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CLINICAL NEUROSCIENCE

A bloody brake on myelin repair

In multiple sclerosis, the blood-coagulation factor fibrinogen can enter the brain. It emerges that fibrinogen inhibits the maturation of cells called oligodendrocytes that repair nerve-fibre insulation and maintain neuronal communication.

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Multiple sclerosis (MS) is a debilitating neurological disease in which the body's immune system destroys the myelin sheath that provides electrical insulation for nerve fibres. Myelin repair subsequently fails owing to a lack of new myelin-producing cells called oligodendrocytes, and this contributes to an irreversible loss of neuronal projections called axons. Why oligodendrocyte precursor cells (OPCs) located at sites of MS-related tissue damage fail to differentiate into oligodendrocytes has been poorly understood. Writing in *Neuron*, Petersen *et al.*[1] report that a blood-coagulation factor called fibrinogen (which enters the brain when the blood–brain barrier is damaged in MS[2]) puts a brake on OPC differentiation. This insight offers hope for future treatment strategies.

Myelin is made by oligodendrocyte processes that spiral around axonal segments, and it forms a multilayered membrane sheath that speeds up electrical conduction. Oligodendrocyte processes also support axon metabolism. Myelin growth is a fast process in which oligodendrocyte mass multiplies in just a few days[3]. In mammals, myelination begins around birth and OPCs are maintained throughout life; myelination in the cortex of the adult brain is thought to contribute to learning and higher brain functions[4]. Orchestrating timely OPC generation, oligodendrocyte differentiation and energy-demanding myelin synthesis under changing metabolic conditions and in phases of physiological low-oxygen levels[5] is a major challenge. Unsurprisingly, OPCs must integrate a plethora of external stimuli to determine when to differentiate.

Similarly, myelin repair following acute brain injury depends on optimal timing of OPC proliferation and differentiation. Unless cellular debris and blood clots are cleared and vascular blood supply is reinstated, remyelination will fail[5]. Thus, it is plausible that blood-borne signalling proteins, such as coagulation factors deposited at sites of physical damage, are detected by OPCs and act as surrogate markers of ongoing repair of the primary injury. This could put differentiation on hold until the damaged environment is ready for remyelination.

Demyelinated areas that arise in MS can also be considered as local 'brain injuries'. Although there is no bleeding and subsequent blood clotting involving coagulation factors in MS, chronic inflammation causes a persistent opening of the blood–brain barrier (BBB), across which these factors might pass in large amounts. Could the permanent entry of blood-borne coagulation factors prevent OPC differentiation and myelin repair?

With this question in mind, Petersen *et al.* revisited the observation that the soluble glycoprotein fibrinogen, which is abundant in blood plasma, is deposited in demyelinated brain regions[2]. First, the authors added physiological concentrations of fibrinogen to OPCs in cell culture, and showed that this coagulation factor strongly inhibited OPC differentiation and prevented axon myelination. Among the many genes in OPCs whose expression was affected by fibrinogen, the researchers detected upregulation of members of a signalling pathway known to inhibit oligodendrocyte differentiation[6] — genes encoding bone morphogenetic proteins (BMPs) and their downstream effectors, including the transcription factor ID2. Indeed, Petersen and colleagues showed that fibrinogen and ID2 could be readily visualized in regions in which remyelination had failed in the brains of people who had died with MS.

Interestingly, the authors found that OPCs exposed to fibrinogen either *in vitro* or in the brains of live mice often underwent a developmental switch to become a different neuron-supporting cell type called an astrocyte. This raises the possibility that astrocytic scars (a form of tissue growth that occurs in response to injury in MS brains and that might prevent myelin repair) arise from a switch in OPC identity. Such a hypothesis will require testing in mouse models of MS.

Fibrinogen drives the activation of brain-specific immune cells, which can indirectly inhibit remyelination. However, the effects reported by Petersen and co-workers are direct: they result from fibrinogen binding to the BMP type I receptor protein ACVR1 on the surface of OPCs to stimulate the BMP signalling cascade in these cells (Fig. 1). This is of interest because inhibitors of BMP signalling have already been developed. Indeed, the authors provide evidence that one such inhibitor can counteract the detrimental effects of fibrinogen on OPC differentiation, pointing to a possible avenue for therapy.

