Concept Paper

Psychosocial Determinants of Immunotherapy Response Through Chronic Inflammation and Immune Senescence

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Posted Date: 30 January 2026

doi: 10.20944/preprints202601.2322.v1

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Psychosocial Determinants of Immunotherapy Response Through Chronic Inflammation and Immune Senescence

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Abstract

Despite revolutionary successes, 60-70% of cancer patients fail to respond to immune checkpoint inhibitors and CAR-T cell therapies, even when tumors harbor predictive biomarkers. We propose "immune biography"—the cumulative encoding of lifetime psychosocial stress in immune system function—as a critical missing variable explaining therapeutic resistance. Chronic stress operates through three neuroendocrine pathways to create dysfunctional T cell states: glucocorticoid receptor signaling programs exhaustion-like transcriptional profiles, chronic inflammation drives bystander T cell dysfunction through IL-6/STAT3/TOX pathways, and catecholamine exposure blocks metabolic reprogramming essential for T cell activation. These stress-programmed T cell phenotypes—measurable through inflammatory markers, exhaustion signatures, and metabolic dysfunction—predict immunotherapy outcomes independently of tumor characteristics. Critically, stress-induced immune dysfunction is modifiable through evidence-based interventions including exercise, β-adrenergic blockade, and IL-6 inhibition. We present immediately actionable strategies for patient stratification and immune enhancement that could improve outcomes by addressing the biological consequences of chronic stress through targeted interventions.

Keywords: immune checkpoint inhibitors; CAR-T cell therapy; cell exhaustion; tumor microenvironment; neuroimmunology

The Immunotherapy Paradox

Two patients with metastatic melanoma present with identical tumor characteristics—high mutational burden, PD-L1 positive, brisk lymphocytic infiltration. One achieves complete remission with pembrolizumab; the other progresses rapidly. This scenario repeats daily in oncology clinics worldwide, highlighting a fundamental gap in our understanding: tumor-intrinsic biomarkers explain only partial variance in immunotherapy outcomes[1–3].

The immunotherapy revolution has transformed cancer treatment, yet persistent realities temper this success. Meta-analyses reveal that checkpoint inhibitor monotherapy produces responses in only 20-30% of unselected patients across solid tumors[4]. Even in melanoma, approximately 50% demonstrate primary resistance to anti-PD-1 therapy[5]. CAR-T cell therapy achieves remarkable responses in specific contexts, yet 40-60% of diffuse large B-cell lymphoma patients fail to respond, with many initial responders relapsing[6].

Accumulating clinical observations point toward a missing variable. Patients with elevated systemic inflammatory markers—neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), interleukin-6 (IL-6)—demonstrate inferior checkpoint inhibitor responses regardless of tumor mutational burden or PD-L1 expression[7,8]. Pre-treatment T cell exhaustion phenotypes predict resistance[9]. For CAR-T therapy, the phenotypic quality of patients® T cells before collection determines manufacturing success and clinical outcomes[10].

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These observations converge on a critical insight: therapeutic efficacy depends not solely on tumor biology but fundamentally on the functional capacity of the patient's immune system—capacity shaped by factors extending far beyond genetics. Emerging evidence suggests that chronic psychosocial stress—accumulated through adverse life experiences, socioeconomic hardship, chronic disease burden, and psychological distress—creates measurable, mechanistic immune dysfunction that predisposes to therapeutic resistance.

Immune Biography: The Biological Basis

We propose "immune biography"—the cumulative record of lifetime psychosocial experiences encoded in immune system structure and function—as the framework explaining this missing variance. Chronic stress operates through well-characterized neuroendocrine pathways that directly reprogram immune cell biology[11,12].

Stress-Programmed T Cell Dysfunction: Three Convergent Pathways

Chronic psychosocial stress creates measurable T cell dysfunction through three neuroendocrine pathways, each generating distinct but overlapping dysfunctional T cell states that predict immunotherapy resistance.

Glucocorticoid-programmed exhaustion: Sustained stress elevates circulating glucocorticoids (cortisol in humans), which access T cells directly through glucocorticoid receptors (GR) expressed on activated lymphocytes. Recent work demonstrates that chronic GR signaling in CD8+ T cells drives a transcriptional program remarkably similar to exhaustion: upregulation of inhibitory receptors (PD-1, LAG-3, TIM-3), expression of TOX (the master regulator of exhaustion), and metabolic reprogramming[13,14]. Mechanistically, GR cooperates with NFAT—a transcription factor activated during T cell receptor signaling—to induce and stabilize exhaustion programs. Critically, genetic deletion of GR in T cells enhances anti-tumor immunity and improves checkpoint inhibitor responses in preclinical models, establishing that glucocorticoid exposure alone, independent of tumor antigens, can create therapeutic resistance.

