

# Immunopathogenesis of Idiopathic Thrombocytopenic Purpura ITP

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

Immunologically an antigenic challenge or an auto-immune 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 antiidiotypic 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-macrocyclic 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.

## THE IMMUNE SYSTEM

In ITP the immunopathogenesis of platelets is antibody mediated under the control of T-helper cells

and related cytokines. Platelets' (auto)antigen driven T-cell clones and Interleukins, mainly Interleukin-2 (IL-2) direct autoreactive B-cells to secrete (auto) antibodies.

In acute ITP specific antibody (e.g. against Varicella zoster virus) may crossreact with platelet antigen: molecular mimicry occurs. Th<sub>0</sub> or Th<sub>2</sub> expression with TGF- $\beta$  as potent immunosuppressive modulator among the cytokine pattern seems to correlate with transient ITP.

In chronic ITP autoimmune targets on platelets are mostly GPIIb/IIIa with different locations of epitopes, GPIb/IX and rarely GPIa/IIa, IV and V. Th<sub>1</sub> pattern and abnormal activation of autoreactive B-cells characterize autoimmunity in chronic ITP. With aberrant immune response circulating and platelet-associated autoantibodies can be detected by capture assays (immunoblot-, MAIPA-assay). The sensitivity (positive results in patients with ITP) is 49 - 66%, the specificity (negative results in patients with nonimmune thrombocytopenia) is 78 - 95%.

(Auto-)antibodies have a hypervariable region with amino-acid sequences which are specific for each individual antibody and which never before were encountered by the host and, therefore, are foreign to the host who starts to produce neutralizing, regulatory antibody. The patients' own antiidiotypic antibodies or those in IVIG preparations regulate/downmodulate the production of (platelet) antibodies.

## PHAGOCYTOSIS AND FC $\gamma$ -RECEPTORS (FC $\gamma$ R)

Among the classes of FC $\gamma$ Rs the low affinity FC $\gamma$ IIA with the capacity of IgG<sub>1</sub> and <sub>3</sub> binding and FC $\gamma$ IIIA

with IgG<sub>2</sub> 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 FcγII 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

see Supplement on State-of-the-Art Expert Meeting on ITP. *J Ped Hematol Oncol* 2003 (in press), especially the articles by R. Kekomäki, A. Crow and A. Lazarus, J. Semple, R. McMillan and D. Cines