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Strategic Diplomats of Immunity: Rethinking Tregs as Rheostats of Immune Regulation

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In the evolving narrative of immunology, regulatory T cells (Tregs) have traditionally been cast as the peacekeepers of the immune system, perceived as constant, stable, and passive enforcers of self-tolerance [1]. The expression of the transcription factor FOXP3 has long been regarded as indispensable for the development and suppressive function of Tregs [2]. However, recent discoveries prompt a critical reappraisal of this notion, revealing a more nuanced, dynamic, and context-sensitive character of Tregs. Three seminal studies in particular have accelerated this conceptual pivot. Jäger et al. demonstrated that Tregs can maintain suppressive function in steady-state tissues despite a near-complete loss of FOXP3 protein, yet this flexibility is lost in inflammatory settings, where Treg function becomes acutely FOXP3-dependent [3]. Wang et al. further revealed that succinate, a citric acid cycle intermediate elevated in inflammatory bowel disease, disrupts Treg function by promoting FOXP3 degradation through inhibition of its succinylation, linking metabolic stress to epigenetic instability [4]. In parallel, Klawon et al. illustrated that self-antigen-specific Tregs can suppress autoimmunity even during infection while sparing the immune system's ability to combat pathogens, highlighting a remarkable degree of antigen-specific discrimination [5]. Together, these findings present a portrait of Tregs as active integrators of environmental, metabolic, and antigenic signals, thus reimaging them as immune regulators whose function is far more strategic and adaptive than previously appreciated.

This reconceptualization is elegantly captured in the phrase "Strategic Diplomats of Immunity," a metaphor that shifts the image of Tregs from passive peacekeepers to context-aware moderators of immune decisions. Like diplomats, Tregs exhibit strategic restraint and engagement depending on the immunological landscape. In non-inflamed tissues, their function persists even in the absence of FOXP3, indicating a form of baseline regulation when threats are minimal. In inflamed tissues, however, FOXP3 becomes indispensable, suggesting a transition to active suppression mode when the immune environment becomes turbulent. This context-dependence aligns well with the concept of diplomatic engagement, i.e., not all situations demand intervention, but when they do, precise and contextually appropriate responses are critical, performed by skilled negotiators, as by Tregs in this case. The metabolic insight provided by Wang et al. further refines this analogy. Just as external pressures can destabilize geopolitical negotiations, internal metabolic stress, such as elevated succinate, can erode FOXP3 stability and undermine Treg functionality [4]. The result is a subtle yet

potent weakening of immune regulation, not through outright removal of Tregs but via a reduction in their molecular integrity. These findings converge on a model of immune modulation that is scalar rather than binary, where Tregs fine-tune their suppressive output in response to dynamic physiological cues. Hence, the analogy of a “rheostat” aptly fits Tregs, which function as dials rather than switches, adjusting their suppressive activity based on the inflammatory tone, antigenic landscape, and metabolic state.

This dynamic **perspective** of Treg activity is essential, considering that unchecked suppression would impair effective immune responses, while sub-optimal Treg function could lead to autoimmunity. Therefore, a framework wherein external **stimuli dynamically scale Treg function** offers a better understanding with respect to the function of Tregs in the context of inflammation. Importantly, this dynamic view also has profound clinical implications. It suggests that therapeutic manipulation of Tregs need not be absolute, but can be calibrated, such as dialed up in autoimmune disease to restore tolerance, or dialed down in cancer to enable anti-tumor immunity. This nuanced understanding also raises the possibility that Treg induction in cancer may result from chronic inflammation rather than being a direct outcome of tumorigenesis. The study by Klawon et al. further reinforces this idea by showing that Treg suppression is not indiscriminate but antigen specific [5]. Self-peptide-specific Tregs can selectively suppress autoimmune responses while preserving anti-pathogen immunity. Such specificity represents immune regulation at its most refined, i.e., **resolving internal immune conflicts without compromising host defense.** Such precision suggests that Tregs are not merely general suppressors but active decision-makers within the immune hierarchy, equipped to discriminate between friend and foe even under inflammatory pressure. Indeed, under overwhelming inflammation, this antigen-specific regulation might collapse into indiscriminate suppression, aligning with classical Treg biology associated with pathology. Additionally, the integration of antigen specificity with metabolic and transcriptional contexts constructs a compelling model of Tregs as intelligent immune sensors and responders. These cells do not suppress indiscriminately, rather, they assess, interpret, and respond. This behavior validates their reclassification as strategic regulators within the immune hierarchy.

