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Inhibition of IgE and IgE/anti-IgE mediated responses in mast cells by Omalizumab

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Background

IgE binding via the high affinity FcεRI receptor modulates FcεRI expression and cytokine production in mast cells. Antigen crosslinking of bound IgE further activates mast cells, inducing degranulation and inflammatory mediator release. Omalizumab (Xolair; Genentech Inc) is a recombinant human monoclonal anti-IgE antibody that prevents IgE binding to FcεRI.

Objective

We investigated the effects of omalizumab on IgE-mediated responses in human mast cells.

Methods

LAD2 and $CD34^+$-derived human mast cell degranulation was determined by measuring the release of the granular enzyme, β-hexosaminidase. Toll-like receptor (TLR) expression was measured by quantitative (qPCR) and western blot analysis. IgE binding and FcεRI expression was determined by flow cytometry.

Results

Omalizumab (10 ug/mL) inhibited IgE binding to LAD2 cells by 78% (P=0.007) compared to untreated control. Omalizumab (10 ug/mL) further blocked IgE-dependent upregulation of FcεRI expression by 90% (P=0.03). In addition, omalizumab removed FcεRI-bound IgE in a time-dependent manner; an effect that was detected as early as 24 hrs (57% removal; P<0.001) after addition of omalizumab resulting in a concomitant decrease in IgE-dependent FcεRI expression (30%; P<0.001). Omalizumab attenuated degranulation induced by anti-IgE cross-linking of bound IgE in a dose dependent manner, with 66% inhibition (P<0.0001) at 25 ug/ml. Furthermore, 100 ug/ml omaluzimab prevented cysteinyl leukotriene production and FcεRI–dependent modulation of TLR expression.

Conclusions

Omalizumab inhibits IgE and IgE/anti-IgE dependent degranulation and receptor expression by human mast cells. Furthermore, omalizumab is able to remove pre-bound IgE from sensitized mast cells thereby reducing their response to FcεRI-dependent signals. This data suggests that omalizumab is an effective inhibitor of both sensitized and unsensitized human mast cells.

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