IN BRIEF

ION CHANNELS

Crystal structure of a bacterial homologue of Na^+/Cl^--dependent neurotransmitter transporters.

Yamashita, A. *et al*. *Nature* **437**, 215–223 (2005)

Na^+/Cl^--dependent neurotransmitter transporters are drug targets for a variety of neurological disorders, but there is currently no crystal structure to aid further drug discovery efforts. This paper reports the crystal structure of a leucine-bound bacterial homologue, $LeuT_{Aa}$, which will help to define the residues and domains that form the extracellular and intracellular gates of this transporter class.

GENE THERAPY

In vitro-generated regulatory T cells induced by Foxp3-retrovirus infection control murine contact allergy and systemic autoimmunity.

Loser, K. *et al*. *Gene Ther*. **12**, 1294–1304 (2005)

Impaired suppressor function of regulatory $CD4^+CD25^+$ T cells is implicated in many autoimmune diseases, but efforts to use regulatory T cells to treat these disorders have been hindered by the poor availability of this T cell subtype. Loser *et al.* generated regulatory T cells *in vitro* by infecting naive T cells with a retrovirus encoding Foxp3, a transcription factor involved in the development of $CD4^+CD25^+$ T cells. Injection of Foxp3-infected cells inhibited contact hypersensitivity and prevented the ongoing development of autoimmune dermatitis in sensitized mice.

INFECTIOUS DISEASE

Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry.

Simmons, G. *et al*. *Proc*. *Natl Acad*. *Sci*. *USA* **102**, 11876–11881 (2005)

Infection by the coronavirus that causes severe acute respiratory syndrome (SARS-CoV) has been shown to be sensitive to endosomal pH perturbations. Simmons *et al.* searched for pH-dependent endosomal proteins that might be involved in infectivity and found that specific inhibitors of cathepsin L block SARS-CoV infection of cells in culture. Infection was shown to involve three steps: receptor binding, conformational change of the viral spike glycoprotein, and subsequent cathepsin L-mediated proteolysis within endosomes. Inhibitors that target cathepsin L could be beneficial as anti-infective drugs against SARS.

ANTICANCER DRUGS

Pleiotropic effects of HIF-1 blockade on tumor radiosensitivity.

Moeller, B. J. *et al*. *Cancer Cell* **8**, 99–110 (2005)

Activation of hypoxia-inducible factor-1 (HIF1) can cause resistance to radiotherapy in tumours and it is proposed that HIF1 inhibitors could be used to sensitize tumours to radiation. This paper reports on the complexity of HIF1 signalling under various tumour conditions and reveals that HIF1 radiosensitizes tumours by promoting radiation-induced p53 activation, ATP metabolism and proliferation, yet causes radioresistance by stimulating endothelial cell survival. The success of HIF1 inhibitors as a complement to radiotherapy will therefore depend on the 'sequencing' of treatment.

VACCINES

β-Glucan conjugate provides protection

At present, there are no antifungal vaccines available for the numerous people — in particular, immunocompromised individuals — who are at risk of infection with opportunistic fungal pathogens. However, new hope for the development of an effective vaccine has been provided by data published in *The Journal of Experimental Medicine* that indicate that immunization with the β-glucan laminarin conjugated to the diphtheria toxoid CRM197 protects mice from infection with *Candida albicans* and *Aspergillus fumigatus*.

Fungal infections such as aspergillosis and candidiasis are a serious threat to immunocompromised individuals and have a high mortality rate, even when patients are treated with antifungal drugs, thereby highlighting the pressing need for an effective vaccine. Because β-glucans, a polysaccharide component of fungal cell walls, are essential for fungal viability, they are not expected to mutate readily. So, to develop an immunogen that is likely to induce a β-glucan-specific immune response, Torosantucci *et al*. linked laminarin, a well-characterized and weakly immunogenic β-glucan from the brown alga *Laminaria digitata*, to the highly immunogenic diphtheria toxoid CRM197, a protein carrier that is a component of some current human vaccines. Treatment of mice with this conjugate (Lam–CRM) before lethal systemic challenge with *C. albicans* was protective, in terms of both median survival time and overall mortality. Protection was associated with the presence of β-glucan-specific antibodies, and, when transferred to naive animals, these antibodies markedly reduced the fungal burden in the kidneys of recipients that were subsequently challenged with *C. albicans*. Similarly, prophylactic treatment of rats with Lam–CRM protected them from disease in a rat model of vaginal candidiasis, and vaginal fluid from immunized rats transferred protection to non-immunized animals in a β-glucan-specific-antibody-dependent manner. Importantly, initial studies also showed that Lam–CRM protects mice against a lethal systemic challenge with another major human fungal pathogen, *A. fumigatus*.

The β-glucan-specific antibodies were shown to bind the hyphae and germ tubes of *C. albicans* and the hyphal threads of *A. fumigatus* and to inhibit fungal growth, providing one potential mechanism by which these antibodies can protect against fungal infection.

These data show that a single carrier-protein-conjugated β-glucan can induce a protective immune response to subsequent challenge with distinct fungal pathogens that cause markedly disparate disease states. Because the authors also showed that a β-glucan-specific monoclonal antibody could reduce fungal burden, they suggest that β-glucan-specific antibodies might also be an effective immunotherapy for patients who are already infected with a fungal pathogen.

Karen Honey, Senior Editor, Nature Reviews Immunology

References and links

ORIGINAL RESEARCH PAPER Torosantucci, A. *et al*. A novel glyco-conjugate vaccine against fungal pathogens. *J. Exp. Med.* **202**, 597–606 (2005)

FURTHER READING Romani, L. Immunity to fungal infections. *Nature Rev. Immunol.* **4**, 11–23 (2004)