Notably, the modern understanding of Treg function is **not limited to canonical CD4+FOXP3+ cells**. Recent studies have highlighted roles for **CD8+FOXP3+ Tregs and regulatory B cells (Bregs)**, particularly under experimental or pathological conditions. Though rare, these populations possess distinct regulatory roles in cancer, transplantation, and viral infections [6,7]. Their inducible expansion and antigen-specificity reinforce the notion that immune suppression is a **flexible and strategic response** tailored to the context. These populations complement CD4+ Tregs, contributing to a broader, more coordinated immune regulation. For example, induced Tregs (iTregs), generated in vitro, have demonstrated reparative functions in models of viral pneumonia. This layered model of regulation highlights that the rheostat-like behavior attributed to these regulatory cells is, in fact, a distributed function, shaped by the collective contribution of multiple cell types and molecular programs. Much like how different materials are chosen to construct rheostats tailored to specific electrical loads, the immune system employs diverse regulatory players depending on the inflammatory context and physiological demand, emphasizing that no single mechanism fits all scenarios. However, the efficacy of these regulatory cells is **tightly coupled to their epigenetic integrity.** The maintenance of FOXP3 expression via DNA methylation, governed by UHRF1, is crucial. In the absence of UHRF1, iTregs lose their identity, acquire effector traits, and exhibit reduced reparative capacity [8]. These findings underscore that epigenetic anchoring is

essential for Tregs to execute contextually appropriate immunoregulatory functions, acting as the molecular grounding that enables their rheostat-like responsiveness to immune fluctuations.

While the metaphors of diplomacy and rheostats are evocative, they risk **oversimplifying complex immune dynamics**. The term "strategic diplomats" might anthropomorphize cellular behavior. However, these analogies are **heuristically valuable**, offering a conceptual bridge between immunological data and systems-level understanding. They encourage **more granular experimental designs** and **precision-based therapeutic strategies**. By embracing the model of Tregs as adaptive, context-responsive regulators, the field can **transcend static suppression paradigms** and approach a systems biology framework for immune balance.

Thus, the title "**Strategic Diplomats of Immunity: Rethinking Treg Cells as Rheostats of Immune Regulation**" encapsulates this evolution with clarity. It calls on immunologists to re-examine long-held assumptions, explore Treg context-specific behaviors with greater resolution, and design **precision immunotherapies** that reflect the nuanced spectrum of Treg functions. In doing so, we honor the complexity of Treg biology and chart a thoughtful path forward for translational immunology.

References

1. Sakaguchi S, Yamaguchi T, Nomura T, Ono M. Regulatory T cells and immune tolerance. *Cell*. 2008
2. Hori S, Nomura T, Sakaguchi S. Control of regulatory T cell development by the transcription factor Foxp3. *Science*. 2003
3. Jäger C, Dimitrova P, Sun Q, et al. Inducible protein degradation reveals inflammation-dependent function of the T_{reg} cell lineage-defining transcription factor Foxp3. *Sci Immunol*. 2025
4. Wang H, Hu D, Cheng Y, et al. Succinate drives gut inflammation by promoting FOXP3 degradation through a molecular switch. *Nat Immunol*. 2025
5. Klawon DEJ, Pagane N, Walker MT, et al. Regulatory T cells constrain T cells of shared specificity to enforce tolerance during infection. *Science*. 2025
6. Luo S, Larson JH, Blazar BR, Abdi R, Bromberg JS. $Foxp3^{+}CD8^{+}$ regulatory T cells: bona fide Tregs with cytotoxic function. *Trends Immunol*. 2025
7. Rosser EC, Mauri C. Regulatory B cells: origin, phenotype, and function. *Immunity*. 2015
8. Joudi AM, Gurkan JK, Liu Q, et al. Maintenance DNA methylation is required for induced regulatory T cell reparative function following viral pneumonia. Preprint. *bioRxiv*. 2025