New insight into immune tolerance furthers understanding of autoimmune disease

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It is no easy task to preserve the delicate balance that allows us to maintain a strong immune system that can defend us from harmful pathogens, but that is sensitive enough to correctly identify and spare our own cells. Therefore, it is not surprising that the mechanisms that underlie immune activation and tolerance are not completely understood. Now, a new research study published by Cell Press in the journal *Immunity* and available online on September 15th provides intriguing insight into the complex immune regulatory mechanisms that underlie immune tolerance.

Cells called Foxp3-expressing regulatory T cells, or "Treg cells," are a subpopulation of immune cells that suppress the immune system to maintain self tolerance. These regulatory "suppressor" cells have to recognize our own cells as "self" in order to turn off the effector arm of the immune system so that it does not attack our own healthy tissues and cause an autoimmune or inflammatory disease. There has been a lot of interest in Treg cells because it has been hypothesized that these cells might be useful for treating autoimmune disease or facilitating organ transplantation. "Foxp3 is a transcription factor that is important for Treg cell function," explains senior study author, Dr. Yisong Y. Wan, from the University of North Carolina at Chapel Hill. "If we are going to fully understand immune tolerance and regulation, it is critical to understand how Treg and Foxp3 function are controlled."

Dr. Wan and colleagues were interested looking at a second transcription factor, GATA-3, best known as a master regulator of another type of immune cell. "GATA-3 plays multi-faceted roles of regulating immune function in a cell-type specific fashion," says Dr. Wan. "However, whether and how GATA-3 is involved in controlling Treg function was unknown." The researchers discovered that when GATA-3 was deleted from Treg cells, mice developed a spontaneous inflammatory disorder and that Treg cells were defective in their ability to suppress the immune system. They went on to show that GATA-3 controls Foxp3 expression by binding to a regulatory region in the Foxp3 gene and that defects in both GATA-3 and Foxp3 resulted in substantially impaired Treg cells.

Therefore, the investigators have shown that one transcription factor (GATA-3) can control the expression of another transcription factor (FoxP3) to drive functional differentiation of Treg cells. By evolutionarily engineering a multi-layered process of transcriptional regulation, nature has provided for the opportunity to finely tune the generation of Treg cells. "Our study provides novel insights into the modulation of Treg function, revealing an indispensible role of GATA-3 in regulating Treg function and immune tolerance," concludes Dr. Wan. "We suggest that GATA-3 expression in Treg cells is important for the modulation of Treg function and immune response, and thus needs to be considered in order to fully understand how protective (to clear pathogen) and pathogenic (to cause autoimmunity and inflammatory disease) immune responses are controlled."

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