

Uncovering the Heterogeneity of Signaling Pathways in Skin Cutaneous Melanoma: Insights into Prognostic Values and Immune Interactions

Yufang Liu^{1,*}, Chunyan Li^{2,*}, Weiwei Deng^{1D}²

¹Department of Dermatology and Venereology, Fuyang People's Hospital, Fuyang, Anhui, 236000, People's Republic of China; ²Department of Dermatology and Venereology, Dermatology Hospital of Southern Medical University, Department of Dermatology, Guangzhou, People's Republic of China

*These authors contributed equally to this work

Correspondence: Weiwei Deng, Email dengww@smu.edu.cn

Background: Signaling pathways play crucial roles in tumor cells. However, functional heterogeneity of signaling pathways in skin cutaneous melanoma (SKCM) has not been established.

Methods: Based on a recent computational pipeline, pathway activities between SKCM and normal samples were identified.

Results: The results showed that high activities in 12 pathways were associated with poor prognoses, while high activities in 17 pathways were associated with favorable prognoses. Interestingly, elevated metabolic pathway activity was unfavorable, whereas elevated immune activity was favorable for SKCM. Unfavorably elevated metabolic pathways strongly correlated with Wnt/beta-catenin signaling. Conversely, favorable pathways, such as glycosaminoglycan biosynthesis and keratan sulfate, were strongly correlated with anti-tumor pathways. Moreover, the activities of favorable pathways were strongly positively correlated with infiltrating CD8⁺ T cells, macrophages M1, immune score, and stromal score, all of which were favorable for SKCM.

Conclusion: Taken together, our study provides insights into the characteristics of several pathways in SKCM.

Keywords: skin cutaneous melanoma, pathway activity, immune infiltration, prognosis, bioinformatics, tumor microenvironment

Introduction

Metabolic pathways play a vital role in providing cancer cells with energy, maintaining redox balance, and supplying the raw materials for biomacromolecule synthesis.^{1,2} Metabolic reprogramming, which is the abnormal metabolic change in tumor cells, has been recognized as a critical factor in the local nutrient environment, pentose phosphate pathway, tissue origin, synthesis of nucleic acids, somatic mutations, and oxygen-derived free radicals.^{3–8} The immune system is a key component of the body's defense mechanism. The innate immune system has the ability to inhibit tumor metastasis and proliferation by recognizing malignant cells and displaying anti-tumor functions.^{9–11} Studies on mice models and patients have demonstrated that boosting the adaptive immune response can significantly improve antitumor immunity and extend survival time.^{12–14} Other pathways, such as genetic information processing, environmental information processing, cellular processes, and human diseases, may also play a role in tumor proliferation, metastasis, progression, pathogenesis, or the antitumor response. Given the significance of these pathways, it is imperative to clarify their impact on tumor cells.

Over the last few decades, advances in the study of the tumor microenvironment (TME) have revealed the roles of infiltrating immune cells and non-immune cells in TME. For instance, the presence of immune cell infiltration and non-immune stromal cells within TME is closely tied to the prognosis of tumor patients.¹⁵ Recently, various bioinformatic algorithms have been developed to evaluate the immune status of TME, including the reliable and fast CIBERSORT and ESTIMATE algorithms.^{16–20} However, no studies have comprehensively investigated the relationship between pathway activities and immune infiltration in SKCM.

In recent years, metabolic reprogramming and immune infiltration have gained significant attention as critical factors in cancer progression and therapy response. However, the heterogeneity of signaling pathways in SKCM presents unique challenges. While metabolic and immune-related pathways are well-documented in cancer biology, the complex interactions and differential activities of these pathways in SKCM remain underexplored. This gap is particularly pronounced in SKCM due to its distinct tumor TME, where immune cells, stromal cells, and metabolic shifts can create unique cellular landscapes that influence tumor progression and therapeutic responses. Additionally, existing SKCM treatments, including immune checkpoint inhibitors, often show limited success due to the variability in immune infiltration and the unpredictable activity of key signaling pathways. The need for a deeper understanding of how pathway heterogeneity and immune infiltration influence SKCM prognosis is critical for identifying new therapeutic strategies and biomarkers. In this study, we aim to address this gap by investigating the relationship between pathway activities and immune cell infiltration in SKCM, providing novel insights into how these factors affect clinical outcomes and may guide more effective treatment approaches.

