Table of Contents

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Distinct Inflammatory Mechanisms Underlie Lichen Planus and Lichenoid Reactions to Checkpoint Inhibition

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Keywords

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Abstract

Cancer treatment has advanced rapidly in the past decade, with checkpoint inhibitors (CPIs) delivering improved outcomes across a variety of malignant indications. However, their application is associated with the development of immune-related adverse events (irAEs), which are linked to the physiological role of checkpoint molecules like PD-1 and CTLA-4 in regulating immunological self-tolerance and safeguarding non-malignant tissues from the immune response. CPIs disrupt these checkpoints, restoring the immune system's cytotoxic function to recognize and eliminate cancer cells, potentially leading to immune dysregulation and the onset of irAEs.

The incidence rate of irAEs ranges significantly across treatment contexts, ranging from 27% to 72% of patients. Neoadjuvant therapy for melanoma poses a heightened risk, with up to 73% of patients experiencing severe treatment-related adverse events. Cutaneous irAEs exhibit morphologies that resemble clinical and histologic features of inflammatory skin diseases. Selection of nonsteroidal therapies is guided by the resemblance of irAEs to established dermatoses, but varying success rates suggest a fundamental difference in underlying mechanisms, impacting patient response to therapy.

Lichen planus (LP) is a chronic inflammatory skin condition characterized by distinct lesion morphology, distribution, and histologic patterns, while lichenoid c-irAE refers to a skin reaction induced by CPIs that is similar but presents variable clinical and histologic distinctions from typical LP. To assess mechanistic differences between lichenoid irAE and LP, we combined two global transcriptomic approaches with more targeted interrogation using RNA in situ hybridization and immunofluorescence. Combining scRNA-seq with spatial sequencing allowed us to compare transcriptional activation and local cell-cell interaction networks with single-cell resolution while maintaining the microenvironmental context. The results of our investigations suggest broad similarities between cell populations and transcriptional programs within these two dermatoses, but

also highlight key (and potentially actionable) differences, including higher IL-6 expression and increased IFNg pathway activation in lichenoid irAE compared to LP.