, Stephen K. Burley, commented the collaboration: 'This partnership with Roche is consistent with our integrated business strategy, which is to apply FAST™ to generate novel lead candidates in key therapeutic areas for strategic partners, as well as oncology candidates for further development by SGX.'

SGX has developed a preclinical pipeline leveraging FAST™ lead generation, a proprietary fragment-based method of characterizing novel drug candidates based on the core expertise of SGX in high-throughput protein crystallography, computational chemistry and automated parallel synthesis. One of the lead product candidates at SGX is a novel cancer treatment for acute myelogenous leukemia and other malignancies that is at Phase 1/2 clinical trials.

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