cytoplasmic CD4 detected in mice deficient in both Irf2 and IFN- α/β receptor 1 were comparable to those found in littermate controls, indicating that the role of Irf2 in regulating the development of these DC subsets was to attenuate type 1 IFN-induced signals.

This report confirms the previous study identifying Irf2 as a molecular regulator of a specific DC subset, namely that characterized as CD4⁺CD11b⁺ or CD8 α -CD11b⁺CD11c⁺. Combined with other studies indicating a crucial role for Irf8 in the development of CD8 α ⁺ DCs and plasmacytoid DCs, these data begin to provide insight into the distinct molecular pathways responsible for the differentiation of discrete DC subsets.

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References and links

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MAST CELLS

Size does matter

It seems that mast cells haven't heard the familiar adage 'quality not quantity' — a new study published in *Blood* shows that their responses are based on the strength rather than type of stimulation. Depending on the amount of IgE with which the mast cell comes into contact and the duration of the interaction, crosslinking of Fc ϵ RI can induce mast-cell degranulation or survival.

IgE bound to multivalent antigen [IgE(+Ag)] crosslinks Fc ϵ RI on the surface of mast cells, resulting in degranulation and the release of allergic mediators such as histamine. However, researchers have also shown that IgE in the absence of antigen [IgE(–Ag)] can induce cell survival without degranulation. As the degranulation and survival responses both rely on signalling through the common γ -subunits (Fc γ R) of Fc ϵ RI, Saito and colleagues set out to determine the importance of strength of signalling for the differential responses.

They transfected bone-marrow-derived mast cells (BMMCs) from Fc γ -deficient mice with a construct encoding a chimeric molecule consisting of the cytoplasmic domain of mouse Fc γ R linked to the extracellular and transmembrane domains of mouse CD8 α . The strength of signalling through Fc γ R could then be altered using different concentrations of a CD8-specific antibody. Whereas high levels of antibody were necessary for degranulation, increased survival resulted from stimulation with both low and high concentrations of CD8-specific antibody.

To confirm that the signalling threshold for survival is lower than that for degranulation, the authors also looked at the effects of receptor valency. CD8 α normally dimerizes through a disulphide bond between its extracellular

domains, so that the chimeric CD8 α -Fc γ R construct exists as a homodimer. When the crucial cysteine residues of CD8 α were mutated to prevent dimerization, mast cells had a similar survival response to treatment with CD8-specific antibody, but signalling through the monovalent receptor did not induce degranulation even in response to high concentrations of antibody.

In other cell types, activation of extracellular-signal-regulated kinase (Erk) is known to induce cell survival, and in this system, both high and low concentrations of CD8-specific antibody induced Erk activation. Also, introduction of an active form of the kinase Mek into the BMMCs, which directly activates Erk, increased cell viability, confirming the link between survival and Erk activation in mast cells.

However, in contrast to this artificial system in which degranulation and increased survival can occur together, in wild-type mast cells, IgE(–Ag) increases cell survival, whereas IgE(+Ag) induces degranulation in the absence of cell survival. Previous studies have shown that IgE(–Ag) elicits more prolonged Erk activation than IgE(+Ag), so the authors suggest that sustained Erk activity is necessary for survival. When the CD8-specific antibody was crosslinked with another antibody (mimicking IgE crosslinked with multivalent antigen), the initial Erk activation decreased rapidly due to receptor internalization, and the viability of these cells was significantly lower than cells treated only with the CD8-specific antibody. Mast cells treated with IgE(+immobilized Ag), which does not cause Fc ϵ RI internalization, both degranulated and survived for longer.

Therefore, signals through Fc γ R can induce both degranulation and survival according to signal strength and duration, respectively.

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References and links

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