Inflammation-driven bystander exhaustion: Chronic stress elevates systemic inflammatory cytokines, particularly IL-6, which signals through STAT3 in T cells. This pathway directly induces TOX expression and upregulates inhibitory receptors, creating exhaustion-like dysfunction even in T cells not encountering cognate antigen—a phenomenon termed "bystander exhaustion"[14,15]. Combined blockade of IL-6 and PD-1 shows synergistic anti-tumor effects in preclinical models, reversing the mutual reinforcement between inflammation and T cell dysfunction[16]. Clinically, elevated pre-treatment IL-6 predicts checkpoint inhibitor failure independently of tumor characteristics[8], consistent with inflammation pre-programming T cells toward resistant states before therapy initiation.

Catecholamine-mediated metabolic suppression: Stress-induced catecholamines (epinephrine, norepinephrine) signal through β-adrenergic receptors on T cells, blocking the metabolic reprogramming essential for T cell activation and effector function. β-adrenergic stimulation impairs upregulation of glucose transporters, reduces glycolytic flux, and suppresses oxidative phosphorylation, creating metabolically compromised T cells unable to sustain proliferation or cytotoxic activity[17]. This "adrenergically suppressed" state is mechanistically distinct from classical exhaustion but produces similar functional consequences: reduced proliferation, impaired cytokine production, and therapeutic resistance.

Why These Mechanisms Matter for Immunotherapy

These stress-programmed T cell states exist *before* immunotherapy and predict resistance. Patients with chronic stress exposure—whether from disease burden, socioeconomic adversity, or psychological distress—may present with T cell populations already carrying exhaustion transcriptional programs, inflammatory priming, and metabolic suppression.

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For checkpoint inhibitor therapy, this creates a fundamental problem: the therapy attempts to reverse exhaustion in cells already programmed toward dysfunction through stress pathways that checkpoint blockade does not address. Anti-PD-1 antibodies can block one inhibitory receptor, but if T cells carry stable exhaustion programs induced by chronic glucocorticoid exposure, inflammation-driven TOX expression, and metabolic suppression from catecholamine signaling, removing PD-1 blockade alone may be insufficient for functional restoration.

For CAR-T therapy, the challenge is even more direct. Autologous cell collection from stressed patients yields starting material carrying these dysfunction signatures. Manufacturing processes cannot fully erase stable exhaustion programs or restore metabolic fitness compromised by chronic stress exposure, limiting both production success and clinical efficacy[10]. Studies demonstrate that the phenotypic and metabolic state of pre-manufacturing T cells—determined by the patient's immune biology—predicts CAR-T product quality and clinical outcomes better than tumor characteristics[18–20].

Accelerated Immune Senescence: The Broader Context

Beyond creating acutely dysfunctional T cell states, chronic stress accelerates fundamental immune aging processes. Stress drives thymic involution, reducing naive T cell generation[21,22]. Repeated activation accelerates telomere attrition, limiting proliferative capacity[23]. T cell receptor (TCR) repertoire diversity contracts through reduced naive input and oligoclonal expansion[24]. The result is premature immunological aging, chronologically young individuals with immune phenotypes characteristic of advanced age[25,26].

These changes become biologically embedded through epigenetic modifications—DNA methylation and histone modifications creating stable alterations in gene expression persisting long after initial stressors[27,28]. This "epigenetic scarring" fundamentally limits T cell functional potential regardless of subsequent interventions. Epigenetic clocks based on DNA methylation patterns provide quantitative measures of this biological aging, predicting health outcomes better than chronological age and correlating with cumulative stress exposure[29–31].

The Evidence Base

Inflammatory biomarkers predict outcomes: Elevated NLR (≥5) associates with reduced response rates, shorter progression-free survival, and worse overall survival across melanoma, non-small cell lung cancer, and renal cell carcinoma treated with checkpoint inhibitors[7,32]. Meta-analyses including thousands of patients establish NLR as an independent prognostic factor beyond PD-L1 expression and tumor mutational burden. Elevated pre-treatment IL-6 and CRP similarly predict checkpoint inhibitor failure[8]. For CAR-T therapy, pre-infusion inflammatory markers predict both severe cytokine release syndrome and inferior efficacy[33].

