

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].

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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.

References

- Tomaras GD, Haynes BF (2010) Strategies for eliciting HIV-1 inhibitory antibodies. *Curr Opin HIV AIDS*. 5: 421-7.
- Lu S (2009) Heterologous prime-boost vaccination. *Curr Opin Immunol*. 21: 346-51.
- Streeck H, D'Souza MP, Littman DR, Crotty S (2013) Harnessing CD4(+) T cell responses in HIV vaccine development. *Nat Med*. 19: 143-9.
- Pantophlet R, Burton DR (2006) GP120: target for neutralizing HIV-1 antibodies. *Annu Rev Immunol*. 24: 739-69.
- Gray ES, Taylor N, Wycuff D, Moore PL, Tomaras GD, et al. (2009) Antibody specificities associated with neutralization breadth in plasma from human immunodeficiency virus type 1 subtype C-infected blood donors. *J Virol*. 83: 8925-37.
- Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, et al. (2001) The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. *J Virol*. 85: 4828-40.
- Doria-Rose NA, Klein RM, Manion MM, O'Dell S, Phogat A, et al. (2009) Frequency and phenotype of human immunodeficiency virus envelope-specific B cells from patients with broadly cross-neutralizing antibodies. *J Virol*. 83: 188-99.
- Binley JM, Lybarger EA, Crooks ET, Seaman MS, Gray E, et al. Profiling the specificity of neutralizing antibodies in a large panel of plasmas from patients chronically infected with human immunodeficiency virus type 1 subtypes B and C. *J Virol*. 82: 11651-68.
- Liao HX, Lynch R, Zhou T, Gao F, Alam SM, et al. (2013) Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus. *Nature*. 496: 469-76.
- Bonsignori M, Montefiori DC, Wu X, Chen X, Hwang KK, et al. (2012) Two distinct broadly neutralizing antibody specificities of different clonal lineages in a single HIV-1-infected donor: implications for vaccine design. *J Virol*. 86: 4688-92.
- Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, et al. (2009) Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. *Science*. 326: 285-9.
- Walker LM, Simek MD, Priddy F, Gach JS, Wagner D, et al. (2010) A limited number of antibody specificities mediate broad and potent serum neutralization in selected HIV-1 infected individuals. *PLoS Pathog*. 6: e1001028.
- Clapham PR, Lu S (2011) Vaccinology: precisely tuned antibodies nab HIV. *Nature*. 477: 416-7.
- Klein F, Diskin R, Scheid JF, Gaebler C, Mouquet H, et al. (2013) Somatic mutations of the immunoglobulin framework are generally required for broad and potent HIV-1 neutralization. *Cell*. 153: 126-38.
- Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, Kaewkungwal J, Chiu J, et al. (2009) Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. *N Engl J Med*. 361: 2209-20.
- Andersson KM, Paltiel AD, Owens DK (2011) The potential impact of an HIV vaccine with rapidly waning protection on the epidemic in Southern Africa: examining the RV144 trial results. *Vaccine*. 29: 6107-12.
- Wang S, Kennedy JS, West K, Montefiori DC, Coley S, et al. (2008) Cross-subtype antibody and cellular immune responses induced by a polyvalent DNA prime-protein boost HIV-1 vaccine in healthy human volunteers. *Vaccine*. 26: 3947-57.
- Victoria GD, Nussenzweig MC (2012) Germinal centers. *Annu Rev Immunol*. 30: 429-57.
- Klein U, Dalla-Favera R (2008) Germinal centres: role in B-cell physiology and malignancy. *Nat Rev Immunol*. 8: 22-33.
- Crotty S (2011) Follicular helper CD4 T cells (TFH). *Annu Rev Immunol*. 29: 621-63.
- Crotty S, Johnston RJ, Schoenberger SP (2010) Effectors and memories: Bcl-6 and Blimp-1 in T and B lymphocyte differentiation. *Nat Immunol*. 11: 114-20.
- Fazilleau N, Mark L, McHeyzer-Williams LJ, McHeyzer-Williams MG. (2009) Follicular helper T cells: lineage and location. *Immunity*. 30: 324-35.
- Zuccarino-Catania GV, Sadanand S, Weisel FJ, Tomayko MM, Meng H, et al. (2014) CD80 and PD-L2 define functionally distinct memory B cell subsets that are independent of antibody isotype. *Nat Immunol*. 15: 631-7.
- Dogan I, Bertocci B, Vilmont V, Delbos F, Mégret J, et al. (2009) Multiple layers of B cell memory with different effector functions. *Nat Immunol*. 10: 1292-9.
- Pape KA, Taylor JJ, Maul RW, Gearhart PJ, Jenkins MK (2011) Different B cell populations mediate early and late memory during an endogenous immune response. *Science*. 331: 1203-7.
- Chung Y, Tanaka S, Chu F, Nurieva RI, Martinez GJ, et al. (2011) Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions. *Nat Med*. 17: 983-8.
- Linterman MA, Pierson W, Lee SK, Kallies A, Kawamoto S, et al. (2011) Foxp3(+) follicular regulatory T cells control the germinal center response. *Nat Med*. 17: 975-82.
- Sage PT, Francisco LM, Carman CV, Sharpe AH (2012) The receptor PD-1 controls follicular regulatory T cells in the lymph nodes and blood. *Nat Immunol*. 14: 152-61.
- Wollenberg I, Agua-Doce A, Hernandez A, Almeida C, Oliveira VG, et al. (2011) Regulation of the germinal center reaction by Foxp3+ follicular regulatory T cells. *J Immunol*. 187: 4553-60.

