Review Article

The role of immune metabolism in skin cancers: implications for pathogenesis and therapy

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Abstract: The skin is a complex organ that serves as a critical barrier against external pathogens and environmental impact. Recent advances in immunometabolism have highlighted the intricate link between cellular metabolism and immune function, particularly in the context of skin cancers. This review aims to provide a comprehensive overview of the key metabolic pathways and adaptations that occur in immune cells during homeostasis and activation, and explore how metabolic reprogramming contributes to the pathogenesis of specific skin cancers. We discuss the complex interplay between tumor cells and infiltrating immune cells, which shapes the tumor microenvironment and influences disease outcomes. The review delves into the role of various metabolic pathways, such as glycolysis, oxidative phosphorylation, and lipid metabolism, in the regulation of immune cell function and their impact on the development and progression of skin cancers. Furthermore, we examine the potential of targeting metabolic pathways as a therapeutic strategy in skin cancers and discuss the challenges and future perspectives in this rapidly evolving field. By understanding the metabolic basis of skin immune responses, we can develop novel, personalized therapies for the treatment of skin cancers, ultimately improving patient outcomes and quality of life. The insights gained from this review will contribute to the growing body of knowledge in immunometabolism and its application in the management of skin cancers, paving the way for more effective and targeted interventions in the future.

Keywords: Immunometabolism; skin cancer; metabolic reprogramming; immune cell function; targeted therapies

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Introduction

The skin is the largest organ of the human body, serving as a critical barrier against external pathogens and environmental impact (1). As such, the skin is home to a complex network of immune cells that work in concert to maintain tissue homeostasis and mount appropriate responses to potential threats (2). In recent years, the field of immunometabolism has emerged as a crucial area of research, highlighting the intricate link between cellular metabolism and immune function (3,4). This connection is particularly relevant in the context of skin cancers, where aberrant immune responses and metabolic dysregulation often go hand in hand (5).

Immune cells, like all other cells in the body, require energy and biosynthetic precursors to carry out their functions (6). However, it has become increasingly clear that immune cells undergo dynamic metabolic reprogramming

in response to activation signals, which can have profound effects on their differentiation, effector functions, and ultimately, their impact on cancer pathogenesis (7,8). In the skin, where immune cells are constantly exposed to a variety of stimuli, understanding the metabolic underpinnings of immune responses could provide valuable insights into the mechanisms driving various skin disorders (9). Moreover, many carcinogenic environmental factors, such as ultraviolet (UV) radiation, can significantly impact the metabolic reprogramming of skin cells, contributing to the development and progression of skin cancers. These factors can alter the metabolic landscape of skin cells, creating a microenvironment that favors tumor growth and immune evasion. This review aims to provide a comprehensive and up-to-date synthesis of the current literature on immune metabolism in skin cancers. Unlike previous studies that have focused on specific aspects of this field, our review offers a holistic perspective, integrating the latest findings on novel metabolic pathways, tumor-host metabolic crosstalk, and the potential of metabolic interventions as therapeutic strategies. By doing so, we seek to highlight the unique contributions of this review to the field and stimulate further research into the metabolic basis of skin immune responses.

This review aims to address these gaps by providing a comprehensive and integrative analysis of immune metabolism in skin cancers. Our innovative approach lies in the holistic examination of the metabolic landscape of skin immune responses, considering the intricate interplay between various immune cell types, tumor cells, and the skin microenvironment. By synthesizing the latest findings on novel metabolic pathways, tumor-host metabolic crosstalk, and the potential of metabolic interventions as therapeutic strategies, we seek to provide a more nuanced understanding of the metabolic basis of skin immunity and its implications for cancer pathogenesis. Furthermore, we discuss the translational potential of targeting immune metabolism in skin cancers, highlighting the challenges and opportunities in developing metabolic therapies. By doing so, we aim to stimulate further research into the immunometabolic dysregulation underlying skin cancers and inspire the development of novel therapeutic strategies that harness the power of metabolic reprogramming to enhance anti-tumor immunity.

In this review, we seek to provide a comprehensive overview of the current state of knowledge regarding immune metabolism in the context of skin cancer. We begin by discussing the key metabolic pathways and adaptations that occur in immune cells, both under homeostatic conditions and during activation. We then delve into the role of immune metabolism in specific skin cancers, highlighting the metabolic alterations that contribute to cancer progression and exploring potential therapeutic targets. By providing a comprehensive synthesis of the current literature on immune metabolism in skin cancers, this review aims to highlight the importance of this emerging field and stimulate further research into the metabolic basis of skin immune responses, with the ultimate goal of developing novel, targeted therapies for the treatment of skin disorders.

