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Retinoic acid promotes long lasting mucosal and systemic immune responses after mucosal priming and systemic boosting in mice

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The vast majority of pathogens invade through or cause disease at mucosal surfaces. Development of novel immunization strategies suitable for mucosal vaccines is widely desired to protect against infectious diseases. However, very few mucosal vaccines are available for human use, none of which are recombinant proteins or subunits of pathogens, owing to the lack of potent and safe mucosal adjuvants. Therefore, novel approaches to elicit mucosal immune responses are highly needed. Given the crucial role of Vitamin A metabolites, such as retinoic acid (RA) in imprinting a mucosal homing capacity on T and B cells, as well as its potential to promote the differentiation of IgA-producing plasma cells, we evaluated the capacity of RA to improve mucosal vaccinations.

We found that mice treated with RA as compared with untreated ones, showed enhanced systemic (IgG) and mucosal (IgA) tetanus toxoid (TT)-specific antibody responses after intranasal administration of TT as antigen and cholera toxin (CT) as adjuvant. Of note, in these set of experiments, we observed an appreciable TT-specific antibodies responses after intranasal priming with Ag alone in the absence of CT in RA treated as compared with untreated intranasally primed mice. Therefore, we asked whether we could amplify this response by giving a systemic boost with Ag in the presence of systemic adjuvant alum. We found that mice treated with RA and primed intranasally with Ag alone showed a higher titer of both systemic TT-specific IgG and mucosal IgA as compared with untreated mice after systemic boost with TT and alum. Furthermore, we detected higher frequencies of TT-specific IgG and IgA secreting cells in the bone marrow of mice treated with RA after intranasal priming with Ag alone followed by systemic boost with Ag and alum as compared to untreated mice. The persistence of the antigen-specific responses was evaluated and after 8 months we found still higher IgG TT-specific antibodies in the serum and, even if at lesser extent, higher IgA TT-specific antibodies in the vaginal compartment in RA treated as compared with untreated mice. This approach can contribute to progress beyond the state of the art in adjuvant research by achieving mucosal immunity in the absence of mucosal adjuvants or improve the effectiveness of mucosal delivered vaccine.

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