ENHANCED ANTI-DIABETOGENIC EFFECT OF INTRAVENOUS IMMUNE GLOBULIN MODIFIED BY FERROUS ION EXPOSURE

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The aim of this study was to investigate the immunomodulatory capacity of native and Fe(II)-exposed intravenous immune globulin (IVIg) in multiple low dose streptozotocin-induced diabetes and to delineate the mechanisms of their influence on immune cell functions. Optimal doses (200-600mg/kg) of IVIg prevented the development of hyperglycemia, glycosuria and attenuated mononuclear cell infiltration in pancreatic islets. Fe(II) exposure of IVIg decreased their optimal therapeutic dose to 100mg/kg which significantly decreased the serum levels of proinflammatory cytokines compared to the same dose of native IVIg. This was accompanied by lower numbers of TNF-α, IFN-γ and IL-17 producing $CD4^+$ T cells and increased frequencies of $CD4^+IL\text{-}10^+$ and $CD4^+IL\text{-}4^+$ T cells in the pancreatic lymph nodes and islets on day 16 after diabetes induction. Ferrous ion-exposed IVIg enhanced the bias towards Th2 response while the regulatory $Foxp3^+$ T cells were not affected.

Intravenous immunoglobulins (IVIg) are widely used for treatment of patients with several autoimmune and inflammatory diseases. A variety of mutually non-exclusive Fc- and $F(ab)_2$-fragment-dependent mechanisms have been proposed to explain the beneficial therapeutic effects observed (1-4). FcγR-mediated effects are the most favored explanation of IVIg infusion-mediated amelioration of antibody-mediated immunopathological conditions such as autoimmune thrombocytopenia. They cannot be fully responsible for the beneficial effects of IVIg in autoreactive T cell-mediated diseases. Indeed, Ephrem at al. (5) have reported that IVIg induced an increase in the number of peripheral $CD4^+CD25^+Foxp3^+$ regulatory T cells and the improvement of their functions in experimental allergic encephalomyelitis. They have shown that these effects could also be achieved by the infusion of an equimolar amount of $F(ab)_2$ fragments of IVIg (5).

Polyspecificity (polyreactivity) is currently considered as an intrinsic property of a subset of antibodies, primarily of naturally occurring IgM antibodies (6). Furthermore, the spectrum of antigens, bound by a single antibody, could be modified by some physical or chemical agents - the so called "induced polyspecificity," which is not a laboratory artifact, but can also be observed *in vivo* (7). It was therefore postulated that transient exposure of some IgG molecules to protein-destabilizing agents may lead to a significant expansion of the spectrum of recognized epitopes without their concomitant

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