NEURODEGENERATIVE DISEASE

Capturing MS targets

Lack of knowledge of the pathology that underlies multiple sclerosis (MS), a chronic inflammatory neurodegenerative disease that is estimated to affect approximately one million people worldwide, has hampered the development of improved therapeutics. Reporting in *Nature*, Steinman and colleagues show that large-scale proteomic analyses of MS lesions (or 'plaques') in the CNS are useful for the identification of new drug targets for this disease.

MS plaques have distinct characteristics that depend on the level of disease activity. By using laser-capture microdissection and mass spectrometry, the authors examined the protein profile of human MS lesions at three different pathological stages: acute plaque, chronic active plaque (CAP) and chronic plaque. Over 1,000 proteins were identified in each lesion type, more than 100 of which were unique to that particular type of plaque. Surprisingly, five proteins that are known to be involved in the blood-clotting cascade were unique to CAPs, suggesting a previously unsuspected role for coagulation factors in the immune system dysregulation that occurs in MS.

The authors focused their attention on two of these proteins, tissue factor and protein C inhibitor (PCI). Both are known to signal through protease-activated receptor (PAR) proteins to promote pro-inflammatory thrombin signalling, and PCI also functions as an inhibitor of activated protein C (aPC), a major physiological anti-coagulant. The presence of tissue factor and PCI in CAPs implicates an upregulation of thrombin signalling and a suppression of the protein C pathway in MS pathogenesis.

To investigate the therapeutic potential of targeting the activity of tissue factor and PCI in MS, the thrombin inhibitor hirudin or recombinant aPC was injected daily into an experimental autoimmune encephalomyelitis (EAE) mouse model, which is commonly used to model MS. In both cases a marked reduction of disease severity was observed. In addition to decreasing immune cell proliferation and cytokine production from splenocytes and lymph node cells, these treatments also led to a reduction in the number of inflammatory foci in the CNS after 35 days of treatment. Although treatment with an anticoagulant increases the risk of bleeding, and although the protective effects of hirudin were observed only until day 35 (probably owing to the development of anti-hirudin antibodies), recombinant aPC could be further developed as a drug for MS. Experiments with aPC mutants showed that both the anticoagulant and the anti-inflammatory (through PAR1) activities of aPC are required to suppress EAE in mice, but it might be possible to design an effective variant with reduced bleeding potential.

This study highlights the value of large-scale proteomic profiling of diseased tissue, not only for furthering understanding of the underlying pathology but also for the identification of new drug targets. The ability of hirudin and, in particular, of aPC to reverse the effects of two of the newly identified proteins in MS plaques opens promising directions of research for the discovery of improved MS therapeutics.

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