Platelets Provide a Bounty of Potential Targets for Therapy in Multiple Sclerosis

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Multiple sclerosis (MS) and related demyelinating conditions like neuromyelitis optica are mediated via migration of leukocytes and monocytes from the peripheral circulation. This is particularly relevant in the initial phases of disease that manifests clinically with relapses and remission and dominates the pace of the evolution of these chronic diseases in the first decade. The most effective approved therapeutic approach for relapsing remitting MS, Natalizumab, blocks lymphocyte migration into the brain by targeting α4 integrin.1 Scant attention has been given to platelets in the pathophysiology of these diseases. And yet there have been hints that platelets play an important role in MS. For instance, an early study of MS lesions using gene microarrays indicated that glycoprotein IIb/IIIa was highly expressed in MS lesions and, surprisingly, particularly in the more chronic stages of the disease.2 Leukocyte–platelet interactions are mediated by α4 integrin, although α2, α5, and α6 are the primary integrins on platelets themselves.3

The coagulation cascade itself plays a major role in the development of an inflammatory response in MS. Proteomic studies of laser-captured microdissected lesions reported in the transcriptional profiling in MS2 illuminated a key role for the thrombin cascade in the development of inflammation in MS.4 In vivo administration of hirudin or recombinant activated protein C reduced paralytic disease and inflammation in experimental autoimmune encephalomyelitis. Key Th1 and Th17 cytokines were suppressed in the immune system and in the nervous system.4 Administration of recombinant activated protein C showed that both its anticoagulant properties and its downstream signal functions were critical in demyelinating disease.4

Langer et al5 break new ground in describing a key role for platelets in the pathogenesis of demyelinating disease. They show that platelets are present in chronic active lesions of MS and in the related collection of animal models referred to as EAE (Figure). They were also able to show that blockade of key receptors on platelets like glycoprotein IIb/IIIa ameliorates paralysis and reduces experimental autoimmune encephalomyelitis. This, of course, opens an opportunity to consider glycoprotein IIb/IIIa blockers like Abciximab in MS and other demyelinating diseases.

The platelet also may be participating in pathways that intersect with key pathophysiological mechanisms at play in demyelinating disease. Platelets are a major component of neutrophil traps that are found in conditions like neuromyelitis optica.6 Modulation of platelet function may help prevent the release of active proteases such as elastase in exacerbations of neuromyelitis optica.6

The platelets are more than a plug for halting hemorrhage in the physiology of coagulation cascade. They are a storehouse of potent mediators, such as the most aptly named platelet-derived growth factor. Remarkably, modulation of platelet-derived growth factor with drugs like imatinib has strong effects in the EAE model to reverse paralytic disease.7 Modulation of the blood–brain barrier by inhibition of platelet-derived growth factor with drugs like imatinib has been shown to impair transendothelial migration of small and large molecules across the blood–brain barrier.8 The platelets themselves may provide a key switch for modulation of the blood–brain barrier to restore homeostasis or for promoting drug delivery.

As the pathophysiology of demyelinating disease is unraveled, an unexpected role of platelets emerges. Understanding platelet physiology in the pathobiological processes associated with venules in the inflamed brain will provide new opportunities for therapeutic development.
targets for therapy in MS. Platelet-activating factor and platelet-derived growth factor are certainly two molecules that merit consideration as targets for therapy. Some of these targets already have available drugs that could be merely repurposed for use in demyelinating diseases. Finally, there is evidence that platelets themselves are highly activated in some patients with MS, again emphasizing that modulating platelet activity may be beneficial. The work by Langer et al has now opened a new frontier for research on platelets and their role in multiple sclerosis.

Disclosures

None.

References


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