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Immunological responses to influenza vaccination: lessons for improving vaccine efficacy

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A critical factor in the maturation of influenza vaccine responses is the nearly inevitable binding of vaccine antigens by exiting anti-influenza IgGs. These antigen-IgG immune complexes direct the response to immunization by modulating cellular processes that determine antibody and T-cell repertoires: maturation of dendritic cells, processing and presentation of antigens to T cells, trafficking of antigens to the germinal center, and selection of B cells for antibody production. By focusing on the recent advances in the study of the immunomodulatory processes mediated by IgG immune complexes upon influenza vaccination, we discuss a pathway that is critical for modulating the breadth and potency of anti-HA antibody responses and has previously led to the development of strategies to improve influenza vaccine efficacy.

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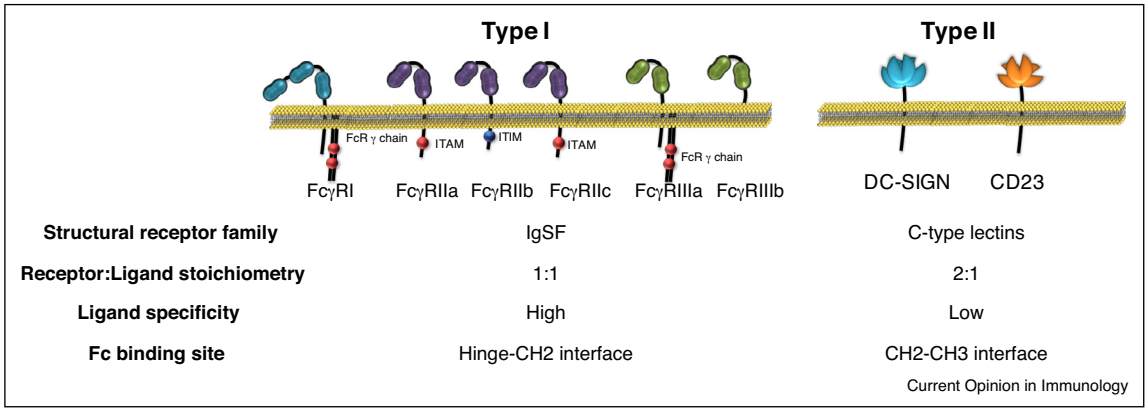
This year marks the 100-year anniversary of the 1918 influenza pandemic, one of the deadliest natural disasters in the history of mankind, accounting for 100 million deaths and infecting over half billion of the global population. Although pandemic influenza outbreaks occur on a periodic basis (the most recent being the 2009 H1N1 pandemic), every year seasonal influenza epidemics cause hundreds of thousands of deaths and account for over 5 million cases of severe illness worldwide, having a tremendous socioeconomic impact on global health. For over half a century, vaccination has been the main approach for the prevention of influenza outbreaks; however, licensed influenza vaccines commonly provide sub-optimal protection (typically ranging from as low as 10% to 60%), as they largely elicit strain-specific immunity against circulating influenza strains, necessitating annual reformulation to provide adequate protection. More importantly, conventional influenza vaccines provide little or no protection against antigenically drifted strains, which have the capacity to cause pandemic outbreaks with devastating effects on global public health. Intensive research efforts over the past recent years focusing on influenza immune evasion mechanisms and the immune responses elicited against influenza have led to exciting new findings that could guide strategies for the optimization of the influenza vaccine efficacy to elicit universal protection against diverse influenza strains that would minimize morbidity and mortality caused by seasonal influenza and prevent potential pandemic outbreaks in the future. Indeed, these studies have renewed optimism in the field and made the development of a universal influenza vaccine a more realistic prospect.

By focusing on the study of B-cell responses against influenza, a number of key immune determinants of antibody-mediated immunity against influenza have been identified. For example, recent epidemiologic studies on the immune responses against influenza revealed that circulating influenza strains that are dominant during childhood shape immunological memory and impact future responses against influenza during adulthood [1••], supporting a clear role for pre-existing influenza immunity in modulating the magnitude and quality of the antibody responses against future antigenic encounters [2–5]. Additionally, systematic characterization of the B-cell responses against influenza resulted in the discovery of panels of monoclonal antibodies (mAbs) that specifically recognize influenza hemagglutinin (HA) and neuraminidase (NA) proteins and exhibit broadly protective activity against diverse influenza strains [6–10,11••]. Indeed, the isolation and pre-clinical evaluation of anti-influenza antibodies capable of neutralizing a broad range of influenza viruses — with some even recognizing both group 1 and group 2 hemagglutinins (HAs) — has led not only to the development of novel mediators that could potentially be used for the prevention or treatment of pandemic influenza infections, but also provided evidence on the capacity of the human immune system to elicit specific IgG responses to target highly conserved viral epitopes [6–10,11••]. These studies have, in turn, provided useful insights into the functional properties and immunogenicity of influenza antigens, leading to the identification and characterization of highly conserved epitopes that have guided the design of novel influenza immunogens to elicit immune responses with broadly

