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Immune history and influenza virus susceptibility

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Abstract

Antibody responses to influenza viruses are critical for protection, but the ways in which repeated viral exposures shape antibody evolution and effectiveness over time remain controversial. Early observations demonstrated that the history of viral exposures has a profound effect on the specificity and magnitude of antibody responses to a new viral strain, a phenomenon called "original antigenic sin." Although "sin" might suppress some aspects of the immune response, so far there is little indication that hosts with pre-existing immunity are more susceptible to viral infections compared to naïve hosts. However, the tendency of the immune response to focus on previously recognized conserved epitopes when encountering new viral strains can create an opportunity cost when mutations arise in these conserved epitopes. Hosts with different exposure histories may continue to experience distinct patterns of infection over time, which may influence influenza viruses' continued antigenic evolution. Understanding the dynamics of B cell competition that underlie the development of antibody responses might help explain the low effectiveness of current influenza vaccines and lead to better vaccination strategies.

Introduction

Antibodies impose strong selection on influenza viruses and largely determine susceptibility to infection. Frequent mutations in viral surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) allow influenza viruses to continuously evade antibodies and infect human hosts repeatedly during their lifetime. Despite nearly seventy years of research, a coherent picture of the induction of human antibody responses and how these antibodies shape viral evolution and vaccine effectiveness is still emerging.

In this review, we propose that immunological and epidemiological evidence is remarkably consistent with one of the oldest and most notorious theories in influenza virus literature. In a series of studies in the 1940s and 1950s, Thomas Francis and colleagues demonstrated that humans have high antibody titers to influenza virus strains that they likely encountered early

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in life and that subsequent exposures with antigenically drifted viral strains boost antibody responses initiated by early childhood infections [1,2]. They also found that compared to primary exposures, antibodies generated during subsequent infections were more likely to cross-react with previous strains. Francis coined the phrase “original antigenic sin” to describe the preferential boosting of antibody responses to viral strains encountered early in life. Here, we review studies that led to the concept of original antigenic sin, and we describe more generally how prior viral exposures can have positive and negative effects on the generation of antibody responses. We present a working model of how prior exposures influence susceptibility to new influenza virus strains, which has important implications for viral evolution and vaccination strategies.

A short history of original antigenic sin

In 1947, a new antigenic variant of H1N1 influenza A viruses caused a severe epidemic. College students who had been vaccinated a few months earlier with the previously circulating viral strain (PR8) and naturally infected with the new viral strain developed higher acute antibody titers to PR8 upon infection than did unvaccinated students [3]. Infected students from both groups had higher acute and convalescent antibody titers to PR8 than to the new viral strain, and antibody titers to the new strain did not differ between the two groups. A preliminary explanation for these phenomena would take several years to unfold.

Davenport et al. [4] soon found that humans of all ages have higher antibody titers to strains they likely encountered in childhood. Sera from 1,250 Michigan residents showed that children possessed a narrower range of antibodies specific to recent strains of influenza A and B viruses, whereas older cohorts had higher antibody titers to older strains and more cross-reactive responses against recent strains. A cross-sectional study in Sheffield, England, revealed similar trends [5]. For each age cohort, antibody titers were usually highest against viral strains circulating in childhood and declined steadily against more recent viral strains [6,7]. Nearly sixty years later, studies of H3N2 antibody responses also found higher titers to older viral strains, although titers were not necessarily highest to strains from childhood [8,9].

As early as 1953, it was suspected that preexisting antibody responses were boosted when new strains shared cross-reactive antigens [4], but the first confirmation appeared when Jensen et al. analyzed the composition of sera from immunized humans and sequentially infected ferrets [10]. Sera from secondary exposures contained a high fraction of antibodies that cross-reacted with early viral strains and relatively few antibodies specific to later viral strains. Ten years later, de St. Groth and Webster showed that the secondary response, in contrast to the primary, was highly cross-reactive and surprisingly uniform in its affinity [11]. These results provided preliminary support for Francis’s claim that the response to the “first dominant antigen” would be repeatedly stimulated over a person’s lifetime, even as the original antigen became a “secondary or lesser component” of subsequent strains [2,12].

