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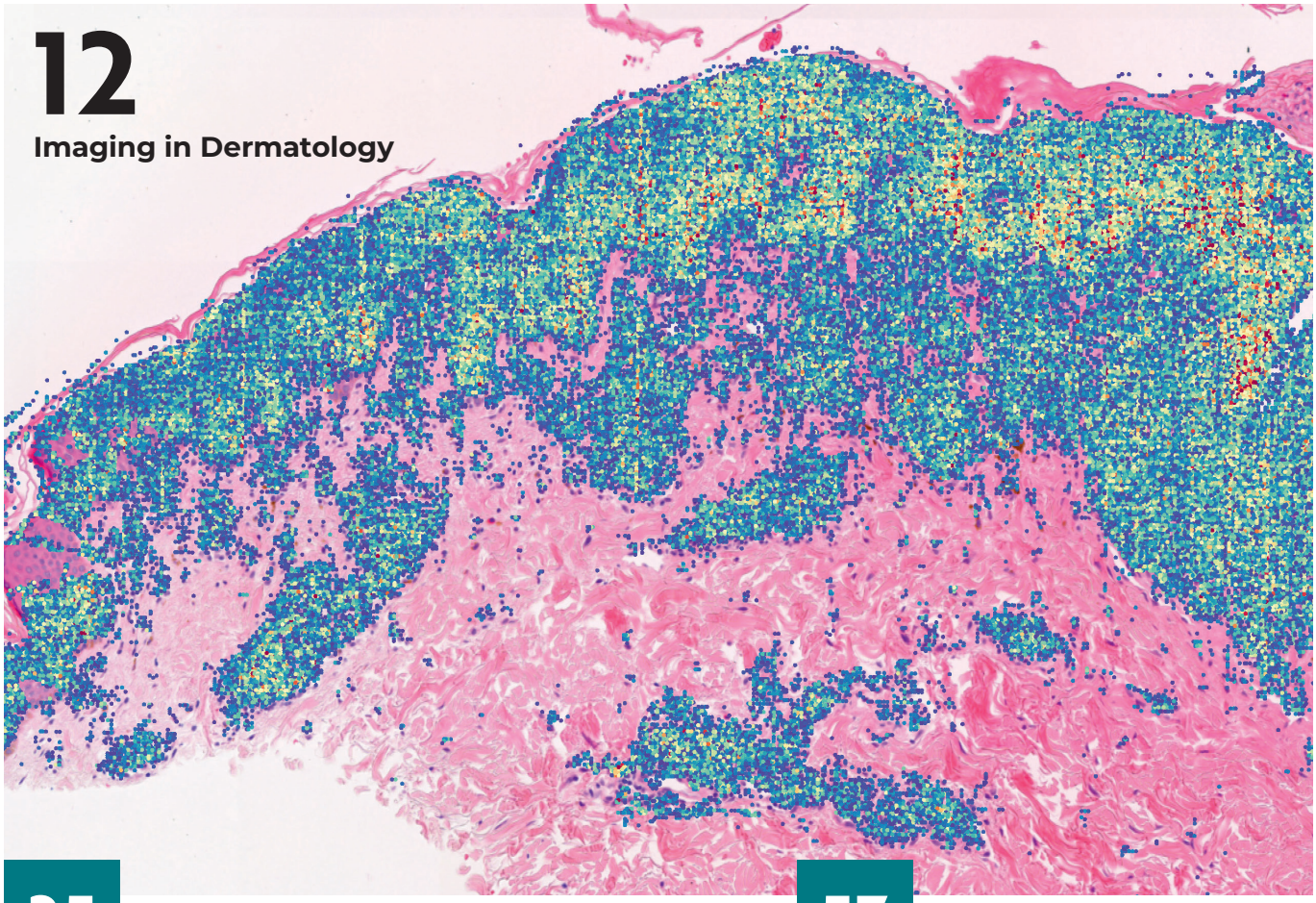

Société Suisse de Dermatologie et Vénéréologie
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WHAT'S NEW

MHC-I Upregulation Safeguards Neoplastic T Cells in the Skin Against NK Cell-mediated Eradication in Mycosis Fungoides

This section is a contribution from the SKINTEGRITY.CH interdisciplinary research consortium. The present work was performed by Dr. Yun-Tsan Chang and colleagues, including SKINTEGRITY.CH Principal Investigators, Prof. Mitchell Levesque, PD François Kuonen, Prof. Lars French and Prof. Emmanuella Guenova.