T cell phenotypes determine responses: Higher frequencies of exhausted T cells (PD-1+TIM-3+LAG-3+) before checkpoint inhibitor therapy associate with non-response[9]. Conversely, patients with higher frequencies of less differentiated T cells with progenitor potential demonstrate superior responses[34]³¹. For CAR-T therapy, the phenotypic composition of apheresed T cells predicts outcomes: products with higher naive and central memory content show superior expansion, persistence, and anti-tumor efficacy[18,19].

Metabolic fitness predicts efficacy: For CAR-T therapy, the metabolic state of starting T cells—measured as spare respiratory capacity and glycolytic reserve—predicts product quality and clinical outcomes[35]. Cells with robust metabolic fitness demonstrate superior expansion, cytokine production, and anti-tumor activity. This validates mechanistic predictions that stress-induced metabolic dysfunction constrains therapeutic responses.

TCR diversity and telomere length: Higher baseline TCR diversity associates with better checkpoint inhibitor outcomes[36]. For CAR-T therapy, greater diversity in manufactured products predicts superior responses[20]. Shortened leukocyte telomeres correlate with checkpoint inhibitor

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resistance[37], while longer telomeres in CAR-T products predict superior expansion and persistence[38].

Clinical Implications: Actionable Strategies Now

Patient Stratification

Oncologists can implement immune biology assessment using currently available tools. Routine blood tests provide inflammatory markers (NLR, CRP, IL-6). Flow cytometry, where available, quantifies exhaustion markers and naive:memory T cell ratios. Brief questionnaires assess stress exposure and psychological distress. This stratification identifies high-risk patients (NLR ≥5, elevated IL-6/CRP, high stress burden) who may require enhanced therapeutic approaches or preferential enrollment in intervention trials.

Immune Enhancement Interventions

Evidence-based strategies exist today for improving immune function before and during immunotherapy. Importantly, the stress-programmed dysfunction mechanisms suggest *specific* therapeutic targets beyond generic "immune boosting."

Exercise demonstrates the strongest evidence. Structured exercise programs reduce systemic inflammation (decreased IL-6, CRP, TNF-α), improve T cell phenotypes (increased naive frequencies, reduced exhaustion markers), and enhance metabolic fitness[39,40]. Mechanistically, exercise modulates neuroendocrine signaling, reduces adipose tissue inflammation, and may influence epigenetic programming. A practical protocol: 150 minutes weekly moderate-intensity aerobic exercise plus resistance training, initiated 2-4 weeks before immunotherapy and continued during treatment.

β-adrenergic blockade directly interrupts catecholamine-mediated metabolic suppression and reduces immunosuppressive myeloid expansion. A phase I trial combining propranolol with pembrolizumab in metastatic melanoma demonstrated 50% response rates with acceptable toxicity[41]. Propranolol is widely available, well-tolerated, and could be implemented immediately in clinical trials. This represents a mechanism-targeted intervention directly addressing stress-pathway-mediated dysfunction.

IL-6 pathway inhibition could interrupt inflammation-driven bystander exhaustion. While combining IL-6 blockade (tocilizumab, siltuximab) with checkpoint inhibitors has been tested primarily for managing immune-related adverse events, preclinical data support testing whether IL-6 inhibition *before and during* immunotherapy enhances efficacy by preventing inflammation-driven T cell dysfunction[16]. This requires prospective trials but has strong mechanistic rationale.

Metabolic optimization includes metformin, which improves insulin sensitivity, reduces inflammation, and enhances T cell metabolic fitness. Retrospective analyses suggest improved checkpoint inhibitor outcomes in patients taking metformin for diabetes[42]. For CAR-T therapy, brief ex vivo metabolic enhancement during manufacturing—providing metabolic substrates, modulating signaling pathways—could improve product quality from stress-compromised starting material[35].

Glucocorticoid receptor modulation represents a novel approach suggested by mechanistic studies. Selective glucocorticoid receptor modulators (SEGRMs) that block pathological stress-induced GR signaling while preserving beneficial anti-inflammatory effects could prevent glucocorticoid-programmed exhaustion. While such compounds remain in early development, they represent mechanism-based therapeutic strategies directly targeting stress biology[43].

Combination Strategies

Optimal enhancement likely requires combination approaches targeting multiple stress-pathway mechanisms simultaneously: exercise reduces inflammation and improves metabolism; β-

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blockers interrupt catecholamine signaling; IL-6 inhibition prevents inflammation-driven exhaustion; metabolic optimization addresses bioenergetic dysfunction. Testing such combinations requires systematic trials but could address the multifactorial nature of stress-induced immune dysfunction more comprehensively than single interventions.

