-Corruption of human follicular B-lymphocyte trafficking by a B cell superantigen.

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Abstract:

Protein A (SpA) of Staphylococcus aureus is known to target the paratope of immunoglobulins expressing V(H)3 genes, and to delete marginal zone B cells and B-1a in vivo. We have discovered that SpA endows S. aureus with the potential to subvert B-cell trafficking in the host. We found that SpA, whose Fc-binding site has been inactivated, binds essentially to naïve B cells and induces a long-lasting decrease in CXCR4 expression and in B-cell chemotaxis to CXCL12. Competition experiments indicated that SpA does not interfere with binding of CXCR4 ligands and does not directly bind to CXCR4. This conclusion is strongly supported by the inability of SpA to modulate clathrin-mediated CXCR4 internalization, which contrasts with the potent effect of anti-immunoglobulin M (IgM) antibodies. Microscopy and biochemical experiments confirmed that SpA binds to the surface IgM/IgD complex and induces its clathrin-dependent internalization. Concomitantly, the SpA-induced signaling leads to protein kinase C-dependent CXCR4 downmodulation, suggesting that SpA impairs the recycling of CXCR4, a postclathrin process that leads to either degradation into lysosomes or de novo expression at the cell surface. In addition to providing novel insight into disruption of B-cell trafficking by an infectious agent, our findings may have therapeutic implications. Because CXCR4 has been associated with cancer metastasis and with certain autoimmune diseases, SpA behaves as an evolutionary tailored highly specific, chemokine receptor inhibitor that may have value in addition to conventional cytotoxic therapy in patients with various malignancies and immune-mediated diseases.

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