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SUPPLEMENT ARTICLE

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Novel artful applications of vaccines at the horizon

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Abstract

Some live vaccines, particularly Bacillus Calmette-Guérin (BCG), oral polio vaccine (OPV), and measles vaccine, can reduce the incidence of all-cause mortality by outreaching the mere control of specific infections and exerting off-target effects. Asides from the prevention of viral infection, some other vaccines, such as those against flu or rotavirus, could reduce the risk of developing autoimmunity. The nonspecific effects of vaccines are mediated by the innate immune system, mainly through the so-called trained innate immunity. These observations paved the way for developing tolerogenic and trained immunity-based vaccines with substantial implications for more effective use of vaccines and combat vaccine hesitancy.

KEYWORDS
autoimmunity, BCG, diabetes, measles, mRNA vaccines, nonspecific effects, vaccines

1 | INTRODUCTION

Vaccines represent a milestone in preventive and social medicine since the 19th century. Apart from specific effects against infectious diseases and their complications, vaccines intriguingly emerge with nonspecific protective effects. Further knowledge of how they work and the availability of novel manufacturing techniques can open new avenues in vaccine policy.

Key Messages

Bacillus Calmette-Guérin (BCG), oral polio vaccine (OPV), measles, and smallpox vaccines reduce the incidence of all-cause mortality, outreaching the mere prevention of their target infection. Nonspecific effects of vaccines are largely related to "trained innate immunity," a mechanism due to epigenetic changes occurring in innate immune system cells. Flu and rotavirus vaccines have proven safe in individuals at risk of T1D or coeliac disease. By preventing viral infections, vaccines can rather be protective over developing autoimmunity. Recently, a tolerogenic vaccine has been developed to treat experimental autoimmune encephalomyelitis (EAE), the mouse model for multiple sclerosis. Besides, trained immunity-based vaccines are also in development.

2 | CAN VACCINES HAVE NONSPECIFIC PROTECTIVE EFFECTS?

Off-target effects of vaccines were observed almost a century ago, but only recently, further interest has been raised to impact overall human health.[1] A growing body of literature is suggesting that several live vaccines, remarkably Bacillus Calmette-Guérin (BCG), oral polio vaccine (OPV), measles, and smallpox vaccines, reduce the incidence of all-cause mortality in vaccinated compared to unvaccinated populations outreaching the mere prevention of their target infection. Although most evidence derives from epidemiological observational studies, which are exposed at risk of bias, several randomized controlled trials seem to confirm these data, too.[2] Some pediatric studies showed that revaccination with live vaccines is associated with a marked reduction in mortality and lower hospital admission risk for severe non-targeted infections.[3] Also, maternal antibodies have been shown to enhance a beneficial nonspecific effect on survival in infants who received measles and BCG live vaccines.[1] Furthermore, some studies reported the association of BCG vaccination with a reduced risk of atopy and atopic asthma improvement.[4] As observed in several studies, sex and timing of vaccinations seem to affect nonspecific effects of vaccines.[1]

The recent SARS-CoV-2 pandemic has fostered concern about the heterologous effects of vaccines. Some studies have suggested that confirmed COVID-19 and mortality rates were lower in countries with a BCG vaccination program at birth.[5] However, when different confounding variables were considered, including testing rates, BCG vaccination policy, and COVID-19, spread and mortality rates appear to be uncorrelated.[6]

3 | HOW DO VACCINES PROVIDE NONSPECIFIC EFFECTS?

Although clinical and epidemiological evidence of nonspecific immunomodulation by vaccines has been known for a long time, the immunological mechanisms behind these reports have long remained elusive. An assumption involves the role of heterologous immunity in immunopathology by molecular mimicry. As such, host immune response to a specific pathogen can provide partial protective immunity to unrelated microorganisms. In fact, as well as pathogen-specific T cells cross-react to different peptide-MHC combinations, a similar response might be elicited when T cells are challenged with vaccine antigens. Of note, detrimental effects of triggered cross-reactive immunity can also occur due to excessive activation of Th1 or Th2 compartments that can result in solicited autoimmune or allergic manifestations, respectively. On the other hand, a crucial role of innate immunity for nonspecific protective effects to subsequent unrelated infections after immunization has been recently postulated. How human innate immunity maintains a level of memory to previously encountered pathogens has been only recently investigated. This process has been described as "trained innate immunity" and appears to be related to epigenetic changes occurring in innate immune system cells.[7] In particular, methylation levels of specific lysine residues on the H3 histone tail cause the transition of chromatin from a condensed, transcriptionally inactive form to open, and transcriptionally permissive euchromatin; these epigenetic modifications are detected both in terminally differentiated and in stem cells, are stable over time and can be induced by some pathogen-associated molecular patterns (PAMPs) such as beta-glucan.[8] Proof of principle of this mechanism has been provided by preclinical models, where NOD-SCID mice have been injected with BCG vaccine and showed significant immune protection toward subsequent encounters with *Candida albicans*, even in the absence of adaptive immunity.[9]

