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Follicular Helper, Follicular Regulatory T cells and the Germinal Center In HIV Vaccine Development

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The development of a vaccine to prevent human immunodeficiency virus type I (HIV-1) infection remains an important task in global health. An ideal HIV-1 vaccine would elicit long lasting high quality protective antibody (Ab) responses including broadly neutralizing antibodies (bnAbs) that would inhibit infection [1-4]. One of the major obstacles to development of an effective HIV-1 vaccine, besides the high degree of diversity in the envelope proteins (Env) of HIV-1 [1-4], is the time required to elicit potent bnAbs. As demonstrated by several recent reports, only a small percentage of HIV-1-infected people were able to develop bnAbs and only after several years of infection [5-13]. One peculiar feature of bnAbs is that they are heavily mutated from germline immunoglobulin sequences, indicating that the B cells producing these bnAbs have undergone several rounds of mutation and selection in the germinal center (GC) reaction [3,9,14]. Thus, in order to generate HIV-1-specific bnAbs through vaccination, strategies must be employed that maximize somatic hyper mutation (SHM) of immunoglobulin genes in the GC, as well as the selection of B cell clones that produce bnAbs. Recent results from the RV144 clinical trial has shown that a viral vector prime and protein boost HIV-1 vaccine was able to elicit 31% protection, while protection levels may be higher if the efficacy is calculated within the first year of vaccinations [15,16]. Additionally, an HIV-1 vaccine phase 1 clinical study led by Dr. Shan Lu tested a DNA prime and protein boost vaccination system [17]. This study revealed a highly immunogenic protocol where a 100% positive response rate of HIV-1 specific antibody and T cell immune responses was elicited in study volunteers [17]. With this vaccine regimen, high titer and persisting Env-specific Ab responses and lower titer cross-neutralizing antibody responses for HIV-1 clades A to E were generated [17]. However, information about the basic immunological mechanisms behind such gene-based prime and protein boost vaccines is almost completely lacking. More information is needed about the immunological mechanisms involved in development of robust, high-affinity Ab responses to HIV-1 gp120. Specifically, how the DNA prime and protein boost system affects the generation of memory B cells and the responsiveness of the memory B cells is a key question.

Germinal centers (GCs) and memory B cells

In the GC response, antigen (Ag)-specific B cells proliferate and undergo somatic hyper mutation of Ig genes; high-affinity Abs results by selecting rare B cells that have undergone advantageous mutation of their Abs [18-22]. The major outcomes of the GC are plasma cells that directly produce Ab and long-lived memory B cells (MBCs), however the mechanisms that control whether a GC B cell becomes a plasma cell or an MBC are poorly understood. MBC responses to Ag rechallenge are also poorly understood, although recent work has defined separate subpopulations of MBCs based on the expression of IgM or CD80 and PD-L2 [23-25]. Historically, it was thought that MBCs had undergone class Ig switching and thus didn't express IgM. However more recent work has shown the existence of an IgM+ MBC population [23-25]. Interestingly, CD80 and PD-L2 expression define functional subpopulations of MBCs [23]. MBCs that express both CD80 and PD-L2 and are "double positive" (DP) tend to differentiate into plasma cells upon re-exposure to Ag, whereas MBCs that lack expression of CD80 and PD-L2 (thus are "double negative" or DN) tend to re-enter the GC after re-exposure to Ag. The mechanism for this difference is not yet understood, but it may depend on affinity of the MBC Ab for Ag and/or the maturation state of the MBC. CD80+PD-L2+ DP MBCs appear to have higher affinity for Ag and are more differentiated than CD80-PD-L2- DN MBCs [23]. DN MBCs express higher levels of the GC B cell transcription factor BCL6, and thus are more GC-like than DP MBCs [23]. An important question is how to promote the formation of DN MBCs that can travel back into the GC to allow for further Ig somatic hyper mutation, which will help the formation of bnAbs to HIV-1.

TFH cells and TFR cells

Follicular T helper (TFH) cells are a recently characterized CD4 T cell lineage located in the GC whose specific function is to help GC B cells to produce high-affinity Abs [18-22]. TFH cells have an activated, effector T cell phenotype among CD4 T cells and uniquely express very high levels of PD1. TFH cells are critical for the development of the germinal center reaction and the resulting memory B cells, plasma cells and T cell dependent Ab response. A key cytokine produced by TFH cells is IL-21, a factor that potently promotes B cell activation and Ab secretion. The BCL6 transcriptional repressor protein is highly expressed in TFH cells and is considered the master regulator for TFH cells [20-22]. Additionally, a subpopulation of follicular CD4 T cells was discovered that can act as suppressors of the GC reaction [26-29]. These cells express both FoxP3 and BCL6 and have been termed follicular regulatory T (TFR) cells. Like TFH cells, TFR cells are dependent on BCL6 for their function. Although TFR cells are not well understood, TFR cells appear to suppress the number of TFH cells and GC B cells during the immune response and also regulate affinity maturation of Abs. Thus, TFR cells have an important role in affinity selection of Abs during the B cell response. Whether TFR cells regulate MBCs is not yet clear, however, it seems likely that TFR cells can alter MBC differentiation. A TFH-like cell population has been identified circulating in blood ("blood-TFH" cells) [30-36]. Although they are not true TFH cells, since they lack high-level expression of BCL6 and PD1, these cells are related to TFH cells as they express CXCR5 and IL-21 and they have strong B cell help activity. TFR-like cells have also been found circulating in blood [28]. Although also not well understood, blood-TFH cells appear to be TFH precursors that disseminate early in an immune response to provide TFH activity to other parts of the body

[31]. Most strikingly, the percentage of blood-TFH cells increases with an ongoing Ab response in autoimmunity, vaccination and infection [30-36]. Notably, higher levels of blood-TFH cells correlate with bnAbs in HIV-1-infected patients [34]. Blood-TFH cells are therefore an attractive marker for examining TFH cell responses in humans. However, blood-TFH and blood-TFR cells have not yet been analyzed in an HIV-1 vaccine setting.

Heterologous prime-boost vaccination

This type of vaccine regimen is often termed simply "prime-boost vaccination", and has been shown to be an effective approach for generating strong, protective immune responses in several different experimental systems, against several types of pathogens [1,2,17,37-48]. In the prime-boost approach, the Ag is given in two different forms. Plasmid DNA- or viral vector-encoded Ag is typically used in the initial "priming" stage, and then purified protein Ag is given in the subsequent "boost" stages. The prime-boost approach has been shown to have a unique advantage in promoting the formation of high affinity bnAbs in HIV-1 vaccine systems [39,49-51]. Work over the last 15 years in a number of labs has shown DNA priming to be a very promising vaccination approach. Although DNA vaccines originally gave low immunogenicity in humans when used alone, the combination of DNA priming and protein boosting has shown promise. The NIH-sponsored HIV Vaccine Trial Network is organizing expanded clinical studies with DNA vaccines.

Conclusion

The over-arching goal of the field is to develop approaches to improve vaccination against HIV-1, such that there is predictable and stable production of bnAbs. Future work is needed to clarify how GC B cells and GC-derived MB cells are regulated by TFH and TFR cells, particularly in the context of vaccination to HIV-1. This will allow for the development of new approaches to augment bnAb production following HIV-1 vaccination.

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