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REVIEW

Immune Microenvironment of Hair Follicles in Tumor Immunotherapy

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Abstract: Although tumor immunotherapy has shown significant efficacy against solid tumors, it frequently causes cutaneous and follicular adverse events resulting from disruption of the hair follicle immune microenvironment. This microenvironment is maintained through careful regulation by immune cells and cytokine networks to support normal hair cycling. Immune checkpoint inhibitors disturb this balance by activating T cells, promoting macrophage polarization toward pro-inflammatory phenotypes, upregulating inflammatory cytokines such as tumor necrosis factor-alpha, and activating Toll-like receptor/nuclear factor-kappa B signaling pathways, ultimately leading to follicular toxicity including alopecia. Encompass relies mainly on topical corticosteroids and other immunomodulatory agents. A deeper understanding of these mechanisms is essential to identify key regulatory nodes for future targeted interventions.

Keywords: immune microenvironment, hair follicles, tumor immunotherapy

Introduction

Solid tumors remain a leading cause of mortality worldwide, with cancer immunotherapy emerging as a transformative approach that mobilizes the host's immune system to combat malignant cells.[1–4] The underlying mechanism involves reversing tumor-induced immunosuppression; tumor cells often overexpress immune checkpoint molecules such as Programmed Cell Death Ligand 1 (PD-L1), which binds Programmed Cell Death Protein 1 (PD-1) on T cells and dampens their antitumor activity.[5] Immune checkpoint inhibitors (ICIs) block this interaction, thereby reinvigorating T cell–mediated tumor killing and establishing durable antitumor immunity.[6] These advances have reshaped the treatment landscape for multiple solid tumors.[7–10]

Nevertheless, not all patients benefit. Primary or acquired resistance remains common, driven by tumor-intrinsic evasion mechanisms and immunosuppressive microenvironmental cues.[11–13] Moreover, immune-related adverse events (irAEs) frequently occur, limiting treatment sustainability. Among these, cutaneous toxicities are prevalent, with follicular adverse events—such as alopecia, hair repigmentation, and alopecia areata—affecting a substantial proportion of patients.[14] Epidemiological studies suggest that dermatologic irAEs occur in over 30% of patients receiving ICIs, with hair-related manifestations contributing significantly to this burden.[15,16] These events not complicate clinical management but also impair quality of life, underscoring the need for cross-disciplinary collaboration between dermatologists and oncologists.

The hair follicle operates as a dynamic immune-privileged site under physiological conditions, maintained by finely tuned interactions between immune cells (eg, T cells and macrophages) and cytokine networks.[17] Immunotherapy-induced systemic immune activation can disrupt this homeostasis, provoking inflammatory cascades involving T cell activation, macrophage polarization, and upregulation of cytokines such as tumor necrosis factor-alpha, along with

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activation of Toll-like receptor/nuclear factor-kappa B (TLR/NF-κB) signaling. These changes contribute to follicular damage and hair cycle abnormalities.[18–20] In this review, we integrate current understanding of the hair follicle immune microenvironment, elucidate the mechanisms by which ICIs disrupt follicular homeostasis to induce irAEs, evaluate clinical management strategies, and identify key directions for future research aimed at mitigating these adverse effects and improving patient care.

Immunoregulatory Mechanisms of the Hair Follicle Immune Microenvironment

Synergistic Regulation by Immune Cells

The hair follicle immune microenvironment is a sophisticated system regulated by a diverse array of immune cells and cytokines. T lymphocytes play a central role in this system, wherein T helper 1 cells secrete interferon-gamma (IFN-γ) to activate the phagocytic function of macrophages, participating in anti-infection immune responses.[21] In contrast, regulatory T cells (Tregs) maintain immune tolerance by producing inhibitory cytokines such as Interleukin-10 (IL-10) and Transforming Growth Factor-beta (TGF-β), preventing autoimmune-mediated damage to hair follicles.[22] As a key component of innate immunity, natural killer (NK) cells directly recognize and eliminate abnormal cells, playing a critical role in immune surveillance within hair follicles.[23] Antigen-presenting cells (APCs), including macrophages and dendritic cells (DCs), constitute another essential element of this system.[24] These cells not only phagocytose pathogens and cellular debris but also process and present antigens to activate antigen-specific T cell responses.[25] Macrophages exhibit dual functionality, promoting both inflammatory responses and tissue repair.[26] Dendritic cells serve as a bridge between innate and adaptive immunity by priming naïve T cells to initiate antigen-specific immune responses.[27]