4 | COULD VACCINES PREVENT AUTOIMMUNITY?

Among nonspecific beneficial effects of vaccines, protection against autoimmunity deserves to be mentioned. Several studies have suggested the role of viral infections, especially those caused by RNA viruses (i.e., measles and rotavirus), as triggers of autoimmunity. For instance, in type 1 diabetes (T1D), the interaction between predisposing genes and environmental factors seems to be responsible for the autoimmune attack against β cells. After all, mutations in some genes, such as MDA5 (IFIH1), PTPN2, and TYK2, playing a pivotal role in innate response against RNA viruses, have been associated with T1D development. In this context, it is conceivable that vaccinations, preventing viral infections, could have a protective role against autoimmunity. The potential protective effect of the measles vaccine and Pandemrix flu

vaccine on T1D has been reported.[10] In the same way, a decrease in the incidence of T1D has been recently observed after introducing the routine immunization schedule of the oral Rotavirus vaccine.[11] Rotavirus vaccine has proven safe in individuals at risk of T1D and those at risk of coeliac disease (CD).[12] Moreover, it has been recently reported a higher prevalence of CD in rotavirus-non-vaccinated children than in vaccinated ones, suggesting a role of rotavirus infection, in combination with other genetic and environmental factors, in causing CD.[13]

Despite these limited data, some vaccines seem to be a promising tool to turn down autoimmunity.

5 | ARE THERE NOVEL ARTFUL APPLICATIONS OF VACCINES ON THE HORIZON?

Novel mRNA technology has been recently applied to achieve tolerogenic vaccines. To treat experimental autoimmune encephalomyelitis (EAE), the mouse model for multiple sclerosis, Krienke et al. have developed a vaccine encapsulating an engineered mRNA encoding a myelin antigen in liposomes with a lack of pro-inflammatory activity. The absence of innate immune activation and subsequent production of pro-inflammatory cytokines makes the mRNA transcripted antigen able to induce tolerance instead of sensitization. Even more critical, the mRNA was synthesized, replacing the uridine with 1-methylpseudouridine with consequent inability to engage TLR7.[14] This strategy is highly effective in treating EAE and warrants further applications in the field of organ-specific autoimmunity.

Additional knowledge of those immunologic mechanisms underlying vaccine nonspecific effects can lead to trained immunity-based vaccines. As such, two novel experimental live vaccines, intranasal pertussis, and a new oral Salmonella Typhi vaccine seem to induce an increased immune response to unrelated pathogens.[1]

Although some off-target effects of vaccines have been documented, further issues are to be clarified. For example, optimal administration time of live vaccines, the effects of simultaneous administration of live and non-live vaccines, or the interactions with other concomitant health interventions deserve further investigations. Addressing these unsolved questions could bring significant changes to vaccine schedules, including repositioning existing vaccines more effectively.

Last but not least, emphasizing the off-target effects of vaccines could help combat vaccine hesitancy and sustain the undeniable benefits of vaccination.

CONFLICT OF INTEREST

None of the authors reported conflicts of interest.

AUTHOR CONTRIBUTIONS

Davide Montin: Conceptualization (equal); writing-original draft (equal). **Giorgio Ottaviano**: Writing-review and editing (equal). **Maria Sangerardi**: Writing-review and editing (equal). **Mayla Sgrulletti**: Writing-review and editing (equal). **Loredana Chini**: Writing-review and editing (equal). **Rosa Maria Dellepiane**: Writing-review and editing (equal). **Baldassarre Martire**: Writing-review and editing (equal). **Caterina Rizzo**: Writing-review and editing (equal). **Viviana Moschese**: Conceptualization (equal); supervision (lead); writing-review and editing (equal).

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