Artificial Intelligence–Enabled Dissection of Regulatory T Cells in the Tumor Immune Microenvironment: From Mechanistic Insight to Population-Scale Inference

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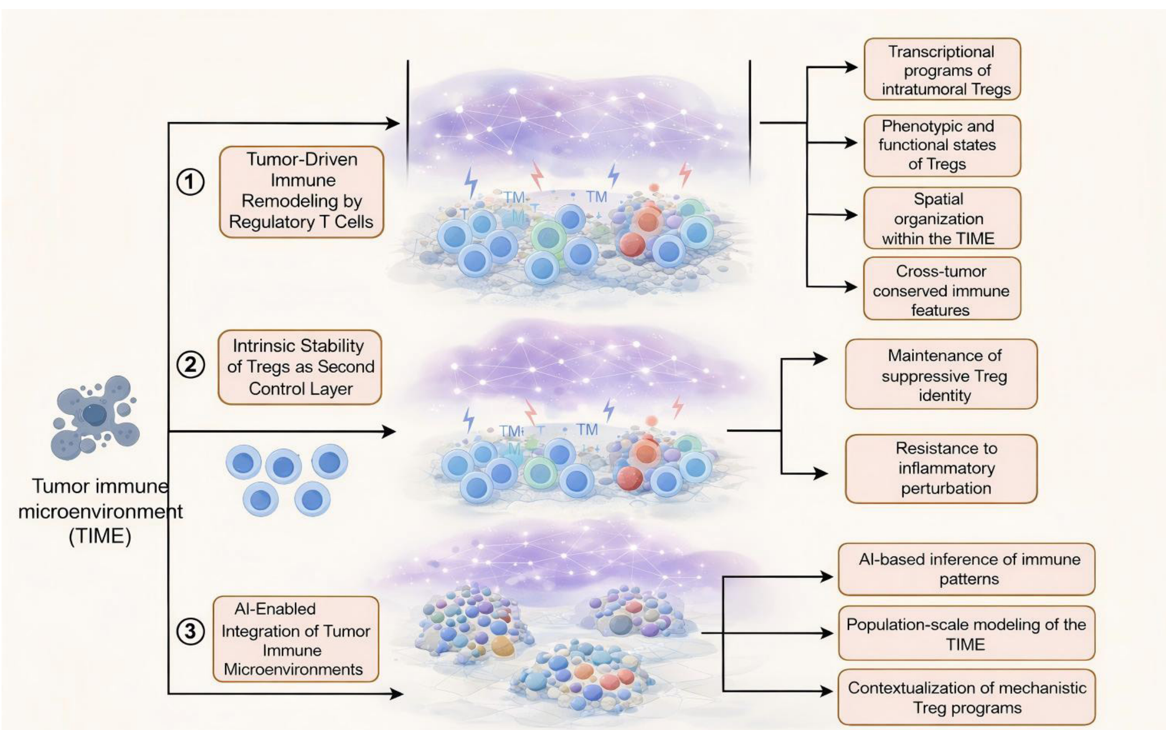
Graphical Abstract



AI-enabled integration of mechanistic Treg biology with scalable modeling of the tumor immune microenvironment.

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Artificial Intelligence–Enabled Dissection of Regulatory T Cells in the Tumor Immune Microenvironment: From Mechanistic Insight to Population-Scale Inference

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Abstract

Background: Regulatory T cells (Tregs) are central regulators of immune tolerance in the tumor immune microenvironment (TIME) and are increasingly implicated in tumor immune evasion and immunotherapy resistance. While mechanistic studies have delineated pathways governing Treg recruitment and functional stability, extending these insights to spatial organization and population-level heterogeneity remains a major challenge.

Methods: In this correspondence, we integrate recent advances in tumor immunology with emerging artificial intelligence (AI)–based analytical frameworks to highlight how Treg-driven immune programs can be interrogated at scale. We draw on representative experimental mechanisms and AI-enabled multimodal modeling approaches, including virtual tumor microenvironment reconstruction and vision–language foundation models, to illustrate a mechanism-informed computational perspective.

