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Investigating the role of neutrophils and NETs in staphylococcus aureus endocarditis

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Funding Acknowledgement: FWO SB

Background/Introduction: Infective endocarditis (IE) remains one of the deadliest cardiac diseases. Despite optimal antibiotic and surgical treatment, still one in three patients do not survive Staphylococcus aureus (S. aureus) IE. In order to cause this disease, bacteria need to first overcome shear stress and adhere to cardiac valves. Secondly, they need be able to progress into a complex lesion. Previously, we have shown that S. aureus adheres to cardiac valves via platelets and von Willebrand factor. However, the process of progression from initial bacterial adhesion to a complex vegetation, particularly how bacteria bypass the immune system and thrive in the host environment, remains unclear.

Purpose: We aimed to determine the role of neutrophils and neutrophil extracellular traps (NETs) in IE progression using a novel mouse model.

Methods: We intravenously injected mice with S. aureus and locally stimulated the endothelium with histamine, resulting in IE lesions that originate on inflamed heart valves. After three days we determined the development of IE on the aortic valves with Gram staining and echocardiography. We investigated the presence of NETs in 14 mice by immunostaining for citrullinated histone H3 (H3Cit), extracellular DNA, and myeloperoxidase. Of these 14 mice, 9 developed endocarditis. In a separate set of experiments, we investigated the role of neutrophils in IE development by injecting a neutrophil-depleting or control antibody 24h before surgery.

Results: Echocardiography revealed real IE lesions attached on inflamed aortic valves. Mice with endocarditis had significantly (P=0.005) more detectable H3Cit (9/9) than those without (1/5). More specifically, four mice had H3Cit+ neutrophils within thrombi, indicating early NETosis. Seven mice had an extracellular H3Cit staining pattern within the thrombus. These extracellular H3Cit-positive regions were associated with DNA and myeloperoxidase, indicating the presence of a network of NETs. When we depleted neutrophils, mice developed significantly more endocarditis (7/16 vs. 1/15, P=0.03).

Conclusion: Endocarditis lesions contained NETs or neutrophils undergoing NETosis, and neutrophil depletion led to increased IE incidence. Further investigating these two players in IE could potentially provide new strategies to combat this deadly disease.