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Review article

Original antigenic sin: A comprehensive review

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ABSTRACT

The concept of "original antigenic sin" was first proposed by Thomas Francis, Jr. in 1960. This phenomenon has the potential to rewrite what we understand about how the immune system responds to infections and its mechanistic implications on how vaccines should be designed. Antigenic sin has been demonstrated to occur in several infectious diseases in both animals and humans, including human influenza infection and dengue fever. The basis of "original antigenic sin" requires immunological memory, and our immune system ability to autocorrect. In the context of viral infections, it is expected that if we are exposed to a native strain of a pathogen, we should be able to mount a secondary immune response on subsequent exposure to the same pathogen. "Original antigenic sin" will not contradict this well-established immunological process, as long as the subsequent infectious antigen is identical to the original one. But "original antigenic sin" implies that when the epitope varies slightly, then the immune system relies on memory of the earlier infection, rather than mount another primary or secondary response to the new epitope which would allow faster and stronger responses. The result is that the immunological response may be inadequate against the new strain, because the immune system does not adapt and instead relies on its memory to mount a response. In the case of vaccines, if we only immunize to a single strain or epitope, and if that strain/epitope changes over time, then the immune system is unable to mount an accurate secondary response. In addition, depending of the first viral exposure the secondary immune response can result in an antibody-dependent enhancement of the disease or at the opposite, it could induce anergy. Both of them triggering loss of pathogen control and inducing aberrant clinical consequences.

Contents

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1. Introduction

The concept of "original antigenic sin" was first proposed by Thomas Francis Jr., in his treatise "On the Doctrine of Original Antigenic Sin" and has been advocated to explain a number of immunological phenomena. In the 1940s the concept of "original antigenic sin" was used to explain the way by which the immune system contributed to the requirement for yearly influenza vaccines. As early as 1958, there was evidence that the clinical pandemics of influenza in the early 20th century depended on interaction between immunological patterns of the human host and viral characteristics [1]. "Original antigenic sin" is not limited to humans [2–4], this was demonstrated in a study in rabbits primed with beef myoglobulin, and thence boosted with myoglobulin from other species including sheep, chicken, pig and sperm whale, that mounted an increased antibody response to the original beef myoglobulin [5].

With many viruses, the clinical presentation of an infection can be quite different depending on the original virus or first serotype to which the individual was exposed. For example, human Bocavirus 1 (HBoV1) infects the respiratory tract, causes lower respiratory infections including pneumonia with high prevalence in children [6]. However, the serotype HBoV2, affects the gastrointestinal tract causing gastroenteritis. At first sight, the topic of evolving serotypes should not be a problem, as the immune system, in theory, should be able to combat each subsequent serotype effectively. However, as we delve deeper, a strange phenomenon emerges. After prior exposure to a virus, the immune system has an ineffective to no response to a subsequent exposure of a different serotype of the virus [6]. This observation can be explained with the concept of "original antigenic sin".

Although simple, the concept has extreme implications. It can be explained in the following way. A body contacts a hypothetical first virus, since the body has no prior exposure to this virus; it must establish a primary response, a slow and intricate process of identifying an antigen of a virus and develop the classic immune response through innate and adaptive components with the aim to activate both cellular and humoral defenses to combat the virus. Subsequent exposure to the virus elicits a secondary amplified response, in which the body responds much quicker against the signal of a familiar antigen. Normally, classical understanding of the mammalian immune system would suggest that exposure to a closely related form of the virus, should trigger a secondary response. If the virus is significantly different, the body should recognize this as a completely new infection and undergoes a primary response (Fig. 1).

But according to "original antigenic sin", reality is somewhere in between, and it is indeed this hole that can trigger immune evasion by the pathogen. In "original antigenic sin", if an individual is exposed to a serotype very similar to the pioneer virus, the immune system can mistakenly identify the secondary virus antigens as antigens from the first virus encountered, and progress to a classical memory response producing virus1-specific antibodies, which may be ineffective towards the second virus. Another way of looking at this is that the immune system is unable to differentiate between the two serotypes (Fig. 1) [7], and makes a misdirection error [8]. Actual clinical events that illustrate the effects of "original antigenic sin" include the influenza epidemics, as it was observed that people born prior to 1956 had a worse outcome than young people exposed to influenza virus for the first time. This effect was modeled in rats in a study by Angelova and Schvartzman in 1982 [9]. "Original antigenic sin" can affect a varied array of microbials, including RNA viruses, bacteria and parasites [10]. In this manuscript we will describe the mechanism of "original antigenic sin" and its relevance in different human pathogens and clinical outcomes.

2. Mechanism

The cellular mechanism of "original antigenic sin" has been discussed in a triad of papers by Deutsch et al. in the 1970s [11–13]. The pathophysiologic mechanism of "original antigenic sin" includes two immunological components, the innate and adaptive immune systems, which influence the way by which the body mounts a secondary response on re-exposure to an antigen. Normally, on first exposure to a pathogenic antigen, the initial response involves the innate immune system, which recognize the antigen as being "new", foreign and/or dangerous and prime the antigen presenting cells (APCs) to further mount an adaptive immune response. APCs process and present the antigens to naïve T lymphocytes through the major histocompatibility complex (MHC) activating this way antigenic-specific lymphocytes. This leads to effector B-cells, effector T-cells, memory B-cells, and memory T-cells being produced en masse in a process called clonal expansion. The activated B-cells, or plasma cells, then proceed to produce specific antibodies to identify, flag, and "catch" the pathogenic antigens, which are then engulfed by phagocytes and destroyed, thus protecting the body from the harmful effects of the infection. The adaptive immune response to the first exposure of the antigen takes time to occur, and has to go through the steps of recognition, amplification and response. This whole process is known as the primary response, which occurs after exposure to a completely new pathogen, and takes approximately two weeks to run its course.

Upon a second exposure to the same pathogen, the response occurs in a similar fashion but at a much faster pace due to the B and T-cells having already seen the antigen of the pathogen and being able to recognize it much quicker. The subsequent steps are much faster and antibodies are produced more rapidly as well. This secondary response allows for rapid clearance of the pathogen, and is the basis for the mechanism of vaccines. The function of vaccines is to provide a less harmful exposure to a pathogen so that if in future the body is re-exposed to the wild type virus, the body can respond much quicker. However, it is during this secondary response that the problem of "original antigenic sin" can worsen the pathogenicity of the infection.

The mechanism of "original antigen sin" occurs when the body is re-exposed to a slightly evolved or different pathogen during a subsequent exposure. In this case, due to the prior exposure of the first antigen, memory lymphocytes do not respond to the variant antigen itself, but instead use their memory, interprets the second antigen as the original antigen and proceeds with a secondary response to the original antigen. At first glance, this may seem like a favorable phenomenon. The immune system is thus able to more quickly respond to the intrusion. However, the problem arises