Composition of pertussis vaccine given to infants determines long-term T cell polarization

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The introduction of a whole-cell vaccine against *Bordetella pertussis*, the causative agent of whooping cough, dramatically reduced disease incidence. Unfortunately, the whole-cell formulation also induces severe reactions in some infants. Because of this, acellular vaccines have been developed, but they are used exclusively in high-income countries. However, the acellular vaccines do not provide long-term protection, and despite the use of routine boosters, the disease is on the rise. In this issue of the *JCI*, da Silva Antunes and colleagues demonstrate that the whole-cell vaccines promote long-term polarization toward Th1 and Th17 responses, while the acellular vaccines induce Th2 polarization. Moreover, this polarization is long term, as the response to acellular boosters is dependent on the initial vaccine given in infancy. The authors speculate that Tregs may be induced by initial acellular vaccine administration. The results of this study have important implications for the development of pertussis vaccination strategies that would induce Th1 and Th17 polarization.

From whole-cell to acellular pertussis vaccines

The current state of vaccination against whooping cough (also referred to as pertussis and caused by the bacteria *Bordetella pertussis*) supports the old adage, "Be careful what you wish for." A whole-cell pertussis vaccine (wP) was developed in the early years of the 20th century and was quite successful at controlling pertussis in children, but unfortunately, it also caused serious reactions, including convulsions, encephalopathy, and hypotonic episodes (1). As wP consists of formalin-inactivated *B. pertussis* to which aluminum adjuvant is added, adverse reactions to the multiple bacterial antigens present and other innate-immune stimulating factors were not surprising.

Complaints by parents in high-income countries about reactions to wP vaccination of their children motivated attempts to develop a less reactogenic vaccine, and multiple attempts were made in the 1990s to generate pertussis vaccines based on purified protein components of the bacteria. During that decade, a number of acellular pertussis (aP) vaccines were tested in large-field trials, leading to licensing in some cases. The content of these vaccines was variable, ranging from the inclusion of pertussis toxoid (PT) alone to combinations of PT with filamentous hemagglutinin, pertactin, and/or fimbrial agglutinogens. All aP vaccines were shown to be safer than the wP vaccine, and although their efficacy was arguably slightly lower than that of the wP vaccines in the same trials, aP vaccines were licensed in many developed countries (2, 3).

The initial results with aP vaccines were gratifying, as serious reactions virtually disappeared and pertussis continued to be under control. However, with the passage of time, and particularly after the aP vaccine began to be used for initial vaccination of infants, the incidence of pertussis began to increase in vaccinated children and adolescents. Soon studies appeared showing that immunity after aP vaccination wanes substantially within several years. The incidence of pertussis began to increase, reaching epidemic proportions in multiple countries using aP, with the highest age incidence in school children and adolescents (4–10).

Many reasons for the recrudescence of pertussis, including improved diagnostics, variation in secular pertussis trends, and differences between the older strains in the vaccine and circulating strains with respect to toxin production or antigenic variation, were proposed (11, 12). However, two observations overturned complacency and awakened us to the real problems with the aP vaccine. First, using murine models, Kingston Mills in Dublin showed that there are important differences in T cell responses to wP compared with aP. Specifically, wP induced Th1 and Th17 polarization in response to pertussis antigens, whereas aP stimulated Th2 polarization (13, 14). Second, Tod Merkel's laboratory at the US FDA demonstrated that baboons vaccinated with wP and challenged with *B. pertussis* were resistant to both disease and carriage of the organism, while those vaccinated with aP could become carriers of *B. pertussis* despite being protected against disease (15).

These observations led to the realization that, as shown in mice, the recrudescence of pertussis was due in large part to the immunologic orientation induced in infants in response to aP vaccination during the first year of life. Those vaccinated with wP developed a Th1 and Th17 orientation, whereas those vaccinated with aP developed a Th2 orientation (16–19).

Initial vaccine determines long-term T cell responses

In this issue of the *JCI*, da Silva Antunes et al. (20) extend our understanding of immu-

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nological imprinting after the two kinds of pertussis vaccines. The authors show that IL-4, IL-9, and TGF-β drive polarization in aP recipients, whereas IFN-γ and IL-17 responses underlie immune polarization in wP recipients. The orientation of the immune response persists into adulthood, despite administration of aP boosters, as shown in the study of subjects 15 years and older given aP booster after either aP or wP immunization in infancy. Moreover, the study by da Silva Antunes demonstrates that protection against pertussis is relatively persistent in wP vaccinees and can be boosted by aP; however, those vaccinated with aP as infants received only temporary boosts of immunity by those same aP boosters. The authors speculate that priming with aP results in production of IL-1 and IFN-β, which in turn promotes generation of cytokines that block Th17 generation and induce Tregs, which inhibit the development of later proliferation and long-lasting antibody responses to aP booster vaccines. Although this study did not verify the contribution and role of Tregs, future studies to evaluate the presence of these cells would provide an explanation for the inability to correct T cell orientation in response to aP.

As a return to the sole use of wP vaccines in developed countries is unlikely, the question remains at to how T cell orientation after aP can be altered. da Silva Antunes and colleagues suggest the possible use of a single vaccination with wP as the first dose in infancy or the addition of an adjuvant to aP that would shift the immune response toward Th1 and Th17. However, reverting to even a single dose of wP would be difficult to put into practice. Studies to evaluate the immune response in aP recipients who developed pertussis later in life to determine whether infection changes T cell orientation would be interesting. If pertussis infection after aP vaccination does shift polarization, then the attenuated strain of *B. pertussis* developed by Locht et al. (21) might conceivably be used later in life to promote a shift of Th2 to Th1 and Th17. The baboon model could also conceivably be employed to determine whether or not reorientation is feasible (22).

The introduction of new adjuvants to acellular vaccines may be a more feasible approach to solving the problem, although it is not yet known if an adjuvant could reorient T cell responses. For such an approach to be feasible, the adjuvant would need to stimulate innate immune functions and be well tolerated by infants. At the moment, the most promising approach is to use LPS from *B. pertussis*, which is capable of stimulating the TLR2 receptor; however, careful studies of reactogenicity are required (23).

Collaborations with immunologists in developing countries in which wP is still given to infants would also be informative. In these countries, trials of aP boosters later in life would allow specimen collection to characterize possible changes in T cell polarization in response to aP. Moreover, such results could be compared with those obtained from cells collected from people from high-income countries given aP at birth. The hypothesis that Tregs are induced in the latter vaccinees could then be tested with proper controls.

Conclusions

In any case, the study by da Silva Antunes et al. elucidates a fundamental problem in vaccine immunology. Specifically, these results indicate that T cell phenotype may be fixed early in life and may create problems for efficacy later in life. In some respects, this issue is related to the observed nonspecific effects of vaccination with live or killed vaccines in infancy on innate immune responses and protection (24). Importantly, the definition of immunologic imprinting and the study of ways to change it is a key problem in vaccinology and must be the subject of intensive study.

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