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Balancing fire and healing: A human-touch exploration of immune responses in inflammation

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ABSTRACT

The immune system operates through a tightly timed orchestration of attack and repair. Inflammation embodies this duality it is both a necessary defense and, if unchecked, a driver of pathology. While individual cytokine biology is well established, the dynamic transition between a pro-inflammatory "alarm" phase and a regulatory "resolution" phase remains underappreciated. We investigated cytokine kinetics using two complementary models: standardized murine inflammation and primary human peripheral blood mononuclear cells (PBMCs), both stimulated with ovalbumin (the specified "antigen X"). Interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) surged within six hours, marking the alarm phase, followed by expansion of $CD25^{+}FoxP3^{+}$ regulatory T cells (Tregs) and increased interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) at 48–72 hours. In Treg-deficient models, resolution failed and fibrosis ensued. Mirrored kinetics in human PBMCs suggest an evolutionarily conserved mechanism. These findings emphasize that immune success depends not on unrestrained strength but on timely restraint, indicating that therapeutics should modulate this rhythm rather than suppress it outright.

KEY WORDS

Cytokines; Inflammation; Regulatory T cells; Immune balance; Immunopathology; Translational immunology

ARTICLE HISTORY

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Introduction

The immune system is often framed as a battlefield between host and invader; however, beyond warfare, immunity is a dialogue between destruction and healing [1,2]. When this transition fails, pathology emerges. Controlled inflammation confines pathogens and initiates tissue repair, but chronic activation causes harm, as seen in rheumatoid arthritis or sepsis [3,4]. Immune checkpoint therapy rejuvenates anti-tumor immunity yet risks autoimmunity [5]. Understanding these outcomes require viewing immunity as a temporal process cytokines acting like notes in a symphony, where timing and amplitude determine harmony or chaos [6].

Molecular orchestration of NF-κB and STAT3 in inflammation

During the early alarm phase, activation of Toll-like and cytokine receptors rapidly triggers the NF-κB pathway. In resting cells, NF-κB remains sequestered in the cytoplasm by IκB proteins; upon stimulation, the IKK complex phosphorylates IκB, targeting it for degradation and enabling NF-κB nuclear translocation to drive IL-6, TNF-α, and other pro-inflammatory genes.

Concurrently, the IL-6–JAK–STAT3 axis is activated. Phosphorylated STAT3 (Tyr705) forms dimers that translocate to the nucleus and promote IL-10 and TGF-β transcription, bridging inflammatory and regulatory phases. Crosstalk between NF-κB and STAT3 NF-κB upregulates IL-6, which activates STAT3, which in turn modulates NF-κB target genes creates a rhythmic loop essential for balanced immunity [7].

Macrophage polarization and the healing switch

Macrophages are pivotal regulators of immune tone. Classically activated M1 macrophages (induced by IFN-γ or LPS) secrete IL-6, IL-1β, and TNF-α, promoting pathogen clearance but also tissue damage if sustained. Alternatively activated M2 macrophages (induced by IL-4 or IL-13) release IL-10 and TGF-β, facilitating tissue repair and matrix remodeling. The temporal M1→M2 shift marks the onset of the healing phase. In our model, the 48–72-hour rise in IL-10/TGF-β alongside $CD206^{+}$ macrophages align with this transition, suggesting coordinated regulation by STAT3 signaling [8-10].

Materials and Methods

Murine model

Female BALB/c mice (6–8 weeks; n=6/group) were maintained under specific pathogen-free conditions. Mice received intraperitoneal injections of 100 μg ovalbumin emulsified in alum; controls received adjuvant alone. Physiological parameters (temperature, mobility, local swelling) were monitored for 72 hours. Each experiment was repeated three times with IACUC approval.

Human PBMCs

PBMCs from healthy donors (n=4) were isolated by Ficoll gradient, cultured at 1×10^{6} cells/mL in complete RPMI-1640, and stimulated with 10 μg/mL ovalbumin for 72 hours. Cytokine quantification: IL-6, TNF-α, IL-10, and TGF-β were measured using ELISA and multiplex bead-based assays.

