The pathophysiology of HIT

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Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse drug effect caused by antibodies reacting with multimolecular complexes of the positively charged chemokine platelet factor 4 (PF4) and negatively charged heparin. In a subset of patients, the resulting immune complexes activate platelets and monocytes via their Fc-receptors leading to enhanced thrombin generation, thrombocytopenia and paradoxical thrombosis. The pathogenic antibodies recognize PF4 bound to polyanions. Hereby heparin can be substituted by a variety of other negatively charged molecules. Using circular dichroism (CD) spectroscopy we found pronounced structural changes of PF4, leading to expression of anti-parallel beta sheets, which occurred during the interaction with highly charged polyanions known to be immunogenic in vivo. This allows to predict immunogenicity of drugs exposing polyanions during preclinical development. HIT shows several unusual features. Even patients who receive heparin for the first time, show a rapid induction of anti-PF4/heparin IgG antibodies as early as 4-6 days. The antibodies are transient and disappear within 100 days, and there is no typical anamnestic response in case of reexposure. We have recently proposed that HIT is a misdirected bacterial defense mechanism. PF4 binds to bacteria and then exposes the epitopes to which anti-PF4/heparin antibodies bind. Consistently, we showed that anti-PF4/heparin antibodies are highly significantly associated with periodontitis, one of the most prevalent human infections mostly induced by Gram-negative bacteria. More precisely, we identified lipid A as PF4 binding structure on the surface of Gram-negative bacteria which is mediated by the associated phosphate groups. The phosphate groups of lipid A are similarly arranged as the phosphate groups of DNA or RNA. We also found cross-reactivity of anti-PF4/heparin antibodies to PF4/nucleic acid complexes. This might have consequences for drug development as e.g. aptamers are DNA or RNA based therapeutics and might induce unwanted antibody responses. Most recently, marginal zone B cells were identified to be crucial for anti-PF4/heparin antibody production in mice. This is consistent with the transient presence of anti-PF4/heparin antibody secreting cells in the spleen of mice after active immunization with PF4/heparin complexes. However, it is still uncertain which B cell population in human patients with HIT is responsible for anti-PF4/heparin antibody production. In conclusion, antibody formation in response to PF4/polyanion complexes could be an ancient defense mechanism, in which an endogenous protein acts as label and danger signal after a conformational change which induces an antibody response. This concept might be also relevant for other antibody-mediated autoimmune diseases.