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EDITORIAL

How regulatory T cells sense and adapt to inflammation

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The immune system exists in harmony and also with the potential for dynamic control in healthy individuals. Our healthy body needs to sense the presence of microbes and react through both innate and adaptive immunity to eliminate infection. How our immune system senses the initiation, progression, and termination of the inflammatory process is critical for maintaining immune homeostasis. Thanks to the elegant experimental progress in using conditional knockout animal models, we have, over the past decade, gained a deep understanding of the contributions of thymus-derived $CD4^+CD25^+Foxp3^+$ natural regulatory T cells (Tregs) to this process.

Although there have been many advances in our understanding, it remains unclear how the adaptive immune system, including natural and induced $Foxp3^+$ Tregs, plays a central role in suppressing immune responses, sensing inflammation, and ensuring appropriately timed and localized immune responses, especially in humans.[1,2] It is still actively debated whether Treg plasticity exists and/or how it is dynamically controlled both in healthy and inflammation states. On the one hand, it has been convincingly demonstrated that the Foxp3 gene locus

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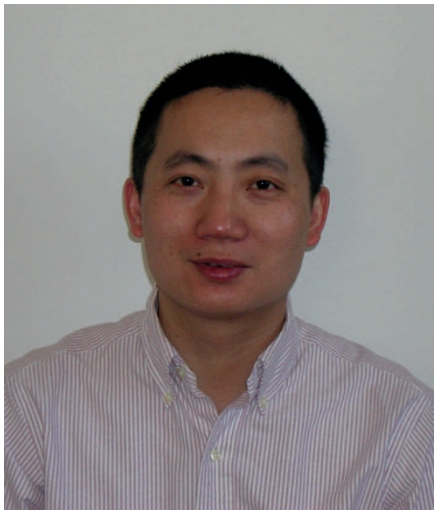
is consistently demethylated and actively transcribed in natural Treg cells.[3–5] On the other hand, the Foxp3 protein is regulated at the posttranslational level by acetylation, phosphorylation, and ubiquitination, which detemine its DNA binding, protein stability, and degradation under inflammation.[6–10] Understanding functional plasticity and stability could provide new insights in promoting Treg-based clinical therapies for autoimmune disease, organ transplantation, and cancer.[11]

In this issue, we have assembled a series of up-to-date reviews on the functional plasticity of Tregs to address and discuss how Tregs may sense the initiation and progression of inflammation in different physiological microenvironments. In an inflammatory micro-



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environment, a small subpopulation of Treg cells may lose the expression and/or function of the Treg cell lineage master regulator Foxp3 and function as inflammatory cytokine-producing pathogenic effector T cells (Teff cells), which were initially identified by and have been reviewed by Xuyu Zhou *et al.*[12,13] The induction and function of recently identified inflammatory Teff cells, called Th17 cells, are tightly controlled by differential nuclear receptors, as reviewed by Benjamin V. Park and Fan Pan.[14] Moreover, Treg cells may function locally and adapt to the tissue microenvironment in lymphoid and non-lymphoid tissues, including skin, muscle, adipocytes, and tumors, as reviewed by Zhou *et al.*[15] Over a decade ago, it was discovered that $Foxp3^+$ Treg cells could also be differentiated and induced from naive T cells *in vitro* and *in vivo* under TCR activation and costimulation by anti-inflammatory cytokines

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such as TGF-β. Liu *et al.* summarize recent progress in understanding the induction and function of induced Treg cells and their functional stability as modified by all-trans retinoic acid.[16] Zhiyuan Li *et al.* provide an update on the molecular mechanism by which the Foxp3 protein is dynamically regulated at the posttranslational level by inflammatory stimuli, as well as functional applications for clinical therapies.[17] In addition to Foxp3-expressing Treg cells, IL-10-producing but Foxp3-negative T regulatory cells, called Type 1 regulatory T (Tr1) cells, may also play a critical role in controlling immune homeostasis. Hanyu Zeng *et al.* summarize the induction and functional characterization of this important subset of Treg cells and their potential clinical applications.[18] More recently, it has been found that during the terminal and recovery phases of inflammation, inflammatory Th17 cells can transdifferentiate into immune suppressive Tr1 cells.[19] Future studies on the plasticity and transdifferentiation of Treg and Teff cells could provide therapeutic applications for treating human inflammatory diseases.

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