Network Regulation of Cytokines and Signaling Pathways

The cytokine network serves as a core mediator in regulating hair follicle immune balance. Pro-inflammatory cytokines promote immune cell activation and inflammatory responses, while anti-inflammatory cytokines maintain immune homeostasis through Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) and Suppressor of Mothers Against Decapentaplegic (SMAD) signaling pathways.[28] Growth factors, including Epidermal Growth Factor (EGF) and Fibroblast Growth Factor (FGF), are not only involved in the proliferation and differentiation of hair follicle cells but also modulate the functions of immune cells.[29]

Multiple signaling pathways are involved in the regulation of the hair follicle immune microenvironment. Recent work by Kirby et al has revealed a critical negative regulatory mechanism in this context. The RNase L-caspase-1 axis can cleave the TLR adaptor protein TIR-domain-containing adapter-inducing interferon-β (TRIF), thereby restraining the pro-regenerative dsRNA-TLR3 signaling cascade and functionally repressing hair follicle regeneration.[30] Beyond inflammation, NF-κB activity in the hair follicle matrix and inner root sheath, as demonstrated by Krieger et al is essential for hair shaft morphogenesis and cyclic regeneration, with its suppression leading to distinct hair-type-specific cycling defects. Specifically, NF-κB translocation upregulates pro-inflammatory gene expression;[31] NF-κB regulates the expression of inflammatory cytokines, and its aberrant activation may lead to pathological inflammation.[32,33]

Maintenance of Immune Homeostasis in the Hair Follicle Growth Cycle

Hair follicles normally possess immune privilege status as specialized organs. The normal immune microenvironment of hair follicles is crucial for maintaining the normal growth cycle of hair and the physiological functions of hair follicles, involving multiple mechanisms. The growth of hair exhibits periodic changes, including the anagen (growth phase), catagen (regression phase), and telogen (resting phase).[34] During the anagen phase, the immune microenvironment of hair follicles is in a relatively active but balanced state. Immune cells and cytokines work together to provide necessary immune protection for hair follicles, defending against the invasion of external pathogens, and at the same time, promoting the proliferation and differentiation of hair follicle cells.[17] Immune cells such as T cells and macrophages

promptly eliminate pathogens, while growth factors like epidermal growth factor (EGF) and fibroblast growth factor (FGF) stimulate the division and proliferation of hair follicle cells, enabling the continuous growth of hair.[35]

When entering the catagen phase, corresponding changes occur in the cytokines and signaling pathways within the immune microenvironment of hair follicles, regulating the apoptosis of hair follicle cells and the remodeling of the hair follicle structure.[36] The expression of cytokines such as tumor necrosis factor-alpha (TNF-α) increases, inducing the apoptosis of some hair follicle cells, causing the hair follicles to gradually atrophy, and the hair stops growing and transitions to the telogen phase.[37–39] During the telogen phase, the immune microenvironment of hair follicles is in a relatively quiescent state, maintaining the basic structure and functions of hair follicles, awaiting the initiation of the next anagen phase (Figure 1).

