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Harnessing immune history to combat influenza viruses

Jenna J Guthmiller and Patrick C Wilson

Individuals are exposed to influenza viruses throughout their lifetime. Accumulating evidence shows the first viruses an individual is exposed to leaves an imprint on the antibody response induced by subsequent drifted and novel influenza viral exposures. Imprinted humoral immunity against influenza viruses relies on biased immune memory to influenza viruses for which memory B cell responses were initially generated against. Imprinting allows for antibodies to adapt to drifted influenza viruses while maintaining binding potential for the first influenza viruses an individual is exposed to. However, imprinting can increase susceptibility to non-imprinted influenza viruses and mismatched influenza viruses. This review highlights the role of imprinting on the regulation of antibody responses induced by influenza viruses and explores potential vaccine strategies to harness imprinted antibody responses to increase protection against influenza.

Address
Department of Medicine, Section of Rheumatology, The Knapp Center for Lupus and Immunology, University of Chicago, Chicago, USA

Corresponding author: Wilson, Patrick C (wilsonp@uchicago.edu)

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Introduction

The goal of influenza vaccines is to induce antibodies that upon exposure can rapidly neutralize and clear influenza viruses. While seasonal vaccination decreases influenza virus infection burdens [1], the vaccine effectiveness is low at an estimated 36% for 2017–2018 [2]. Mounting a broadly protective antibody response against influenza viruses requires the induction of antibodies targeting conserved epitopes found amongst group 1 and 2 influenza A viruses and influenza B viruses. Current annual vaccination largely induces strain specific antibody responses with little cross-reactivity to drifted viruses [3,4].

Prior influenza virus exposure has a profound effect on antibody responses induced by subsequent exposures. The two current leading hypotheses of how influenza virus exposure affects humoral immunity are original antigenic sin (OAS) [5–7] and immune imprinting, also commonly referred to as antigenic seniority [8••,9•,10]. Both OAS and imprinting rely on immune memory rather than *de novo* immune responses to combat an altered version of the original pathogen. OAS and imprinted immune responses result in the activation of MBCs that secrete antibodies against current strains while also 'back-boosting' antibody responses against historical influenza strains. Therefore, OAS and imprinting rely on immune memory that is biased towards the first influenza viruses an individual is exposed to. Unlike OAS, the hypothesis of imprinting accounts for positive impacts on anti-influenza humoral immunity including continued affinity maturation of influenza-specific MBCs and protection against drifted and shifted influenza viruses. However, imprinting increases the odds of infection by non-imprinted influenza viruses and mismatched influenza viruses in an OAS fashion.

The 2009 pandemic H1N1 (pH1N1) outbreak allowed for a greater understanding of how immune history shapes anti-influenza humoral immunity and allowed for researchers to test the hypotheses of OAS and imprinting. Since the pH1N1 outbreak, our understanding of anti-influenza virus humoral immunity has shifted to fit more inline with a generalized concept of imprinting, in which the anti-pH1N1 antibody responses after first pH1N1 exposure relied on a biased MBC response targeting conserved epitopes and naïve B cell responses against novel epitopes [3,11]. Subsequent exposures to pH1N1 preferentially induced MBCs originally induced by both childhood influenza viruses and the first exposure to pH1N1 [3]. Similarly vaccination with the avian influenza viruses H5N1 and H7N9 induces MBC responses against conserved epitopes and naïve B cell responses against antigenically novel epitopes [4,12]. Therefore, the term immune imprinting should be defined as the bias to use immune memory, independent of whether that immune memory was induced by the very first influenza strain an individual is exposed to or an antigenically novel influenza virus that an individual is exposed to later in life. This new definition of imprinting maintains the role of continued affinity maturation of biased immune memory to drifted influenza viruses. For this review, imprinting will be referred to as the bias to use immune memory, including serological memory and MBCs, to combat influenza viruses.

Mechanisms of imprinting

Upon first exposure to an influenza virus, naïve B cells become activated, undergo affinity maturation and

