Computational modeling of FcεRI signaling during mast cell activation.

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Summary

Mast cell activation is a pivotal event in the initiation of inflammatory reactions associated with allergic disorders. It is triggered by the aggregation of high-affinity IgE receptors (FcεRI), on the mast cell surface [1]. FcεRI aggregation is induced by the binding of a multivalent allergen to FcεRI-bound IgE antibodies. Mast cell activation is a complex process relying on multiple layers of tightly controlled intracellular signaling molecules, which form an intricate network [2, 3].

A global and rigorous understanding of the signaling and cross-regulatory processes involved in mast cell activation requires the integration of public and novel data into a comprehensive computational model.

Based on a survey of relevant data published in scientific journals or available in public databases, we are currently building and annotating a comprehensive regulatory map using the sofware CellDesigner [4]. This regulatory map currently encompasses 60 components, and more than 300 interactions, including the FcγRIIB negative regulatory pathway, along with annotations and links to databases (PubMED, EntrezGene, UniProt).

This mast cell activation map now serves as a scaffold to generate a dynamical model of the underlying network, using a sophisticated logical modeling approach and the software GINsim [5, 6, 7]. Logical modeling has already been used to address successfully the regulation of Th cell differentiation [6, 8].

In parallel, MS data derived from knock-in mice with tagged signaling component are used to delineate salient dynamical features of mast cell response under different conditions (e.g. how the FcεRI signaling network operates in the absence or in the presence of negative regulatory signals triggered by the FcγRIIB or by the transmembrane adaptor LAT2).

In this respect, the data already gathered in collaboration with the groups of B Malissen (CIML Marseille) and J Garin (CEA, Grenoble) point to novel SLP-76 interactants, some previously reported in T or B cell activation processes, but now specifically identified in mastocytes.

Ultimately, our modeling study should contribute towards a better understanding of how the different functional outcomes of mast cell activation (degranulation, synthesis of lipidic mediators, induction of cytokine transcription) are articulated at the level of the underlying molecular network, and to delineate means to uncouple these functions and control them separately or collectively.

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