DBC1 negatively modulates regulatory T cells function under the inflammation

With the support by the National Natural Science Foundation of China, Dr. Li Bin and colleagues at the Institut Pasteur of Shanghai, in collaboration with Dr. Zheng Songguo and colleagues, have published their study entitled "Inflammation negatively regulates FOXP3 and regulatory T-cell function via DBC1" in *PNAS* (2015, 112(25): E3246—3254).

Regulatory T cells (Treg) are actively engaged in the prevention of autoimmunity and mitigation of aberrant or excessive immune responses. FOXP3, a master transcription factor in Treg cells, is essential for Treg function. Furthermore, FOXP3 could modulate Treg functions through binding with other regulators or/and co-factors. Here, we found Deleted in breast cancer 1 (DBC1) is a previously unidentified subunit of the FOXP3 complex. DBC1 physically interacts with FOXP3 and DBC1 depletion maintains FOXP3 expression and Treg suppressive function during inflammatory insult. Moreover, DBC1-deficient mice showed alleviated clinical symptoms in both EAE and colitis models and had reduced production of IL-17a. Inhibition of caspase 8 activity rescued FOXP3 expression during TNF-α treatment, suggesting that DBC1 negatively regulates FOXP3 and Treg cells function through the caspase 8 mediated pathway. These findings establish a previously unidentified mechanism regulating FOXP3 stability during inflammation and reveal a pathway for potential therapeutic modulation and intervention in inflammatory diseases.

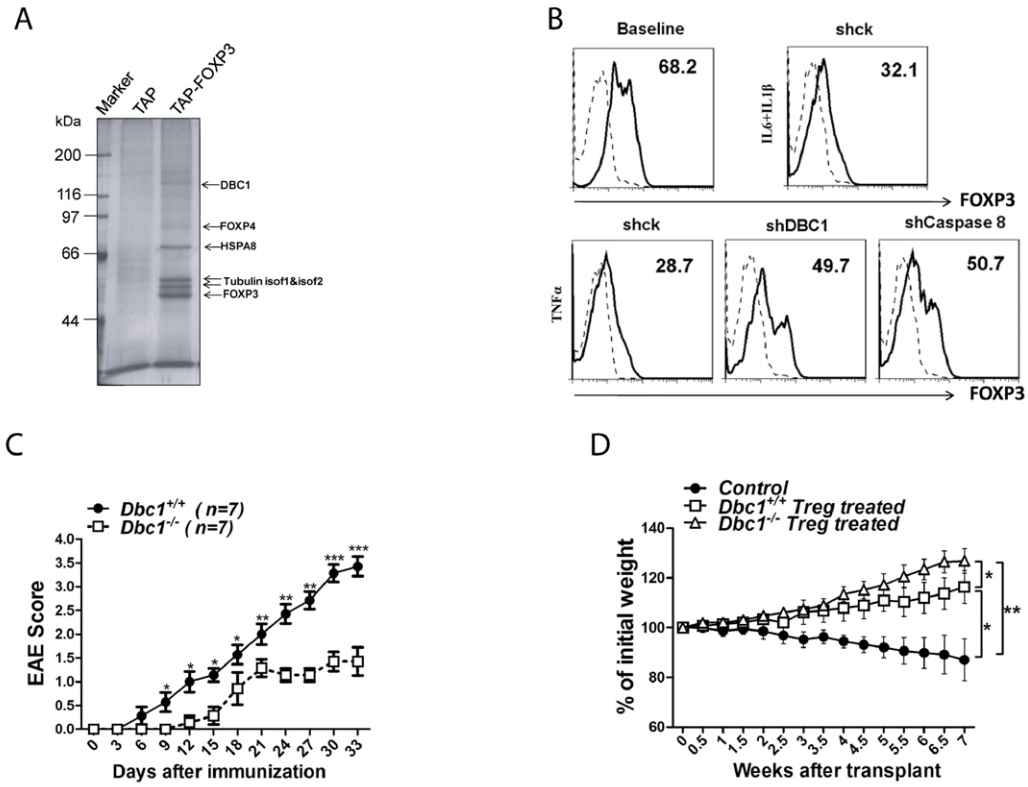

Figure A. FOXP3 complex was purified by tandem affinity purification in T cells. B. DBC1 knockdown or Caspase 8 knockdown human Treg cells maintain more FOXP3 proteins. C. *Dbc1*$^{-/-}$ mice develop less severe autoimmune disease symptoms during EAE induction. D. *Dbc1*$^{-/-}$Treg cells function profoundly in preventing colitis.