Stub1 negatively modulates regulatory T cell suppressive activity

Under a research project funded by the National Natural Science Foundation of China, Prof. Li Bin, a member of Institut Pasteur of Shanghai, Chinese Academy of Sciences and colleagues have published their study entitled "The Ubiquitin Ligase Stub1 Negatively Modulates Regulatory T cell Suppressive Activity by Promoting Degradation of the Transcription Factor Foxp3" in *Immunity* (**2013**, 39(2): 272—285).

In this study, the findings showed a molecular pathway by which Foxp3 is downregulated at the protein level in response to inflammatory cues, thus allowing for initial robust effector responses that are required for combating imminent threats to the host. Foxp3 was found to interact with the E3 Ligase Stub1, induced by inflammatory stimuli (LPS, IL-1β, etc.). Stub1 was found to mediate the ubiquitination and subsequent degradation of Foxp3. This Stub1-mediated Foxp3 protein down-modulation was further found to be dependent on the inducible heat-shock protein HSP70, which acts as a co-factor for the interaction between Stub1 and Foxp3. Furthermore, by utilizing both overexpression and knock-down approaches, Stub1-mediated Foxp3 degradation had profound effects toward Treg stability and function *in vitro* and *in vivo*. In particular, the downregulation of Foxp3 coincided with the loss of suppressive function and the acquisition of a Th1-like effector phenotype in Tregs ectopically expressing Stub1.

These findings may have significant implications for the fields of Regulatory T cell (Treg) biology and immune homeostasis. Firstly, while they contribute to mounting observations of instability or flexibility in the Treg lineage, they also provide a mechanistic explanation for the reported tendency of Treg cells to lose Foxp3 expression under conditions such as hyper-inflammation. Importantly, the hitherto unrecognized pathway of Foxp3 regulation characterized in this manuscript may provide several opportunities for novel therapeutic interventions aimed at modulating Foxp3 expression. Future exploration and exploitation of this Stub1-dependent regulatory pathway could potentially be used to benefit treatments targeting autoimmune diseases, chronic inflammation, and cancer.

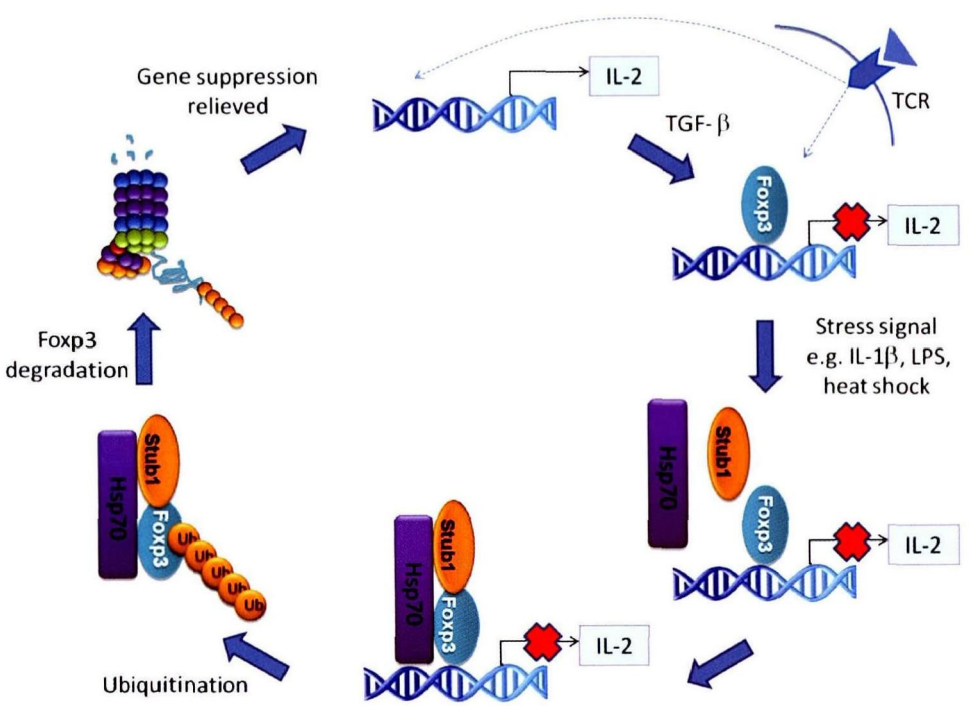

Figure A working model for Stub1-mediated loss of Foxp3 protein and Treg cell mediated immune suppression.