In addition, fibrinogen itself might be

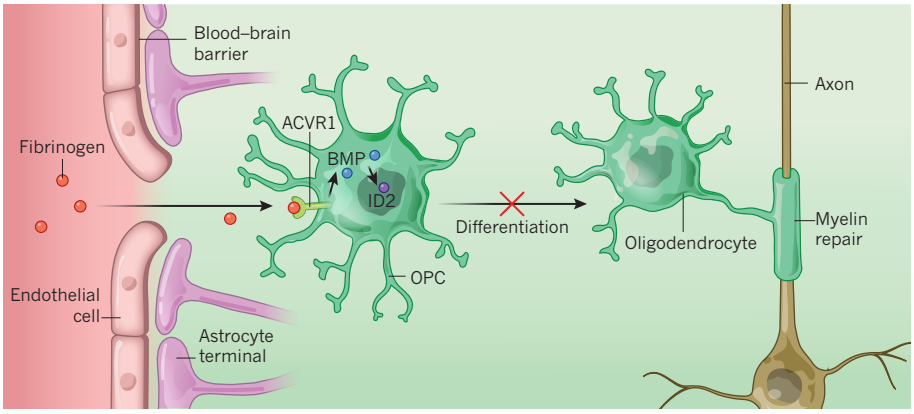

Figure 1 | A coagulation factor and multiple sclerosis (MS). In MS, neuronal projections called axons are stripped of their insulating myelin sheath. Subsequent myelin repair often fails, but the reason for this has been unclear. The blood-coagulation factor fibrinogen crosses the blood–brain barrier (composed of endothelial cells lined with the termini of cells called astrocytes) in MS, and Petersen *et al.*[1] provide evidence that fibrinogen acts to inhibit myelin repair. They show that it binds to the receptor protein ACVR1 on the surface of oligodendrocyte precursor cells (OPCs), triggering an intracellular signalling cascade in which bone morphogenetic protein (BMP) activates the transcription factor ID2. BMP signalling prevents OPCs from differentiating into mature oligodendrocyte cells, which would produce myelin and so drive myelin repair.

a drug target. Petersen *et al.* show that the fibrinogen-cleaving enzyme ancrod — an anticoagulant from a snake venom that has been proposed (although not approved) as a treatment for ischaemic stroke — enhanced the remyelination of demyelinated axons. A mouse model of MS has previously been shown to benefit from ancrod and fibrinogen depletion[7], owing in part to anti-inflammatory effects. However, it is possible that myelin repair is also improved in these animals. Regardless of the relative contributions of indirect and direct effects of ancrod on OPCs, clinical tests would be needed to determine the drug's efficacy in people with MS. Unfortunately, given that the drug is off-patent, such trials are unlikely to find support in the pharmaceutical industry.

It is becoming apparent that coagulation factors do much more than simply act in the blood-coagulation cascade. The research group that performed the current study has previously shown[8] that the enzyme thrombin, which cleaves fibrinogen to produce fibrin, is activated in demyelinated tissue. This leads to the formation of large fibrin complexes, which are equivalent to blood clots. Moreover, tissue plasminogen activator protein, which is routinely given to people who have had an ischaemic stroke to promote the breakdown of fibrin-containing blood clots, inhibits the death of oligodendrocytes[9] and promotes axonal regeneration[10]. One must assume that these factors, like fibrinogen, access the brain in the absence of a functional BBB, and have roles in determining the success or failure of myelin repair. And although fibrinogen is apparently not expressed in the brain, other coagulation factors are[8]. Their uncontrolled transfer from the blood when the BBB leaks will no doubt perturb the 'coagulation-unrelated' functions of these factors in the brain; these effects await exploration.

If a compromised BBB is an entry port for blood-borne inhibitors of myelination, does fibrinogen entry reduce cortical myelination and affect higher brain functions in chronic conditions other than MS? The brains of people with Alzheimer's disease have a leaky BBB and show fibrinogen infiltration[11]. Individuals carrying a form of the *APOE* gene that increases the risk of Alzheimer's disease display reduced BBB integrity, and this variant has been associated with age-dependent myelin breakdown[12]. Petersen and colleagues' findings might thus have implications beyond MS — these should be investigated soon. ■

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