The immunoregulatory mechanism plays a central role in this process. Tregs prevent excessive immune responses from damaging hair follicles by suppressing the activity of effector T cells.[22] When hair follicles are mildly stimulated, Tregs rapidly activate, secreting inhibitory cytokines to suppress the overactivation of immune cells and maintain the balance of the immune microenvironment.[40] Immune tolerance is also a critical mechanism for maintaining the homeostasis of the hair follicle immune microenvironment.[41] Hair follicle cells express immunoregulatory molecules such as PD-L1, which binds to PD-1 on the surface of immune cells, inhibiting T cell activation and inducing immune tolerance, thereby preventing the immune system from mounting an attack against hair follicle self-antigens.[42]

Moreover, the balance of the cytokine network is essential for maintaining the homeostasis of the hair follicle immune microenvironment.[43] Various cytokines interact and constrain each other, forming a complex network. When hair follicles are injured or infected, pro-inflammatory cytokines such as TNF-α are upregulated, initiating an immune response.[44] Simultaneously, anti-inflammatory cytokines such as IL-10 and TGF-β are also actiIL-10ated to suppress excessive inflammatory responses, restoring equilibrium to the immune microenvironment.[45] Precise regulation of signaling pathways is also key to maintaining homeostasis. Different signaling pathways function at various stages of the hair follicle growth cycle and coordinate with each other.[46,47] For instance, The Wingless-type MMTV integration site family (Wnt) signaling pathway plays an important role in the activation of hair follicle stem cells and hair follicle growth, while the Notch signaling pathway is involved in the differentiation and fate determination of hair follicle cells.[48,49] The orderly activation and inhibition of these signaling pathways ensure the stability of the hair follicle immune microenvironment and the normal physiological function of hair follicles (Figure 2).

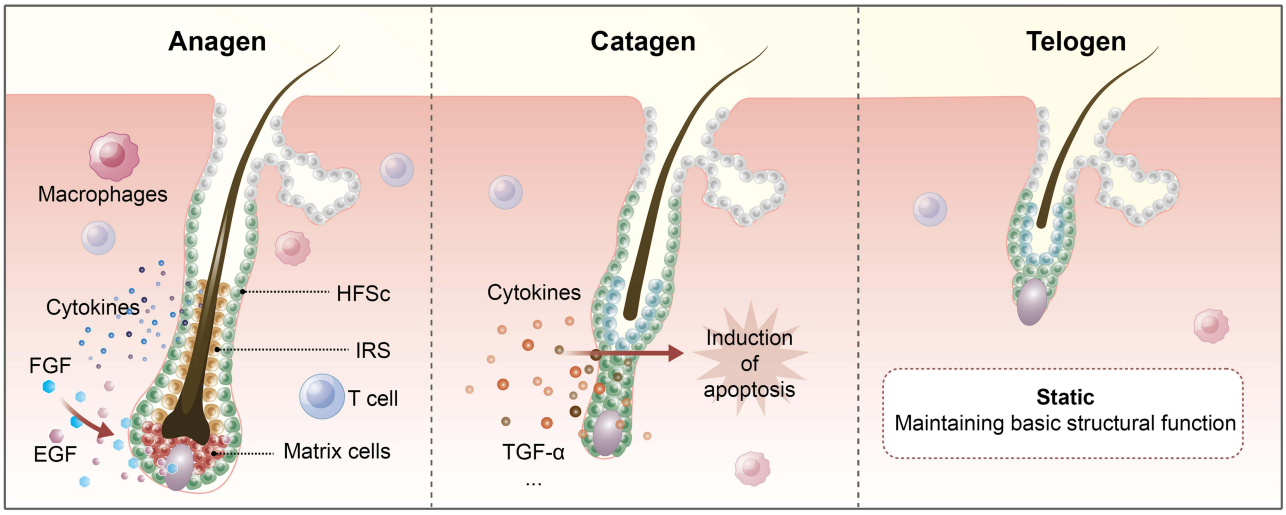

Figure 1 Immune microenvironment characteristics during distinct phases of the hair follicle growth cycle. During anagen, macrophages and other cells secrete cytokines, FGF, and EGF to promote proliferation and differentiation of hair follicle cells; during catagen, cytokines such as TGF-α induce apoptosis and structural remodeling; during telogen, the immune microenvironment remains relatively quiescent, maintaining basic hair follicle structure and function.