Is original antigenic sin detrimental?

While it is clear that antibody responses against childhood viral strains are efficiently boosted by antigenically novel strains, early reports conflicted about whether boosting comes at the expense of generating strong antibody responses against the new strain. The original study by Francis in 1947 found no difference in post-infection antibody titers to the new viral strain between recent recipients of the mismatched vaccine strain, whose titers were boosted, and non-recipients [3]. Similar results were found in animals sequentially infected with different influenza viruses [11]. The magnitude of the responses elicited by an antigenically distinct influenza virus in these studies was the same in animals with and without prior influenza exposure.

Other studies have suggested that prior exposures actively suppress the magnitude or quality of antibody responses to new viral strains. For example, Davenport & Hennessy [6] noted a “suppressive effect” on the antibody response to some viral strains in children, depending on the order in which they received monovalent vaccinations, and cited similar patterns of apparent suppression in other immunization studies [4,13]. Antibody responses tend to decline during repeated vaccinations [14]. de St. Groth & Webster [11] described the secondary response in immunized rabbits as “inadequate” because antibodies in the secondary response reacted better with the first antigen than the second. However, most studies that report inhibitory effects of prior exposures rely on the hemagglutination-inhibition assay, which only measures antibodies that block viral attachment to sialic acid. It is possible that sequential vaccinations in these studies elicit cross-reactive antibodies against other epitopes (such as the HA stalk) that are not detected in classical hemagglutination-inhibition assays. Thus, these studies might indicate that prior exposures affect the specificity of antibody responses, but this change in specificity might not affect overall protection.

There is currently minimal evidence that hosts with preexisting, cross-reactive immunity to influenza viruses experience greater susceptibility or more severe infections compared to naïve hosts. Cross-reactive antibody responses to influenza viruses appear generally beneficial. Early studies speculated that antibodies elicited against older viral strains were partially protective and that these cross-reactive antibodies reduced susceptibility and the opportunity to develop immunity to new strains [4,5,13]. A robust relationship between pre-existing antibody titers and reduced susceptibility has been repeatedly observed [15–17]. Cross-reactive antibodies elicited by initial infections limit virus replication during secondary viral exposures and reduce disease in experimental infections [18,19]. However, as discussed below, the direct benefits of preexisting responses against influenza viruses may be inevitably associated with opportunity costs. These costs can make some types of pre-existing antibody responses appear less beneficial than others, but they do not demonstrate that original antigenic sin has a net cost.

A contemporary synthesis

Nearly seventy years of accumulated evidence suggests how pre-existing responses, coupled with repeated exposures to antigenically evolving influenza viruses, might generate the

immunological and epidemiological patterns associated with original antigenic sin. A central element is the competitive dominance of memory versus naïve B cells for antigen. The anamnestic basis of secondary responses to influenza viruses has been demonstrated by Jensen et al. [10], de St. Groth and Webster [11], and others [20–23]. Memory B cells targeting epitopes shared with the original strain are reactivated, and these cells dominate secondary immune responses because they presumably outcompete naïve B cells, which have a higher threshold of activation [24,25]. The recall of memory B cells can be advantageous because these cells can acquire additional somatic mutations that increase affinity to new viral strains [22]. The level of activation of naïve B cells in secondary immune responses is likely partially dependent on antigen dose. For example, naïve B cells can be activated and the antibody response broadened if high doses of secondary antigen are administered [11], the antigen is given with adjuvants [26], or repeated doses of antigen are given [7].

