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Cytokine networks and immune endotypes for precision immunotherapy in sepsis

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INTRODUCTION

Sepsis is defined by life-threatening organ dysfunction caused by a dysregulated host response to infection[1], but this clinical definition encompasses diverse and changing immune states. Inflammatory activation and immunosuppression vary among patients, can coexist, and may change in relative intensity during illness[2,3]. Decades of unsuccessful translation of immunomodulatory therapies may reflect limitations in target selection, experimental models that incompletely represent human immunity, and trial enrollment that inadequately accounts for immune heterogeneity[4].

The pairwise cytokine study by Takahama *et al.* and the ImmunoSep randomized trial address this translational challenge from mechanistic and clinical perspectives, respectively: defining cytokine interactions across organs and selecting treatment by immune endotype[5,6]. Their findings support moving beyond isolated cytokine targets to consider pairwise and broader network interactions. Translating these interactions into treatment decisions will require attention to patient endotype, organ compartment, and disease phase. A key unresolved question is how mechanistic insights into cytokine networks can inform patient selection and guide treatment.

PAIRWISE CYTOKINE INTERACTIONS IN SEPSIS

Takahama *et al.* combined multi-organ transcriptomic profiling in murine cecal ligation and puncture (CLP) and lipopolysaccharide (LPS)-induced endotoxemia models with comparisons of single cytokines and pairwise combinations. Tumor necrosis factor (TNF), paired with interleukin-18 (IL-18), interferon-γ (IFN-γ), or interleukin-1β (IL-1β), was sufficient to reproduce many model-associated transcriptional, cellular, and tissue responses. Whole-tissue RNA-seq profiles were used to compute cell-type abundance scores for 195 cell types across nine organs,

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with selected predictions examined by whole-mouse spatial profiling and orthogonal assays. For example, TNF plus IL-18 depleted splenic B-cell subsets, particularly marginal-zone B cells[5].

In CLP, TNF neutralization combined with *Il1b*, *Il18* or *Ifng* deletion counteracted changes in gene expression, with differentially expressed gene sets overlapping 31.9%, 45.6% or 63.3% of CLP-regulated genes, respectively. Hypothermia was significantly attenuated with the *Il1b* and *Ifng* combinations, while the *Il18* comparison did not reach significance[5]. These perturbations support a functional role for cytokine interactions within the experimental models, but their implications for treatment after sepsis onset remain uncertain. The experiments used antibody pretreatment or constitutive gene deletion in LPS-induced endotoxemia without live infection or in controlled CLP infection, leaving the efficacy of treatment initiated after disease onset untested.

PRECISION IMMUNOTHERAPY GUIDED BY IMMUNE ENDOTYPES

ImmunoSep tested a precision immunotherapy strategy tailored to the patient's immune state. An immune endotype is a subgroup within a clinical syndrome defined by distinct underlying immune mechanisms[7]. In patients with sepsis due to pneumonia or primary bacteremia, blood ferritin concentrations and human leukocyte antigen-DR (HLA-DR) expression on monocytes were used to classify patients as having macrophage activation-like syndrome (ferritin > 4,420 ng/mL) or sepsis-induced immunoparalysis (ferritin ≤ 4,420 ng/mL and < 5,000 HLA-DR receptors per CD45/CD14 monocyte). In the double-dummy design, patients in the precision immunotherapy group received intravenous anakinra plus subcutaneous placebo for the former, or intravenous placebo plus subcutaneous recombinant human IFN-γ for the latter; controls received both placebos[6].

The trial provided evidence that this strategy improved organ dysfunction by day 9 in the selected population. Its primary endpoint was a reduction of at least 1.4 points from the baseline day-1 Sequential Organ Failure Assessment (SOFA) score to the mean SOFA score over days 2-9. The primary endpoint was attained by 46/131 (35.1%) patients receiving precision immunotherapy *vs.* 26/145 (17.9%) receiving placebo [difference, 17.2 percentage points; 95% confidence interval (CI): 6.8 to 27.2; $P = .002$]. The trial was designed with 90% power at $\alpha = .05$ to detect a difference in primary endpoint attainment rates of 40% *vs.* 20%. At 28 days, mortality was 43.5% *vs.* 49.7%; the reported reduction, placebo minus active treatment, was 6.1 percentage points (95%CI: -5.6 to 17.6; $P = .34$)[6]. The trial did not demonstrate a 28-day survival benefit. Its sample size was determined for the SOFA-based primary endpoint, which may have limited its ability to detect a difference in 28-day mortality[6]. Whether improved organ function translates into improved survival therefore remains to be established; SOFA's association with mortality alone does not validate it as a surrogate for this treatment's survival effect[8].

