

A study of the contribution of mast cells to vaccination
- Regulatory functions of Fc γ receptors

Akademisk avhandling

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- I. Fang Y, Larsson L, Mattsson J, Lycke N & Xiang Z. Mast cells contribute to the mucosal adjuvant effect of CTA1-DD after IgG-complex formation. *J. Immunol.* 2010; 185(5):2935-2941.
- II. Fang Y*, Zhang T*, Lidell L, Xu X, Lycke N & Xiang Z. The immune complex CTA1-DD/IgG adjuvant specifically targets connective tissue mast cells through Fc γ RIIIA and augments anti-HPV immunity after nasal immunization. *Mucosal Immunol.* 2013; doi: 10.1038/mi.2013.16.
- III. Fang Y*, Larsson L*, Bruhns P & Xiang Z. Apoptosis of mouse mast cells is reciprocally regulated by the IgG receptors Fc γ RIIB and Fc γ RIIIA. *Allergy.* 2012; 67(10):1233-1240.

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Abstract

This thesis aimed to explore the regulatory roles of mast cells in vaccination. Mast cells have been increasingly recognized as important orchestrators of immune regulation in both health and disease, in addition to their classically defined roles in allergic diseases. One of the recently appreciated beneficial roles of mast cells is their involvement in augmenting the adjuvant effects that are critically important in successful vaccination.

This study has focused on the interaction of mast cells with an adjuvant complex composed of IgG and CTA1-DD, a fusion protein consisting of the A1 subunit of cholera toxin (CT) linked to a synthetic dimer of fragment-D of *Staphylococcus aureus* protein A (DD). As the DD domain unspecifically binds immunoglobulins, CTA1-DD and IgG form complexes potentially able to activate mast cells through Fc γ receptors. Indeed, CTA1-DD, in combination with polyclonal IgG, induced mast cell degranulation and the production of TNF- α , a cytokine important for the maturation and migration of antigen presenting cells, resulting in enhanced antigen-specific immune responses following immunization.

Furthermore, only connective tissue mast cells (CTMCs), but not mucosal mast cells (MMC)s, were found to be activated by CTA1-DD/IgG complexes. This effect was mediated by Fc γ RIIA, an activating receptor that has been described to be only expressed on connective tissue mast cells. Indeed, Fc γ RIIA-expressing connective tissue mast cells were found in the nasal submucosa. Responses to immunization facilitated by CTA1-DD/IgG were compromised in Fc γ RIIA-deficient mice, and in mice pre-treated with a CTMC inhibitor.

Interestingly, MMCs, which were present in mouse nasal mucosa, were not entirely bystanders in CTA1-DD/IgG-mediated adjuvanticity. We discovered that a balanced expression of Fc γ RIIB and Fc γ RIIA was required for mast cells to resist apoptosis mediated by IgG immune complexes. Therefore, MMCs, which only expressed Fc γ RIIB, but not Fc γ RIIA, underwent apoptosis as a result of treatment by CTA1-DD/IgG. MMCs were capable of phagocytosing ovalbumin (OVA), and engulfment of these MMCs by antigen presenting cells (APCs) could occur if the MMCs were induced to apoptose. Finally, the APCs were able to present OVA peptide to OVA-specific T cells. Thus, MMCs may also contribute to vaccination through cross-presentation.

Safety is always a prioritized concern for developing adjuvants, especially when mast cells are involved. Remarkably, CTA1-DD did not function as a superantigen to activate mast cells which had captured IgE molecules with their Fc ϵ RI, indicating that CTA1-DD is safe for use in allergic patients in which mast cell Fc ϵ RI is occupied by antigen-specific IgE molecules. Furthermore, CTA1-DD/IgG immune complexes administered intranasally did not trigger systemic anaphylaxis.

In conclusion, CTA1-DD/IgG may target both CTMCs and MMC through Fc γ receptors to enhance antigen-specific immune responses, probably through two distinct mechanisms. We propose that IgG immune complex-induced mast cell activation may be considered as a component of rationally designed mucosal adjuvants.

Keywords: mast cell, vaccine, adjuvant, CTA1-DD, Fc γ receptor, apoptosis

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