PREDICTING TOLERANCE IN VACCINE ANTIGENS: APPLICATION TO INFLUENZA, HCV AND HIV

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JanusMatrix, a newly developed algorithm by EpiVax, Inc, identifies cross-reactive T cell epitopes by matching the T cell receptor (TCR)-accessible amino acids (the TCR face) of peptides that bind the same human leukocyte antigen (HLA) [1]. Taking into both HLA binding and TCR contact account, JanusMatrix is uniquely able to compare T cell epitope conservation between protein sequences from bacterial and viral organisms that make up the human gut microbiome, autologous proteins from the human genome, and human viral and bacterial pathogens.

We recently discovered that pathogens might escape human immune response by mutating their epitopes to present “human-like” amino acid sequences to TCR when displayed on antigen-presenting cells [2]. We hypothesized that such “human-like” T cell epitopes contained in pathogens may trigger autologous regulatory T cells (Tregs), actively suppress immune response to themselves, thus improving their ability to survive in the host. We have used JanusMatrix to identify such “human-like” pathogen sequences that both bind HLA and share the same TCR-face patterns as human proteins.

In a large scale analysis of viruses that infect humans, we found that chronic viruses that establish persistent infection in human (such as Epstein-Barr, Herpes Simplex Virus and Cytomegalovirus) contain a significantly higher number of T cell epitopes that are cross-conserved (at the TCR face) with human proteins than viruses that do not establish chronic infection (such as Ebola and Marburg) [3]. Using JanusMatrix, we identified human-like T cell epioteps in H7N9 influenza hemagglutinin (HA) protein [4]. A promiscuous T cell epitope from H7N9 HA expanded Tregs and suppressed responses to other H7N9 peptides. This may explain the low titer of H7N9 HA inhibiting antibody responses and diminished seroconversion rates. Depletion the Treg-activating epitope increased antibody titers by 5 fold and B cell response by 20 fold (Unpublished). We also identified a “human-like” HCV T cell epitope, HCV_G1_p7_794, induced a marked increase of Tregs in PBMC derived from HCV-infected patients [5]. In HIV-1 Env, we found a human-like epitope that shares a TCR-face with a large number of human leukocyte antigen (HLA) class I molecule sequences. This highly conserved epitope is found in both the HIV-1 E and B Env antigens used in the ‘moderately effective’ HIV RV144 trial. It was found that this HIV Env-derived T cell epitope trigger functional Treg responses in HIV negative individuals. All these results suggest that JanusMatrix tool opens up a new window on the networks of cross-reactive T cell epitopes in human immune response, which may lead to significant improvements in the efficacy of vaccines.

References:

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