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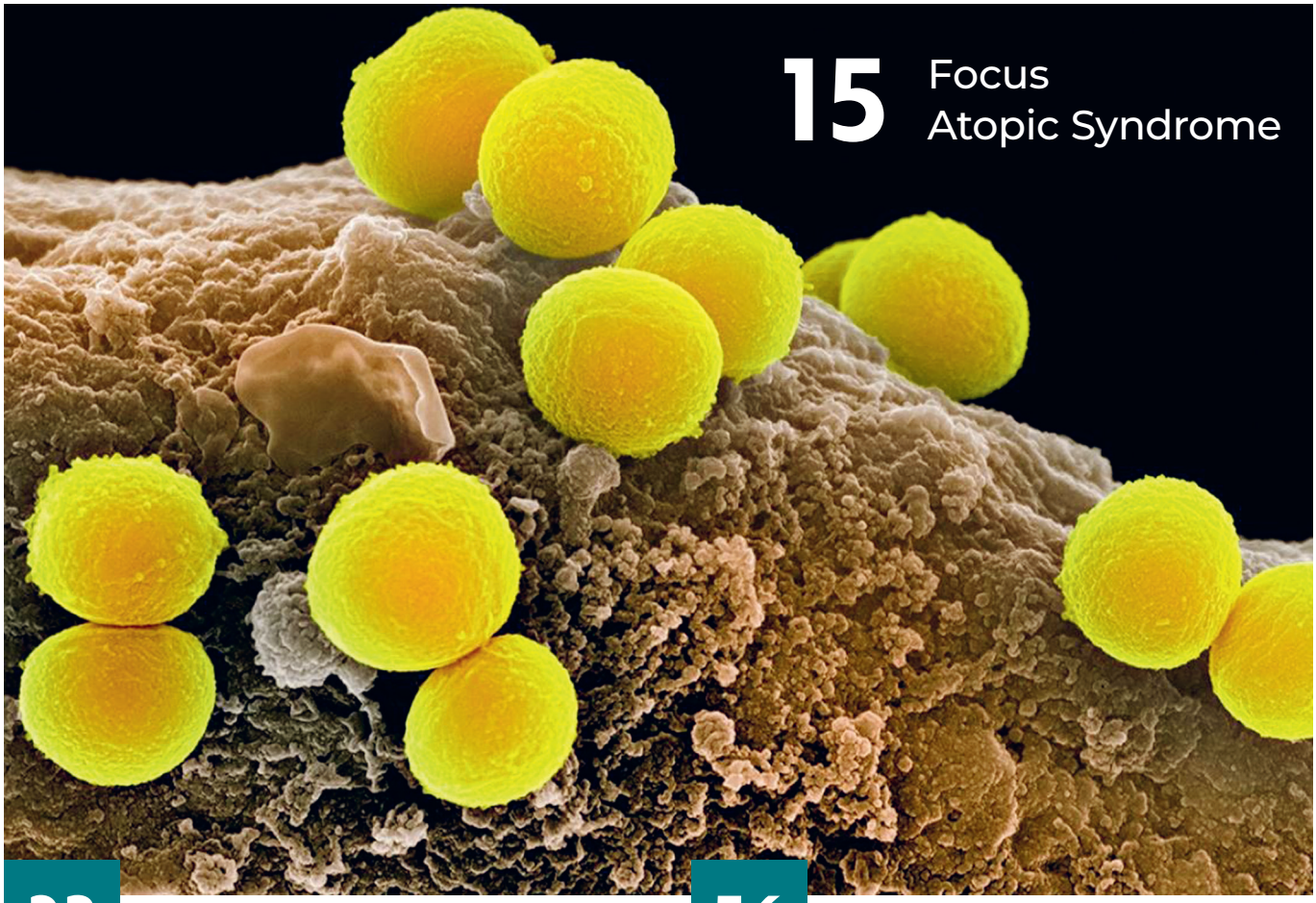

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WHAT'S NEW

Beyond tumor control: reduced lymphedema risk under anti-CTLA-4 therapy

This section is a contribution from the SKINTEGRITY.CH interdisciplinary research consortium. The collaborative work was performed by Dr. Stefan Wolf and colleagues, led by Prof. Epameinondas Gousopoulos in collaboration with SKINTEGRITY.CH PIs Profs. Reinhard Dummer, Nicole Lindenblatt, Cornelia Halin, Michael Detmar, and Mitchell Levesque and their teams.

