The impact of early-life B cell activation on aging immune responses

ABSTRACT

Immunological memory is critical for effective adaptive immune responses, particularly in aging populations where immunosenescence contributes to increased vulnerability to infections and diminished vaccine efficacy. As the global population ages, understanding how the immune system evolves is essential for improving vaccines and therapeutic interventions for older adults.

This project aims to investigate the differential impacts of aging on B cell compartments, challenging the prevailing notion of immunosenescence. While it is recognized that older adults exhibit diminished responses to new infections and recent vaccines, we propose that older adults can maintain robust antibody responses to antigens encountered earlier in life before the onset of immunosenescence. Specifically, we explore the hypothesis that "young" activated memory B cells, induced early in life during an individual's immunocompetent years, exhibit greater longevity and functionality than those activated later in life.

Preliminary data from our lab indicate a reversal in antibody response effectiveness, with older individuals showing the most robust responses to early-life vaccinations. To further explore this phenomenon, we will employ an interdisciplinary approach that incorporates cutting-edge methodologies, including human organoid models, B cell receptor sequencing, and single telomere length assays. To assess B cell biology, repertoire diversity, activation, and aging, we will compare memory B cells from young adults vaccinated early in life with those from older adults vaccinated either early or later in life. In contrast to traditional studies that compare different age groups, we will determine how the timing of B cell activation affects their longevity and repertoire breadth by examine cell death pathways, telomere dynamics, and repertoire diversity. Furthermore, to provide a comprehensive overview of B cell compartments, we will extend our analysis beyond human blood samples to include tissue samples from bone marrow, lymph nodes, spleen, and tonsils. Our initial data indicate that we can evaluate antigen-specific memory responses in organoids derived from spleen and lymph nodes in older individuals post-mortem.

By focusing on the differential impacts of aging on B cell types and the timing of their activation, our research will provide a new body knowledge on immunological memory and aging. This has the potential to revolutionize therapeutics and vaccines for aging populations by providing critical insights into the mechanisms of B cell maintenance and function.