IN BRIEF

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PRION DISEASES

Hot spots in prion protein for pathogenic conversion.

Kuwata, K. *et al. Proc. Natl Acad. Sci. USA* **104**, 11921–11926 (2007)

Prion proteins are key molecules in transmissible spongiform encephalopathies (TSEs), but the precise mechanism of the conversion from the normal cellular form (PRP^{c}) to the pathogenic form (PRP^{sc}) is unknown. Kuwata and colleagues discovered a chemical chaperone that stabilized the PRP^{c} confirmation and identified the distinct hot spots that prevented the pathogenic conversion. *In silico* screening identified compounds that fitted into a pocket created by residues undergoing conformational rearrangements, one of which reduced PRP^{sc} levels in a TSE-infected cell model, and prolonged the survival of TSE-infected mice. Therefore, focusing on the hot spots of the PRP^{c} could open the way to the development of novel antiprion drugs.

INFLAMMATORY DISORDERS

Crucial role of the protein C pathway in governing microvascular inflammation in inflammatory bowel disease.

Scaldaferri, F. *et al. J. Clin. Invest.* **117**, 1951–1960 (2007)

Activated protein C (PC) is a potent anticoagulant and anti-inflammatory molecule. Scaldaferri and colleagues showed that in human inflammatory bowel disease (IBD) there was loss of expression of endothelial PC receptor and thrombomodulin, which in turn caused an impairment of PC activation by the inflamed mucosal microvasculature. In isolated human intestinal endothelial cells, administration of recombinant activated PC had a potent anti-inflammatory effect and *in vivo*, activated PC ameliorated experimental colitis. These results suggest that restoring the PC pathway may represent a new approach to suppress intestinal inflammation in IBD.

PROTEIN STRUCTURE

LeuT-desipramine structure reveals how antidepressants block neurotransmitter reuptake.

Zhou, Z. *et al. Science* 9 Aug 2007 (doi:10.1126/science.1147641)

Antidepressant binding site in a bacterial homologue of neurotransmitter transporters.

Singh, S. K *et al. Nature* 8 Aug 2007 (doi:10.1038/nature06038)

Tricyclic antidepressants inhibit the reuptake of serotonin, noradrenaline and dopamine by blocking transporters, but the drug-binding site and mechanism of inhibition are poorly understood. Two studies have determined the crystal structure of the bacterial leucine transporter — a homologue of human neurotransmitter transporters — in combination with tricyclic antidepressants. Zhou and colleagues showed that desipramine binds at the inner end of the extracellular cavity of the transporter and is held in place by a hairpin loop and a salt bridge. This binding site is separated from the leucine-binding site by the extracellular gate of the transporter, and by locking the gate desipramine prevents conformational changes and blocks substrate transport. In the second paper, Singh and colleagues demonstrated that clomipramine binds in an extracellular-facing vestibule above the substrate, again stabilizing the extracellular gate in a closed conformation, and slows substrate release. These studies suggest that tricyclic antidepressants exert a gate-locking mechanism on the transporter and pinpoint regions that might be exploited for the development of new inhibitors.