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Stefan Wolf. *Immune checkpoint inhibitors have revolutionized the treatment of malignant melanoma and a growing number of advanced solid tumors. Antibodies targeting cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) act primarily by blocking inhibitory signals during early T-cell activation, thereby enhancing effector T-cell priming and antitumor immune responses. While the oncologic efficacy of CTLA-4 blockade is well established, accumulating evidence suggests that its systemic immunological effects extend beyond tumor immunity. In particular, modulation of immune regulatory pathways may influence inflammatory processes and tissue homeostasis in non-tumor compartments, including the lymphatic system. In this context, our study provides novel mechanistic insight into the immunobiology of lymphedema.*

Inflammatory and fibrotic mechanisms in lymphedema

Lymphedema is a chronic, progressive disease caused by impaired lymphatic drainage, most frequently occurring as a secondary complication following oncologic surgery, lymph node dissection, or radiotherapy. Its pathophysiology is characterized by persistent interstitial fluid accumulation, chronic inflammation, immune cell infiltration, adipose tissue deposition, and progressive fibrosis. Chronic inflammation plays a central role in disease progression by promoting lymphatic vessel dysfunction and irreversible tissue remodelling. Despite its clinical relevance and increasing prevalence among cancer survivors, therapeutic options remain largely symptomatic, highlighting the urgent need for preventive and disease-modifying strategies.

Anti-CTLA-4 therapy reduces lymphedema risk

Given the critical role of immune-mediated inflammation in lymphedema development, we hypothesized that immune checkpoint inhibition might modulate lymphatic pathology. To test

