Mechanism for the regulation of antibody quality

-Regulation of germinal center B cell proliferation by Foxo1-

Keywords: Adaptive immunity, Germinal center B cell, Foxo1 transcription factor

A group of researchers, Takeshi Inoue (Assistant Professor), Ryo Shinnakasu (Assistant Professor), Wataru Ise (Associate Professor), led by Tomohiro Kurosaki (Professor, WPI Immunology Frontier Research Center [IFReC], Osaka University, and RIKEN Center for Integrative Medical Sciences) has revealed the mechanism of the B cell function in the germinal centers, which are important sites within the secondary lymphoid organs to generate high affinity antibodies. They have clarified that Foxo1 transcription factor has an essential role for the regulation of germinal center B cell proliferation and differentiation.

When exposed to antigens, such as viruses or bacteria, “germinal center” is generated in the lymphoid organs including spleens and lymph nodes. B cells in the germinal center hypermutate their immunoglobulin genes during proliferation to produce higher affinity antibodies, which get rid of antigens. The mechanisms how germinal center B cell proliferation and differentiation are regulated remain largely unknown.

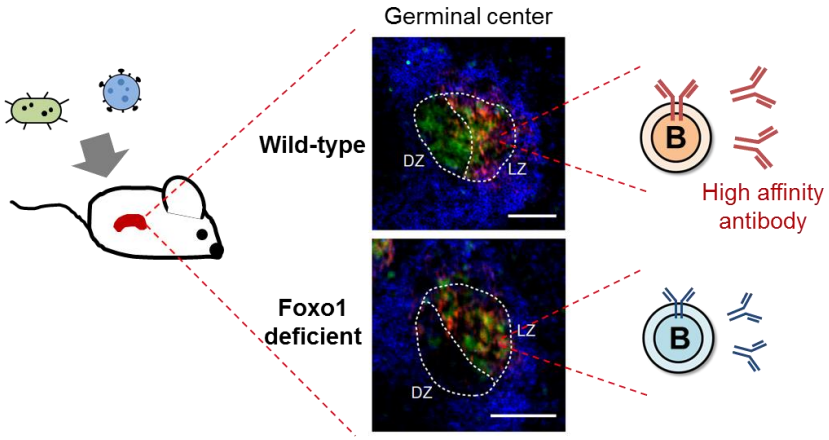
By using mouse model system, this research group clarified that transcription factor Foxo1 has an essential role in the regulation of germinal center B cell proliferation and differentiation, and also has important functions of the germinal center B cell biology.

This group’s achievement will help to develop new vaccine strategies by targeting Foxo1 to modulate germinal center B cell biology.

Abstract

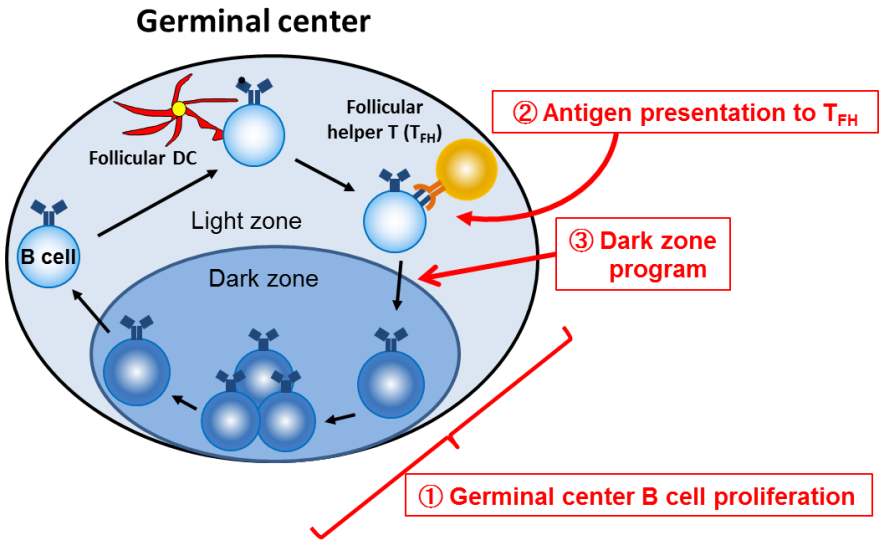
Germinal center (GC) B cells cycle between two states, the light zone (LZ) and the dark zone (DZ), and in the latter they proliferate and hypermutate their immunoglobulin genes. How this functional transition takes place is still controversial. In this study, we demonstrate that ablation of Foxo1 after GC development led to the loss of the DZ GC B cells and disruption of the GC

architecture, being consistent with recent reports. Mechanistically, even upon provision of adequate T cell help, Foxo1-deficient GC B cells showed less proliferative expansion than controls. Moreover, we found that the transcription factor BATF was transiently induced in LZ GC B cells in a Foxo1-dependent manner and that deletion of BATF similarly led to GC disruption. Thus, our results are consistent with a model where the switch from the LZ to the DZ is triggered after receipt of T cell help, and suggest that Foxo1-mediated BATF up-regulation is at least partly involved in this switch.



Foxo1 is required for high affinity antibody production

Without Foxo1, germinal center structure is disorganized and mice could not produce high affinity antibodies against foreign antigens.



①②③ Functions of Foxo1 in the germinal center B cells

Dark zone is lost and the germinal center is collapsed upon Foxo1 ablation. Foxo1 has also important roles in the light zone B cells, including antigen presentation to T_{FH} cells and

expression of dark zone program genes.