Live-attenuated vaccination increases the diversity of pathogen-specific T cell repertoire triggered in chronic infection responses

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The immunity is an outcome of a defense strategy system that ensures the resolution of infection and pathogen clearance aiming to promote a sterilizing condition of the host. However, many pathogens deploy diverse immune evasion tactics in the host in order to establish persistent or chronic infections (1,2). In these cases, the pathogen burden is maintained under control by protective immunity to avoid a worst-case scenario in which host resources would be vanished by the infection in order to guarantee the host viability. Infection control by protective immunity requires the host defense system to build an effective and rapid immune response immediately after the pathogen enters the host (3).

The ability of the immune system to initiate and maintain the control of infections relies on its capacity to recognize not only dominant antigens involved in the protective immunity but also their variants that can arise during pathogen colonization of the hosts (3). In natural infections, modulations of the pathogen antigens exist in a way to subvert the acquisition of acquired immunity. Pathogens can alternate the expression of immunodominant antigens during the acute and latent phases of infection, or even evade the host defense mechanism by mutation in only one amino acid of the presented peptide from those immunodominant antigens in order to completely abrogate pathogen-recognition by the host. These modulations guarantee the perpetuation of pathogens in chronic persistent infections (1,2).

In fact, the modulation of immunodominant antigens has a strong impact on the oligoclonal immune responses that contains a limited number of T cell clonotypes, with lower diversity in epitope recognition (4). This condition is seen in varicella zoster virus (VZV) infections, for instance, which are able to establish latency during infancy and later with increasing age in adults, when the virus can escape from immune control responses in relapse infection episodes. Recent investigations have determined the T cell receptor (TCR) diversity of VZV-specific $CD4^+$ T cells in cohort studies with individuals older than 50 years, including identical twin pairs and unrelated individuals (4).

The analysis of VZV-specific T cell repertoire before and after vaccination with live-attenuated VZV shows that there is no genetic significance in the diversity and selection of dominant T cell clones. However, analysis of T cell repertoire after vaccination in the cohort of individuals has shown an increased ratio of infrequent virus-specific T cell clones. These clonotypes include the VZV-specific T cells recruited from the naïve compartment that in the natural VZV infections would have reduced capacity to compete for growth and viability signals during activation as compared to dominant T cell clones (4).

Importantly, the studies conducted by Cavanagh *et al.* (4) have shown that vaccination increases the heterogeneity of T cell clonotypes within the repertoire of T cells acting against the virus infection. Although this increase in the repertoire diversification of VZV-specific T cells occurred upon immunization, this event seems not able to influence a rebalance of the clonal dominance characteristic of chronic VZV infections (4). Further studies will be necessary to address the implication of a wide TCR diversity repertoire generation against VZV on the type of T cell subsets and their differentiation programs that ultimately would establish different outcomes in the pathogen-host interplay.

The insufficient increase in clonal T cell diversity characteristic of natural VZV infections may depends on the poor nonmicrobial adjuvanticity needed to initiate

broad pathogen-specific adaptive responses. The effect of adjuvants used in booster immunizations would overcome this issue (5). It has yet to be determined whether protective immune responses induced by vaccination tend to be represented by many different clonotypes containing several structurally related TCRs that would either focus their recognition on the same antigen determinant and/or alternatively to a variety of epitope variants from distinct antigens. The generation of a diverse clonotypic repertoire incorporating multiple TCRs with different recognition patterns would easily overcome the antigen variations that may occur in chronic infections thus promoting an effective immunity able to reduce the ability of pathogens to establish a persistent infection.

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Footnote

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