Overview of immune metabolism

Key metabolic pathways in immune cells

Immune cells rely on a variety of metabolic pathways to meet their energy demands and support their effector functions (10,11). The two primary pathways are glycolysis and oxidative phosphorylation (OXPHOS) (12,13). Glycolysis is a cytoplasmic process that converts glucose into pyruvate, generating adenosine triphosphate (ATP) and intermediates for biosynthesis. OXPHOS, on the other hand, occurs in the mitochondria and involves the complete oxidation of glucose or fatty acids to generate large amounts of ATP (14). In addition to these central pathways, immune cells also utilize other metabolic routes, such as the pentose phosphate pathway (PPP), which generates nicotinamide adenine nucleotide phosphate (NADPH) and pentose sugars for nucleotide synthesis and redox balance, and amino acid metabolism, which provides precursors for protein synthesis and supports cell proliferation (15). Fatty acid synthesis and oxidation also play crucial roles in immune cell function, with fatty acid synthesis supporting membrane biosynthesis and signaling, while fatty acid oxidation provides an alternative energy source during nutrient-limited conditions (16). Metabolism plays a critical role in supporting various aspects of cellular function, and metabolic reprogramming is a key driver of cell differentiation and fate. In immune cells, distinct metabolic signatures are associated with specific functional states. For example, pro-inflammatory immune cells, such as M1 macrophages and Th1/Th17 cells, exhibit a highly glycolytic phenotype, while anti-inflammatory subsets, such as M2 macrophages and regulatory T cells, rely more on OXPHOS and fatty acid oxidation (17-19). These metabolic profiles are not merely a consequence of differentiation but

actively shape the functional outcomes of these cells.

Metabolic reprogramming during immune cell activation and differentiation

Upon activation by pathogens or inflammatory signals, immune cells undergo profound metabolic reprogramming to meet the increased energy and biosynthetic demands associated with cell proliferation, cytokine production, and effector functions (20,21). This metabolic shift is characterized by a transition from a quiescent state, relying primarily on OXPHOS, to an activated state, marked by a significant upregulation of glycolysis. For example, when naive T cells encounter an antigen, they rapidly increase their glucose uptake and glycolytic flux, a process driven by the transcription factors hypoxia-inducible factor-1alpha (HIF-1) and Myc. This glycolytic switch supports the biosynthesis of macromolecules needed for cell growth and proliferation (22,23). Similarly, activated macrophages and dendritic cells also upregulate glycolysis, which is crucial for supporting their phagocytic and antigen-presenting functions (24). Importantly, the metabolic profile of immune cells can also dictate their differentiation and effector functions. These distinct metabolic signatures are not merely a consequence of differentiation but actively shape the functional outcomes of these cells.

Role of immune metabolism in maintaining skin homeostasis

In the skin, immune cells play a critical role in maintaining tissue homeostasis and preventing pathogen invasion (25). The metabolic state of these cells is finely tuned to support their functions in the unique microenvironment of the skin. For example, skin-resident memory T cells (TRMs) have been shown to rely on fatty acid oxidation and mitochondrial respiration to support their long-term survival and protective functions in the skin (26,27). Moreover, the metabolic interplay between immune cells and skin-resident cells, such as keratinocytes and fibroblasts, is crucial for maintaining skin homeostasis (28-30). Keratinocytes, for instance, can modulate the metabolic microenvironment of the skin through the production of lactate, which can influence the function of local immune cells (31). Disruption of this metabolic cross-talk can contribute to the development of skin disorders, highlighting the importance of immune metabolism in maintaining healthy skin. In summary, immune metabolism plays a central role in shaping the function and fate of immune cells in the skin. By understanding the metabolic pathways and adaptations that occur during immune cell activation and differentiation, we can gain valuable insights into the mechanisms underlying skin homeostasis and disease pathogenesis.

Immune metabolism in skin cancers

Metabolic reprogramming is a hallmark of cancer cells, and skin cancers, such as melanoma and squamous cell carcinoma (SCC), are no exception. Tumor cells often exhibit increased glycolysis (the Warburg effect) and glutamine metabolism to support their rapid growth and proliferation (32). However, the metabolic interplay between tumor cells and infiltrating immune cells also plays a crucial role in shaping the tumor microenvironment and determining disease outcomes. In melanoma, tumor cells exhibit a high glycolytic flux, which not only provides energy for their growth but also generates metabolic intermediates for biosynthesis and redox balance (33). The increased expression of glycolytic enzymes, such as HK2, has been associated with poor prognosis and resistance to therapy in melanoma patients (34). Moreover, melanoma cells can also utilize glutamine as an alternative fuel source, with the upregulation of glutaminase (GLS) and other glutamine-metabolizing enzymes supporting their metabolic flexibility and survival under stress conditions (35). Recent studies (36-38) have also unveiled novel metabolic pathways and tumor-host metabolic crosstalk mechanisms that contribute to skin cancer progression and drug resistance. For example, the kynurenine pathway, which is involved in tryptophan catabolism, has been shown to create an immunosuppressive microenvironment in melanoma, promoting tumor growth and immune evasion. Additionally, the metabolic interplay between melanoma cells and cancer-associated fibroblasts (CAFs) has been found to support tumor progression through the exchange of metabolites such as lactate (39). Targeting these novel metabolic pathways and crosstalk mechanisms may provide new therapeutic opportunities for skin cancers.

