COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Impact Of Gut Microbial Complexity On The Host Response To Vaccination Against A Viral Pathogen

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Vaccination continues to be a proven strategy to prevent morbidity and mortality associated with infectious diseases. However, for many infectious agents, there are currently no approved vaccines available. Even when developed, new, first generation vaccines may only induce marginal protective immunity. Another concern is that protection can be highly variable among recipients, leaving some individuals at greater risk for disease. It is now well-recognized that the intestinal microorganisms (i.e., the gut microbiome) play important roles in modulating the immune system. Current evidence suggests that this host-microbe interaction can influence vaccine effectiveness, and may explain why some individuals respond better to vaccination than others. However, it is unknown whether the gut microbiome can be modified to enhance vaccine effectiveness; moreover, the shear complexity of the microbiome complicates our ability to elucidate its role of the microbiome on host immune responses. To address these challenges, we have performed experiments to compare the response to vaccination of gnotobiotic mice and conventionally-reared (Conv-R) mice. Specifically, Conv-R C3H/HeN and gnotobiotic C3H/HeN mice harboring the eight members of the altered Schaedler flora (ASF) were immunized with killed VEEV virions administered subcutaneously with one of three separate adjuvants: monophosphoryl lipid A (MPLA), cyclic dinucleotide (CDN), or CpG ODN. All mice were immunized twice (day 0 and day 42). Serum samples were collected at various timepoints following immunization out to 180 days to assess the kinetics and magnitude of the immune response. Total anti-VEEV serum antibody (Ab) response was evaluated by ELISA and serum samples were also evaluated for the presence of VEEV neutralizing antibody (nAb). In addition, serum samples collected two days post-immunization were collected to assess differences in the cytokine response. With respect to total IgG anti-VEEV Ab titers, the ASF mice developed higher Ab titers than did the Conv-R mice. Relative to the adjuvant used, the mice immunized with CDN formulations developed the highest Ab titers compared mice receiving the MPLA and CpG ODN formulations. While the Ab titers induced by MPLA and CpG ODN began to wane by day 70 all mice, the IgG titer remained elevated in the mice immunized with the VEEV antigen plus CDNs. With respect to nAb titers measured at 180 days post-immunization (DPI), seven of the eight Conv-R mice immunized with VEEV Ag plus CDNs had demonstratable nAb titers > 640 while only two of the eight ASF mice had a nAb titer ≥ 320 at 180 DPI. Few of the ASF or Conv-R mice immunized with either MPLA or CpG ODN developed nAb titers above 160. By using gnotobiotic and Conv-R mice, we have demonstrated differential responses to total anti-VEEV IgG and nAb titers relative to the complexity of the microbiome in otherwise syngeneic mice. These data and our ongoing studies demonstrate the feasibility of our long-term goals to identify specific targets for intervention within the gut microbiota to improve the effectiveness of vaccines in order to better protect the warfighter against current and emerging infectious agents.

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