From these immune dynamics, complex patterns of serology and infection can arise as a function of hosts' exposure histories. Due to influenza viruses' rapid spread and fast antigenic evolution, these differences are partly recognizable as contrasting patterns by birth year (Figure 1A). Hosts infected for the first time develop antibodies that target multiple epitopes on the surface of influenza viruses' HA, although antibodies with particular specificities may dominate due to differences in epitopes' immunogenicity, chance, or host-specific factors [27]. Hosts remain protected as long as circulating viral strains conserve at least one epitope to which hosts have high concentrations of neutralizing antibodies. If exposure induces mild infection (many influenza virus infections are mild [28,29]), then these responses are boosted, and additional cross-reactive antibodies may continue to evolve. This model is consistent with the gradual increase with age in concentrations of cross-reactive anti-HA stalk antibodies [30], which are normally subdominant [21]. It also shares features with other models of immune dynamics that allow preexisting responses to outcompete new responses via resource limitation or suppression [31–33].

The focusing of antibody responses to epitopes conserved in older influenza virus strains can have dangerous consequences when viruses acquire mutations in these epitopes. An example of this was seen following the 2009 H1N1 pandemic. Most individuals infected with the 2009 pandemic H1N1 virus mounted antibody responses against epitopes that were conserved in older seasonal H1N1 viruses [20,23,34,35]. Following exposure with the 2009 H1N1 virus, humans produced antibodies of different specificities depending on the specific seasonal H1N1 virus that they were exposed to in childhood [20,35,36]. In some individuals, this led to a very focused antibody response. This focus became a problem during the 2013–2014 influenza season when pandemic H1N1 viruses acquired a new mutation in an exposed region of HA that was targeted by antibodies present in many middle-aged individuals [20]. This region of HA was conserved between seasonal H1N1 viruses from the late 1970s and the 2009 pandemic H1N1 virus. Since antibodies failed to bind to the 2013–2014 H1N1 strain that possessed a mutation in this epitope, middle-aged individuals were disproportionately affected by the new drifted H1N1 strain [37]. This season revealed the opportunity cost of preexisting immunity: because middle-aged humans were more protected than younger cohorts to the original 2009 strain, they missed opportunities to develop antibodies to other epitopes that would have protected them in 2013–2014.

Immune history may shape patterns of infection not only with different strains within the same subtype but also with different subtypes. Several lines of evidence suggest that birth year, a proxy for early exposure to particular subtypes, affects susceptibility to others. In 1953, Francis speculated that the peculiarly high incidence in young adults of a pandemic influenza-like illness in 1782 resulted from preexisting immunity [1]. Francis and others proposed that in 1918, primary exposures to previously circulating H1 subtypes lowered susceptibility in children and older adults [1,38]: although young adults had probably already been infected with other H1 viruses, their first exposure (presumably to an H3 virus that emerged in 1889–1890) may have precluded the development of a robust response to H1. Other evidence suggesting that the subtype of first exposure affects immunity to other subtypes in an original antigenic sin-like way comes from age-specific mortality patterns in 2009 [39] and the age distribution of H5N1 and H7N9 cases [40]. Neutralizing cross-reactive heterosubtypic antibodies appear uncommon [21], and thus a reduction in heterosubtypic antigen availability mediated by other cross-reactive immune responses, such as memory T cells, might explain this sin-like phenomenon. Repeated exposures may gradually erode this effect [41,42]. This erosion is consistent with the observation that subtype-specific stalk antibodies accumulate in proportion to total exposure to each subtype [30].

Implications for viral evolution and vaccination

Influenza virus populations evolve through competition for susceptible hosts, and the existence of host subpopulations targeting different epitopes suggests a mechanism for influenza viruses' regular antigenic evolution. In theory, assuming mutations that change the antigenic phenotype do not otherwise affect viral fitness, mutated strains that have the most susceptible hosts should spread fastest. If antigenic mutations occur slowly relative to the timescale of transmission, then influenza viruses could evolve to escape immunity in one subpopulation after another [43,44].

