Immune Homeostasis by FoxP3^{+} Regulatory T Cells

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The regulatory T cells (a.k.a Treg) are unique population of T cells that has central importance in immunological tolerance to self and in the control of inflammatory processes. Tregs are generally considered to suppress all types of inflammatory responses triggered by various types of immune & non-immune cells. Hence, they play versatile roles to balance homeostasis, regarding both immunological (autoimmunity, allergy, responses to pathogenic and commensal microbes, cancer) and non-immunological (tissue regeneration, metabolic control) contexts. Initially, Treg has unique phenotypic markers including CD4, CD25, and FoxP3. Since shared expression of CD25 with activated T cells, only FoxP3 act as bona fide marker for Treg.

Foxp3, a winged-helix transcription factor (TF) of the Forkhead family, is specifically expressed in Treg cells, where it has pivotal roles for differentiation and function, and is considered to be the defining factor of the lineage. Germline deletion of Foxp3 leads to Treg deficiency and to devastating multi-organ inflammation in *scurfy* mice. In human IPEX (Immunodysregulation polyendocrinopathy enteropathy X-linked) patients, total loss of FoxP3 function also leads to the absence of Treg cells, but there is also a spectrum of missense mutations that allow the differentiation and maintenance of some Treg cells with partial functional deficiencies. Hence, FoxP3 generally considered the key factor to be Treg as the Treg.

Treg cells share a core transcriptional signature, genes that are over- or under-expressed in Treg cells relative to their naive CD4+ T cell counterparts (Tconv). Much of this signature is controlled by FoxP3, the lineage's defining TF, although FoxP3 cannot alone drive the entire Treg signature, and other TFs, such as Foxo1 or the Nr4a family, seem to play independent roles in specifying some Treg functions. The Treg signature contains a number of transcripts typically induced (or repressed) in activated T cells, in keeping with the self-reactive nature of the TCR in many Treg cells, but an important aspect of Foxp3 function in maintaining Treg identity is the suppression of effector cytokines produced by activated Tconv cells such as IL-2, IL-4, or IL-17.

Beyond this shared signature, Treg transcriptomes are further modified and adapted to their location and function to maximize local specific immuno-suppression known as 'Tissue Treg'. For instance, PPARγ-controlled transcripts that promote metabolic adaptation to the adipose tissue are uniquely found in Tregs that reside visceral adipose tissue (VAT) to control local/chronic inflammation to protect against metabolic disorders such as obesity and type II diabetes. Furthermore, the control of different types of effector Th cells involves the re-use, in Tregs, of TFs, known as Th lineage determining factors that govern those functions in Th cells (e.g. Irf4: Th2 type Tregs, Stat3: Th17 type Tregs, Tbet: Th1 type Tregs or Bcl6: Tfh type Treg).

Since Tregs act as 'Peace keeper' with the double-edge sword in immune system, the key questions in the fields of Treg immunology are how the Treg is modulated during the course of various ongoing immune responses and how to specifically modulate their functionalities in the context dependent manner to maximize therapeutic benefits during the course of immune responses. Conclusively, like Dr. Dipayan Rudra's comment on his review article, looking at the diversity of responses ranging from maintaining immune tolerance to tissue repair, to becoming a major stakeholder in maintenance of physiological function of tissues, it would be apt to say that Tregs are the proverbial "Jack of all trades," and certainly, "master" of some.