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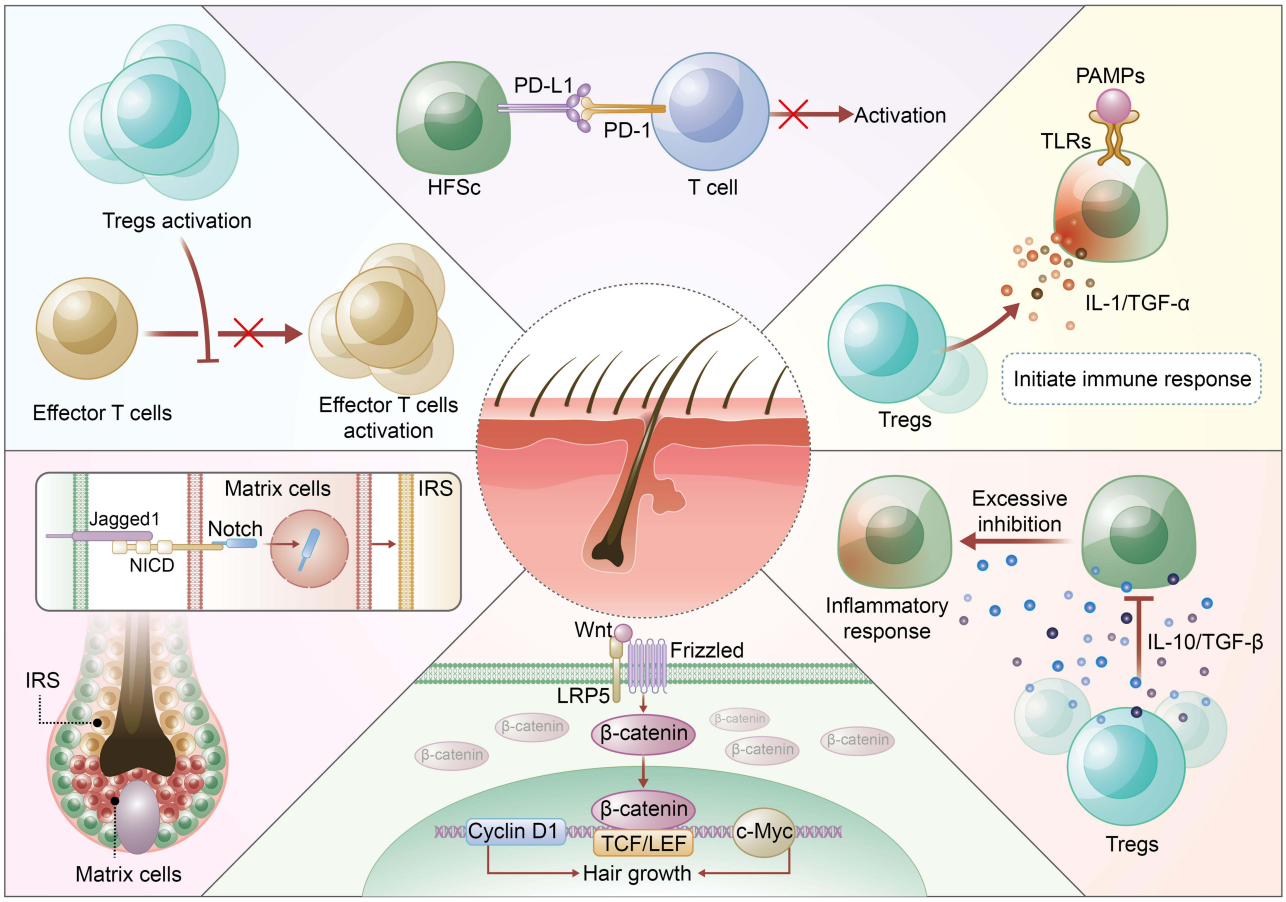

Figure 2 Schematic diagram of the regulatory mechanisms for immune homeostasis and the growth cycle in the hair follicle microenvironment. This figure integrates six core components: PD-L1-mediated immune tolerance, PAMP-TLR initiated immune activation, the activation and regulation of effector T cells, Treg-mediated suppression via IL-10/TGF-β, the precise control of effector T cell activation, and the matrix cell-driven hair growth process via signaling pathways such as Wnt/β-catenin and Notch, which regulate TCF/LEF, Cyclin D1, and c-Myc.