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Mycosis fungoides (MF), a malignancy of skin-homing T cells, represents the most common form of cutaneous T-cell lymphoma (CTCL). Progressive impairment of cell-mediated immunity is a hallmark of cancer, and in patients with CTCL, inadequate immune response has been reported. Tumorous T cells play a significant role in suppressing the patient's immune system, thereby blunting the response of other immune cells that would otherwise mount an anti-tumor defense. This impairment of cellular immunity may negatively affect all therapeutic approaches that rely on a functional immune system.

Therapeutic approaches harnessing immune responses are hallmarks of modern oncology. Monoclonal antibodies (mAbs), specialized proteins designed to target tumor cell-surface antigens, have emerged as powerful agents capable of eliminating malignant cells and inducing disease remission. In addition to inducing tumor-cell apoptosis, therapeutic mAbs initiate immune effector signaling cascades that rely on the complement system and natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC) as anti-cancer modes of action. Cancer-associated immune dysfunction is a major challenge for effective therapies. The emergence of antibodies targeting tumor cell-surface antigens led to remarkable advancements in the treatment of hematopoietic malignancies, particularly blood cancers. Yet their impact is constrained against tumors of hematopoi-

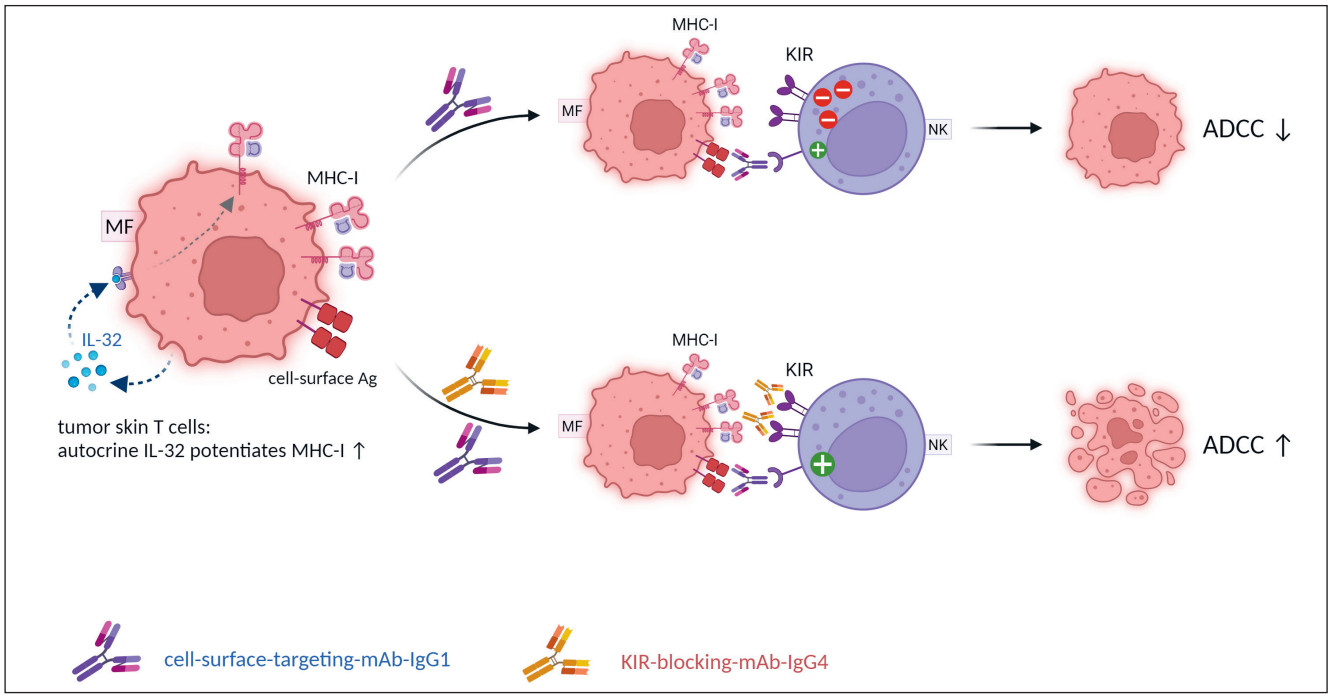

Figure 1: A high expression of major histocompatibility complex (MHC)-I, potentiated by IL32β, on skin tumor T cells serves as a mechanism that blocks ADCC and renders tumor cell-surface antigen targeted therapy ineffective in MF. Blockade of the MHC-I-KIR interaction restores NK cell-mediated ADCC activity against malignant T cells in MF skin lesions. Figure created with BioRender.com.

etic origin manifesting in the skin. In CTCL, the therapeutic mAbs are highly effective in treating blood tumoral disease in patients with Sézary syndrome (leukemic CTCL) but have been shown to be less effective in treating skin lesions in patients with MF.