class-switch recombination in a germinal center, and differentiate into antibody-secreting cells (plasmablasts and plasma cells) or MBCs (Figure 1a). Initial secreted antibodies and MBC responses are targeted against a variety of conserved and non-conserved epitopes found predominantly on the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). Notably, antibodies are elicited against poorly conserved epitopes on the HA head and highly conserved epitopes within the receptor binding domain (RBD) on the HA head and the HA stalk. Influenza infection also induces antibodies against conserved epitopes in the NA enzymatic site [13•]. Exposure to subsequent influenza viruses preferentially drives MBC reactivation rather than *de novo* B cell responses, boosting the antibody response to epitopes shared by prior and current influenza strains [14]. Upon re-exposure to drifted homosubtypic influenza viruses, circulating antibodies bind shared epitopes amongst homosubtypic viruses, outcompeting and limiting the activation of MBCs with specificity for conserved epitopes. Instead, MBCs with specificity to easily accessible epitopes in the polymorphic HA head are activated (Figure 1b) [[13•],15••,16,17]. MBCs targeting conserved epitopes are preferentially activated upon exposure to antigenically novel viruses, such as pH1N1 or avian influenza strains, for which there is little to no circulating antibody for the poorly conserved epitopes (Figure 1c) [[13•],11,12,18]. Naïve B cells targeting novel HA head epitopes are also activated upon novel influenza virus exposure and can contribute to subsequent MBC responses (Figure 1c) [[13•],11]. This model suggests that the breadth of the circulating antibodies induced by subsequent drifted influenza strain exposure becomes narrower with time and titers increase against easily accessible epitopes (Figure 1b). Narrowing the circulating antibody response to a few epitopes pressures the virus to mutate to avoid immune detection [19,20]. Despite this, circulating antibodies and MBCs with specificity for conserved epitopes are maintained and can provide protection upon exposure to antigenically novel influenza viruses [18]. Additionally, naïve B cells against antigenically novel viruses can affinity mature and contribute to future biased immune memory against antigenically similar viruses.

Serological memory, via circulating antibodies, can limit humoral immunity against conserved epitopes on influenza viruses by means of epitope masking. Epitope masking occurs when circulating antibodies recognize and bind viral epitopes, limiting the amount of free antigen to be recognized by naïve B cells and MBCs [14,15••]. Despite the obvious perk of immediate recognition of virus by circulating antibodies, epitope masking prevents the activation of B cells with specificity for conserved epitopes while preferentially activating MBCs to poorly conserved epitopes on the polymorphic HA head [3,15••,17,21]. Via steric hindrance, circulating antibodies binding poorly conserved epitopes on the HA-head prevent access of antibodies to bind conserved epitopes found within the RBD and the stalk [3,22•,23]. Continuous immune pressure against HA head epitopes increases the frequency of mutation at these sites leading to viral drifting [19,20] and makes antibodies induced by prior strains obsolete. Additionally, influenza viruses can mask epitopes by introducing glycosylation sites on epitopes previously recognized by circulating antibodies and MBCs [24]. Recently, circulating H3N2 viruses acquired a glycosylation site within epitope B [25•,26], effectively masking epitopes previously recognized by circulating antibodies. The introduction of glycosylations on the HA head further hampers antibody responses against the RBD and stalk as these epitopes may become masked with glycans. Antibodies targeting the RBD and the stalk are limited, as they require distinct biochemical characteristics such as a long complementarity determining region 3 or hydrophobic patches, respectively [27–29].

Biased immune memory can benefit anti-influenza antibody responses by promoting continued affinity maturation of MBCs. Secondary humoral immunity to drifted or antigenically novel influenza strains relies heavily on recalling MBCs from prior exposures. After each additional exposure, MBCs can undergo further affinity maturation to increase the affinity of viral binding [3,30••,31]. Many broadly neutralizing antibodies characterized against viruses are highly mutated [3,30••,32], suggesting a positive role for biased immune memory on affinity maturation. Furthermore, imprinted MBC responses allow for the maintenance and further affinity maturation of MBCs with specificity for conserved epitopes that can be recalled after novel influenza exposure. MBCs that target conserved epitopes are believed to have a greater capability of recognizing escape mutant viruses [33,34], which may function by inducing B cells with receptors that are polyreactive [35,36]. In support of this, the 2009 pH1N1 outbreak lead to the induction of polyreactive stalk-binding antibodies derived from affinity matured MBCs [3,11,18]. Polyreactivity is common for human antibodies and likely has important immune functions [37–39]. Polyreactivity may allow for greater flexibility in the influenza-reactive MBC repertoire with broad protection against influenza viruses outweighing potential self-reactivity. Furthermore, experimental vaccination with either H5N1 or H7N9 drives highly mutated stalk-reactive antibodies that are cross-reactive with H1N1 or H3N2 viruses, respectively [4,12,40]. Therefore, biased immune memory allows for the maintenance and maturation of MBCs targeting conserved influenza virus epitopes and potentially provides protection from divergent influenza strains. Together, imprinting can both positively and negatively regulate humoral immunity by maintaining and maturing MBC responses and masking epitopes, respectively. Imprinting may be a common feature of humoral immunity induced by other