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DIAGNOSTIC SIGNIFICANCE OF IL-15 IN SJS/TEN SYNDROME

Razikova I.S. Republican Specialized Scientific-Practical Medical Center of Allergology and Clinical Immunology, Tashkent, Uzbekistan
Turaev N.T. Tashkent State Medical University, Tashkent, Uzbekistan

Abstract: Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening severe cutaneous adverse reactions characterized by widespread epidermal and mucosal necrosis. Although clinical scoring systems such as SCORTEN play an important role in severity assessment, they have limited predictive value during early disease stages. Consequently, immunological biomarkers—including cytokines—are being actively investigated to improve early diagnostics and prognostication. Interleukin-15 (IL-15) has emerged as a potent activator of $CD8^+$ T lymphocytes and NK cells, enhancing cytotoxic pathways and amplifying keratinocyte apoptosis. This paper reviews the role of IL-15 in SJS/TEN pathogenesis, its association with cytotoxic lymphocyte activity, and its diagnostic and prognostic significance.

Introduction

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe mucocutaneous reactions characterized by extensive keratinocyte apoptosis, epidermal detachment, and high mortality rates. Drug hypersensitivity is the leading cause, often triggered by anticonvulsants, sulfonamides, allopurinol, and certain antibiotics. Despite advances in supportive care, early diagnosis and prognostication remain major clinical challenges.

Traditional severity scoring methods such as SCORTEN are useful but insufficient, as they are not designed to detect early immunological changes occurring before extensive epidermal necrolysis. Therefore, the identification of novel biomarkers reflecting real-time immune activation is of great clinical interest. Interleukin-15 (IL-15) has gained attention as a key cytokine involved in the activation and survival of cytotoxic lymphocytes, making it a promising biomarker for evaluating disease activity and predicting outcomes.

Pathogenesis of SJS/TEN

SJS/TEN is driven by a T-cell–mediated immune reaction, with apoptosis—not acantholysis—being the primary mechanism of keratinocyte death. Several key processes shape its immunopathology:

1. **Massive keratinocyte apoptosis** mediated by cytotoxic molecules such as perforin, granzyme B, FasL, and especially granulysin, the major mediator responsible for widespread epidermal detachment.
2. **Central role of $CD8^+$ T cells and NK cells.** These cytotoxic effectors infiltrate lesional skin and mucosa, releasing apoptotic mediators that destroy keratinocytes.
3. **Mucosal involvement**, which often precedes skin lesions, reflecting rapid immune activation and contributing to severe morbidity.

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Drug-induced immune dysregulation, where medications bind to MHC-I complexes on keratinocytes, altering antigenicity and triggering abnormal $CD8^+$ T-cell activation.
Within this cascade, IL-15 acts as a potent amplifier of cytotoxic responses.
Role of IL-15 as an Immunoregulatory Cytokine
IL-15 is essential for the survival, proliferation, and cytotoxic activity of $CD8^+$ T cells and NK cells. Its major functions include:

- promoting differentiation and long-term survival of $CD8^+$ cytotoxic T cells (Steel et al., 2020)

enhancing NK-cell proliferation and cytolytic activity (Croce et al., 2021)
functioning through a trans-presentation mechanism via IL-15Rα (Wu et al., 2022)
increasing localized immune injury within severely affected mucosal tissues
Due to these roles, IL-15 acts as an upstream regulator of cytotoxic lymphocyte activation in SJS/TEN.

IL-15 and Cytotoxic Lymphocyte Activation
IL-15 enhances keratinocyte apoptosis by stimulating $CD8^+$ T cells to produce higher amounts of:
granulysin
perforin
granzyme B
Fas ligand (FasL)
Studies demonstrate a positive correlation between IL-15 levels and cytotoxic mediator production (X et al., 2023), indicating that IL-15 directly influences disease severity. Higher IL-15 levels are associated with:
faster epidermal detachment
more rapid clinical progression
increased mucosal involvement

IL-15 Levels and Disease Severity / Prognosis
Clinical findings show that elevated serum IL-15 correlates with:
percentage of body surface area detachment
higher SCORTEN scores
intensive care requirement
increased mortality risk
A pivotal study demonstrated that IL-15 levels strongly correlate with disease severity and mortality ($r = 0.401$; $P < 0.001$) (Su et al., 2019).
IL-15 rises early in the disease course—before extensive necrolysis—making it a valuable **early** dynamic biomarker.

Diagnostic and Therapeutic Implications
Diagnostic Role
Although IL-15 alone cannot distinguish SJS/TEN from other dermatoses, it:
reflects real-time immune activation
correlates with keratinocyte apoptosis
improves prognostic accuracy when combined with SCORTEN or granulysin
may assist in monitoring treatment response

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Therapeutic Potential

Experimental strategies targeting the IL-15 axis include:
IL-15Rα inhibitors
IL-15 neutralizing antibodies
JAK/STAT pathway inhibitors
These approaches may reduce cytotoxic lymphocyte activation and keratinocyte apoptosis, offering future therapeutic promise.

Conclusion

IL-15 plays a crucial role in SJS/TEN pathogenesis by activating $CD8^+$ T cells and NK cells, thereby intensifying keratinocyte apoptosis. Although IL-15 alone has limited diagnostic utility, its strong association with disease severity and mortality underscores its value as a prognostic biomarker. Future research should focus on large-scale cohort studies, dynamic IL-15 profiling during therapy, and clinical evaluation of IL-15 signaling inhibitors as potential treatments.

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