In this study, we perform single-cell sequencing of skin T cells from MF patients, mathematically reconstruct the natural identifiers of T cells - the T-cell receptors (TCRs) of individual T cells - and categorize them into clonal (tumoral) and non-clonal (non-tumoral) groups based on TCR similarity. Based on the separation of tumoral and non-tumoral T cells, we employ a clonality-guided deep learning approach to dissect key pathological features and tumor-related genes implicated in mycosis fungoides (MF). We functionally characterized that a high expression of classical major histocompatibility complex class I (MHC-I) on malignant skin T cells as a mechanism rendering targeted therapy ineffective in MF. Notably, in patients' skin, we find upregulated classical MHC-I to detrimentally impact the functionality of NK cells, diminishing ADCC and promoting resistance of tumor skin T-cells to cell-surface targeting therapies. Ex vivo, we confirm that the inhibition of the interaction between classical MHC-I on MF malignant T cells and inhibitory killer cell immunoglobulin-like receptors (KIRs) on NK cells effectively reinstates ADCC activity in autologous NK cells against MF malignant T cells. Through murine experiments, we demonstrate that disruption of the MHC-I interaction with NK cell inhibitory Ly49 receptors restores NK cell anti-tumor activity and targeted T-cell lymphoma elimination in vivo. A noteworthy observation is the malignant skin T cells display increased expression of IL32 and elevated levels of IL32 binding sites, and the supplementation of IL32 leads to an increase in MHC-I expression. This underscores the significance of IL32 – MHC-I axis in MF skin T cells, implying that IL32β functions as a crucial autocrine signal for survival and expansion of malignant T cells and a critical determinant in tumor T-cell immune evasion within the human skin environment *(Figure 1)*.

Overall, our investigations unveil the prominence of the IL32 – MHC-I axis as a critical determinant in tumor T-cell immune evasion within the skin microenvironment and our study introduces a novel strategy to block NK-cell inhibition and reinvigorate NK cell-mediated anti-tumor responses to overcome treatment resistance to existing cell-surface targeted therapies for skin lymphoma.

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Reference

Chang, YT., Prompsy, P., Kimeswenger, S. et al. MHC-I upregulation safeguards neoplastic T cells in the skin against NK cell-mediated eradication in mycosis fungoides. Nat Commun 15, 752 (2024). https://doi.org/10.1038/s41467-024-45083-8

Guenova Lab. From left to right: Yi-Chien Tsai, Karine Salamin, Olesya Pavlova, Emmanuella Guenova, Christoph Iselin, Gabriela Blanchard, Yun-Tsan Chang and Maël Blanchard.