

Correspondence

Increase in human basophils IgE-mediated stimulation by omalizumab: A role for membrane FcγRs?

To the Editor:

In a recent issue of the *Journal of Allergy and Clinical Immunology*, MacGlashan and Saini¹ reported that treatment of allergic patients with omalizumab induced increased sensitivity in the circulating basophil. Although there was some discussion of changes in Syk expression in the cells during treatment as a possible explanation for the increased sensitivity, the underlying explanation yet remains unknown. We suggest that the presence of low-affinity IgG receptors on human basophils² and the known existence of IgE-omalizumab immunocomplexes^{3,4} might offer a mechanism for the modulation of these cells that has not been previously considered and is unrelated directly to the decrease in FcεRI expression.

The clearance of most immune complexes (ICs) is mediated via interaction with Fc-gamma receptors (FcγRs), and the mechanism was also reported for IgE-anti-IgE complexes as the primary mode of their elimination from plasma. Complexes are very small in human patients treated with omalizumab; therefore, they are unlikely to cause tissue damage⁵ and clearance by FcγR assesses the role of omalizumab as an IgG₁. During the formation of omalizumab-IgE heterodimers in serum,⁴ the monoclonal IgG₁-anti-Cε3(IgE) complex can be recognized by FcγRs in immune and dendritic cells and removed from circulation.³ Clearance of allergens by ICs-mediated competition or trap mechanism³ also elicits a downregulation mechanism of FcεRI on the basophil membrane, thereby reducing basophil IgE-mediated response and allergy symptoms.^{5,6} The effect of omalizumab on IgE sequestering has also been shown in mast cell, as this mAb is able to remove FcεRI-prebound IgEs within 24 hours from treatment and reduce to 92% by 5 days.⁷ FcγR-mediated clearance of ICs should suggest that omalizumab may also interact with basophil FcγRs. Basophils express low-affinity IgG receptors, which, in turn, regulate membrane expression of the high-affinity FcεRI.⁸ Recent data have reported that basophils also express FcγRIII.⁹ IgG-FcγR regulation of histamine release and degranulation has also been reported for mast cells.¹⁰ Despite the evidence showing a rapid dampening in allergic response following omalizumab, basophils from subjects suffering from cat allergy and treated with the mAb in a randomized controlled trial protocol exhibited an increase by 3- to 125-fold in cell intrinsic sensitivity, as measured by the release of histamine and LTC₄.¹ MacGlashan and Saini reported that the basis for the observed increase during treatment with omalizumab is yet unknown. They suggested that in some reported cases of cat and peanut allergy, basophils from treated patients showed a better response following stimulation with anti-IgE antibodies and exhibited an increase in the level of spleen tyrosine kinase (Syk), though relatively low to explain alone the observed 12-fold increase in basophil IgE-mediated response.¹ Regulation of Syk activity is a complex mechanism depending on a wide panoply of factors. Therefore, suggestions about the observed increase in basophil intrinsic sensitivity¹ are only presumptive at this stage and need further investigation.

A reduced expression of Syk, in the term of tyrosine phosphorylation, has been described during FcγR-mediated

regulation of allergy, by using chimeric proteins that were able to cross-link both FcεRI and FcγRIIB and dampen basophil response to allergens.¹¹ A reduction was also reported during chronic aggregation of FcεRI.¹² Syk inhibition or dephosphorylation is associated with downregulation of IgE-mediated allergy. This mechanism may be altered in basophils with downregulated surface FcεRI. FcγRs exert a regulatory role on the basis of their interaction with membrane FcεRI. However, because of the strong reduction in surface FcεRI density following therapy, both the role and the function of basophil FcγRs may change dramatically. The inhibitory activity exerted by FcγRII needs co-aggregation with FcεRI¹² and a decrease in high-affinity IgE receptors on cell membrane may reduce and modify the inhibitory mechanism. In this context, the role of FcγRs may lead to some paradoxical mechanism. At least in mast cells, chronic aggregation of FcγRs leads to a phosphorylation/activation of src kinases and Syk.¹³ These cells, as do basophils, compete for FcRβ in the allergy IgE-mediated mechanism.¹⁴ The subunit FcRβ is shared by both FcεRI and FcγRIIBs and functions as an amplifier of allergy response, able to increase Syk phosphorylation and activity.^{14,15} FcγRIII are downregulated by high-density surface FcεRI-IgE and in atopic subjects; therefore, it is presumable that a decrease in FcεRI may enhance basophil FcγRIII function.⁹ Whether heterogenous Fc receptor aggregates or FcεRI/FcγRs competition plays a role in basophil sensitivity and Syk level is still a matter of debate because the complexity of mechanisms involved needs further insights. Finally, FcγRIIB can phosphorylate Lyn, which, in turn, should activate a signaling pathway through protein kinase C leading to IL-3 production, although this evidence was reported in murine mast cells.¹³ However, changes in the cytokine milieu and in IL-3 production together with the suggested mechanisms involving surface Fc receptors and intracellular Syk might give rise to a highly sensitive basophil phenotype, apparently despite omalizumab treatment. FcγRs are highly polymorphic in man and might also account for the wide variability in IgE-mediated response reported in allergic people during treatment with an anti-IgE-mAbIgG, probably by contributing to the regulation of FcεRI membrane density.

In this sense, the article by MacGlashan and Saini merits further attention and prompts researchers to deepen the described mechanism and address models of investigation to optimize monoclonal anti-IgE therapy. Whether or not basophil FcγRs are really involved in the described mechanism cannot be totally excluded but needs the investigation of FcγRs (CD32, CD16b) membrane expression in association with Syk phosphorylation level during omalizumab therapy.

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