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Immune history and influenza virus susceptibility

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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 viral exposure history 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.

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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 in life and that subsequent exposures with antigenically drifted viral strains boost antibody responses initiated by early childhood infections [1–5]. 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 1250 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).