IN BRIEF

ALZHEIMER'S DISEASE

Regulation of NMDA receptor trafficking by amyloid β.

Snyder, E. M. *et al*. *Nature Neurosci*. **8**, 1051–1058 (2005)

Tau suppression in a neurodegenerative mouse model improves memory function.

SantaCruz, K. *et al*. *Science* **309**, 476–481 (2005)

Two recent papers shed new light on the pathological processes involved in neurodegenerative diseases. Snyder and colleagues provide evidence for the synaptic amyloid β (Aβ) hypothesis of Alzheimer's disease by showing that non-fibrillar Aβ acts at synapses and disrupts glutamergic transmission. Addition of Aβ42 to cortical neurons in culture promoted the endocytosis of *N*-methyl-D-aspartate (NMDA) receptors, reducing long-term potentiation (LTP) and therefore decreasing the synaptic plasticity required for memory and learning. In the second paper, SantaCruz *et al*. studied the role of neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau protein in neurodegeneration. The authors used mice expressing a tau variant that can be suppressed with doxycycline and found that expression of the tau variant in mice causes NFTs, neuronal loss and behavioural defects such as memory loss. Suppression of tau with doxycycline resulted in recovery of memory loss and neuron numbers despite the continued accumulation of NFTs.

ANTI-THROMBOTICS

Defective thrombus formation in mice lacking coagulation factor XII.

Renné, T. *et al*. *J. Exp. Med.* **202**, 271–281 (2005)

Coagulation factor XII (FXII), a protein not previously considered as important for blood coagulation in humans, has now emerged as a potential drug target for anti-thrombotic drugs. Renné *et al*. used three mouse models of platelet recruitment and thrombus formation and found that mice lacking FXII have a severe defect in the formation and stabilization of platelet-rich occlusive thrombi, and are also protected against thromboembolism brought on by the administration of collagen or adrenaline. Restoring FXII function by infusing human FXII into the mice restored their ability to form thrombi. These initial studies suggest further investigation of the role of FXII in human thrombus formation is warranted.

INFLAMMATION

Oxygenation inhibits the physiological tissue-protecting mechanism and thereby exacerbates acute inflammatory lung injury.

Thiel, M. *et al*. *PLoS Biol*. **3**, e174 (2005)

This study, carried out using mouse models of lung infection, suggests that the use of high oxygen concentrations to treat acute respiratory distress syndrome in humans might actually worsen the condition by interfering with a hypoxia-driven anti-inflammatory pathway involving the adenosine A_{2A} receptor. The authors proposed that oxygen-mediated inhibition of the hypoxia–adenosine–A_{2A}-receptor pathway caused a lack of endogenously formed adenosine, which has recently been shown to downregulate inflammation. Administration of an A_{2A} receptor agonist restored the lack of adenosine and prevented further inflammation in the inflamed lungs of oxygenated mice.

INFECTIOUS DISEASE

Unravelling SARS lethality

Severe acute respiratory syndrome (SARS), an illness identified in 2003 that spread throughout the world for several months, re-awakened nightmares of a lethal global pandemic. Caused by the SARS coronavirus (SARS-CoV), therapeutic options are limited, and fears of renewed outbreaks highlight the paramount importance of understanding its pathogenicity. Reporting in *Nature Medicine*, a multinational research team now provides a molecular explanation for the high lethality associated with SARS, and highlight a potential therapeutic strategy for tackling SARS and possibly other respiratory disease viruses.

Recently, the renin–angiotensin system, an endocrine cascade best known for regulating blood pressure, has been implicated in the respiratory damage responsible for SARS lethality. Angiotensin II, which is produced through the action of angiotensin-converting enzyme (ACE), has been identified as a potent vasoconstrictor that can aggravate lung injury and produce lung oedema.

Intriguingly, *in vitro* experiments have indicated that ACE2 — a homologue of ACE that negatively regulates angiotensin II — is a cellular receptor for SARS-CoV. Now, by using mice deficient for ACE2, Kuba *et al.* provide the first *in vivo* evidence for the importance of this enzyme in SARS-CoV replication, and show that infection with SARS leads to downregulation of ACE2. The authors identified the SARS-CoV Spike protein as an interaction partner for ACE2, and demonstrated that recombinant Spike exacerbates acute lung injury through down-modulation of ACE2 and subsequent accumulation of angiotensin II. Recombinant ACE2, as well as angiotensin II receptor type 1 (AT1R) inhibitors, which are already in clinical use for the control of blood pressure, were shown to protect against Spike-mediated lung injury in mice.

Underscoring the relevance of these findings in humans, recent data in a small cohort of individuals with SARS suggested that an insertion deletion ACE polymorphism that affects ACE function correlates with disease severity. Furthermore, the SARS-CoV–ACE2 interaction might also provide a molecular explanation for the long-standing puzzle as to why SARS-CoV is so much more lethal than other coronavirus infections, which are responsible for ~30% of common colds.

These findings are a crucial step towards the development of treatments for individuals infected with SARS-CoV. Furthermore, evidence of the link between the renin–angiotensin system and acute lung failure could also provide an opportunity to treat other viral infections that owe their lethality to a respiratory syndrome — for example the avian influenza A H5N1 strain, whose recent outbreak in South East Asia resulted in 70% lethality due to acute respiratory failure.

Alexandra Flemming

References and links

ORIGINAL RESEARCH PAPER Kuba, K. *et al.* A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature Med.* **11**, 875–879 (2005)
FURTHER READING Imai, Y. *et al*. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* **436**, 112–116 (2005)