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Faster, higher, stronger: A protein that enables powerful initial immune response

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Your first response to an infectious agent or antigen ordinarily takes about a week, and is relatively weak. However, if your immune system encounters that antigen a second time, the so-called memory response is rapid, powerful, and very effective.

Now, a team of researchers at The Wistar Institute offers evidence that a protein, called Foxp1, is a key component of these antibody responses. Manipulating this protein's activity, they say, could provide a useful pathway to boosting antibody responses to treat infectious diseases, for example, or suppressing them to treat autoimmune disorders. Their findings appear online in the journal *Nature Immunology*.

"Foxp1 has an important role in our antibody immune responses, and if we could find a way to regulate Foxp1 activity in a subset of T cells, the CD4+ T cells, it could have some profound impact on the antibody responses," said Hui Hu, Ph.D., senior author of the study and associate professor at Wistar's National Cancer Institute-designated Cancer Center.

"Repressing Foxp1 activity, for example, we may be able to make antibody responses faster-acting and more effective, which could be crucial in, say, a pandemic when time is a critical factor," Hu said. "Alternatively, if we could enhance the effectiveness of this protein, we may be able to significantly dampen the antibody responses that are unwanted in some cases of autoimmune diseases such as lupus."

Previously, the Hu laboratory determined that Foxp1 was responsible for keeping T cells—the white blood cells that mediate our immune system—on "active stand-by mode," a process called quiescence. In the present study, Hu teamed with the laboratories of Louise C. Showe, Ph.D., professor in the Wistar Cancer Center's Molecular and Cellular Oncogenesis program, which provided crucial genomics expertise, and Jan Erickson, Ph.D., professor in the Tumor Microenvironment and Metastasis program, which offered expertise in the study of autoimmunity and the activation of B cells, the cells that generate antibodies.

According to their *Nature Immunology* report, variants (or isoforms) of Foxp1 (called Foxp1A and Foxp1D) are critical regulators for the formation of a type of T cells, called T Follicular Helper (TFH) cells. These TFH cells then go on to enable B cells in creating long-lived, highly reactive antibodies. The proteins are transcription factors, meaning they work by binding to DNA to control which genes in these T cells are "read" or translated into protein.

In the initial days of an immune response, the Foxp1 proteins determine how TFH cells arise from activated T cells. "The two isoforms act as regulators of TFH differentiation in the early moments of the immune response, where they effectively act as gatekeepers to slow TFH development, " Hu said. "They constitute a 'double-check' system that prevents the humoral branch of the immune system from acting too hastily."

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