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Innate myeloid cells under the control of adaptive immunity: the example of mast cells and basophils

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Mast cells and basophils are mostly known as the initiators of IgE-dependent allergic reactions. They, however, contribute to innate immunity against pathogens and venoms. Like other myeloid cells, they also express receptors for the Fc portion of IgG antibodies. These include activating receptors and inhibitory receptors. Because IgG antibodies are produced in exceedingly higher amounts than IgE antibodies, IgG receptors are co-engaged with IgE receptors under physiological conditions. Mast cells and basophils are examples of the many innate myeloid cells whose effector functions are used and finely tuned by antibodies. They can be thus enrolled in a variety of adaptive immune responses, their activation can be regulated, positively and negatively and their biological responses can be modulated qualitatively by antibodies.

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Introduction

Adaptive immunity is well-known to require cells of the innate immune system for being initiated. Antigen presentation is indeed primarily ensured by dendritic cells. Adaptive immunity is less well known to require also innate cells for being efficient. Antibodies generated during adaptive immune responses indeed exert little effect if any, when binding to antigen, unless they activate effector systems through their Fc portion. Effector systems include complement and the many cells that express Fc receptors (FcRs). When bound to FcRs, antibodies function as *bona fide* antigen receptors that enable FcR-expressing cells to recognize specific antigen. Most if not all innate cells express FcRs.

In a recent review [1], Akiko Iwasaki and Ruslan Medzhitov emphasized that the roles of immunogenicity, *i.e.* mechanisms by which antigens and pathogens can elicit immune responses, have been thoroughly investigated and that the challenge is now to define the rules of protective immunity, *i.e.* mechanisms by which the effectors of immune responses can act on antigen and pathogens. This review discusses how adaptive immunity uses FcR-expressing innate cells to act on antigen. It focuses on mast cells and basophils as examples of innate cells whose multiple functions are under the control of antibodies.

Fc receptors as adaptive immunoreceptors on innate myeloid and lymphoid cells

Innate cells include most of the many myeloid cells (dendritic cells, monocytes, macrophages, polymorphonuclear cells of the three types, platelets and mast cells of the serosal and mucosal types) and some lymphoid cells (NK cells and ILCs subsets). Innate myeloid cells (IMCs) interact with pathogens via a variety of pattern-recognition receptors. Innate lymphoid cells (ILCs) interact with infected or transformed cells via other non-clonally expressed receptors. All IMCs and NK cells express FcRs. Whether FcRs are expressed by other ILCs is unknown.

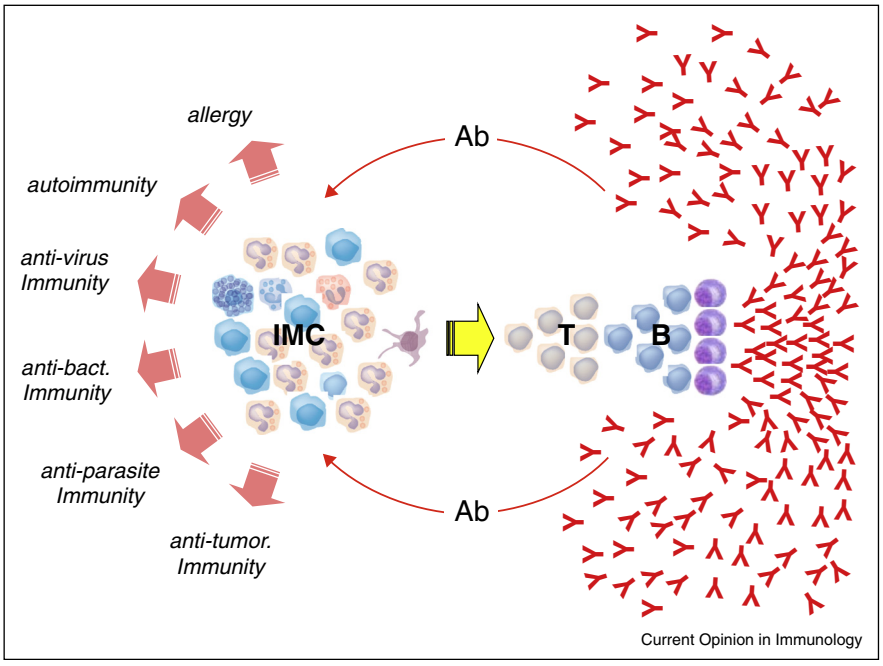
Having no intrinsic antigen-recognition structures, innate cells have no predetermined antigen specificity. FcR-bound antibodies can provide them with the innumerable specificities of the B cell repertoire. Consequently, unlike lymphocytes, every single IMC can respond to a multitude of antigens, depending the antibodies that happen to bind to their FcRs. Altogether, these cells have a wide functional repertoire. Antibodies thereby enroll innate cells in adaptive immunity, which benefits of their many biological functions. IMCs are the main effector cells of adaptive immunity (Figure 1).