30. Feng X, Wang D, Chen J, Lu L, Hua B, et al. (2012) Inhibition of aberrant circulating Tfh cell proportions by corticosteroids in patients with systemic lupus erythematosus. *PLoS One*. 7: e51982.
31. He J, Tsai LM, Leong YA, Hu X, Ma CS, et al. (2013) Circulating precursor CCR7(lo)PD-1(hi) CXCR5(+) CD4(+) T cells indicate Tfh cell activity and promote antibody responses upon antigen re exposure. *Immunity*. 39: 770-81.
32. Pallikkuth S, Parmigiani A, Silva SY, George VK, Fischl M, et al. (2012) Impaired peripheral blood T-follicular helper cell function in HIV-infected nonresponders to the 2009 H1N1/09 vaccine. *Blood*. 120: 985-93.
33. Simpson N, Gatenby PA, Wilson A, Malik S, Fulcher DA, et al. (2010) Expansion of circulating T cells resembling follicular helper T cells is a fixed phenotype that identifies a subset of severe systemic lupus erythematosus. *Arthritis Rheum*. 62: 234-44.
34. Locci M, Havenar-Daughton C, Landais E, Wu J, Kroenke MA, et al. (2013) Human circulating PD-(+)CXCR3(-)CXCR5(+) memory Tfh cells are highly functional and correlate with broadly neutralizing HIV antibody responses. *Immunity*. 39: 758-69.
35. Luo C, Li Y, Liu W, Feng H, Wang H, et al. (2013) Expansion of circulating counterparts of follicular helper T cells in patients with myasthenia gravis. *J Neuroimmunol*. 256: 55-61.
36. Morita R, Schmitt N, Bentebibel SE, Ranganathan R, Bourdery L, et al. (2011) Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion. *Immunity*. 34: 108-21.
37. Cristillo AD, Ferrari MG, Hudacik L, Lewis B, Galmin L, et al. (2011) Induction of mucosal and systemic antibody and T-cell responses following prime-boost immunization with novel adjuvanted human immunodeficiency virus-1-vaccine formulations. *J Gen Virol*. 92: 128-40.
38. De Rosa SC, Thomas EP, Bui J, Huang Y, deCamp A, et al. (2011) HIV-DNA priming alters T cell responses to HIV-adenovirus vaccine even when responses to DNA are undetectable. *J Immunol*. 187: 3391-401.
39. Narayan KM, Agrawal N, Du SX, Muranaka JE, Bauer K, et al. (2013) Prime-boost immunization of rabbits with HIV-1 gp120 elicits potent neutralization activity against a primary viral isolate. *PLoS One*. 8: e52732.
40. Stambas J, Brown SA, Gutierrez A, Sealy R, Yue W, et al. (2005) Long lived multi-isotype anti-HIV antibody responses following a prime-double boost immunization strategy. *Vaccine*. 23: 2454-64.
41. Editorial (2009) A (prime) boost for HIV vaccine research? *Lancet*. 374: 1119.
42. Buchbinder SP, Mehrotra DV, Duerr A, Fitzgerald DW, Mogg R, et al. (2008) Efficacy assessment of a cell-mediated immunity HIV-1 vaccine (the Step Study): a double-blind, randomised, placebo-controlled, test-of-concept trial. *Lancet*. 372: 1881-93.
43. Wei CJ, Boyington JC, McTamney PM, Kong WP, Pearce MB, et al. (2010) Induction of broadly neutralizing H1N1 influenza antibodies by vaccination. *Science*. 329: 1060-4.
44. Chuang I, Sedegah M, Cicutelli S, Spring M, Polhemus M, et al. (2013) DNA prime/Adenovirus boost malaria vaccine encoding P. falciparum CSP and AMA1 induces sterile protection associated with cell-mediated immunity. *PLoS One*. 8: e55571.
45. Dalmia N, Ramsay AJ (2012) Prime-boost approaches to tuberculosis vaccine development. *Expert Rev Vaccines*. 11: 1221-33.
46. Dou J, Wang Y, Yu F, Yang H, Wang J, et al. (2012) Protection against Mycobacterium tuberculosis challenge in mice by DNA vaccine Ag85A-ESAT-6-IL-21 priming and BCG boosting. *Int J Immunogenet*. 39: 183-90.
47. Feng G, Jiang Q, Xia M, Lu Y, Qiu W, et al. (2013) Enhanced immune response and protective effects of nano-chitosan-based DNA vaccine encoding T cell epitopes of Esat-6 and FL against Mycobacterium tuberculosis infection. *PLoS One*. 8: e61135.
48. Lu J, Wang C, Zhou Z, Zhang Y, Cao T, et al. (2011) Immunogenicity and protective efficacy against murine tuberculosis of a prime-boost regimen with BCG and a DNA vaccine expressing ESAT-6 and Ag85A fusion protein. *Clin Dev Immunol*. 2011: 617892.
49. Zolla-Pazner S, Kong XP, Jiang X, Cardozo T, Nádas A, et al. (2011) Cross-clade HIV-1 neutralizing antibodies induced with V3-scaffold protein immunogens following priming with gp120 DNA. *J Virol*. 85: 9887-98.
50. Vaine M, Wang S, Liu Q, Arthos J, Montefiori D, et al. (2010) Profiles of human serum antibody responses elicited by three leading HIV vaccines focusing on the induction of Env-specific antibodies. *PLoS One*. 5: e13916.
51. Luo Z, Ren L, Zheng Y, Qi Z, Liang H, et al. (2012) Eliciting broad neutralizing antibody to HIV-1: envelopes of different lentivirus cross immunization by prime-boost vaccination. *Vaccine*. 30: 5316-23.