Clinical Trial Priorities

Window-of-opportunity trials testing brief enhancement interventions (2-4 weeks of exercise, β-blockers, or combination approaches) before immunotherapy initiation could rapidly establish proof-of-concept while minimizing treatment delays. Designs should stratify by baseline immune biology (high versus low inflammatory markers, exhaustion phenotypes) and include biomarker endpoints demonstrating that interventions improve immune phenotypes (reduced NLR, reduced exhaustion markers, improved metabolic fitness, increased naive T cells) alongside clinical outcomes.

Mechanism-targeted trials could test specific hypotheses: Does β-blockade improve responses specifically in patients with high baseline catecholamine levels or sympathetic nervous system activity? Does IL-6 inhibition enhance efficacy in patients with elevated pre-treatment IL-6? Does exercise preferentially benefit metabolically compromised patients? Biomarker-stratified designs could identify which interventions work for which patients, enabling precision immune enhancement approaches.

CAR-T manufacturing optimization could test whether brief interventions before apheresis (exercise, β-blockers, metabolic optimization) improve starting material quality, manufacturing success, and clinical outcomes. Alternatively, ex vivo enhancement strategies during manufacturing—metabolic reprogramming, epigenetic modulation, rest periods to reduce exhaustion features—could compensate for stress-compromised starting material[19].

Broader Implications and Future Directions

Beyond cancer, immune biography principles apply wherever immune function determines outcomes—vaccines, infections, aging. Cancer immunotherapy provides compelling proof-of-concept in a context where immune capacity directly and measurably determines therapeutic success.

Allogeneic cellular therapies manufactured from healthy donors with favorable immune biology (low inflammatory markers, high naive T cell frequencies, robust metabolic fitness, long telomeres) could avoid limitations of autologous approaches using stress-compromised patient cells[44]. Donor selection criteria should include immune health assessment, not just HLA matching.

Addressing root causes requires acknowledging that the most effective intervention is preventing chronic stress exposure. Social policies reducing poverty, discrimination, and cumulative adversity would prevent immune dysfunction more effectively than biological interventions treating consequences. However, such upstream solutions require societal changes extending beyond medical practice. In the interim, biological interventions targeting stress pathways offer nearer-term opportunities to improve outcomes while advocacy continues for addressing root causes.

Research priorities include prospective validation of comprehensive immune biology assessment predicting outcomes across diverse populations, intervention trials testing combinations of enhancement strategies, mechanistic studies identifying which immune deficits are most rate-limiting and most reversible, and health equity research ensuring discoveries benefit populations experiencing greatest stress burdens.

The convergence of mechanistic understanding (stress-programmed T cell dysfunction through defined pathways), measurement feasibility (inflammatory markers, immune phenotyping, metabolic assessment using existing tools), and evidence-based interventions (exercise, β-blockers, IL-6 inhibition, metabolic optimization) creates an unprecedented opportunity to address a fundamental determinant of immunotherapy outcomes previously dismissed as unmeasurable "host factors."

 doi:10.20944/preprints202601.2322.v1

Conclusions

Immunotherapy efficacy depends not only on tumor biology but fundamentally on host immune competence shaped by lifetime experiences. Chronic stress creates measurable immune dysfunction—inflammation-driven bystander exhaustion, glucocorticoid-programmed T cell dysfunction, catecholamine-mediated metabolic suppression, and accelerated immunosenescence—that predicts therapeutic resistance through well-characterized neuroendocrine pathways accessing immune cells directly.

We already have tools to assess immune biography (inflammatory markers, immune phenotyping, stress assessments) and evidence-based interventions to enhance immune function (exercise, β-blockers, IL-6 inhibition, metabolic optimization). The field must move beyond tumor-centric biomarkers to embrace immune biology assessment and enhancement as integral components of precision immunotherapy. Window-of-opportunity trials testing brief, mechanism-targeted interventions before therapy initiation could rapidly establish proof-of-concept.

The missing variable in immunotherapy is not missing—it is measurable, mechanistic, and modifiable. Understanding immune biography as the biological record of lifetime stress exposure provides a framework for improving outcomes by addressing the fundamental determinants of immune competence through targeted interventions. This represents a paradigm shift from accepting therapeutic resistance as inevitable to recognizing it as potentially preventable through systematic attention to patient immune biology shaped by life experiences.

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