The Journal of Immunology
IN BRIEF | MAY 01 2023

Top Reads

J Immunol (2023) 210 (9): 1179–1180.
https://doi.org/10.4049/jimmunol.2390006

Related Content

IL-4 Predicts the Efficacy of a Candidate Antioxycodone Vaccine and Alters Vaccine-Specific Antibody-Secreting Cell Proliferation in Mice

J Immunol (March,2023)

Prime-Pull Immunization of Mice with a BcfA-Adjuvanted Vaccine Elicits Sustained Mucosal Immunity That Prevents SARS-CoV-2 Infection and Pathology

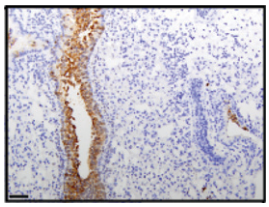
J Immunol (March,2023)

A Small Molecule RIG-I Agonist Serves as an Adjuvant to Induce Broad Multifaceted Influenza Virus Vaccine Immunity

J Immunol (March,2023)

The Journal of Immunology

BcfA-Adjuvanted Vaccine against SARS-CoV-2

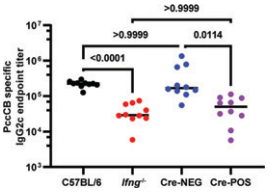


In this Top Read, Shamseldin et al. (p. 1257) describe a prime-pull vaccination strategy that provides long-term systemic and mucosal protection from SARS-CoV-2 infection in mice. Mice were primed i.m. with either SARS-CoV-2 spike (S) plus alum (A) or with S, A, and *Bordetella* colonization factor A (BcfA, B), then boosted intranasally with either S, S/A, or S/B combinations. Only mice that were primed with the S/A/B combination and boosted with S/B elicited Th17-polarized systemic responses with an attenuated IL-5 response, and Ag-specific tissue-resident T cells (T_{RM}) in the lungs. This prime-pull vaccine also generated T follicular helper cells and activated germinal center B cells in the draining lymph node, increased lung resident and circulating IgA Abs, and increased circulating S-specific IgG that suggested a skewed Th1 Ab response. Only immunizations incorporating BcfA in both prime and boost prevented SARS-CoV-2–associated weight loss, lung pathology, and viral replication in the upper and lower respiratory tracts. This strategy also maintained pulmonary IL-17$^+$ T_{RM} cells and circulating neutralizing Abs 3 mo after the boost. Together, the data demonstrate in mice that a BcfA-adjuvanted prime-pull SARS-CoV-2 subunit vaccine strategy can elicit long-lived local and systemic immune responses that prevent disease and impede viral replication, which may prevent asymptomatic transmission.

Low IL-4 Enhances Antiopioid Vaccine Efficacy

In this Top Read, Crouse et al. (p. 1272) sought to understand the mechanisms underlying involvement of IL-4 in the variation in anti-oxycodone vaccine efficacy among individuals. Initial experiments ruled out insulin receptor substrate 2 signaling downstream of the IL-4R, as well as the effect of IL-4 on somatic hypermutation, Ab avidity, and class switching to IgE after immunization. Whereas a previous report showed that IL-4 depletion during immunization enhances class switching to IgG_{2a}, the authors now show that IgG_{2a} and IgG_1 provide equivalent protection, ruling out significant impact from IL-4–mediated increase in IgG_{2a}. IL-4 depletion also increased vaccine-mediated plasmablast formation, but it did not promote long-lived oxycodone-specific plasma cells. Interestingly, preimmunization IL-4 levels produced by ex vivo–stimulated T cells negatively correlated with oxycodone-specific IgG concentration and vaccine efficacy. In summary, the data show that preimmunization IL-4 status may predict anti-oxycodone vaccine efficacy, and its depletion increases the number of oxycodone-specific Ab-secreting cells.

Role for IFN-γ in Blood-Stage Malaria



Previous studies have shown that total ablation of IFN-γ results in higher parasite burden during plasmodium infections. In this Top Read, Drewry et al. (p. 1305) show that IFN-γ derived from CD4 T cells limits parasite burden in chronic-stage malarial infections. Using a mouse model with inducible excision of *Ifng* in mature CD4 T cells (CD4Cre*Ifng* mice), the authors found similar parasite burdens between CD4Cre*Ifng* mice and their Cre$^-$ littermates during the acute phase of infection. However, during chronic infection, CD4Cre*Ifng* mice had elevated parasite burdens compared with littermate controls. Unlike what has previously been reported in complete IFN-γ knockout mice, phagocytic activity in the CD4Cre*Ifng* mice was unaffected. The CD4Cre*Ifng* mice had lower titers of IgG2c Abs, suggesting a role for IFN-γ in class switching. Together, these data provide a CD4-independent role for IFN-γ in chronic blood-stage malaria infection.

DGKα Limits CD8 T Cell Activation in Chronic Viral Infection

In this Top Read, Kudek et al. (p. 1281) demonstrate that diacylglycerol kinase α (DGKα) deficiency during a chronic viral infection leads to increased CD8 T cell activation, resulting in increased mortality. Following infection with lymphocytic choriomeningitis virus (LCMV) Clone 13, mice deficient in DGKα showed increased mortality, while having lower viral titers compared with controls. The frequency of activated, virus-specific CD8 T cells in DGKα-deficient mice was significantly higher than in the controls. Additionally, these CD8 T cells showed no signs of increased exhaustion. Mice with CD8 T cell–specific deletion of DGKα, which were infected with LCMV Clone 13, showed a similar increased mortality to the germline DGKα-deficient mice, suggesting that CD8 T cells are responsible for the increased morbidity and mortality. Further, ablating CD8 T cells from DGKα-deficient mice prior to LCMV Clone 13 infection rescued animals from lethal outcomes. Finally, RNA sequencing revealed DGKα may inhibit many cell-cycle signaling pathways. Together, these data demonstrate that DGKα may act to limit CD8 T cell activation during chronic viral infection.

RIG-I Activator Enhances Influenza Vaccine Response

The small molecule KIN1148 was designed as an agonist of IRF3- and NF-κB–dependent innate immune responses. In this Top Read, Hemann et al. (p. 1247) showed that KIN1148 enhances vaccine-mediated antiviral immune responses

www.jimmunol.org/cgi/doi/10.4049/jimmunol.2390006

in mice upon infection with H1N1 and H5N1 influenza A virus (IAV). The mechanism of action for this adjuvant is binding to and activation of RIG-I. In RIG-I–deficient cells, KIN1148 failed to increase phosphorylation of IRF3 and NF-κB or to enhance the expression of IRF3 target genes such as *Ifit1* and *Il6*. Among RIG-I–like receptors (RLRs) and RLR adaptor proteins tested, KIN1148 bound only to RIG-I at the C-terminal repressor and helicase domains without affecting RIG-I adenosine triphosphatase activity. In human macrophage-like THP-1 cells, KIN1148 led to increased expression of genes involved in Ag presentation but did not impact expression of genes involved in type I or type III IFN responses. In mice immunized with suboptimal doses of split vaccines against H1N1 or H5N1 IAVs and challenged with lethal IAV doses, KIN1148 reduced pulmonary virus titer, decreased illness and mortality, induced germinal center B cells in the draining lymph node, and increased both broadly neutralizing Ab production and IAV-specific $CD4^+$ and $CD8^+$ T cell responses. Together, the data show that KIN1148 is a promising antiviral vaccine adjuvant that acts via noncanonical RIG activation.