Flow cytometry

Cells were stained for CD4, CD8, CD25, and FoxP3; macrophage polarization was assessed by CD80 (M1) and CD206 (M2). Data were acquired on a BD FACSCanto II and analyzed in FlowJo.

Histology and fibrosis scoring

Liver and peritoneal sections (5 μm) were stained with H&E and Masson's trichrome; fibrosis was scored using the Ashcroft scale (0–8) by two blinded observers.

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Statistics

Data are mean±SEM. One-way ANOVA with Tukey's post-hoc testing was used; $p<0.05$ was considered significant.

Results

Early alarm phase (IL-6 and TNF-α)

Within six hours, IL-6 and TNF-α rose sharply ($p<0.01$), correlating with macrophage activation ($CD80^+/CD206^-$) [1,11]. This defines the alarm phase (Table 1) (Figure 1).

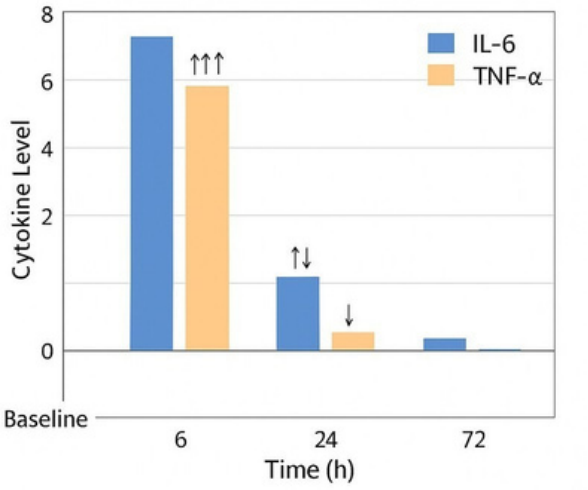

Figure 1. Bar graph showing IL-6 and TNF-α levels at 0–72 h in mice and PBMCs, illustrating cytokine kinetics during the inflammatory alarm phase.

Table 1. Cytokine kinetics summary.

Time (h)	IL-6	TNF-α	IL-10	TGF-β	Treg %
6	↑↑	↑↑	–	–	–
24	↑	↑	↑	–	↑
48	↓	↓	↑↑	↑↑	↑↑
72	–	–	↑	↑↑	↑↑↑

Legend: ↑↑ = sharp rise; ↑ = mild rise; ↓ = decline; ↔ = baseline; – = not detected.

Pathology in the absence of tregs

FoxP3-deficient mice failed to down-regulate inflammation, exhibiting necrosis and fibrosis ($p<0.001$) (Figure 2).

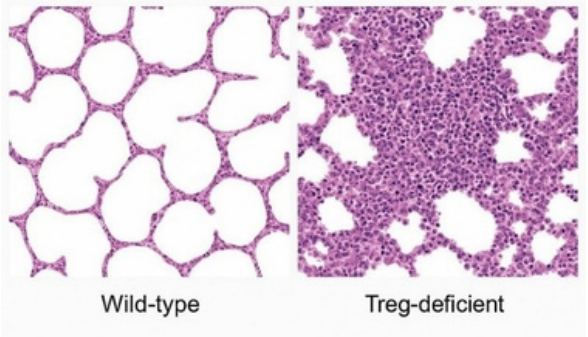

Figure 2. Histology comparison: wild-type vs. treg-deficient.

Cross-species conservation

Human PBMC kinetics mirrored murine patterns (Pearson $r>0.9$) (Figure 3) [12-14].

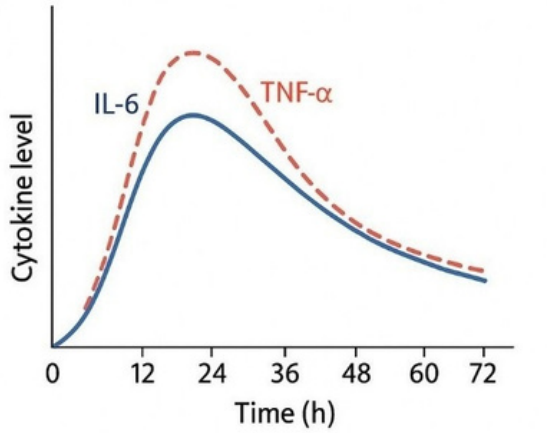

Figure 3. Line graphs of cytokine profiles in mice vs. PBMCs.

