Bacterial DNA mimetics activate platelets and promote thrombosis via CLEC-2

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Bacterial DNA activates the innate immune system through recognition of unmethylated CG dinucleotides (CpG motifs) by Toll-like receptor 9 (TLR9). Short nuclease-resistant phosphorothioate synthetic oligodeoxynucleotides mimic bacterial DNA immunostimulatory activity and are being used in clinical trials as vaccine adjuvants. Targeted cells include plasmacytoid dendritic cells and B lymphocytes. Whether these bacterial DNA mimetics affect platelet function and thrombosis is currently unknown.

We presently show that phosphorothioate-modified oligodeoxynucleotides with CpG motifs (PT-CpG ODN) bind on platelet surface and are internalized. They activate platelets and induce their aggregation. PT-ODN without CpG motifs were as efficient as PT-CpG ODN to elicit these platelet responses, whereas non modified phosphodiester CpG ODN had no effect. TLR9- or MyD88-deficient platelets aggregated normally in response to PT-CpG ODN stimulation. Interestingly, platelets deficient for the C-type lectin receptor CLEC-2 were unable to capture and internalize PT-ODN. CLEC-2 deficiency fully abolished PT-ODN-induced platelet activation and aggregation. PT-CpG ODN stimulated CLEC-2 dependent tyrosine kinase pathway and Syk phosphorylation. In vivo, intravenously injected PT-CpG ODN interacted with platelets adhered to laser injured endothelia of mouse cremaster and promoted fibrin generation and thrombus growth.

Thus, CLEC-2 mediates platelet activation and aggregation induced by bacterial DNA mimetics, which might serve an important role in the interplay between platelets and immunity.