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

Lawrence Steinman

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 autoimmu

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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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