The effects of immune history on susceptibility to influenza viruses have several consequences for current vaccination strategies. Antigenic distances are typically measured using sera isolated from ferrets recovering from influenza virus infections [45]. With epitope-specific immunity, the antigenic distance between two strains can differ among hosts with different immune histories (Figure 1B,C) [46,47]. Thus, strains that appear antigenically similar according to antibodies raised in ferrets (i.e., in animals without prior influenza virus exposures) might be distinct from antibodies in adults [36]. The World Health Organization has recognized this problem and recently updated the 2017 Southern Hemisphere H1N1 vaccine strain based on human serology (http://www.who.int/influenza/vaccines/virus/recommendations/2017_south/en/). Antibodies elicited in ferrets do not antigenically distinguish the old and new H1N1 vaccine strains, but antibodies elicited in a subset of humans do differentially recognize these H1N1 strains. Due to the primacy of antibody titers in determining susceptibility and strain fitness, cross-sectional serologic testing could be useful not only for identifying the need for vaccine updates but also as a complementary—or even alternative—method to predict the evolution of seasonal viruses [48–52].

Immune history also matters for the development of new vaccination strategies. In 1957, Davenport and colleagues immunized differently aged individuals with a polyvalent vaccine containing four antigenic variants of H1N1 [7]. Broad antibody titers arose after repeated immunizations, and more recent studies confirm that multiple immunizations can elicit antibodies that target conserved epitopes [23,53]. An important consideration is whether such responses are protective, because it is possible that sequential exposures might elicit antibody responses toward conserved epitopes that are non-neutralizing. It will also be important to determine how to maintain levels of specific types of antibodies via vaccination. For example, in 2009 many individuals mounted antibodies that recognize the conserved HA stalk of the pandemic H1N1 virus [23]. However, these HA stalk-specific antibody responses dissipated after repeated vaccinations [21]. Understanding interactions between preexisting and new responses might also illuminate seemingly low vaccine effectiveness among repeat vaccinees [54–58].

Future directions

The majority of this manuscript has focused on neutralizing HA antibodies, but it is clear that other types of antibodies can limit influenza virus replication and spread. For example, some anti-HA antibodies limit virus replication *in vivo* through mechanisms involving ADCC [59,60]. These antibodies are not accounted for in most influenza virus serological assays. Similarly, NA antibodies can limit influenza virus spread and disease severity [61], and there is evidence that NAs of human influenza viruses undergo antigenic drift [62]. It will be important to continue to identify new correlates of protection against influenza virus infection and determine how prior exposures influence these processes.

We propose that quantitative, predictive models that relate previous exposures to susceptibility to different strains are within reach. The main hurdle is to understand fundamental dynamics of the immune system. There is evidence that “antigenic sin” occurs in humans, but the mechanisms involved in this process remain underdeveloped. What determines which viral epitopes are targeted by antibodies in primary infections, what determines variation between individuals, and how do immune repertoires evolve over time? New sequencing methods to examine B cell receptors, combined with animal experiments and longitudinal studies in humans, have the potential to provide fine-scale observations of the development of immunity to influenza viruses and related pathogens [21,63–65]. These large data sets can be used to evaluate mathematical models that capture the complex immune dynamics involved in secondary responses to influenza viruses [31,32,66]. Understanding the interactions that shape immunity over time will aid in our understanding of the selective pressures that shape the fitness of circulating influenza virus strains, and could potentially reveal strategies to increase vaccine effectiveness.

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Highlights

- Early viral infections shape B cell response recalled against future viral strains
- Competition between memory and naïve B cells occurs in secondary viral exposures
- Antibodies become focused on epitopes conserved in past influenza virus strains
- Focused antibody responses fail to protect against mutated viral strains

