RHEUMATOID ARTHRITIS

SLAYGLR revealed!

Buffy the Vampire Slayer spends a lot of her time killing vampires, demons and other freaks that pose a threat to the town of Sunnydale. Mostly, the Slayer's identity is a well-kept secret. Now the role of a malevolent kind of slayer has been uncovered. SLAYGLR, an epitope of the bone molecule osteopontin (OPN), has been found to have a destructive role in the development of rheumatoid arthritis (RA), according to research published in the 15 July issue of *The Journal of Clinical Investigation*.

RA is a chronic inflammatory disease characterized by synovial inflammation and subsequent cartilage and bone destruction. Development of the disease involves complicated cytokine signalling cascades that in part cause macrophages to differentiate into cells known as osteoclasts, which resorb and destroy bone. OPN, which is abundant in bone, is thought to play an important role in the pathogenesis of RA, but until now the molecular mechanism of action was unknown.

OPN acts as a bridge between bone and the immune system, mediating cell adhesion and modulation of the immune response. One of its roles is to faciliate attachment of osteoclasts to the bone matrix via cell-surface adhesion molecules called integrins, using the specific integrin-binding motif RGD. However, other sequences within OPN have been shown to mediate cell adhesion; a second sequence (SLAYGLR in mice and SVVYGLR in humans), created as a result of cleavage by the protease thrombin, has recently been shown to mediate cell adhesion, particularly to cells expressing integrin types α4 and α9. Interestingly, patients who suffer from RA have higher ratios of the thrombin-cleaved form of OPN to the noncleaved form, compared with healthy controls and patients with osteoarthritis.

Nobuchika Yamamoto and colleagues from the Fujisawa Pharmaceutical Company and Hokkaido University observed that immune cells called monocytes from arthritic mice had a greater tendency to migrate toward thrombin-cleaved OPN than full-length OPN, and that these monocytes expressed integrins α4 and α9, which bind the exposed SLAYGLR epitope. To investigate the role of the exposed SLAYGLR epitope in RA, the authors generated an antibody that binds the epitope. Antibody blockade of the SLAYGLR sequence stopped monocyte migration to the cleaved OPN and significantly suppressed the development of arthritis in mice. Furthermore, the authors showed that OPN blockade prevented osteoclast-mediated bone resorption and osteoclast formation *in vitro*.

The data indicate the crucial role of OPN and the SLAYGLR sequence in the formation of osteoclasts and development of RA, and indicate that blocking SLAYGLR could be a useful therapeutic approach. Death and disease might be the only things the Vampire Slayer cannot fight; Buffy would say that new strong weapons are needed.

Melanie Brazil

References and links

ORIGINAL RESEARCH PAPER Yamamoto, N. *et al*. Essential role of the cryptic epitope SLAYGLR within osteopontin in a murine model of rheumatoid arthritis. *J. Clin. Invest.* **112**, 181–188 (2003)

FURTHER READING

Smolen, J. S. & Steiner, G. Therapeutic strategies for rheumatoid arthritis. *Nature Rev. Drug Discov.* **2**, 473–488 (2003) | Palladino, M. A. *et al*. Anti-TNF-α therapies: the next generation. *Nature Rev. Drug Discov.* **2**, 736–746 (2003)

IN BRIEF

TRANSPORT PROTEINS

Structure and mechanism of the lactose permease of *Escherichia coli*.

Abramson, J. *et al. Science* **301**, 610–615 (2003).

Structure and mechanism of the glycerol-3-phosphate transporter of *Escherichia coli*.

Huang, Y. *et al. Science* **301**, 616–620 (2003).

Membrane transport proteins have been shown to have important roles in depression, stroke and diabetes, and are the targets of widely used drugs, such as fluoxetine and omeprazole. However, structural information on these proteins, which could aid in future drug design, has been lacking owing to the challenges associated with obtaining suitable crystals for X-ray structure determination. These two papers report the first crystal structures of proteins from the major facilitator superfamily, the largest group of secondary membrane transporters.

ANTICANCER DRUGS

Functionalized glycomers as growth inhibitors and inducers of apoptosis in human glioblastoma cells.

Hanessian, S. *et al. J. Med. Chem.* (2003) July 16 (doi:10.1021/jm0205853).

Glioblastomas are brain tumours that have a very poor prognosis, as they are often resistant to traditional drugs and their high migratory potential in the central nervous system precludes surgical removal. Hanessian *et al.* show that monosaccharide derivatives can inhibit the growth and/or induce apoptosis of human glioblastoma cells, and so represent a new class of molecules that are potentially able to control the progression of brain tumours.

NEURODEGENERATIVE DISEASE

Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Aβ and synaptic dysfunction.

Oddo, S. *et al. Neuron* **39**, 409–421 (2003).

Alzheimer's disease is characterized by two hallmark lesions: neuritic plaques containing amyloid-β, and neurofibrillary tangles composed of aggregates of hyperphosphorylated tau protein. Oddo *et al.* have created a mouse model that recapitulates these salient features of Alzheimer's disease, which will be valuable for evaluating the efficacy of therapies in mitigating the neurodegenerative effects mediated by both signature lesions.

HIGH-THROUGHPUT SCREENING

Effects of detergent on "promiscuous" inhibitors.

Ryan, A. J. *et al. J. Med. Chem.* **46**, 3448–3551 (2003).

The term 'promiscuous inhibitor' has been used to describe compounds that inhibit a range of unrelated enzymes through an inhibition mechanism that involves the formation of aggregates, rather than the binding of individual molecules, which are therefore unlikely to be good starting points for drug discovery programmes. Ryan *et al.* show that promiscuous inhibitors can be differentiated from classical inhibitors by the judicious use of detergents, without compromising assay performance.