Rapidly responsive CD73+CD80+ memory B cells are BCL6-dependent but can form outside a germinal center response

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Abstract

Humoral immunity depends upon long-lived, antibody-secreting plasma cells and memory B cells (MBCs). MBCs exhibit significant phenotypic and functional heterogenity. Upon rechallenge, MBCs that express surface molecules associated with germinal center (GC) experience, including CD80 and CD73, rapidly form plasmablasts, while those that do not preferentially form secondary GCs. Yet, there is heterogeneity even within the CD73+CD80+ MBCs with regard to isotype, levels of somatic hypermutation and recall responsiveness. Here, we interrogated the mechanisms that regulate the differentiation of unique populations of MBCs. Using various genetically modified mice, we demonstrate a hierarchy of T-B interactions that leads to the generation of the distinct populations. CD73+CD80+ MBCs require cognate interactions with CD4+ T cells and intrinsic BCL6 expression, while CD73-CD80- IgD+IgMlo do not. Furthermore, the development of most IgM+IgDlo CD73+CD80+ MBCs and some isotype switched CD73+CD80+ MBCs does not require GC experience for somatic hypermutation and the ability to rapidly respond upon secondary antigen encounter.