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Our preliminary studies revealed the dynamic evolution of B cell subsets as a function of age in the human thymus. An initial contingent of medullary B cells present at birth and displaying a phenotype of naive B cells is progressively replaced by antigen-experienced, antibody-secreting, class-switched plasma cells confined within the perivascular space (PVS). Plasma cells start to appear in the PVS a few months after birth at a time that is consistent with early exposure to common endemic viruses and vaccination antigens. We propose that this latter subset results from previous immunization and constitute an important pool of memory B cells and plasma cells. The maturing thymus would therefore represent an unrecognized niche for B cell memory alongside the bone marrow. We also hypothesize that thymic resident plasma cells significantly contribute to the humoral immunity through their constitutive antibody-secreting capacity. Our proposed studies will use a large collection of human specimens obtained from donors aged 0-2 years to further characterize this niche during its early development. Using mice immunized with model antigens, we will then investigate mechanisms whereby PC accumulate in the thymus and contribute to the overall serum immunity.

Aim 1. To characterize the thymic plasma cell niche in the human infant thymus. We will examine the kinetics of development of the thymic PC niche in ~250 human thymus specimens from donors aged 0-2 years. Using immunochemistry, multicolor flow cytometry, gene expression profiling and next generation sequencing based IGVH repertoire analysis, we will characterize the architecture, molecular signature and clonal composition of thymic PC in human infants. A comparison with PC subsets in the spleen and bone marrow of the same donors will reveal whether thymic PC have unique features.

Aim 2. To determine the reactivity profile of thymic plasma cells in human infants. In aim 2, we will assess the frequency of thymic PC reactive to a broad range of antigens towards which human infants are exposed. These include vaccination viral and bacterial antigens, common food antigens as well as ABO blood group antigens. The possible correlation between antigen-specific B cells in the thymus and the presence of serum IgG specific to the same antigens will be examined.

Aim 3. To verify the origin of thymic PC and evaluate their role in serological immunity. Mice immunized with model T cell-dependent and T cell-independent antigens, will be used to verified that thymic PC originate from peripheral immune responses. We will then use a series of genetically-deficient mouse strains to investigate the implication of specific chemokines and chemokine receptors as well as survival factors in the migration and maintenance of thymic PC. Lastly, we will evaluate the capacity of antigen-experienced thymic PC to confer humoral immunity upon adoptive transfer to or transplantation of thymus fragments under the renal capsule of recipient animals.