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EDITORIAL

CTI special feature on innate immune responses and vaccine design

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The challenge of developing next generation vaccines against some of the most burdensome diseases—both infectious and inflammatory, will require an injection of basic knowledge as well as scientific innovation. As highlighted in this collection of expert reviews, the innate immune response is a critical stepping-stone between vaccination and the development of effective adaptive immunity, triggering and shaping the ensuing cellular and humoral responses that will ultimately control the disease. An enhanced understanding of how innate immunity develops in different disease states will help inform the design and formulation of new vaccine components. Conversely, an increased understanding of the mechanism of action of novel adjuvants will aid in their rational selection for different diseases and delivery platforms. In this Special Feature of *Clinical and Translational Immunology*, we present a number of papers that jointly highlight the interplay between innate immune responses and the resulting functional vaccine responses.

An immune response is initiated through the sensing of pathogens or danger signals in the microenvironment by innate immune cells, such as macrophages and dendritic cells (DC). Macrophages and DCs display very dynamic cell membranes with extensive membrane ruffling and active uptake of environmental antigens through phagocytosis and macropinocytosis. In this issue, Stow and Condon[1] discuss how these processes facilitate signaling and antigen processing, and potential presentation in macrophages and DCs, but also how it creates a vulnerability to pathogens that can subvert the system to avoid immune recognition and instead use it for cell entry and productive infection. Interestingly, these pathways apply to vaccinia virus, which is being developed as a potential viral vaccine vector and enters DCs via macropinocytosis. Furthermore, DCs use these active uptake processes to engulf fragments of virally infected, dying/apoptotic cells. In the case of herpes simplex virus, Sandgren *et al.*[2] describe, in this special feature, how this innate response could have an important impact on the type of adaptive response generated. Understanding these complex and nuanced pathways to immunity, on a disease-specific basis, will provide clues to developing effective vaccines.

One of the major pathogen recognition systems are the Toll-like receptors (TLRs). Different cell types express unique repertoires of TLRs, allowing specific activation or suppression of immune cells depending on which TLR is stimulated. TLR agonists tailor immune responses by activating DCs, which then mature and secrete cytokines that condition the innate immune response and polarize the T-cell response appropriately. The TLR agonists can enhance both humoral and cellular adaptive immune responses but also augment suppressive immune responses such as regulatory T cells, which could have applications in autoimmune/inflammatory diseases to limit tissue damage. Although the mechanism of action of many adjuvants is still a mystery, TLR agonists are often defined molecules that interact with specific cell types based on their receptor expression. The unique signatures of TLR expression across different immune cell subsets thus allows for the tuning of the breadth and specificity of immune activation in response to the adjuvant. Several TLR agonists have been evaluated in clinical trials with promising results, as discussed in this special feature by Dowling and Mansell.[3] Another method to target specific immune cells, reviewed here by Macri *et al.*,[4] is to administer antigens chemically coupled or genetically fused to antibodies directed against specific cell surface receptors. The benefit of this approach is that specific DC subsets can be targeted based on their distinct repertoire of surface receptors. When accompanied by an in-depth knowledge of the functional capacity of these DCs, this targeted approach is one way to tailor the resulting immune response. The importance of targeting antigen and adjuvant to the same cell has been demonstrated in multiple experimental systems.

Although the targeting of specific immune cells has progressed rapidly and shows significant promise, as discussed above, the majority of current vaccines contain adjuvant components with a less defined mechanism of action. Liang and Loré[5] highlight this lack of knowledge when discussing the complexity of the early innate immune response following intramuscular vaccination, where muscle cells themselves may initiate inflammation and immune cell recruitment, and the induction of cell death may be a contributing factor to adjuvant action. The plethora of immune cells that respond to different adjuvants and the cross-talk between these cells further complicates our understanding of their roles and highlights the need to learn more about the receptors and mechanisms targeted by non-TLR-based adjuvants. A more targeted vaccine delivery platform, as described by Sandgren *et al.*,[2] is the developing technology of microneedle arrays for skin vaccination, which holds much promise in terms of both tailoring immune responses (targeting epidermal and/or dermal dendritic cells with different functional capacities) and improving efficiency in manufacturing costs, transport logistics and vaccine administration.

We thank the distinguished experts who contributed as authors and reviewers to make this special feature timely and enlightening. Collectively, these articles illustrate that we are at the dawn of a

vaccine revolution. The days of empirical development are long gone and an age of deep mechanistic understanding and deliberate, tailored vaccine formulation is just beginning with an unprecedented appreciation of the complexity of the innate immune response. We anticipate the number of vaccine-preventable and -treatable diseases to balloon with this knowledge.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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4 Macri C, Dumont C, Johnston APR, Mintern J. Targeting dendritic cells: a promising strategy to improve vaccine effectiveness. *Clin Trans Immunol* 2016; **5**: e66.

5 Liang F, Loré K. Local innate immune responses in the vaccine adjuvant-injected muscle. *Clin Trans Immunol* 2016; **5**: e74.