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A flawed immune system and the origins of antigenic sin

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Infectious diseases have been a scourge of humans for millennia. History informs us about many examples of their devastating impact. For example, nearly 2000 years ago the plague reportedly decimated the populations of the Han and Roman Empires, contributing to their eventual collapse (1). In the 12'th century AD, the plague is thought to have killed about 90% of the European population. Several centuries later, smallpox reportedly killed about 25% of the population of the Aztec Empire, facilitating its conquer by the Spanish warrior Hernán Cortés, who had hitherto been defeated by the Aztecs (1). In 1918-1919, an influenza pandemic killed more than 20 million people worldwide (2), including more than a million in sub-Saharan Africa (3). The HIV/AIDS pandemic has thus far led to the deaths of more than 30 million people (4). Meanwhile, malaria still kills about half a million people each year, mostly in sub-Saharan Africa (5).

In response to infectious diseases and other threats to organismal survival, nature evolved a compendium of very useful immune systems. The immune system of humans comprises a collection of white blood cells (e.g. B and T cells), the molecules they secrete, and the organs in which they reside and develop. These different components work together to protect against various threats to human survival. In light of the fact that untreated immune deficiency frequently leads to death from opportunistic infections (6), it is evident that without an immune system the historical record of the human impact of infectious diseases would have been even grimmer.

What is the original antigenic sin?

Despite its usefulness, the human immune system has a number of important functional flaws. Notable instances of these flaws are associated with the mechanisms that temper the immune system's responses in order to prevent them from causing undue harm to the host. In particular, these tempering mechanisms are not always activated at the right time and/or to an appropriate degree. Consequently, much of the pathology associated with many infectious diseases derives from an over-active immune system (7). Recent work (8) indicates that flawed immune tempering is also a key cause of a most puzzling immunological phenomenon called the original antigenic sin (OAS).

The OAS was first observed by an eminent (9) American epidemiologist, Thomas Francis Jr. Francis studied the immune responses of about 100 college students afflicted with influenza in March-April 1947 (10). About 60% of them had been vaccinated several months earlier against a strain of influenza virus called PR8. However, they were mostly infected by a new strain called Rhodes. Early during their illness, the unvaccinated students' immune responses were about three times more reactive with PR8 vs. Rhodes (10). Unexpectedly, during convalescence their immune responses were still about twice more reactive with PR8 vs. Rhodes (10). This suggests that Rhodes boosted existing responses to PR8 while eliciting weaker responses to itself. A subsequent analysis of the immune responses of more than 1000 individuals supported this hypothesis. Specifically, it showed that those individuals' immune responses were much more reactive against the first (*original)* strain they were likely infected with compared to later strains (11). This phenomenon, which Francis called OAS, contradicted the immunological dogma that each strain preferentially activates immune responses to itself. Additional observations consistent with OAS were later made in studies of immune responses to other pathogens and even to non-infectious agents (12).

What is the mechanistic basis for OAS?

Early studies revealed that OAS may occur as a result of competition between B cells (13). To understand the underlying logic, consider an individual who has never been exposed to antigens (i.e. components of pathogens and other substances that induce an immune response) derived from a particular pathogen (either through natural infection or vaccination). The B cells of that individual can be conceptually separated into different, overlapping subsets depending on the antigens they recognise. In general, the subsets that recognise (or are "cognate to") antigens from strains of the pathogen of interest would be in a state called "naive" (meaning that they have never been activated). If a given strain of the pathogen (let's call it strain X) infects that individual, then naïve B cells that are cognate to that strain would become activated. Within a few weeks, these activated B cells would proliferate and differentiate into different classes, including memory B cells. The memory B cells will lie in wait for the next encounter with strain X, whereupon they will quickly be reactivated to proliferate and secrete antibodies that neutralise X. A second infection with X will, therefore, boost immune responses to this strain.

What if the second infection is not with X but with another strain (let's call it strain Y)? If Y is too different from X, then the second infection with Y will be analogous to the first infection with X in the sense that *typical* numbers of naïve B cells that are cognate to Y will be activated to become memory cells. On the other hand, if Y is too similar to X, then the second infection with Y will be analogous to the second infection with X. In contrast, if Y is neither too different from nor too

similar to X, then Y will reactivate existing memory B cells that are cognate to X. Antibodies secreted by these memory B cells will neutralise Y, preventing it from adequately activating naïve B cells that are cognate to Y, whose differentiation into memory B cells takes place on a longer time scale. Therefore, competition for antigens between memory and naïve B cells can explain how a new strain (Y) preferentially boosts immune responses to an older, moderately different strain (X).

However, subsequent experiments (14) brought into sharp relief the inadequacy of this explanation of OAS. Those experiments confirmed that OAS can occur in mice sequentially infected with a suitable pair of strains. They also showed that OAS can be alleviated if, at the time of either the first or the second infection, mice are given certain substances called adjuvants. This observation could not be explained at the time based on the prevailing understanding of the causal mechanisms of OAS (14). A recent study (8) offered a simple, unifying mechanistic explanation of both OAS and its alleviation by adjuvants. This explanation is briefly reviewed below.

How is OAS alleviated by adjuvants?

As mentioned earlier, the immune system has certain tempering mechanisms that help to prevent its responses from causing undue harm to the host. A key effector of such immune tempering is a type of T cell called a T regulatory (Treg) cell. A Treg cell tempers immune responses in various ways, notably by suppressing the activation of a type of immune cell called a dendritic cell. Activated dendritic cells are vital to immune responses because they help to activate B and T cells (8).

A first infection with strain X would activate not only cognate naïve B cells but also cognate naïve Treg cells. These cells will proliferate and differentiate into memory B and Treg cells, respectively. In a second infection with a strain Y that is moderately different from X, Y will reactivate the existing memory B and Treg cells. As previously proposed (13), the reactivated memory B cells will produce antibodies that neutralise Y and prevent it from adequately activating naïve B cells cognate to Y, leading to OAS. There is a second, Treg cell-dependent pathway leading to OAS (8). Specifically, the reactivated memory Treg cells will suppress the activation of dendritic cells, which will in turn prevent naïve B cells cognate to Y from becoming activated. However, because existing memory B cells require much less stimulation from dendritic cells in order to become reactivated, they will be less affected by the memory Treg cells (8); accordingly, this second pathway will enhance the effect of the first one. A mathematical model quantified how different X must be from Y in order elicit OAS (8). Importantly, adjuvants act on this second pathway in accordance with their demonstrated (14) ability to alleviate OAS; adjuvants activate dendritic cells, thereby countering their suppression by Treg cells (8). Therefore, the tempering of immune responses by Treg cells is both a key cause of OAS and the primary reason why adjuvants alleviate OAS. These advances might pave the way towards a more complete understanding of OAS and the development of mitigation strategies that work in humans.

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