Bhlhe40 function in activated B and T follicular helper cells restrains the GC reaction and prevents lymphomagenesis

Rene Rauschmeier [1*], Annika Reinhardt [2,3*], Charlotte Gustafsson[4], Vassilis Glaros [2,3], Artem V. Artemov [3,4], Josefine Dunst [2], Reshma Taneja [5], Igor Adameyko [2,3], Robert Månsson [2], Meinrad Busslinger [1**] and Taras Kreslavsky [2**].

1 Research Institute of Molecular Pathology, Vienna, Austria; 2 Department of Medicine, Karolinska Institutet, Stockholm, Sweden; 3 Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden; 4 Center for Hematology and Regenerative Medicine, Karolinska Institutet, Stockholm, Sweden; 5 Department of Neuroimmunology, Medical University of Vienna, Austria; 6 Endocrinology Research Centre, Moscow, Russian Federation; 7 Department of Physiology, National University of Singapore, 8 Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; 9 Hematology Center, Karolinska University Hospital, Stockholm, Sweden. *equal contribution, **corresponding authors

Abstract

The generation of high-affinity antibodies against pathogens and vaccines requires the germinal center (GC) reaction, which relies on a complex interplay between specialized effector B and CD4 T lymphocytes, the GC B cells and T follicular helper (TFH) cells. Intriguingly, several positive key regulators of the GC reaction are common for both cell types. Here, we report that the transcription factor Bhlhe40 is a crucial cell-intrinsic negative regulator affecting both the B and T cell sides of the GC reaction. In activated CD4 T cells, Bhlhe40 was required to restrain proliferation, thus limiting the number of TFH cells. In B cells, Bhlhe40 executed its function in the first days after immunization by selectively restricting the generation of the earliest GC B cells but not of early memory B cells or plasmablasts. Bhlhe40-deficient mice with progressing age succumbed to a B cell lymphoma characterized by the accumulation of monoclonal GC B-like cells and polyclonal TFH cells in various tissues.

.