Results: Evidence supports a layered model of tumor-driven Treg regulation, combining chemokine-mediated recruitment with intrinsic transcriptional stabilization within the TIME. AI-enabled approaches enable population-scale inference of Treg abundance, spatial distribution, and functional states, revealing clinically relevant heterogeneity and associations with differential immunotherapy responses that are difficult to capture using conventional experimental strategies alone.

Conclusion: The convergence of mechanistic Treg biology and AI-driven TIME modeling offers a conceptual framework for bridging experimental insight with real-world tumor heterogeneity. Mechanism-informed AI has the potential to refine immune stratification and guide Treg-targeted therapeutic strategies, highlighting a translational path forward for precision immuno-oncology.

Keywords: Artificial intelligence; Regulatory T cells; Tumor immune microenvironment; Immunotherapy; Precision oncology

Introduction

The study of regulatory T cells (Tregs) has garnered significant attention due to their pivotal role in modulating the tumor immune microenvironment (TIME). This year, the Nobel Prize in Physiology or Medicine recognized fundamental discoveries in peripheral immune tolerance, centered on Tregs, a lineage now widely implicated in tumor immune evasion. In parallel, last year's Nobel Prize in Physics honored advancements in artificial intelligence (AI) and machine learning, technologies now increasingly integral to understanding cancer biology. As AI begins to unravel the complexities of immune systems, it offers unprecedented tools for analyzing immune interactions at a population scale, which is particularly beneficial for exploring the spatial and functional dynamics of Tregs in cancer.

The convergence of these two fields—the Nobel-winning discoveries of Tregs in cancer immunotherapy and AI's expanding role in precision oncology—lays the foundation for a transformative shift in how we approach cancer research. By leveraging AI, we can begin to address longstanding challenges in oncology, including the intricate mechanisms of immune cell behavior, such as Treg recruitment and function in the tumor context.

Recent advances in artificial intelligence have shifted biomedical research from purely data-driven analysis toward integrated biological intelligence, emphasizing multimodal learning and cross-scale data fusion for complex biological systems [1]. This evolution provides a general methodological foundation for studying tumor immune regulation in a scalable and biologically informed manner.

Within oncology, such integrative strategies are increasingly necessary to contextualize immune mechanisms across heterogeneous tumors. Evidence from molecularly stratified clinical studies demonstrates that tumor-intrinsic alterations, such as FGFR pathway changes, can influence immune checkpoint inhibitor efficacy [2], while multi-omics and machine-learning–based integration of imaging, molecular, and pathological data has emerged as a generalizable approach to resolve biological heterogeneity and support clinically relevant inference [3-4].

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Tregs as Active Targets of Tumor-Driven Immune Remodeling

Rather than passive bystanders, regulatory T cells (Tregs) are increasingly recognized as central executors of tumor-driven immune remodeling. In clear cell renal cell carcinoma (ccRCC), our recent study identified a TGFBI–CCL22–Treg axis, illustrating how tumor- and stroma-derived signals can promote the selective accumulation of FOXP3$^+$ Tregs within the tumor immune microenvironment (TIME) [5]. Importantly, this observation serves primarily as a mechanistic entry point, highlighting the broader concept that tumors actively shape immune tolerance by recruiting and sustaining Tregs.

Accumulating high-impact evidence supports the notion that Tregs are deliberately co-opted by tumors to establish immune privilege. A landmark study in *Nature Medicine* first demonstrated that tumors selectively recruit Tregs through the CCL22–CCR4 chemokine axis, leading to suppressed antitumor immunity and poor clinical outcomes, thereby establishing chemokine-guided Treg trafficking as a conserved immune evasion strategy [6]. Beyond recruitment, Tregs have been shown to critically determine therapeutic responses. Seminal work published in *The Journal of Experimental Medicine* revealed that the efficacy of anti–CTLA-4 therapy depends on Fc-mediated depletion of intratumoral Tregs, redefining immune checkpoint blockade as a Treg-modulating intervention rather than solely an effector T cell–activating strategy [7].

