(Compl)Ex-Th17–T_{reg} cell inter-relationship

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Introduction

While Th17 and regulatory T (T_{reg}) cells functions per se are important to maintain the homeostasis, Th17/T_{reg}-governed sterile (para-)inflammation (a response defined by Medzhitov) is a corollary of immune responses against self-/neo-antigens and Th17–T_{reg} imbalance has a crucial role in the induction and maintenance of sterile chronic inflammation, associated with cancer. The development of Th17 and T_{reg} cells demonstrate common characteristics. Herein, we discuss the newly identified immunological mechanisms involved in the induction of Th17 cells and the development of converted ex-Th17 IL17–FoxP3+ T cells in sterile inflammation. As a novel subpopulation of forkhead box P3 (FoxP3+) cells, ex-Th17–FoxP3+ cells present a paradigm shift with important consequences for tumor initiation, progression and novel therapeutic approaches targeting mutual Th17–T_{reg} pathways of tumor immune surveillance.

Developmental Co-dependence of Th17–T_{reg} Cells

Differentiation of Th17 cells proceeds through a developmental pathway partially shared with the anti-inflammatory FoxP3+ T_{reg} population. This developmental mechanism can present itself in the perplexing co-existence of both populations. Marks et al. demonstrated that the environment may directly regulate the balance between the development of natural T_{reg} and Th17 subsets from a common precursor and implied that T_{reg} enrichment may be a necessary component preceding natural Th17 development. By T_{reg} cell depletion prior to in vivo Th17 priming, resulting in a reduced frequency of antigen-specific IL17 producers and reduced inflammatory skin responses, Chen et al. demonstrated that FoxP3+ T_{reg} cells promote Th17 cell development in vivo, and identified IL2 (single l) signaling to play an important role. Similarly, Pandiyans et al. observed enhanced IL2-dependent induction of Th17 cell differentiation of naïve CD4+ cells in the presence of T_{reg} cells in vivo.

T_{reg} Lineage is Stable

Genetic fate mapping and adoptive T cell transfer approaches led to the notion that the sustained expression of lineage-specifying transcription factors under control of inherent signaling pathways is likely a common feature of late T_{reg} and Th17 cell differentiation, required for the maintenance of a given cell identity in the progeny of dividing differentiated cells. Rubtsov et al. have shown that T_{reg} cell lineage is remarkably stable under physiologic conditions and following a variety of challenges, where stable FoxP3 expression in committed T_{reg} cells is likely facilitated by a positive autoregulatory loop and continuous self-renewal of the established T_{reg} cell population combined with the anti-inflammatory FoxP3+ T_{reg} population. This developmental mechanism can present itself in the perplexing co-existence of both populations. Marks et al. demonstrated that the environment may directly regulate the balance between the development of natural T_{reg} and Th17 subsets from a common precursor and implied that T_{reg} enrichment may be a necessary component preceding natural Th17 development. By T_{reg} cell depletion prior to in vivo Th17 priming, resulting in a reduced frequency of antigen-specific IL17 producers and reduced inflammatory skin responses, Chen et al. demonstrated that FoxP3+ T_{reg} cells promote Th17 cell development in vivo, and identified IL2 (single l) signaling to play an important role. Similarly, Pandiyans et al. observed enhanced IL2-dependent induction of Th17 cell differentiation of naïve CD4+ cells in the presence of T_{reg} cells in vivo.

Keywords: myeloid-derived suppressor cells, regulatory T cells, sterile inflammation, T cell plasticity, Th17 cells

Abbreviations: COX, cyclooxygenase; FoxP3, forkhead box P3; HIF-1α, hypoxia inducible factor 1 α; IDO, indoleamine 2,3-dioxygenase; IFN, interferon regulatory factor; MDSC, myeloid-derived suppressor cell; MMF, mycophenolate mofetil; MSC, mesenchymal stem cell; mTOR, mammalian target of rapamycin; NO, nitric oxide; NOS, nitric oxide synthase; PGE2, prostaglandin E2; PPAR, peroxisome proliferator-activated receptor; RA, retinoic acid; RheumA, rheumatoid arthritis; Rorc, retinoic acid receptor gamma; RA, retinoic acid; ROR, RORγt, retinoid-related orphan receptor gamma; Th17–Treg cell inter-conversion account for the enigmatic coexistence of IL17-producing and FoxP3+ cells in tumor-associated inflammation. In addition to T_{reg} cells, exTh17–FoxP3+ cells present a novel subpopulation of FoxP3+ cells. Yin-yang of IL17+ and FoxP3+ cells presents an important principle for improved approaches in cancer immunotherapy.
With heritable maintenance of FoxP3 expression serves as a major mechanism of maintenance of this lineage. Miyao et al. confirmed that Treg cells constitute a stable cell lineage and identified a minor population of non- regulatory FoxP3+/conventional T cells exhibiting promiscuous and transient FoxP3 expression, which give rise to FoxP3− cells and selectively accumulate in inflammatory milieu.12

Plasticity is an Integral Part of FoxP3+ and IL17+ T Cell Biology

While committed Treg cells are a stable population, ex-FoxP3 IL17A+ cells selectively accumulating in inflammatory milieu reveal the emergence of a plastic and conversion-prone minority within the FoxP3+ population.13-15 IL17+FoxP3+ pathogenic cells that can arise with disrupted immune homeostasis, present a new possibility to restore the balance: rather than focusing on the biology of the differentiated populations, the relevant targets of future clinical interventions could well be the mechanisms regulating plastic subsets.