Figure 1



Structure and properties of Type I and Type II FcγRs. FcγRs are divided into two main types: Type I and II. Despite their common property of interacting with the Fc domain of IgG antibodies, FcγR types present distinct structural and functional differences and have differential capacity to induce diverse immunomodulatory consequences that affect several aspects of immunity.

protective activity against diverse influenza strains [12,13,14•,15••]. These findings clearly illustrate that the in-depth study of the capacity of anti-influenza antibodies to specifically recognize highly conserved epitopes on HA and NA could lead to the development of novel vaccination strategies to elicit broadly protective responses. However, in addition to the study of the Fab-mediated antigenic recognition of broadly protective anti-influenza IgG antibodies, improved influenza vaccine efficacy could be achieved through the systematic characterization of the effector activities mediated through the Fc domain of antibodies elicited upon influenza infection.

IgG Fc domain effector functions

The protective activity of an IgG molecule is mediated through its two functional domains: (i) the Fab domain that facilitates highly specific antigenic recognition and (ii) the Fc domain that contributes to the IgG effector activity through specific interactions with Fcγ receptors (FcγRs) expressed by several leukocyte types [16]. FcγRs comprise a family of immunoreceptors and are broadly divided into two main types: Type I and II, with each type having unique structural and functional characteristics [17] (Figure 1). Upon crosslinking by the Fc domains of IgG immune complexes, FcγRs trigger signaling events through their intracellular signaling motifs, inducing diverse immunomodulatory processes that readily influence the functional activity of effector leukocytes and consequently several aspects of the innate and adaptive immune response [17]. For example, ITAM (immunoreceptor tyrosine-based activation motif)-containing, Type I FcγRs induce the activation of signaling pathways with pro-inflammatory biological consequences, including cellular activation, antibody-dependent cellular cytotoxicity (ADCC), phagocytosis, as well as expression and release of inflammatory cytokines and chemokines. These activities are counterbalanced by the inhibitory Type I FcγR, FcγRIIb, which limits ITAM-mediated signaling in effector leukocytes [17]. Likewise, engagement of Type II FcγRs by the IgG Fc domain has pleiotropic immunomodulatory effects. For example, DC-SIGN engagement on regulatory macrophages leads to the induction of Th2-polarizing immunity that suppresses Th1 and Th17 responses and limits IgG-mediated inflammation through upregulation of FcγRIIb expression on myeloid effector leukocytes [18,19]. On the other hand, engagement by IgG immune complexes of the other Type II FcγR, CD23 on B-cells modulates FcγRIIb expression in an autocrine manner, influencing B-cell selection and the development of high-affinity IgG responses [20].

Given the capacity of Type I and Type II FcγRs to activate diverse immunomodulatory pathways upon engagement, Fc–FcγR interactions are dynamically regulated through specific modulation of the Fc domain structure, either in the primary amino acid sequence (IgG subclasses) or in the Fc-associated glycan composition [17,20,21]. Such differences in the IgG subclass and Fc domain glycan structure contribute to substantial Fc domain heterogeneity and it is estimated that over 10^3 Fc domain variants exist, each with differential FcγR affinity and immunomodulatory potential. For example, IgG glycan variants lacking the branching fucose residue (afucosylated) exhibit improved cytotoxic activity compared to their fucosylated counterparts through enhanced capacity to interact with and activate FcγRIIIa-expressing effector leukocytes [17,22,23]. Likewise, the presence of terminal sialic acid residues at the Fc-associated glycan structure determines the binding specificity of the Fc domain for Type I and Type II FcγRs [17]. Upon sialylation, the IgG Fc domain acquires the capacity to interact with Type II FcγRs (DC-SIGN and CD23),