OMICS Group Conferences
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International Conference & Exhibition on
Vaccines & Vaccination

22-24 Nov 2011 Philadelphia Airport Marriott, USA

Tailoring induction of CD8 T cell quantity and phenotype by vaccine adjuvants

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Induction of $CD8^+$ T cells is often the goal for vaccines against intracellular pathogens and cancer. $CD8^+$ T memory cells are heterogenous and are classified into effector and central phenotypes. It is unclear how $CD8^+$ T cell quantity and quality differentially affect vaccine efficacy. We have developed a panel of vaccine delivery adjuvants that differentially impact the kinetics, quantity, quality of the $CD8^+$ T cell response and immune memory.

Archaeosomes adjuvant (made up of polar lipids derived from the *archaea*, *Methanobrevibacter smithii*), generates a large number of antigen specific CD8 T cells and a balanced phenotype of effector and central memory cells to entrapped antigen (J. Immunol., 278:2396, 2007). Recombinant *Listeria monocytogenes* (LM) and *Salmonella Typhimurium* (ST)-based vaccine delivery vectors are also effective at targeting antigen for CD8 T cell response (Stark et al., Cancer Res., 69:4327, 2009). We have also constructed a novel *Salmonella Typhimurium* vector capable of translocating (ST-T) antigen to the cytosol for effective MHC class I presentation. We evaluated the influence of the adjuvant, antigen processing pathway and vaccination regimen on CD8 T cell response to the same antigen, Ovalbumin (OVA) utilizing these different vaccine delivery approaches.

A single dose of OVA-archaeosomes or *Listeria monocytogenes*-OVA (LM-OVA) primed low numbers of exclusively CD8 central memory T cells. Repetitive boosting with LM-OVA failed to expand the numbers of CD8 T cells further, probably due to rapid neutralization of the live vector during subsequent boosts. In contrast archaeosomes given repetitively stimulated large numbers of OVA-specific CD8 T cells, with each injection increasing the total numbers of antigen-specific CD8 T cells in the lymphoid organ, up to shortly after the third dose. Thereafter a quantitative maximum threshold appeared to have been reached. Furthermore, repetitive boosting resulted in predominately effector memory phenotype CD8 T cells. In contrast, ST-OVA induced low numbers of CD8 T cells with delayed kinetics but predominantly effector memory phenotype. However, ST-OVA-T induced a strong and rapid CD8 T cell response, nevertheless of an effector memory phenotype. The differential responses evoked by each antigen delivery system correlated to the mechanisms of antigen presentation and resulted in varied protection against murine melanoma, in a prophylactic and therapeutic setting. Protection against cancer benefited from a central memory response whereas for clearance of LM and ST infection, a rapid kinetics of CD8 T cell response appeared to be most essential. Thus, the adjuvant and vaccination regimen strategy selected needs to be considered in the context of target application for tailoring the induction of cell-mediated immunity.