Combining two in one: a dual HIV-TB vaccine for vulnerable infants

Infants represent one of the most vulnerable populations to infectious diseases. In 2015, the World Health Organization Global Health report stated that 9.6 million people, including 1 million children, suffered from tuberculosis (TB) during 2014. The goal of the De Paris group is to understand why infants are more susceptible to diseases than adults, and how knowledge about immune system development in infants could be used to influence paediatric vaccine design. In particular, the group is interested in paediatric HIV-1 infection resulting from HIV-1 transmission via breastfeeding. Although there are now effective antiretroviral therapies to reduce in utero (in the uterus) and intra-partum (during birth) HIV-1 infection, the impact on breastfeeding transmission has been more limited. Therefore, an effective HIV-1 vaccine remains a necessary additional measure to prevent paediatric HIV-1 infections.

The majority of HIV-1 infections in infants caused by ingesting breastmilk occur in sub-Saharan Africa. This region also has a high prevalence of TB infections which are caused by the bacterium Mycobacterium tuberculosis (MtB).

The currently licensed TB vaccine is the live-attenuated Bacille Calmette-Guérin (BCG) vaccine which was introduced 95 years ago and is still administered to over 80% of new-born infants worldwide. The BCG vaccine protects against the most serious complications associated with TB and has been linked with a significant drop in overall child mortality. It is not, however, effective in adults, and in vaccinated infants immunity decreases over time. However, the BCG vaccine is contra-indicated in HIV-infected infants or infants at risk for HIV infection. This is because these infants have a much higher risk of developing disseminated BCG disease which mimics the symptoms of tuberculosis and can be life-threatening. Therefore, it is vital that a novel paediatric TB vaccine is developed that can protect this vulnerable population.

COMBINING TWO IN ONE

The aim of Professor De Paris’ group, in collaboration with her colleagues at the Albert Einstein Institute in New York, was to develop a paediatric HIV-TB vaccine which would be capable of preventing both oral HIV acquisition and TB infection. Their hypothesis was that a rationally designed strain of human-adapted MtB may provide better protection than the bovine-adapted BCG. The vaccine proposed comprised an altered MtB strain which co-expressed HIV antigens. It was intentionally designed to retain the immunogenicity of BCG, but with an improved safety profile. The advantages of the BCG vaccine are threefold: it is known to induce a strong immune response, even in infants without a fully mature immune system; it is effective after just a single dose at birth; and it can be administered orally.

In previous work, the group established a paediatric rhesus macaque model of oral simian immunodeficiency virus (SIV) infection to simulate breastfeeding transmission of HIV in human infants. Using this model, it was demonstrated that an attenuated MtB strain, which had been engineered to decrease its virulence, could not disseminate in healthy or SIV-infected infant macaques. The modified MtB was further altered to express SIV antigens. Infant macaques that received an oral MtB-SIV vaccine to prime the immune system and were boosted intramuscularly with modified vaccinia Ankara (MVA)-SIV developed immune responses to both MtB and SIV. However, these vaccinated infant macaques were exposed to a repeated oral SIV challenge, similar to human infants breastfeeding over a period of time, vaccinated animals were more readily infected than the unvaccinated control macaques. This suggested that vaccination with mycobacterium-derived vaccines could potentially increase the risk of HIV infection, rather than reducing it. In areas with a high prevalence of HIV-1. At the same time, this might prove advantageous in inducing immune responses against other pathogens. This phenomenon has been reported in previous studies, including one which looked at risk of HIV-1 infection in South African infants following BCG vaccination.

Infants represent one of the most vulnerable populations to infectious diseases.

Attenuated MtB or BCG vaccine

HIV acquisition by breast-feeding

Potential interplay between mycobacterial vaccines and HIV infection risk. Infant macaques were immunised during the first week of life with attenuated auxotroph MtB vaccines or with BCG. Compared to unvaccinated age-matched control infants, monocytes and dendritic cells in blood and tissues of vaccinated animals had enhanced functional responses for several weeks post immunisation. Concurrently, CD4+ T cells also exhibited increased activation, including the upregulation of CCR5, the co-receptor for HIV and SIV. When these animals were subsequently exposed to weekly oral challenges with SIV by simulating breastfeeding transmission of HIV in human infants, >80% of vaccinated infant macaques became infected after only two exposures, compared to <35% of unvaccinated controls. Whether or not these results are directly translatable to humans remains an unanswered question. The data emphasize the need for larger studies examining interactions between mycobacteria and HIV.
Lab studies by another research group provided further evidence that exposure of human CD4+ T-cells to BCG can enhance HIV-1 infection. The mechanisms by which this occurs are not yet clear but may be associated with a group of BCG-derived molecules that interact with molecules on the immune cell surface, called TOLL-like receptors.

TRAINED IMMUNITY

It was hypothesised that the activation of CD4+ T-cells might be related to trained immunity. The term “trained immunity” was originally applied to an observation in BCG-vaccinated adults, where the term referred to the persistence of enhanced responses of monocytes to not only mycobacterial antigens, but also other unrelated antigens for several months after vaccination. These findings suggested that mycobacterial vaccines, such as BCG, can provide bystander protection against other pathogens. This phenomenon could explain why infant mortality dropped after the introduction of the BCG vaccine. Interestingly, monocytes/macrophages are part of the innate, rapid immune response system that is generally not associated with memory function, yet, trained immunity could potentially confer resistance to reinfection. Trained immunity is thought to be driven by epigenetic changes. Epigenetic changes are heritable, but reversible, alterations that alter gene expression without altering the DNA sequence itself.

The current work of Professor De Paris’ group aims to confirm and further define the molecular mechanisms that may promote the non-specific effects of vaccination with BCG, including epigenetic changes in human infant blood cells after BCG is administered at birth.

THE IMPACT ON VACCINE DESIGN

Vaccines to prevent HIV and TB infection are vital to protect vulnerable infant populations in resource-poor countries where limited access to therapies means that there are high morbidity and mortality rates associated with these diseases. The adjuvant, or enhancing, effects of mycobacterial vaccines may prove highly beneficial for many paediatric vaccines, because they can enhance immune responses in infants in whom responses are generally reduced compared to adults. However, their potential ability to induce long-lasting activation of the immune system in settings with high HIV-1 incidence should be considered. The studies carried out by Professor De Paris and her team provide new insights into paediatric vaccine design which can be used to inform future therapeutic strategies and increase understanding of the complex interactions between vaccine components and host immune responses.