At the cellular and transcriptional levels, recent high-dimensional profiling studies further reinforce the central role of Tregs in the TIME. Comprehensive analyses reported in *Nature Immunology* demonstrated that intratumoral Tregs share conserved gene regulatory and transcriptional programs across diverse cancer types, enabling the maintenance of their suppressive phenotype irrespective of tissue origin [8]. Consistently, distinct but functionally specialized Treg populations have been characterized in human breast cancer, highlighting tumor-specific adaptation of Tregs while preserving core suppressive functions [9].

Collectively, these findings support a unifying framework in which tumors do not merely evade immune surveillance but actively co-opt Tregs as functional mediators of immune suppression. Within this conceptual landscape, the TGFBI–CCL22–Treg axis observed in ccRCC exemplifies one of multiple mechanisms through which tumors orchestrate Treg biology, underscoring the broader relevance of targeting Tregs to disrupt tumor-driven immune remodeling across cancers.

Beyond Recruitment: Intrinsic Stability of Tregs as a Second Control Layer

Recruitment alone, however, does not fully explain the persistence and suppressive potency of Tregs within the TIME. Their functional dominance also depends on intrinsic transcriptional and epigenetic stability, which safeguards Treg identity under inflammatory pressure. Elegant mechanistic studies have revealed that Foxp3, the master regulator of Treg lineage commitment, forms a repressive complex with the transcription factor Ikzf1 to silence effector genes such as *IFNG*, thereby stabilizing the suppressive phenotype of Tregs [10].

Disruption of the Foxp3–Ikzf1 interaction destabilizes Tregs, leading to IFN-γ overproduction, loss of suppressive function, and paradoxically enhanced antitumor immunity. These findings suggest that tumors benefit not only from attracting Tregs into the TIME but also from maintaining their transcriptional integrity once established. Conceptually, Treg regulation in cancer can therefore be viewed as a two-tiered system: tumor-mediated recruitment followed by intrinsic transcriptional reinforcement.

This layered mode of control creates therapeutic opportunities but also introduces substantial analytical challenges. Dissecting where, when, and to what extent recruitment-dependent versus stability-dependent mechanisms dominate across heterogeneous patient populations exceeds the capacity of traditional experimental approaches. This motivates scalable, population-level approaches capable of resolving TIME heterogeneity.

AI and the Emergence of Virtual Tumor Immune Microenvironments

Artificial intelligence has begun to address this scalability problem. Multimodal frameworks such as GigaTIME leverage deep learning to infer spatial proteomic patterns from routine hematoxylin and eosin (H&E) slides, generating virtual multiplex immunofluorescence (mIF) data at population scale [11]. Specifically, such models take whole-slide histopathology images as primary inputs, employ convolutional and transformer-based architectures to learn spatially resolved feature representations, and are trained against matched molecular or imaging-derived ground truth to enable cross-modality inference.

By translating morphological features into immune activation maps, GigaTIME enables the construction of “virtual populations” comprising tens of thousands of tumors across cancer types. This approach fundamentally changes how the TIME can be studied: rare immune configurations, spatial arrangements, and combinatorial protein signatures—previously inaccessible due to cost and throughput limitations—become analyzable at scale. Model robustness is typically assessed through cross-cohort validation and comparison with orthogonal experimental measurements, ensuring that inferred immune patterns are reproducible and biologically meaningful.

For Treg-focused research, such platforms provide a powerful means to contextualize mechanistic immune programs across diverse clinical settings. Rather than asking whether a pathway exists, AI-enabled modeling allows investigators to ask how frequently, in which spatial niches, and in which patient subsets a given immunosuppressive program predominates. Importantly, alignment with biological mechanisms can be achieved by anchoring model interpretation to experimentally validated pathways—such as chemokine-driven Treg recruitment or transcriptional stability programs—thereby enabling AI-derived predictions to inform, and be iteratively refined by, mechanistic immunology.

Vision–Language Foundation Models and Mechanism-Aware Oncology

Beyond spatial inference, vision–language foundation models such as MUSK represent a further evolution in AI-driven oncology [12]. By jointly learning from pathology images and clinical text, these models demonstrate strong zero-shot performance in prognostic prediction and immunotherapy response assessment. Importantly, they move AI from pattern recognition toward integrative reasoning across modalities.