In line with Treg lineage stability, Kryczek et al. reported that only a population of CCR6+ memory FoxP3− and CCR6+ FoxP3+ T cells are preferential precursors of IL17+FoxP3+ Th cells.16 Similar data by Mercer et al. substantiate the selective differentiation of IL17+FoxP3+ T cells from lineage-committed naive CCR6+ FoxP3+ precursors.17 Opposite, Th17 cells can convert to IL17+FoxP3+ cells and express FoxP3+ cells. Whether IL17+FoxP3+ cells represent a stable lineage or a transient state remains to be determined.

Bona fide Th17→Treg transcription factors integrate the functional phenotype of both lineages. While FoxP3 determines the suppressive potential, retinoid-related orphan receptor gamma t (RORγt) instructs the inflammatory phenotype. Cells harboring a FoxP3 reporter null allele exhibit some of the characteristics of FoxP3− Treg cells, but are devoid of suppressor activity and also produce IL17. This phenomenon demonstrates the essential purpose of FoxP3 in Treg cell regulatory function (i.e. in the stable Treg cells and the plastic subsets), but not its suggested requirement in initiating Treg cell lineage commitment.18 FoxP3-mediated repression of IL17 is likely due to a modulation of transcriptional activity of RORγt through a direct interaction.19 Ablation of the RORγt gene in FoxP3+ cells stabilizes Treg anti-inflammatory functions, suppresses inflammation, and improves immune surveillance.14 Further, signal transducer and activator of transcription (Stat) 3 is a transcription factor activated in both, Th17 and Treg cells, and is required for Th17 induction, while it interacts with FoxP3 in Treg cells, limits the expression of soluble mediators of Th17 differentiation, and endows Treg cells with the ability to suppress Th17 responses.20

Lineage specifying cytokine signaling induces a specific metabolic signature of differentiated T cells (extensively reviewed by Pearce et al.21). Metabolic signals (i.e., nutrient, energy, oxygen availability, and stress level) are integrated by mammalian target of rapamycin (mTOR), hypoxia inducible factor 1 α (HIF1α), and AMP-activated kinase (AMPK) and allow for the fine-tuning of the Th17−Treg cell balance (reviewed by Barbi et al.22). That metabolites can help shape Th cell fate was recently demonstrated by Smith et al., showing that short-chain fatty acids regulate colonic Treg cell homeostasis.23 With Th17−Treg inter-conversion, Th cells display a high degree of metabolic plasticity and can adapt their metabolism to support proliferation and viability.

Visceral adipose tissue FoxP3+CD4+ Treg have further revealed an additional association between metabolic regulation and Th17−Treg polarization. Nuclear receptor proliferator-activated receptor gamma (PPARγ) is a key regulator of human and mouse Th17 differentiation and a crucial molecular orchestrator of visceral adipose tissue Treg cell accumulation, phenotype, and function.24 A recent report by Carbo et al. demonstrates that PPARγ activation promotes a phenotype switch from Th17- to Treg cells and can thereby alleviate colitis.25 Th17-to-Treg conversion only occurs in lean fat tissue and allows for insulin sensitivity and homeostasis, while Th17 accumulation in adipose tissue is associated with increased insulin resistance.27

Factors with Dual Treg− and Th17-Promoting Functions

Apart from developmental codependence and Th17–FoxP3+ inter-conversion, an additional level of complexity in discriminating Th17 from Treg lineages is their dependence on the same differentiation factors. Here, the same signal may have either pro-Treg or pro-Th17 driving functions depending on the inflammatory micromilieu.

PGE2, an essential homeostatic factor and a mediator of chronic inflammation, has been shown to exert pro-Th17 effects and expand Th17 cells through both, enhanced macrophage and DC production of IL23 and IL1β and its direct action on Th17 cells.28 On the contrary, PGE2 produced by tumor cells induces the expansion of type-1 Treg cells and induces their endogenous expression of cyclooxygenase (COX2)/PGE2.29

