The challenge of generating lasting mucosal anti-viral sterilising immunity

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Achieving sterilising immunity is often challenging and sometimes even impossible. This article gives a glimpse into the concepts behind and highlights some recent advances and challenges

In its essence, sterilising immunity describes the removal of a virus from the host before it can replicate, and this kind of immunity would be the preferred outcome for vaccination as it efficiently limits the infection of the individual and the spread of disease within the community.

The concept of sterilising immunity

A typical viral infection goes through a four-step cycle: first, the virus attaches to and enters a host cell; second, it copies its genetic material; third, it assembles new viral particles; and finally, it detaches to infect new cells. In its most straightforward form, sterilising immunity is achieved by the neutralisation of the infectious potential in the first step, (Wahl and Wardemann, Immunity, 2022) followed by their removal.

In this scenario, antibodies prevent the pathogen from attaching and entering the host cell, either by specific neutralisation or by decorating the virus with molecules that engage innate immune cells, leading to the destruction of the viral particle. Antibodies are often the main mediators of sterilising immunity, but virus-specific T-cells are also potentially essential contributors due to their ability to eliminate infected host cells ahead of replication.

Viruses show differences in the four infection steps, their efficiency and dynamics; additionally, host-related factors also play an important role, as discussed in the current literature (Wahl and Wardemann, Immunity, 2022. Jones et al., Nature Review Microbiology, 2021. Louten, Essential Human Virology, 2016). Therefore, sterilising immunity might not be achievable for all pathogens and/or in every individual, but its presence in even a fraction of the population might beneficially decrease viral spread during viral outbreaks due to efficient prevention of pathogen transmission in the community.

Another key aspect to consider is the differences in dynamics between the immune response and the viral replication cycle. Both above-described mechanisms, antibodies and T-cells, require a previous encounter with the pathogen, either as infection or immunisation, to be protective. Both effector functions need to be generated through an immune response that takes weeks to complete, too slow compared to the viral replication cycle during the active infection for sterilising immunity.

Indeed, the time until the pathogen replicates remains an important pathogen-related parameter to define the potentially sterilising immune effectors. For example, if replication time is in the range of days, even a memory antibody response that is stimulated and activated upon encountering the pathogen might provide such sterilising immunity. However, often, the presence of soluble antibodies at the time of pathogen encounter is immediately needed to block the pathogen from infecting host cells.

Mucosal and systemic immunity

Over the last decades, distinct compartments of the immune system have been identified within a host, and they have been described as systemic and mucosal immunity. Systemic immunity consists of the cells found in blood, lymphatic tissues and bone marrow, and is stimulated by injected vaccines. Mucosal immunity is associated with the gastrointestinal, genitourinary, and respiratory tracts, and most viruses first meet and infect within these large surfaces. Other immune compartments can be defined, such as central and intratumoral immunity. These are in regular exchange with systemic immunity, (Zang et al., Frontiers Aging Neurosciences, 2022. Bettcher et al., Nature Reviews Neurology, 2021 Fridman et al., Immunity, 2023) whereas mucosal surfaces seem to be largely separated and rely on different mechanisms of protection. In contrast to systemic immunity that produces immunoglobulin G (IgG) and is assessed in serum, mucosal immunity predominantly produces IgA as secretory IgA (sIgA).

These molecules are secreted and protect the host surfaces from pathogens by either aggregation, neutralisation, blocking or promotion of clearance of so-marked pathogens. Furthermore, the mucosal immune system is unique in that it functions in proximity to a ‘dirty’ environment relative to the systemic immune apparatus. Therefore, mucosal immunity differs from systemic immunity on a structural, cellular, molecular, and functional level, and vaccines that induce a good systemic response don’t often lead to a great local mucosal response that protects the host at the viral entry sites. As a result, sterilising immunity (Krammer, Nature, 2020) might often need to engage the mucosal immune system, leading to protective sIgA responses.

Challenges in inducing sterilising immunity with mucosal vaccines

Although much effort has been directed at the development of mucosal vaccines, the number of approved vaccines for human use remains low. While simple to envision, inducing an efficient and lasting IgA response often remains challenging. For instance, various antigenic forms have been developed over the last decades, including live attenuated vaccines, inactivated vaccines, subunit vaccines, conjugate vaccines, mRNA vaccines, viral vector vaccines, and DNA vaccines. So far, the vast majority of these are still only being used for injectable vaccines, and while efficient in triggering a systemic immune response, their ability to trigger localised mucosal immunity is often limited.

For mucosal applications, stability is often a major concern. Here, an essential challenge is the harsh and removal-directed environments prevalent on most mucosal surfaces, providing a serious barrier for many of the above-named antigen formats. The vaccine

components need to be stable enough and stay in place to reach the immune cells nested within the mucosa, passing through a thick physical barrier composed of enzymes, mucus, and epithelial host cells. However, once arrived, they must also allow their contents to interact with the immune system. Therefore, so far, only a handful of these antigen formats have been formulated in a way that allows them to engage mucosal immunity, and other approaches depend on the physical overcoming of the barrier.

A further challenge lies in the often-low memory effect found in mucosal immunity. While strong and long-lasting effector functions can be triggered with current vaccines systemically, the effects found in mucosal immunity are often temporally limited. Here, a better understanding of how (and if) such memory can be generated remains essential.

Once induced, the accurate measurement of mucosal protective immune effectors provides an additional challenge. Mucosal mediators need to be sampled in a reliable and reproducible manner on their respective surfaces so that the correlatives of protection can be assessed and quantified, (Bean et al., mBio, 2024. Bladh et al., Frontiers in Immunology, 2024) which is not always easy to envision within a minimally biased, error-limiting and simple manner.

Lastly, the defined vaccine formulations need to be reliable and reproducible in their delivery of the antigenic cargo. Differences in mucosal accessibility, composition and thickness exist between individuals, and especially for paediatric vaccination, formulations need to be found that are accepted by the recipients.

All these challenges currently represent serious roadblocks and limit the use of mucosal vaccines, but if and when they are overcome, individuals and the herd might profit from their induced sterilising immunity.

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