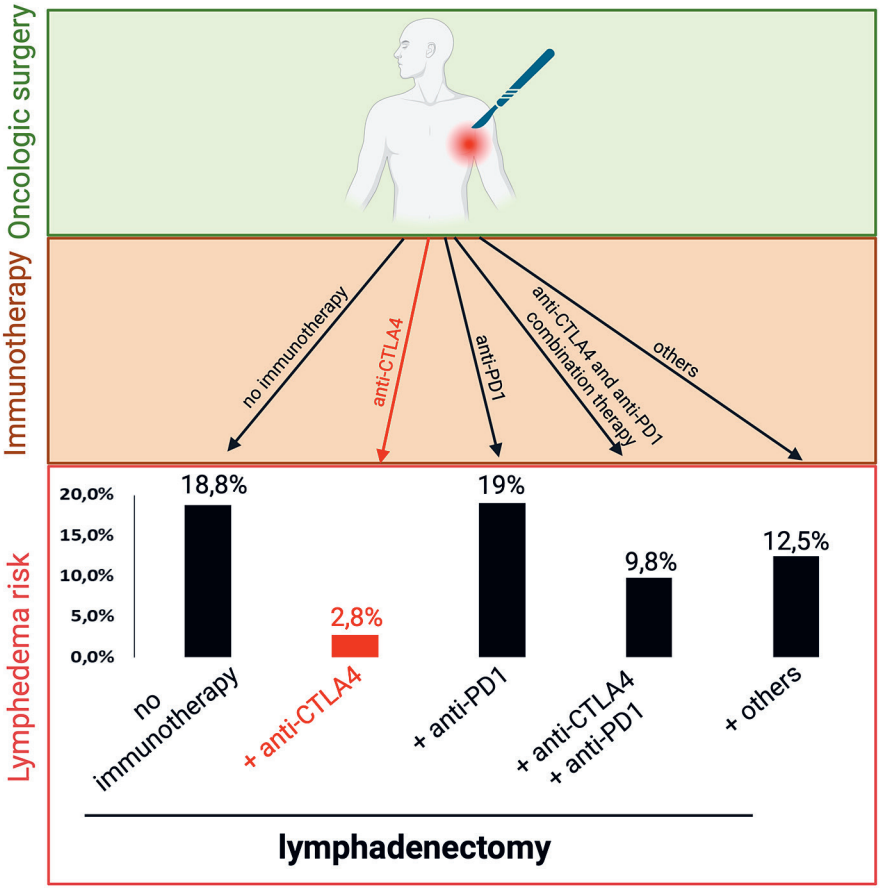

Figure 1: Anti-CTLA4 therapy reduces significantly the risk of lymphedema development upon lymphadenectomy (LAD), whereas the risk in patient receiving anti-PD1 and interferon treatment is comparable to the group receiving only LAD (Image created with BioRender).

this, we conducted a retrospective analysis of 1,464 melanoma patients, assessing the incidence of postoperative secondary lymphedema in relation to systemic therapies. Patients receiving immunotherapy exhibited a significantly reduced lymphedema incidence (10.5 %) compared with untreated individuals (18.8 %). Strikingly, the strongest protective effect was observed in patients treated with the anti-CTLA-4 antibody ipilimumab, in whom only 2.9 % developed lymphedema. In contrast, anti-PD-1–based therapies and interferon-α treatment did not demonstrate comparable protective effects, suggesting a CTLA-4–specific mechanism.

To validate these clinical observations, we employed a well-established murine tail model of secondary lymphedema, induced by surgical disruption of lymphatic vessels. Consistent with the human data, anti-CTLA-4 therapy significantly reduced edema volume, improved lymphatic drainage, and preserved tissue architecture. Histological and functional analyses demonstrated improved lymphatic vessel integrity in treated animals.

FOXP3⁺ regulatory T cells as central mediators

Mechanistically, the protective effects of CTLA-4 blockade were closely associated with a pronounced expansion of FOXP3+ regulatory T cells (Tregs), both systemically and within lymphedematous tissue. Gene expression profiling revealed upregulation of Treg-associated pathways, including FOXP3 and CTLA-4 signalling, alongside interferon-related immune responses. Concurrently, pathways associated with fibrosis and edema formation were significantly downregulated. Flow cytometric analyses confirmed a marked increase in $CD4^+FOXP3^+CD25^+$ Tregs in peripheral blood and affected tissue compartments.

Importantly, these immunological changes were mirrored in human samples. Peripheral blood analyses from melanoma patients demonstrated a significant increase in circulating $CD4^+FOXP3^+CD25^+$ Tregs eight weeks after initiation of ipilimumab therapy, accompanied by elevated serum concentrations of immunoregulatory cytokines, including interleukin-10. These findings support a model in which CTLA-4 blockade induces a context-dependent expansion of Tregs that suppress excessive inflammation in non-tumor tissues, thereby preserving lymphatic function and preventing chronic inflammatory damage.

Translational implications and conclusion

The data presented identify CTLA-4–mediated Treg modulation as a previously unrecognized mechanism influencing lymphatic homeostasis. From a translational perspective, this observation is particularly compelling, as anti-CTLA-4 antibodies are already approved and widely used in clinical oncology. In contrast to nonspecific immunosuppressive approaches, which may compromise antitumor immunity, CTLA-4 blockade appears to confer a dual therapeutic benefit by enhancing tumor control while simultaneously mitigating lymphatic inflammation.

If confirmed in prospective clinical trials, anti-CTLA-4 therapy may represent a disease-modifying factor in the prevention of secondary lymphedema, especially in patients at high risk following lymph node dissection or radiotherapy. Collectively, this work broadens the conceptual framework of immune checkpoint inhibition and provides a rationale for the targeted repurposing of immunomodulatory therapies in lymphedema prevention and management.

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Reference

1. *Wolf, S., Madanchi, M., Turko, P., Hollmén, M., Tugues, S., von Atzigen, J., Giovanoli, P., Dummer, R., Lindenblatt, N., Halin, C., Detmar, M., Levesque, M. & Gousopoulos, E. (2024). Anti-CTLA4 treatment reduces lymphedema risk potentially through a systemic expansion of the FOXP3+ Treg population. Nat Commun, 15(1), 10784. DOI 10.1038/s41467-024-55002-6*