ITP manifests as immune mediated, destructive thrombocytopenia. The etiology of ITP is still unknown.

Immunologically an antigenic challenge or an autoimmune stimulus induces interaction between antigen presenting cells and T-lymphocytes. Through signal mechanisms T-cell activation and B-cell antibody production occur. Regulatory mechanism of T-cells and antidiotype antibodies direct the degree and duration of the physiologic immune response. In ITP the immune response and the selftolerance mechanism are altered in the presence of an antigen stimulus.

Mainly 3 elements are involved in the pathophysiology of ITP: the platelet, the cellular and humoral immune response, the mono-macrocytic phagocytosis mediated by Fc-receptors.

THE PLATELETS

The platelet function is balancing between inflammatory, procoagulant, antithrombic and fibrinolytic properties. When platelet reactive antibodies are overwhelming actively the platelet function gets out of balance: bleeding or thrombosis are symptoms of the advanced state of disorder. Platelets vary in form, size, density, age as well as reactivity according to polymorphism of major glycoproteins (GP's). Platelets trigger the immune response from the first stimulus to irreversible participation in cell to cell reactions. In ITP mainly the numeric balances are disturbed.

PHAGOCYTOSIS AND Fcγ-RECEPTORS (FcγR)

Among the classes of FcγRs the low affinity FcγIIa with the capacity of IgG1 and binding and FcγIIa...
with IgG₃ binding are prominent mediators of platelet clearance in ITP and bind mainly immunocomplexed antibodies. High affinity FcγRI which binds monomeric IgG seems to play a minor role in ITP. Several polymorphisms exist for FcγRII and III in humans which alter affinities for antibodies. The inhibitory FcγRIIb leads to co-crosslinking with B-cell receptors resulting in cell inactivation (no phagocytosis).

The immunologic characteristics of FcγRs are also important in the context of the immunomodulatory effect of IVIG treatment: IVIG dimer and multimer seems to block Fc-receptors more actively than monomeric IVIG. On the other hand the dimers/multimers are responsible for marked side effects of IVIG treatment. IVIG increase the presence of inhibitory FcγRIIB and prevent ITP in a mice model.

The immunopathology of ITP is a model for altered immune response. Similar immunopathologic events are present in other (auto)immune related disorders. The mechanism of action of T-cell regulatory drugs, of IVIG and other biologic therapeutics can be documented by measuring changes of the different components of the immune response.

In the future, monoclonal antibodies against the different steps of the immune response (e.g. anti-T cell antibodies, CD20 antibody (rituximab), anti-Fc-receptor antibodies) may provide specific therapies in ITP and other immune related disorders.

REFERENCES