The metabolic reprogramming in melanoma cells not only supports their own growth but also influences the function of infiltrating immune cells. For example, the high glycolytic activity of melanoma cells can create a glucose-depleted microenvironment, which can impair the metabolic fitness and effector functions of tumor-

infiltrating T cells (40,41). The accumulation of lactate and other metabolic waste products by melanoma cells can further suppress the anti-tumor immune response by inducing the expression of immune checkpoint molecules, such as programmed death-ligand 1 (PD-L1), on tumor cells and promoting the generation of immunosuppressive cell types, such as regulatory T cells and myeloid-derived suppressor cells (MDSCs) (42). In contrast to the metabolic exhaustion observed in tumor-infiltrating T cells, MDSCs in the melanoma microenvironment exhibit a highly glycolytic phenotype, which supports their immunosuppressive functions. The increased glycolytic flux in MDSCs is driven by the upregulation of HIF-1α and other glycolytic regulators, which promote the expression of immunosuppressive factors, such as arginase-1 and inducible nitric oxide synthase (iNOS). The depletion of amino acids, such as arginine and tryptophan, by MDSCs can further impair the metabolic fitness and effector functions of tumor-infiltrating T cells, creating a metabolic barrier to effective anti-tumor immunity (43,44).

Moreover, metabolic interventions that restore the metabolic fitness of tumor-infiltrating T cells have shown remarkable success in treating melanoma. For instance, checkpoint blockade immunotherapy, which targets the programmed cell death protein 1 (PD-1)/PD-L1 axis, has been shown to reinvigorate the metabolic and functional capacity of exhausted T cells, leading to improved anti-tumor responses and durable clinical outcomes (45). Combining checkpoint blockade with metabolic modulators, such as metformin or indoleamine 2,3-dioxygenase (IDO) inhibitors, may further enhance the metabolic reprogramming of T cells and potentiate their anti-tumor functions (46,47).

In summary, metabolic reprogramming is a key driver of skin cancer pathogenesis, contributing to tumor growth, metastasis, and immune evasion. By understanding the specific metabolic vulnerabilities of skin cancer cells and their associated immune cells, we can develop novel therapeutic strategies that target the metabolic basis of these diseases. Combining metabolic modulators with existing therapies, such as chemotherapy and immunotherapy, may help to overcome drug resistance and improve clinical outcomes for patients with advanced skin cancers.

Challenges and future perspectives

As the field of immune metabolism in skin cancers continues to evolve, several challenges must be addressed to fully realize the therapeutic potential of metabolic interventions. One major challenge is the complex and dynamic nature of immune metabolism in the skin (48,49), which requires the development of more sophisticated experimental models and analytical tools. These tools should be capable of dissecting the intricate metabolic circuits that underlie skin immune responses, taking into account the spatial and temporal heterogeneity of the skin microenvironment. Moreover, the translational application of metabolic modulators in skin cancers necessitates careful consideration of the potential off-target effects and long-term safety of these interventions. Identifying the appropriate patient subsets that may benefit most from metabolic therapies is also crucial, as the metabolic dependencies of immune cells may vary depending on the specific cancer biology and stage.

Despite these challenges, the future of immune metabolism in skin cancers holds great promise. The rapid progress in the field of immunometabolism, coupled with the advent of novel technologies and therapeutic modalities, offers a promising outlook for the future of skin cancer management. For example, the integration of single-cell metabolomics, spatial transcriptomics, and advanced imaging techniques (50) may enable the development of high-resolution metabolic maps of the skin, providing unprecedented insights into the metabolic landscape of skin immune responses. Moreover, the growing understanding of the metabolic vulnerabilities of skin cancer cells and their associated immune cells may pave the way for the development of targeted metabolic interventions. By harnessing the power of metabolic reprogramming, we may be able to enhance the efficacy of existing therapies, such as immunotherapy, and overcome drug resistance in skin cancers.

Conclusions

In conclusion, this review has provided a comprehensive synthesis of the current knowledge on immune metabolism in skin cancers, highlighting the critical role of metabolic reprogramming in shaping the pathogenesis and progression of these diseases. By understanding the complex metabolic interplay between tumor cells and immune cells, we can identify novel therapeutic targets and develop more effective strategies for the prevention and treatment of skin cancers. The integration of cutting-edge technologies and the continued exploration of the metabolic landscape of the skin will be crucial in driving future advances in this field. Ultimately, by harnessing the power of immune

metabolism, we may be able to unlock new possibilities for the management of skin cancers and improve patient outcomes.

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