The next conceptual step is to align such models with biological mechanisms. Mechanistic discoveries—such as tumor-derived chemokine gradients driving Treg recruitment or transcriptional circuits stabilizing Treg identity—can serve as interpretive anchors for AI outputs. In turn, AI can highlight unexpected contexts in which these mechanisms are amplified, suppressed, or overridden.

In this sense, AI should not be viewed as a replacement for mechanistic immunology, but as a force multiplier that extends mechanistic insight into real-world complexity.

Toward a Convergent Framework

The convergence of molecular immunology and AI-driven TIME modeling marks a turning point in cancer research. Mechanistic dissection of tumor-driven Treg programs illustrates how focused experimental studies can reveal actionable immune vulnerabilities, while AI frameworks provide the scale and spatial resolution required to translate these insights into population-level relevance. At the same time, the effective application of such AI frameworks remains contingent on the availability of large, well-curated, and standardized datasets, as well as rigorous cross-cohort validation to mitigate bias and ensure biological interpretability.

Future progress will depend on mechanism-informed AI, in which experimentally validated pathways guide model interpretation, validation, and clinical deployment. Conversely, AI-derived hypotheses should inform experimental prioritization, focusing attention on the most clinically impactful immune circuits. Bridging this vision to implementation will require coordinated advances in data harmonization, model transparency, and close integration between computational predictions and experimental validation.

Ultimately, integrating biological depth with computational breadth may redefine how immune evasion is understood and overcome across immunologically complex solid tumors. A clear recognition of current technical and translational constraints will be essential for ensuring that AI-driven insights move beyond conceptual promise toward robust and clinically actionable applications.

Translational and Therapeutic Perspectives

AI-driven analysis of the tumor immune microenvironment offers practical opportunities to translate Treg biology into therapeutic decision-making. By integrating histopathology, molecular profiling, and clinical data at population scale, AI frameworks can enable patient stratification based on Treg abundance, spatial localization, and functional states, thereby identifying tumor subsets more likely to benefit from Treg-modulating strategies. Such stratification may inform the selection of patients for therapies targeting Treg recruitment, stability, or suppressive function, beyond conventional biomarkers that rely solely on tumor genetics or bulk immune signatures.

In addition, AI-enabled approaches can facilitate biomarker discovery and rational combination strategies by linking Treg-associated immune programs with treatment outcomes across large cohorts. For example, population-scale modeling may reveal contexts in which Treg enrichment predicts resistance to immune checkpoint blockade, supporting combination approaches that pair immunotherapy with agents targeting chemokine pathways, stromal cues, or transcriptional programs sustaining Treg stability. Importantly, a mechanism-informed AI framework allows these hypotheses to be grounded in experimentally validated pathways, enabling iterative refinement through focused preclinical and clinical studies. Together, such integrative strategies position AI not only as an analytical tool, but as a translational bridge connecting Treg-centered immunology with precision immunotherapy.

Abbreviations

AI, artificial intelligence; CCR4, C-C motif chemokine receptor 4; ccRCC, clear cell renal cell carcinoma; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; FGFR, fibroblast growth factor receptor; FOXP3, forkhead box P3; Foxp3, forkhead box P3; H&E, hematoxylin and eosin; ICI, immune checkpoint inhibitor; IFNG, interferon gamma; Ikzf1, Ikaros family zinc finger 1; mIF, multiplex immunofluorescence; TIME, tumor immune microenvironment; TGFBI, transforming growth factor beta–induced; Treg(s), regulatory T cell(s).

Author Contributions

Xuexue Hao, Muwei Li and Tao Xiong contributed equally to this work. Xuexue Hao and Muwei Li conceived the central concept and wrote the initial manuscript. Tao Xiong contributed to the integration of immunological mechanisms and AI-related frameworks and participated in critical revisions of the manuscript. Xiaoqiang Liu supervised the overall project, provided conceptual guidance, and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

Not Applicable.

Competing Interests

The authors declare that they have no existing or potential commercial or financial relationships that could create a conflict of interest at the time of conducting this study.

Data Availability

Not Applicable.

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