In this study, we utilized a new computational pipeline²¹ to assess the 186 pathways from 471 SKCM bulk RNA-seq arrays and 1809 normal bulk RNA-seq arrays. Our analysis uncovered differential pathway activities between SKCM and normal samples, and we characterized the prognostic value of these 186 pathways in SKCM. Furthermore, we investigated the relationships between infiltrating immune cells and the pathways, which impact SKCM prognoses. In conclusion, our study sheds light on how pathway activities influence the clinical outcomes of SKCM and immune infiltration within the tumor microenvironment.

Materials and Methods

Ethics Statement

All experimental procedures and protocols used in this research underwent thorough review and received approval from the committee of Dermatology Hospital of Southern Medical University (2023173).

Data Acquiring and Processing

We obtained the bulk RNA-seq samples of skin cutaneous melanoma (SKCM) from the TCGA database (<https://portal.gdc.cancer.gov/>), and normal bulk RNA-seq samples were sourced from the GTEx database (<https://gtexportal.org/home/datasets>). The expression levels of the arrays were quantified using the log₂ (1+TPM) transformation.

Identification of Pathway Activities

The quantification of pathway activities in the bulk RNA-seq samples was carried out using the methods described in a previous study.²¹ Prior to pathway activity quantification, RNA-seq data were preprocessed to ensure high-quality input. This included quality control steps (such as removal of low-quality reads), normalization, and batch effect correction if necessary, to ensure consistency and reduce technical variation. Pathway activity was quantified based on gene expression profiles using established algorithms. To identify differential pathway activities between SKCM and normal samples, we set a threshold of $|\text{SKCM pathway activity} - \text{normal pathway activity}| \geq 0.2$. The resulting pathway activity scores were visualized using the pheatmap package, which generated heatmap representations of high and low pathway activities in SKCM. These modifications provide transparency in our preprocessing and analysis pipeline to facilitate reproducibility.

Kaplan-Meier Survival Analyses

We utilized Kaplan-Meier survival analysis to examine the correlation between the five-year survival rate of SKCM patients and the differential pathway activities. The analysis was conducted using the survival and survminer packages in R. Statistical significance was assessed using the Log rank test, with a significance threshold of $P < 0.05$. Pathways with a significant correlation to clinical outcomes were further investigated in subsequent research. These analyses included the subsequent examination of immune cell infiltration in the tumor microenvironment and Cox regression analyses.

Cox Regression Analyses

Univariate and multivariate Cox regression analyses were performed to examine the relationship between five-year and overall survival of SKCM patients with screened pathways and infiltrating immune cells. The analyses were conducted using the survival package in R, and the results were visualized using the forestplot package.

Immune Infiltration Within TME

The CIBERSORT algorithm was utilized to determine the proportions of 22 immune cell populations present in the TME of SKCM. Meanwhile, the ESTIMATE algorithm was employed to estimate the levels of stromal and immune infiltration, as well as tumor purity, within the TME.