Activating and inhibitory FcRs

FcRs do not signal when they bind antibodies. They do when they are aggregated on cell membranes by antibodies in complex with multivalent antigens. FcR aggregation occurs when a multivalent antigen binds to high-affinity FcR-bound antibodies, or when multivalent antigen–antibody complexes bind to low-affinity FcRs. Neither the quality nor the magnitude of signals depends on the affinity of aggregated FcRs. They depend on the FcR type. Most FcRs are activating receptors, few are inhibitory receptors.

Activating FcRs contain variable numbers of Immunoreceptor Tyrosine-based Activation Motifs (ITAMs) in

Figure 1



The enrolment of innate myeloid cells in adaptive immunity by antibodies. Innate myeloid cells (IMC) of the various types, including mast cells and basophils (cells containing blue granules) and dendritic cells, are schematized in the left panel. Antigen presentation (thick yellow arrow) to T cells by dendritic cells induces an adaptive immune response to this antigen, leading to the secretion of large amounts of specific antibodies by plasma cells (right panel). Antibodies diffuse through the whole body via the blood stream (thin red arrows). When they recognize antigen, antibodies can enroll FcR-expressing IMCs in an array of effector functions that contribute both to immune protection and to immunopathology (thick pink arrows).

their intracytoplasmic domain or in those of subunits they are associated with. Activating FcRs include high-affinity IgA (FcαRI), IgE (FcεRI) and IgG (FcγRI) receptors and several low-affinity IgG receptors (FcγRIIA, FcγRIIC and FcγRIIIA). ITAM-containing FcRs generate activation signals when they are aggregated on cell membranes. This occurs when multivalent antigens bind to antibodies previously bound to high-affinity FcRs or when preformed immune complexes bind to low-affinity FcRs.

Inhibitory FcRs are single-chain receptors. They contain one Immunoreceptor Tyrosine-based Inhibition Motif (ITIM) in their intracytoplasmic domain. ITIM-containing FcRs are low-affinity IgG receptors (FcγRIIB) only. They generate inhibition signals when they are co-aggregated with ITAM-containing receptors. This occurs when immune complexes bind simultaneously to activating and inhibitory low-affinity FcRs via their Fc portions, or to high-affinity activating FcR-bound antibodies via the antigen moiety and to low-affinity inhibitory FcRs via their Fc portions.

FcRs expressed by mast cells and basophils

Mast cells and basophils express high-affinity IgE receptors and several low-affinity IgG receptors (Figure 2). Mouse mast cells express FcεRI, FcγRIIIA and FcγRIIB, whereas human mast cells express FcεRI, FcγRIIA and low levels of FcγRIIB. FcR expression, however, vary with the type of mast cells. Mast cell terminal differentiation takes place in tissues under the influence of cytokines and growth factors that differentially affect FcR expression. Thus, human skin-derived mast cells express no FcγRIIB [2]. Conversely, FcγRI can be induced by IFN-γ in human [3], but not in mouse mast cells [4]. Mouse basophils express FcεRI, FcγRIIIA and FcγRIIB, whereas human basophils express FcεRI, FcγRIIA and FcγRIIB [5•]. Human basophils also express minute amounts of the glycosyl-phopshatidylinositol-anchored FcγRIIIB [6].

FcεRI and FcγRIIIA expressed in mast cell and basophils are associated with two ITAM-containing subunits: the widely expressed FcRγ subunit and the mast cell/basophil-specific FcRβ subunit. FcγRIIA and FcγRIIB are not. They contain one ITAM or an ITIM, respectively. Because they are equipped with FcRs that have antagonistic effects, mast cells and basophils are typical examples of IMCs whose biological activities are under the control of the adaptive immune system *via* antibodies. In the presence of antigen, antibodies 1) enroll mast cells and basophils in various immune responses, 2) modulate