

From the bench

Modulation of CD4⁺ T cells by intravenous immunoglobulin

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CD4⁺ T helper (Th) cells play a prime role in the sustenance and regulation of antigen-specific immune responses.

Th cells come in several subsets with distinct functions and patterns of factor secretion: Th1 (IFN- γ), Th2 (IL-4, IL-5), Th17 (IL-17), and induced regulatory T cells (Tregs) (TGF β , IL-10). In addition to their function in immunity against pathogens, Th1 and Th17 cells are important in autoimmunity, Th2 cells promote allergy, whereas Tregs are crucial for immune homeostasis and tolerance.

Intravenous immunoglobulin (IVIg) is a therapeutic preparation of polyclonal IgG obtained from pooled plasma of several thousand healthy donors.

IVIg is being increasingly used in the treatment of diverse autoimmune and inflammatory diseases, in addition to replacement therapy in immune deficiency diseases.

IVIg exerts sustained beneficial effects in patients and is believed to act through several mutually non-exclusive mechanisms by targeting different cells and their effector molecules. IVIg can directly interact with T cells to induce immunomodulatory effects.

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Some recent stories from the lab ...

IVIg suppresses differentiation and amplification of Th17 cells as well as secretion of IL-17A, IL-17F, IL-21, and CCL20 (1).

IVIg inhibits Th1 cells, but enhances Foxp3⁺Tregs among memory Th cells (1, 2).

IVIg induces the expansion of Tregs and enhances their suppressive functions (2, 3, 4).

IVIg inhibits maturation of human dendritic cells (DCs) and reduces their T cell stimulatory capacity (5).

IVIg suppresses secretion of DC-derived IL-12 and enhances IL-10 expression (5, 6).

Different IVIg preparations have similar effects on Th cells and DCs (5, 7).



- IVIg-derived F(ab)₂ fragments inhibit STAT3 activation and expression of RAR related orphan receptor C (RORC), but enhance Foxp3 expression (1).
- IVIg reciprocally regulates Th17/Tregs and Th1/Th2 cells (8, 9).
- IVIg regulates the cytokine network to alter Th cell subset development and function (9,10).

Open questions ...

- What molecular pathways are involved in IVIg mediated reciprocal regulation of Th cells?
- Does IVIg undergo spontaneous internalization in T cells as it does in activated B cells (11) ?
- How does IVIg modulate antigen presenting cells to regulate Th cell subsets?

Mysteries ...

- Is interaction of alpha 2,6-sialylated IgG Fc with macrophages important in anti-inflammatory therapy with IVIg (12)?
- Does alpha 2,6-sialylated IgG Fc offer a potential therapy for autoimmune diseases (13)?



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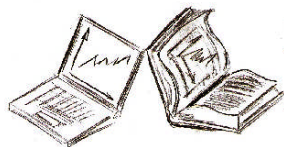
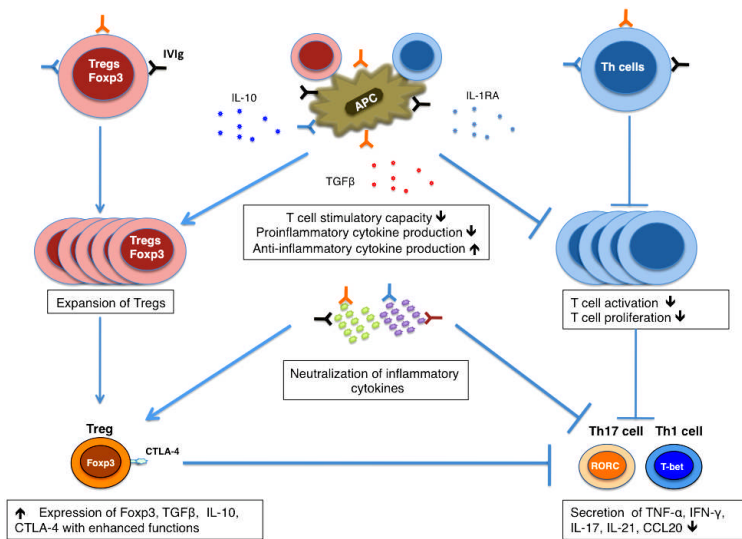


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Background

IVIg is successfully used in the treatment of several autoimmune and inflammatory diseases, which are characterized by dysregulated immune response and chronic inflammation (12). IVIg can act at the initiation, amplification, and effector phase of the immune response to achieve beneficial therapeutic effects (9, 14). IVIg can inhibit antigen presentation, T cell and B cell responses, and neutralize pathogenic autoantibodies, complements, and cytokines (5, 9, 15, 16). In target cells such as fibroblasts, endothelial cells, neutrophils, and macrophages, IVIg suppresses cellular functions, blocks IFN- γ signaling and IFN- γ -induced gene expression, and induces cell death (9, 17, 18).



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Modulation of the immune system by IVIg



DCs, Macrophages, Monocytes

- Differentiation and maturation of DCs ↓
- DC-mediated T cell activation ↓
- Endocytosis ↓
- Expression of inhibitory Fc γ RIIB ↑
- Blockade of activating Fc γ Rs
- Expression of activating Fc γ Rs ↓

T cells, B cells, NK cells

- Activation, proliferation ↓
- IL-2 production by T cells ↓
- Modulation of T cell differentiation
- T cell and B cell apoptosis ↑
- B cell expression of inhibitory Fc γ RIIB ↑
- Modulation of B cell repertoire
- Regulation of cytokine and antibody production
- Modulation of cellular migration
- NK-mediated ADCC ↑

Endothelial cells

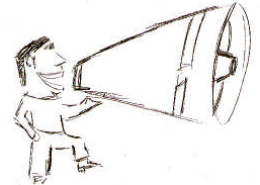
- Saturation of FcRn
- Adhesion molecules ↓
- Regulation of cytokine and chemokine production

Antibodies, Complement, Cytokines

- Idiotypic inhibition of autoantibodies
- Complement activation and tissue damage ↓
- Neutralization of inflammatory cytokines

Neutrophils, Basophils

- Neutrophil activation ↓
- Cell death ↑
- Adhesion to endothelium ↓



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