The trial also illustrates limitations in patient selection and in the evidence available for each endotype. Of 672 patients screened for eligibility, 355 (52.8%) were excluded because their immune state was unclassified; 281 were randomized and 276 analyzed. In prespecified secondary analyses, the SOFA endpoint was attained by 12/25 patients receiving precision immunotherapy *vs.* 4/23 receiving placebo in the macrophage activation-like syndrome group ($n = 48$; $P = .04$), and by 34/106 *vs.* 22/122 in the sepsis-induced immunoparalysis group ($n = 228$; $P = .02$)[6]. The sample size was calculated for the overall strategy, so the small anakinra comparison warrants particular caution. It remains uncertain whether ferritin and HLA-DR sufficiently capture treatment-relevant immune differences and whether adjusting treatment to changes in immune status would improve outcomes. The relationship between patients' immune characteristics and the mechanisms targeted by immunotherapy remains to be defined.

CHALLENGES IN CLINICAL TRANSLATION

Directly linking cytokine networks to clinical immune endotypes could improve patient selection and guide treatment, but neither study establishes that link. IFN-γ illustrates the problem. Paired with TNF, it reproduced some changes in tissue gene expression and cell-type abundance observed in the mouse models; in ImmunoSep, it was administered to patients with predefined sepsis-induced immunoparalysis[5,6]. This contrast suggests that treatment selection requires knowledge of both network mechanisms and the patient's immune state. Differences in species, models, treatment timing and outcome measures limit direct mechanistic comparison; IL-1 receptor blockade also differs from *Il1b* deletion. Cross-study observations alone cannot establish in which patients the corresponding cytokine interactions occur or which intervention they should receive.

The three key cytokine pairs all contain TNF, raising a question about target selection: does inhibiting a partner add to blockade of the common node? TNF neutralization alone induced few statistically significant changes in tissue gene expression at the assessed time point after CLP[5], while a large anti-TNF trial in septic shock did not demonstrate improved survival[9]. Clinical translation will require showing that disrupting these interactions improves patient outcomes.

Even if similar network signatures are found in human samples, their significance would still need to be clarified: they may reflect disease severity, immune dysfunction, or responsiveness to a particular intervention. Biomarkers associated with sepsis susceptibility[10,11] and molecular subgroups associated with different prognoses[12,13] do not necessarily identify patients who will benefit from treatment. Blood expression signatures also cannot be assumed to represent pathway activity in affected organs[2]. Immune classifications require prospective validation of their ability to predict differential treatment response[14].

A TRANSLATIONAL RESEARCH PATHWAY

To guide patient selection, the cytokine interactions observed in mice need to be investigated in human samples. Candidate biomarkers of these interactions can then be tested for their ability to predict benefit from a specific immunotherapy.

1. Identify cytokine interactions and their functional effects in human samples. Blood transcriptomic studies have identified molecular subgroups with distinct immune features and outcomes[12,13], and a recent consensus framework integrates existing classifications to support comparisons across cohorts[15]. These classifications, combined with immune phenotyping, could help identify patient groups in which to study the cytokine interactions observed in mice. Experiments in patient-derived cells or tissues could then test whether the cytokines interact and how those interactions affect cellular responses.

2. Identify clinically measurable biomarkers of these interactions. Findings from human samples could guide the selection of biomarkers that reflect these interactions and can be measured within a clinically useful timeframe. These biomarkers should add information for treatment selection beyond ferritin and HLA-DR, including for patients with an unclassified immune state.

3. Test whether the biomarkers identify patient groups that benefit from treatment. Randomized trials should compare immunotherapy with control within prespecified biomarker groups and test whether the treatment effect differs between groups. These trials should assess patient-centered outcomes, including mortality, with adequate statistical power. Strategies that use repeated immune measurements to adjust treatment should also be tested for additional clinical benefit.

CONCLUSION

Cytokine-network mechanisms and immune endotypes address the target and patient dimensions of precision immunotherapy. Mechanistic insights can inform patient selection through measurable human network features whose ability to predict treatment benefit is tested prospectively, with attention to organ compartment and disease phase. ImmunoSep demonstrated an improvement in organ dysfunction by day 9 in a selected population; a survival benefit and broader applicability remain to be established. Individual targets, target combinations, and combined or sequential strategies require both mechanistic evidence and demonstrated clinical benefit.

DECLARATIONS

Authors' contributions

Literature review and manuscript drafting: Hu D
Supervision and manuscript review: Liu S

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Conflicts of interest

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Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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