

Human immune organoids and immune-on-chip to decode immunity in healthy donors and cancer patients

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Effective antibody production requires naive B cells to differentiate into plasma cells within germinal centers (GCs) of lymphoid tissues, a process critical for immune protection and vaccine efficacy. However, impaired antibody responses are prevalent in patients with cancer, aging individuals, and those with chronic infections, often due to B cell exhaustion. Antibody responses against severe infections are particularly diminished in lymphoma patients, with those undergoing immunotherapy experiencing higher infection rates and reduced vaccine efficacy, even after B cell recovery. Current ex vivo models fail to sustain long-term GC reactions or adequately test B cell responses. To address this, we developed synthetic hydrogels that mimic the lymphoid tissue microenvironment, enabling the generation of human GCs from tonsil-derived and peripheral blood mononuclear cell (PBMC)-derived B cells. PBMC-derived immune organoids sustain GC B cells and plasma cells longer than tonsil-derived ones and exhibit robust B cell programming, including GC compartmentalization, somatic hypermutation, immunoglobulin class switching, and clonal expansion. Chemical inhibitors targeting transcriptional and epigenetic pathways enhanced plasma cell formation, while integrating polarized CXCL12 protein within a lymphoid organ-on-chip modulated GC responses in healthy donor B cells but failed with lymphoma-derived B cells. This system offers a novel platform for modeling immune responses and B cell disorders, providing insights into GC dynamics and paving the way for improved therapeutic strategies and vaccine design. Additionally, the talk will explore the development of immunocompetency within non-lymphoid organ-on-chip systems, such as lung and intestinal, and their potential applications in translational immunology.