TGFβ also drives both, Treg and Th17 cell differentiation in mice, while its role in human Th17 cell differentiation is controversial. While the induction of FoxP3 upon chronic antigen exposure in vivo requires TGFβR signaling,30 TGFβ as well contributes to mouse,32-36 although not human37,38 Th17 cell differentiation. TGFβ drives Treg and Th17 cell differentiation through the repression of Gfi-1, a transcriptional repressor that inhibits the differentiation of both iTreg and Th17 cells.39 It is the IL2, required for TGFβ-mediated induction of FoxP3 in peripheral T cells in vivo40 that opposes differentiation of activated CD4+ T cells into Th17 cells.41 Whereas the latter differentiation pathway is favored when T cell receptor and TGFβR activation in naive CD4+ T cells coincides with IL6R stimulation.42 Interestingly, recent results indicate that only in the presence of TGFβ increased salt (NaCl) conditions in combination with IL1β, IL6, and IL23 drive autoimmune disease by the induction of pathogenic Th17 cells.30
Inherent iNOS expression in CD4⁺ T cells limits Treg induction by repressing TGFβ. This negative regulation of TGFβ in human and mouse CD4⁺ T cells may explain the conflicting data on iNOS-mediated regulation of Th17 differentiation: whereas the NO/iNOS-cGMP-cGK pathway induces Th17 cell differentiation in naive and memory human CD4⁺ T cells, murine T cell-derived iNOS plays a negative role in the regulation of Th17 cell differentiation.

MDSCs – Central Regulators of Th17–Treg Cell Balance

Myeloid-derived suppressor cells (MDSCs) are a cell type that promote Treg cell expansion and/or drive the differentiation of Th17 cells. Most importantly, MDSCs promote IL17⁺FoxP3⁺ CD4⁺ Th cell induction and can skew IL17⁺FoxP3⁻CD4⁺ cells toward IL17⁺FoxP3⁻CD4⁺ cells. When immune homeostasis is disturbed in tissue malfunction, inflammation occurs through activating tissue-resident macrophages and/or recruiting additional myeloid cells. These in turn provoke expansion of MDSCs, which are associated with cancer, autoimmunity, and inflammation. MDSCs are thus a highly plastic key element of para-inflammation. The plasticity of MDSCs is displayed by their heterogeneity, and also helps to explain how various pathological settings can have similar biological effects on myeloid cells. PGE₂ has emerged as one key molecule in MDSC biology and appears to be the common denominator of diverse settings in the induction of MDSCs.

The most prominent cell type to induce MDSCs are cancerous cells. Additionally, bone marrow derived stromal cells, mesenchymal stem cells or adipose cells can also reprogram myeloid cells upon perturbed homeostasis (see Fig. 1). Ericksen et al. have shown that a sole subtle commensal stimulus suffices for sensitization and inflammation of adipose tissue that results in MDSCs mobilization, associated with increased Th17 responses and accelerated preneoplasia. MDSCs inherently express factors and cytokines that instruct the development and plasticity of Th17 or Treg predominance. MDSCs spontaneously produce significant amounts of PGE₂, IL1β, IL6, TGFβ₁, as well as arginase, indoleamine 2,3-dioxygenase (IDO), and...
IL10, all of which are implicated in both the induction of Th17 and Treg cells. In addition, they produce IL23 and NO following CD40 stimulation. The different activation status of MDSCs thereby explain the dual nature of MDSC-derived factors. IDO and iNOS both function as critical molecular “switches” regulating Th17–Treg balance. IDO maintains Treg cells in their normal, potently suppressive state, but when blocked, it allows for IL6-mediated Treg cell conversion into a non-suppressive, pro-inflammatory Th17 phenotype. Contrarily, iNOS/NO from MDSCs induces Th17 responses and its inhibition abrogates IL17 production and results in TGFβ-mediated FoxP3+ Treg cell induction.

Clinical Picture of Th17–FoxP3+ T Cell Inter-conversion

Cancer presents a state of chronic sterile inflammation, where the production of pro-inflammatory cytokines by FoxP3+ cells underlies a pathogenic phenotype of ex-FoxP3+ cells.

Despite a nominally immunosuppressive microenvironment, cancer presents a chronic inflammation infiltrated with high frequency of both Th17 and Treg cells. By virtue of their ability to control cancer-associated Th17 cell-mediated inflammation, FoxP3− and FoxP3+ Treg cells impede cancer progression in an IL10-dependent manner. However, their ability to control inflammation is lost in the course of disease and Treg cells shift from a protective IL10-producing anti-inflammatory to a IL17-producing cancer-promoting pro-inflammatory phenotype, with preserved capacity to suppress protective antitumor immune responses. Blattner et al. found preferential expansion of FoxP3+ in human colon cancer that can suppress T cells but are not anti-inflammatory like classic Treg. These FoxP3+RORγt+ IL17-producing pathogenic Treg cells are directly associated with inflammation and influence disease outcome in colon cancer. Ablating RORγt specifically in Treg stabilizes their anti-inflammatory properties and enhances polyp specific immunity. In analogy, Keerthivasan et al. showed that activation of Wnt/b-catenin signaling in both Th17 and Treg cells is associated with enhanced pro-inflammatory cytokines and correlates with the progression of colitis and colon cancer, which could be reversed in RORγt−/− mice.

Conclusions

Herein discussed data provide a rationale to target Th17–Treg commensalism (and not Treg cells alone) with novel interventional approaches (see Fig. 2). Combinatorial targeting of Th17–Treg interrelationship to promote IFNγ-producing Th1/17 cells will allow for an enhanced antitumor immunity. It will also be valuable to evaluate the Th17–Treg balance together with the plastic potential of Th17 and FoxP3+ cells as prognostic factors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.
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