Discussions

Inflammation is ancient yet perilous; its success lies in resolution. IL-6/TNF-α ignite defense, whereas IL-10/TGF-β restore homeostasis. Treg deficiency drives chronic inflammation [12] and fibrosis, while excessive suppression impairs host defense. The conserved cytokine timing across species [6] suggests an evolutionary immune rhythm. Tracking IL-10/TGF-β phases could refine immunotherapy and predict adverse events [15,16]. A human-centered view sees immunity as wisdom in action knowing not only how to fight but when to stop [17].

Mechanistic insights and evolutionary conservation

The NF-κB–STAT3 circuit represents a deeply conserved mechanism. Primitive metazoans such as Drosophila and Hydra possess homologous pathways, suggesting that the rhythmic transition between inflammation and resolution predates adaptive immunity. Comparative transcriptomics reveal conserved temporal expression of IL-6-like cytokines during injury and IL-10-like cytokines during regeneration. This implies that successful immunity is defined not only by molecular complexity but by timing, emphasizing a need for 'chrono-immunology' in human medicine [14].

Evolutionary significance

Inflammation and healing are evolutionary strategies refined over millions of years. From invertebrate innate systems to mammalian adaptive immunity, the rhythm of attack and resolution remains conserved. NF-κB homologs in Drosophila (Relish) and STAT-like transcription factors in Hydra mediate responses to injury and stress. Oscillatory cytokine patterns mirror circadian and metabolic rhythms, reinforcing that immunity is integrated into broader biological timing systems. Modern immunopathology can be interpreted as a loss of this synchronization; restoring the rhythm may realign immunity with its ancestral blueprint.

Translational relevance

Temporal cytokine profiling tracking IL-6/TNF-α and

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IL-10/TGF-β ratios over time could transform clinical decision-making by predicting whether an immune response is progressing toward resolution or pathology. Persistently high IL-6 early in sepsis correlates with increased mortality risk, whereas a timely IL-10 rise favors recovery [4,14,18]. In autoimmune disease, kinetic insight may define treatment windows: early inhibition of NF-κB-driven mediators followed by promotion of STAT3-dependent regulatory pathways. In oncology, synchronizing checkpoint inhibition with natural regulatory cytokine peaks may reduce immune-related toxicities. This 'chrono-immunotherapy' paradigm aligning therapy with immune timing paired with biosensors and point-of-care cytokine monitoring, could enable real-time, personalized immune modulation [3,19].

Clinical implications

Autoimmunity

Combine IL-6/TNF-α inhibitors with IL-10/TGF-β or Treg-stabilizing agents to restore equilibrium.

Sepsis

Target early cytokine peaks while preserving the 48-hour resolution phase.

Cancer

Use IL-10/TGF-β recovery as biomarkers to predict and prevent checkpoint-inhibitor toxicity (Figure 4).

Figure 4. Conceptual diagramshowing immune balance timing.

Limitations and future work

This study used a single sterile antigenic stimulus (ovalbumin). Future work should test diverse stimuli (viral, bacterial) engaging distinct pattern-recognition receptors. Single-cell and spatial transcriptomics can parse cellular heterogeneity within the cytokine switch. Computational models integrating temporal data could predict system behavior under therapeutic perturbation [20,21].

Future perspectives

Emerging technologies such as single-cell RNA sequencing and spatial transcriptomics can illuminate how individual cells traverse inflammatory and regulatory states. Integrating these datasets with temporal cytokine profiles may enable predictive models of immune dysfunction in autoimmunity, infection, and cancer. Computational immunology can simulate feedback loops within the NF-κB–STAT3 axis to identify key regulatory nodes and optimal intervention windows. Ultimately, systems-level approaches could convert immunity from reactive to programmable, enabling time-synchronized, precision interventions.

Conclusions

Immunity is the art of timing the balance between fire and healing. Our data highlight a conserved transition from IL-6/TNF-α alarm to IL-10/TGF-β/Treg-driven resolution. Therapies that restore this natural rhythm may deliver protection without self-destruction.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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