Results

Heterogeneous Pathway Activities Between SKCM and Normal Samples

We assessed the pathway activities in both SKCM and normal samples, calculating 186 activities in total. The distributions of these activities were comparable between the two types of samples, as depicted in [Figure S1](#), suggesting a lack of global difference between SKCM and normal samples. We analyzed the correlation between pathway activities in SKCM and normal samples using Pearson's correlation analysis. Unexpectedly, we found a strong and significant negative correlation ($r=-1$, $p<0.0001$) between the pathway activities in SKCM and normal samples, as depicted in [Figure S2](#). That suggested significant heterogeneity in pathway activities between the two types of samples. Additionally, our analysis revealed that metabolic pathways were generally more active in SKCM ([Figure 1A](#)), potentially playing a role in the metabolic reprogramming associated with SKCM. We observed that several cell metabolic pathways were up-regulated in SKCM, including glycosaminoglycan biosynthesis keratan sulfate, galactose metabolism, amino sugar and nucleotide sugar metabolism, phenylalanine metabolism and pyruvate metabolism. Additionally, we noted that up-regulated pathways included several immune-associated pathways, such as antigen processing and presentation, B cell receptor signaling, natural killer cell-mediated cytotoxicity, T cell receptor signaling, and chemokine signaling ([Figure 1A](#)). However, only 29 pathways were upregulated in normal samples ([Figure 1B](#)), suggesting that abnormal high activities of pathways may be present in SKCM. Significantly, the TGF beta signaling pathway, p53 signaling pathway, and Wnt signaling pathway were downregulated in SKCM. These results indicate the existence of heterogeneity in pathway activities between SKCM and normal samples.

Identification of Favorable and Unfavorable Pathways in SKCM

To test the hypothesis that the differences in pathway activities between SKCM and normal samples might impact clinical outcomes, we conducted a five-year survival analysis of these differential pathways in SKCM. We found that high activities of 12 pathways were associated with poor prognosis, the majority of which were metabolic pathways ([Figure 2](#)). On the other hand, high activities of 17 pathways were associated with favorable prognoses, where the majority were immune-associated pathways and all were up-regulated in SKCM, with the exception of asthma and linoleic acid metabolism ([Figure S2](#)).

We then investigated the impact of differential pathways on clinical outcomes through Multivariate Cox regression analysis. Surprisingly, the p-values of the unfavorable pathways were all non-significant (above 0.05) in the 5-year analysis, indicating no independent risk factors based on this model ([Figure 3A](#)). However, in the overall survival analysis, aminoacyl tRNA biosynthesis was found to be an unfavorable independent risk factor for SKCM ([Figure 3B](#)). Interestingly, contrary to the 5-year survival analysis, glycosaminoglycan biosynthesis keratan sulfate was found to be a favorable independent factor according to the overall survival analysis ([Figure 3B](#)). This discrepancy may be due to the effect of follow-up data beyond 5 years on the clinical outcomes of glycosaminoglycan biosynthesis keratan sulfate. We also found that B cell receptor signaling pathway and asthma were independent protective factors in SKCM ([Figure 3C](#)). All favorable pathways were not found to be independent factors in the overall survival analysis ([Figure 3D](#)). In conclusion, we have identified several favorable and unfavorable pathways, as well as several independent factors among these pathways.

