Regulation of cell fate decisions in early B cell activation

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Abstract

Cell fate decisions during early B cell activation determine the outcome of responses to pathogens and vaccines. We examined the early B cell response to T-dependent antigen in mice by single-cell RNA sequencing. Early after immunization, a homogeneous population of activated precursors (APs) gave rise to a transient wave of plasmablasts (PBs), followed a day later by the emergence of germinal center B cells (GCBCs). Surprisingly, most APs started to exit the cell cycle very early in the response, giving rise to non-GC-derived early memory B cells (eMBCs) that retained an AP-like transcriptional profile. Rapid decline of antigen availability controlled these events; provision of excess antigen precluded cell cycle exit and induced a new wave of PBs. Fate mapping revealed a prominent contribution of eMBCs to the MBC pool. Quiescent cells with an MBC phenotype dominated the early response to immunization in primates. Thus, excess APs, kept in reserve as eMBCs may enable rapid readjustment of the immune response if failure to contain a threat is manifested by increased antigen availability. Generation of the earliest GCBCs was tightly controlled by the transcriptional repressor Bhlhe40 in the absence of which this population was increased in numbers. Bhlhe40 also restrained in a cell intrinsic fashion the response of T follicular helper (TFH) cells. In B cells, Bhlhe40 executed its function in the first days after immunization by selectively restricting the generation of the earliest GCBCs but not of eMBCs or PBs. In activated CD4 T cells, Bhlhe40 was required to restrain proliferation thus limiting the number of TFH cells. Bhlhe40-deficient mice with progressing age succumbed to a B cell lymphoma characterized by the accumulation of monoclonal GCBC-like cells and polyclonal TFH cells in various tissues.