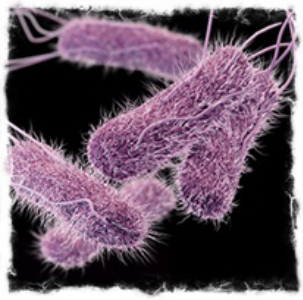

Mechanisms of Adaptive Immunity

Infectious Diseases

Vaccine Design

Immunology

The James McLachlan Lab: 4 Key Questions

Immunity against many types of pathogens relies heavily on helper T cells, a key player that directs many downstream events of the adaptive immune response, such as aiding B cells in making antibodies, or helping macrophages kill bacteria. To address the role these T cells play during an immune response, the lab of **James McLachlan** is working to answer 4 key questions:

How Do Infected Organs Affect Immune Responses

Certain bacterial infections (*i.e. Salmonella*) are never cleared throughout the lifetime of the host. The lab works to understand why the immune system doesn't completely clear these bacterial infections, yet prevents death caused by the pathogen. The formation of this "stalemate immunity" and the mechanisms that regulate it are some of the more interesting concepts facing immunologists studying infectious disease today. We have found that the anatomical site of *Salmonella* persistence leads to very different outcomes with regard to T cell and macrophage function. For example, the liver appears to induce T cells and macrophages that are more tolerant of infection whereas those from the spleen and lymph nodes are much better at bacterial clearance. Additionally, new T cells just "born" out of the thymus are essential for protective immunity to persistent *Salmonella* infection, so it is key to discover the mechanisms that regulate these organ specific responses.

Can Vaccines Optimize Immune Responses

In defining mechanisms of vaccine-mediated immunity, particularly against pathogens that invade via the intestine, it would be desirable to direct immune cells to the gut where they can target the bacteria at their initial entry point; however, it is unclear how this might be achieved. While it is known that vaccines given via traditional routes can protect against many infectious diseases, it is less clear how changing immunization route or vaccine make-up can affect immune cell migration or function. Does immunizing in skin direct a different response compared to other routes? Does the type of adjuvant change the predominant immune response from antibody-dominated to more cell-mediated? Different types of vaccine adjuvants and immunization routes allow us to imprint an anatomical "zip code" for the correct type of cells

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against a particular pathogen based purely on vaccine design.

Mast Cell Control in Adaptive Immune Responses

Mast cells were originally characterized more than 130 years ago, and are tissue-resident cells found at the host-environment interface or localized around blood vessels. Notably, these cells have unusual cytoplasmic granules now known to contain a multitude of physiologically active compounds, including proteases, histamine, heparin and multiple cytokines. These compounds can be released upon stimulation, predominantly with the antibody IgE (the basis for most allergy and asthma). What is less appreciated is how mast cells might contribute to antibacterial immunity, especially with respect to activating the adaptive immune response against pathogens. By activating mast cells using various conditions and determining how downstream immune responses behave, particularly with respect to pathogen-specific T cell responses, the lab hopes to better understand how mast cells initiate and contribute to adaptive immunity. This will answer basic biological questions about how cells communicate within the immune system & may provide opportunities to target mast cells as specific cellular adjuvants.

Sex-Specific Immunological Differences & Vaccines

A great biological conundrum is why men and women differ in how they respond immunologically to various immunological insults. Women respond better to vaccines and many infections, yet it often manifests in an increased susceptibility to autoimmune disease in women (3X more likely to be diagnosed with multiple sclerosis and 9X more likely to have lupus when compared to men of a similar age). A major focus is using mouse models to define how T cell and B cells might behave differently in different tissues and whether the differences seen are cell intrinsic (programmed into the cell when it develops) or cell extrinsic (changes depending on the surrounding environment). Revealing how these disparities are established could lead to potential therapies for autoimmune diseases or help in designing more effective sex-specific vaccines.

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