Effects of Tumor Immunotherapy on the Immune Microenvironment of Hair Follicles

Activation and Polarization Remodeling of Immune Cells

Immunotherapy drugs have multifaceted effects on immune cells in hair follicles. For example, ICIs can activate T cells in hair follicles.[40] Under normal physiological conditions, T cells in hair follicles are in a relatively quiescent state to maintain the stability of the immune microenvironment of hair follicles.[50] However, when patients receive ICIs treatment, the drugs block the immune checkpoint signaling pathways, such as the PD-1/PD-L1 pathway, and relieve the inhibition of T cells. This activates the previously inhibited T cells, promoting their clonal expansion and recruitment to the follicular niche.[51] A study on lung cancer patients treated with pembrolizumab found that after treatment, the number of CD8+ T cells around the hair follicles of patients increased significantly.[52] These activated CD8+ T cells have stronger cytotoxicity and can release substances such as perforin and granzyme, which have a potential killing effect on hair follicle cells.[53]

Macrophages in the immune microenvironment of hair follicles are also affected by immunotherapy drugs. Immunotherapy drugs can regulate the polarization state of macrophages.[54] Under normal circumstances, macrophages in hair follicles are mainly of the M2 type, which has anti-inflammatory and tissue repair-promoting functions and helps maintain the homeostasis of hair follicles. However, after immunotherapy, macrophages may polarize towards the M1 type.[55] M1-type macrophages have strong pro-inflammatory activity and will secrete a large number of inflammatory cytokines. These inflammatory cytokines will trigger a local inflammatory response in the hair follicles, damage hair

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follicle cells, interfere with the normal growth cycle of hair follicles, and lead to the occurrence of hair problems.[56] For example, in mouse model, after administering immunotherapy drugs, it was observed that macrophages around the hair follicles polarized towards the M1 type, the inflammation of hair follicles intensified, and hair loss increased.[54]

Cascade Amplification of Pro-Inflammatory Cytokines

Immunotherapy significantly modulates the expression of immune-related cytokines in hair follicles. The administration of immune checkpoint inhibitors upregulates pro-inflammatory cytokines within the follicular microenvironment.[22] Studies have shown that in breast cancer patients undergoing immunotherapy, local levels of TNF-α, Interleukin-6 (IL-6), and IFN-γ in hair follicles are markedly elevated.[57] TNF-α induces apoptosis of follicular cells while suppressing the proliferation and differentiation of hair follicle stem cells.[58] A clinical study revealed that in lung cancer patients receiving immunotherapy, TNF-α expression in scalp hair follicles increased several-fold post-treatment, correlating positively with the severity of alopecia.[59] IL-6 activates downstream signaling pathways, exacerbating inflammatory responses and disrupting normal follicular function.[60] IFN-γ modulates immune cell activity, enhancing T-cell-mediated attack on follicular cells.[61]

Aberrant Signaling Pathway Activation and Inflammatory Responses

Immunotherapy profoundly influences immune-related signaling pathways in hair follicles by potentially bridging adaptive and innate immunity. We hypothesize that ICI, induced T cell activation and tumor cell apoptosis release damage, associated molecular patterns (DAMPs). These DAMPs may subsequently activate TLRs on follicular cells, initiating an innate immune response that synergizes with the adaptive immune attack.[62] TLR activation then promotes inflammatory cytokine secretion by both follicular and immune cells, further amplifying local immune responses.[63] Concurrently, ICIs directly or indirectly enhance NF-κB signaling, facilitating its nuclear translocation and upregulation of pro-inflammatory genes and adhesion molecules.[32,64] This cascade exacerbates local follicular inflammation and disrupts immune homeostasis, a mechanism supported by in vitro evidence showing that treatment of follicular cells with immunotherapeutic agents leads to significant NF-κB activation and elevated inflammatory cytokine expression.[65]