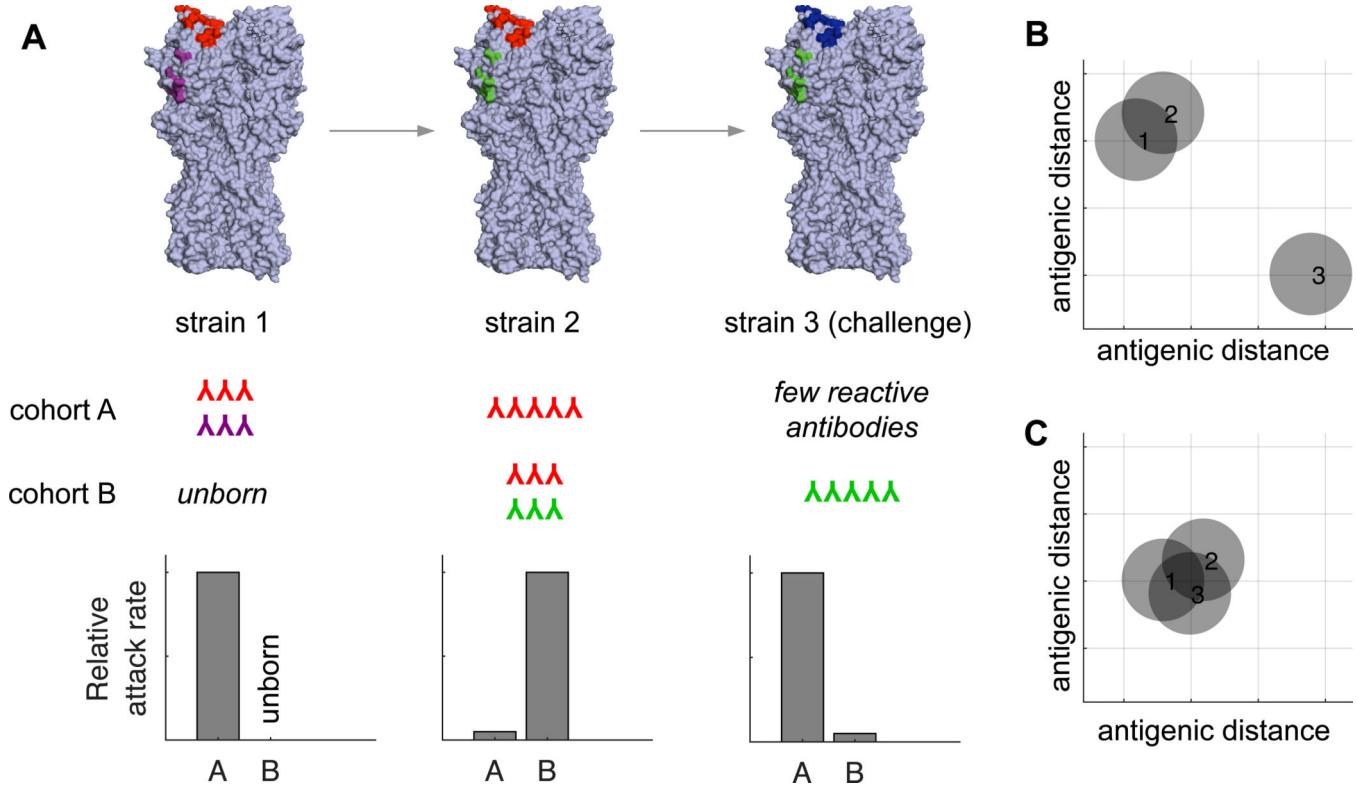

Figure 1. The development of antibody response to drifted influenza virus strains

(A) The population begins completely susceptible to strain 1, which has two epitopes in this example. Upon infection, individuals in cohort A generate antibodies against the red and purple epitopes. The strain then acquires a mutation in the purple epitope (and becomes strain 2). New susceptible hosts (cohort B) that become infected with strain 2 develop antibodies to the red and green epitopes. In contrast, older individuals (cohort A) that are exposed to strain 2 develop an antibody response focused primarily on the red epitope that was conserved in strain 1. Older individuals likely experience mild infections with strain 2 since these individuals possess cross-reactive antibodies against the red epitope. Eventually, immune pressure at the red epitope selects for a virus (strain 3) that possesses a red→blue mutation. Older individuals (cohort A) regain susceptibility since they have an antibody response focused on the former red epitope, and younger individuals (cohort B) are protected against this strain because they possess antibodies against the green epitope conserved in strain 2. (B–C) After exposure to strain 2, antigenic cartography based on the sera from cohort A (B) and cohort B (C) reveals different patterns. Antibodies from individuals in cohort B recognize the red and green epitopes and perceive all strains as identical, whereas antibodies from individuals in cohort A recognize the red epitope and perceive strain 3 to be distinct from strains 1 and 2.