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Identify the Inhibitors ... and Activate Them

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Editorial

Signaling receptors with the potential to impact on cellular effector functions can be classified, in principle, as activating or inhibitory. Whereas inhibitory receptors, such as FcγRIIB (CD32), only have to engage negative signaling elements to fulfill their tasks, activating receptors, such as the high-affinity receptor for IgE (FcεRI), have to manage both initial activation of positive signaling proteins (e.g. kinases) and pathways as well as engagement of attenuating and inhibitory elements (e.g. phosphatases) to allow for well-balanced cellular activation [1]. The FcεRI is mainly expressed on mast cells and basophils, two cell types critically involved in the development of allergic diseases [2]. It belongs to a family of multi-chain immune recognition receptors and in its IgE-bound form is activated by cross-linking via multivalent antigens/allergens. This activation results in immediate release from secretory lysosomes of preformed substances (e.g. histamine and proteases), generation of arachidonic acid metabolites, and production of pro-inflammatory cytokines/chemokines. Activation of the FcεRI follows a particular, bell-shaped dose-response behavior with weak induction of effector responses at both low and high (so-called supra-optimal) antigen concentrations [3]. Careful studies of FcεRI activation and antigen-triggered signaling events in mast cells and basophils in response to supra-optimal antigen concentrations have suggested a molecular explanation for the descending part of this bell-shaped dose-response curve. It is evident now that large FcεRI /IgE/antigen aggregates are generated and inhibitory molecules and/or signalosomes are engaged in response to supra-optimal cross-linking. Hence, mast cell effector responses are actively down-regulated. Known proteins involved in this type of regulation are the Src family kinase Lyn and the inositol-5'-phosphatase SHIP1, which acts as a prominent negative regulator of the phosphatidylinositol 3-kinase (PI3K) pathway [4,5]. In contrast to positively acting signaling elements/pathways that are typically targeted by small-molecule inhibitors, attenuating/inhibiting signaling proteins would have to be pharmacologically activated to accomplish suppression of cellular pro-inflammatory reactions. Indeed, the meroterpenoid pelorol identified in sponge extract was demonstrated to efficiently activate SHIP1 phosphatase function [6] and structural analogs thereof exhibited even greater activity in cell and mouse models of inflammation, such as acute cutaneous anaphylaxis [7]. Thus, analysis of mast cell activation/signaling in response to supra-optimal antigen concentrations might hold great potential for identifying novel targets for pharmacologic therapeutic intervention to benefit patients with allergic diseases.

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