Peer Review File

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Reviewer Comments

The paper titled "The Role of Immune Metabolism in Skin Cancers: Implications for Pathogenesis and Therapy" is interesting. This review discusses 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. However, there are several minor issues that if addressed would significantly improve the manuscript.

RE: We greatly appreciate your thorough review and insightful comments on our manuscript. Your suggestions have been invaluable in helping us improve the quality and clarity of our work. We have carefully considered each of your comments and have made substantial revisions to address them.

1) Please summarize novel tumor metabolic pathways and tumor-host metabolic crosstalk mechanisms leading to skin cancers progression and drug resistance, with an overview on their translational potential as novel therapeutic targets.

RE: In response to your suggestion, we have expanded our discussion on novel tumor metabolic pathways and tumor-host metabolic crosstalk mechanisms that contribute to skin cancer progression and drug resistance. We have added new sections in the Results (paragraphs 1 and 4) that highlight the critical role of metabolic reprogramming in shaping the functional states of immune cells and the immunosuppressive microenvironment in skin cancers. We have also provided examples of specific metabolic pathways, such as the kynurenine pathway and the metabolic interplay between melanoma cells and cancer-associated fibroblasts, that contribute to tumor growth and immune evasion. These additions emphasize the translational potential of targeting these novel metabolic pathways as therapeutic strategies for skin cancers.

Changes in the text: Result – paragraph 1: 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. These metabolic profiles are not merely a consequence of differentiation but actively shape the functional outcomes of these cells.
Result – Paragraph 4: Recent studies 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 and amino acids. Targeting these novel metabolic pathways and crosstalk mechanisms may provide new therapeutic opportunities for skin cancers.

2) Many carcinogenic environmental factors are the cause of early cancer occurrence. What are their effects on metabolic reprogramming? It is recommended to add relevant content.
RE: To address your comment on the effects of carcinogenic environmental factors on metabolic reprogramming, we have incorporated a discussion on this topic in the Introduction (paragraph 2). We now acknowledge the significant impact of these factors, such as UV radiation, on the metabolic landscape of skin cells and their contribution to the development and progression of skin cancers. This addition provides a more comprehensive understanding of the complex interplay between environmental factors and metabolic dysregulation in skin carcinogenesis.
Changes in the text: Introduction – paragraph 2: Moreover, many carcinogenic environmental factors, such as 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.

3) There have been many studies on skin cancers. What is the difference between this study and previous studies? What is the innovation? These need to be described in the introduction.
RE: To clarify the novelty and innovation of our review, we have made changes in the Introduction (paragraph 3). We emphasize the holistic and integrative approach of our review, which sets it apart from previous studies that have focused on specific aspects of immune metabolism in skin cancers. By synthesizing the latest findings on novel metabolic pathways, tumor-host

metabolic crosstalk, and the potential of metabolic interventions as therapeutic strategies, we aim to provide a more nuanced understanding of the metabolic basis of skin immunity and its implications for cancer pathogenesis. We also highlight the translational potential of targeting immune metabolism in skin cancers and the challenges and opportunities in developing metabolic therapies.
Changes in the text: Introduction – paragraph 3: 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 will 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.

4) How metabolism supports many aspects of cellular function, and how metabolic reprogramming drives cell differentiation and fate? It is recommended to add relevant content.

RE: To further explain how metabolism supports cellular function and how metabolic reprogramming drives cell differentiation and fate, we have expanded our discussion in the Introduction (paragraph 2). We now provide a more detailed explanation of the critical role of metabolism in shaping the functional outcomes of immune cells and the unique contributions of our review to the field.
Changes in the text: Introduction – paragraph 2: 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 (13,14), our review will offer 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.

5) How to provide candidate targets for preventing and treating skin cancers? It is recommended to include relevant descriptions in the discussion.

RE: To address your recommendation on providing candidate targets for preventing and treating skin cancers, we have made additions to the Discussion section. We have added two new paragraphs that highlight the future directions and potential of immune metabolism in skin cancer management. We discuss the integration of cutting-edge technologies, such as single-cell metabolomics and spatial transcriptomics, in developing high-resolution metabolic maps of the skin and identifying novel therapeutic targets. We also emphasize the potential of harnessing metabolic reprogramming to enhance the efficacy of existing therapies and overcome drug resistance in skin cancers.

Changes in the text:

Last 2 paragraphs: 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 (46) 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.

Last paragraphs: 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.