SHORT COMMUNICATION

O-8. INTRAVENOUS IMMUNOGLOBULIN INDUCES ANERGY STATE-LIKE OF AUTO-REACTIVE B LYMPHOCYTES IN SJÖGREN'S SYNDROME

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Introduction
Primary Sjögren syndrome (SS) is defined as an autoimmune disease leading to destruction of lacrymal and salivary glands. Contrary to the long-held notion that primary SS is a T-cell-mediated disorder, B-cell appears to be the key actor of its pathogenesis. Recent successes of B-cell depletion therapy in autoimmune diseases are very encouraging.
In this context, Intravenous Immunoglobulins (IVIg) are widely used in supportive therapy of a wide variety of chronic autoimmune and inflammatory diseases. The mechanisms of action of IVIg are still quite misunderstood, particularly in human B-cells. We have already demonstrated that IVIg can modulate BCR-mediated (1) and TLR-mediated (2) B-cell responses. Based on this data, we reasoned that IVIg could modulate B-cell fate and may render autoreactive B-cells tolerant through induction of a functionnally unresponsiveness to BCR stimulation.

Materials and Methods
Tonsil mononuclear cell suspensions were enriched in B cells. They were cultured and stimulated using anti-IgM beads in the presence or absence of IVIg. We analyze subsequent responses of BCR stimulation using confocal microscopy, western blot analysis, and flow cytometry.

Results
IVIg prevents the in vitro activation of B-cells and induces some features characteristic of functionnal silencing. Stimulated B cells exhibit a reduction of PI (3.4.5) P3 generation and a downmodulation of Akt phosphorylation leading to the suppression of PI3K signaling (figure 1). Next, we show that upon BCR stimulation, the presence of IVIg lead to a reduction of tyrosine kinase substrate phosphorylation and a failure to mobilize calcium (figure 2). We also demonstrated that the continuous BCR occupancy by IVIg alter normal basal signaling of this receptor with an impaired agregation in lipid raft.

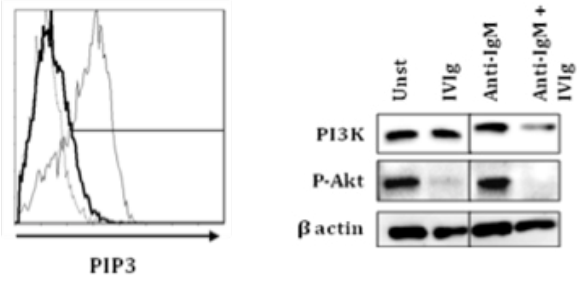

Figure 1: Downregulation of the PI3K-Akt pathway by IVIg. Cells were stimulated with anti-IgM beads alone (thin line) or in presence of IVIg (bold line). PIP3 production was measured by flow cytometry (left column). PI3K and Phospho-Akt expression were analyzed using W-blot (right column)

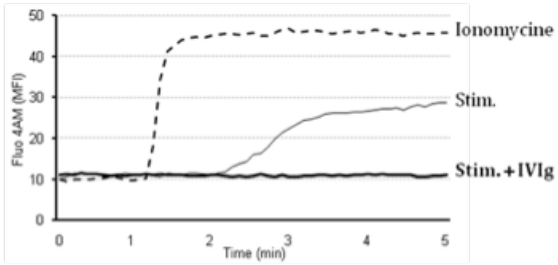

Figure 2: Endoplasmic calcium-store releases are inhibited by IVIg

Discussion

By leading the B cells to an unresponsive state, IVIg could induce functional silencing in human B-cells. Indeed, IVIg-treated B cells show characteristic features of anergic cells such as reduced calcium releases or suppressed PI3K-Akt signaling pathways. Ravetch's group (3) and us have underlined the anti-inflammatory potency of sialylated-IVIg. It will be interesting to determinate the efficacy of this IVIg fraction in inducing the "anergy-like" state on B cells to open up a new therapeutic avenue in B-cells-related autoimmune diseases.

Conclusion

These results bring new insights in the regulation of B-cell physiology and underline the interest of using IVIg as immunomodulatory agents in several B cell-related autoimmune diseases such as Sjögren's syndrome.

References

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