Immunopathological Mechanisms of Hair Abnormalities

Immunotherapy disrupts the equilibrium of the hair follicle immune microenvironment, leading to a cascade of adverse effects, with alopecia being one of the manifestation.[66] By activating the immune system, immunotherapy triggers aberrant immune attacks against follicular cells. Hair follicle antigens, which are normally immune-privileged, become recognized as foreign targets, provoking autoimmune-like reactions.[67] Activated T cells, B cells, and macrophages infiltrate the perifollicular region, releasing excessive pro-inflammatory cytokines (eg, TNF-α) and cytotoxic mediators, ultimately damaging follicular structure and function.[68] The overproduction of these cytokines promotes apoptosis of follicular cells and impairs the proliferation and differentiation of hair follicle stem cells, leading to disrupted hair growth and eventual hair loss.[69]

In clinical practice, a subset of cancer patients receiving immunotherapy have exhibited varying degrees of alopecia.[70] Hair loss represents a rare immune-related adverse event associated with ICIs, with its severity and duration showing considerable interindividual variability.[71] Approximately 1–2% of patients develop alopecia areata or alopecia universalis.[72] Beyond hair loss, immune microenvironment dysregulation in hair follicles may lead to other hair-related abnormalities. For instance, some melanoma patients experience hair whitening and hair loss.[73]

Beyond alopecia, immunotherapy can also induce hair repigmentation, a phenomenon suggesting a dynamic, and potentially reversible, perturbation of the follicular immune microenvironment. The process of repigmentation likely involves the reactivation and differentiation of melanocyte stem cells (McSCs) within the hair follicle bulge and bulb. While the precise mechanisms remain elusive, we propose two non-mutually exclusive hypotheses: first, that ICI-mediated attenuation of immune attack on McSCs may facilitate their survival and subsequent repopulation of the follicle; and second, that specific inflammatory cytokines released during immune activation could directly stimulate melanogenesis or McSC differentiation.[74] Notably, in our ongoing interdisciplinary study on lung cancer patients receiving immunotherapy, preliminary observations indeed suggest a potential correlation between the degree of hair

repigmentation and treatment efficacy. However, this initial dataset has not yet reached statistical significance. To our knowledge, our team is among the first to attempt quantifying this clinically intriguing relationship. We therefore highlight this promising yet preliminary avenue here, hoping to draw broader research attention to the potential of hair follicle immune changes as a biomarker for immunotherapy outcomes. We are optimistic that future collaborative efforts will be pivotal in validating and elucidating this fascinating connection.

Management Strategies and Future Perspectives

Current management strategies for immunotherapy-induced hair follicle irAEs primarily rely on systemic or topical immunomodulatory agents. Topical corticosteroids serve as a first-line approach, exerting potent anti-inflammatory and immunosuppressive effects that suppress perifollicular immune cell activation, reduce pro-inflammatory cytokine secretion, and mitigate inflammatory damage.[17,75–77] For more severe cases, systemic immunosuppressants such as cyclosporine may be employed. Cyclosporine inhibits T-cell activation and proliferation, thereby attenuating immune-mediated attacks on follicular cells, a mechanism supported by animal studies showing reduced follicular damage and promoted hair regrowth.[78–80]

Therefore, we propose investigating the feasibility of topical or localized immunomodulatory approaches as a promising strategy to alleviate follicular irAEs while preserving systemic antitumor immunity. The success of this strategy hinges on developing therapies that spatially confine immunomodulation to the skin microenvironment. Promising candidates include topical JAK inhibitors targeting IFN-γ signaling and specific cytokine antagonists, which could potentially quench the inflammatory cascade within follicles without compromising systemic immune activation. Looking forward, integrating single-cell and spatial transcriptomics of patient lesions will be crucial for identifying novel, tissue-specific therapeutic targets. Successfully decoupling local toxicity from systemic efficacy would not only significantly enhance patients' quality of life but could also potentially broaden the therapeutic window of ICIs, paving the way for more durable and personalized cancer immunotherapy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Bo Li and Sitong Jiang are co-first authors for this study. Lin Li and Jianmin Chang are co-correspondence authors for this study. The authors report no conflicts of interest in this work.

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