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Identificación del proyecto:

Decodificación de la origen y funcionalidad de la inmunoglobulina D secreta (DECONFUSID)

Descripción del proyecto:

B cells thwart antigenic aggressions by differentiating to antibody-secreting plasma cells after establishing cognate interactions with T follicular helper cells. This process involves antibody diversification through somatic hypermutation, which increases the antibody affinity for antigen, and class switching, which modulates the antibody effector functions. Indeed, class-switched IgG, IgA or IgE deploy effector functions distinct from those of IgM. In general, aside from neutralizing or blocking antigen, each antibody class cooperates with innate myeloid or lymphoid cells to clear antigen. In addition to IgM, IgG, IgA and IgE, our antibody arsenal includes IgD, which is mostly known for B cell receptor function. However, also IgD exists as a secreted antibody, but its function remains enigmatic. This gap of knowledge partly stems from earlier findings showing that IgD-deficient mice have no gross phenotype and that IgD is functionally redundant with IgM.

Additional studies showing that IgD lacks a canonical Fc receptor have long suggested that secreted IgD lacks a specific effector function. Nonetheless, recent evidence indicates that secreted IgD binds to and regulates basophils, mast cells and possibly other immune cells both in vitro and in vivo through a receptor complex that encompasses galectin-9, CD44 and additional molecules such as the endocytic and signal-transducing proteins CD36 and CD71. Moreover, allergen-specific IgD responses have been recently shown to negatively correlate with anaphylaxis, but positively correlate with tolerance in children with allergy to food or airborne antigens. Remarkably, IgD responses emerge from a unique subset of nasopharyngeal B cells that undergo unconventional IgM-to-IgD class switching.

Here, we hypothesize that secreted IgD enhances protective tolerance to environmental antigens by linking B cells with both innate and adaptive arms of the immune system. In particular, we argue that tandem-repeat galectins, including galectin-9, link secreted IgD with a multi-protein IgD receptor complex that arms basophils, mast cells and possibly other myeloid cells with an adaptive recognition system specific for common aerodigestive antigens such as food and airborne antigens. We contend that ligation of receptor-bound IgD by these antigens promote immune protection by enhancing T helper type-2 cell-dependent B cell production of antigen-clearing IgG1, IgG4, IgA and IgE antibodies. We also propose that receptor-bound IgD stimulates tolerance to common aerodigestive antigens by attenuating IgEinduced basophil and mast cell degranulation.

The following aims will explore the biology of IgD by combining standard with state-of-the-art approaches. Aim 1 will define the ontogeny, clonal architecture and reactivity of secreted IgD. Aim 2 will determine the distribution, composition and function of the IgDR complex. Aim 3 will characterize the involvement of secreted IgD in immune tolerance. By decoding the role of secreted IgD, the proposed studies could lead to the development of new treatment strategies against severe allergic disorders.

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