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Thanks a clot!

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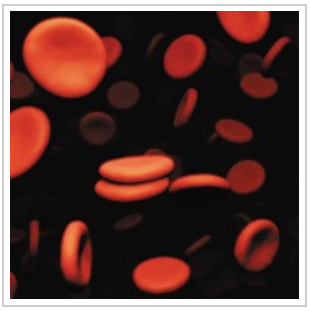
Researchers identify proteins involved in coagulating blood as targets for treatment of multiple sclerosis.



Clues to new treatments for multiple sclerosis (MS) may be in your blood. MS lesions (scleroses) are demyelinated patches of the central nervous system. Han *et al.* identified proteins involved in coagulating blood in MS lesions. They report that anticoagulants improved an animal model of MS in a recent article in *Nature*.

MS symptoms and disease course are variable. MS lesions (plaques) vary depending on disease activity and are characterized as acute, chronic active (CAP) or chronic. Because different stages of MS may be caused by different disease mechanisms, the authors profiled the proteins expressed in each type of MS lesion with tandem mass spectroscopy.

Of the 2574 proteins identified in MS lesions and control brain regions, 158, 416 and 236 proteins were unique to acute, CAP and chronic lesions, respectively. More than half of these proteins had no known functions. Five coagulants (tissue factor, protein C inhibitor (PCI), thrombospondin, fibronectin and vitronectin) were unique to CAP lesions.

Inflammation is involved in MS, and some factors involved in blood coagulation are also involved in inflammation. Tissue factor is expressed in immune cells and astrocytes during inflammation and promotes signaling of the proinflammatory coagulant thrombin. PCI, which is usually found in blood, accumulates in CAP lesions during inflammation. PCI inhibits the anticoagulant activated protein C (aPC).

Mice immunized with myelin proteolipid protein develop an autoimmune response called experimental autoimmune encephalomyelitis (EAE) that, like MS, induces demyelination and inflammation and impairs movement. Hirudin is a Food and Drug Administration (FDA) approved anticoagulant that inhibits thrombin. Hirudin reduced EAE severity, immune cell proliferation and cytokine production. Relative to vehicle-treated mice, hirudin-treated mice also showed fewer areas of inflammation in brain and spinal cord.

Recombinant aPC is approved by the FDA for the treatment of severe sepsis. Like hirudin, recombinant aPC reduced EAE severity, immune cell proliferation, cytokine production and inflammatory foci. The aPC domains important for coagulation and cell signaling are distinct. Mice lacking either of these domains showed brief improvement of EAE severity. However, both domains were necessary for prolonged EAE improvement, suggesting that aPC's roles in both cell signaling and coagulation are important in combating EAE.

Together, these data suggest that some anticoagulants might reduce the severity of MS in people. However, because anticoagulants can cause hemorrhage, clinical trials will be necessary to weigh the benefits against the risks.

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1. Han, M. H. *et al.* Proteomic analysis of active multiple sclerosis lesions reveals therapeutic targets. *Nature* **451**, 1076–1081 (2008). | Article | PubMed | ChemPort |