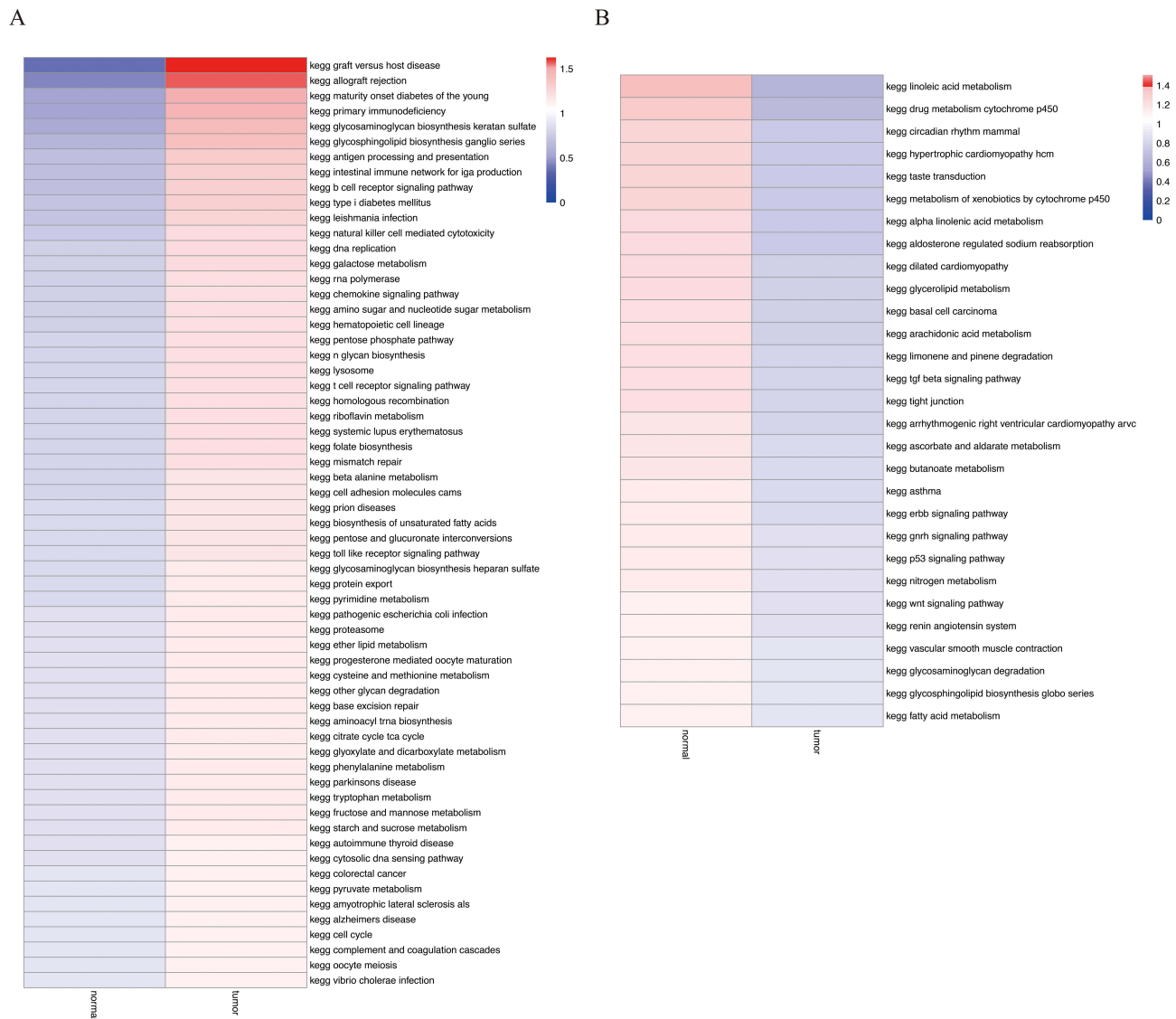


Figure 1 Pathway activities in the bulk RNA-seq samples of SKCM and normal. Up-regulated pathway activity was observed in SKCM (A), while down-regulated pathway activity was seen in normal samples (B). The red color indicates increased pathway activity and blue represents decreased pathway activity.

Favorable Pathways Strongly Positively Correlated with Antitumor Associated Pathways

We analyzed the relationships between the screened pathways and antitumor-associated pathways using Pearson correlation analysis. The results showed that the favorable pathways had strong positive correlations with pathways involved in TNFA signaling via NFKB, Interferon-gamma response, Interferon-alpha response and inflammatory response (Figure 4A). The favorable pathways were also positively correlated with the reactive oxygen species pathway and apoptosis (Figure 4A and B). However, the T cell receptor signaling pathway had a strong positive correlation with TGF beta signaling ($r=0.42$, $p<0.0001$, Figure 4A and B), suggesting a balance in immune regulation in SKCM. Notably, the favorable pathways were generally negatively correlated with DNA repair and WNT beta catenin signaling (Figure 4A and B), enhancing their protective effects. In contrast, the unfavorable pathways were generally negatively correlated with antitumor-associated pathways and even positively correlated with DNA repair and WNT beta catenin signaling (Figure 4A and B). The glycosaminoglycan biosynthesis keratan sulfate was strongly positively correlated with TGF beta signaling ($r=0.41$, $p<0.0001$, Figure 4A and B), and cell cycle had a strong correlation with PI3K AKT mtor

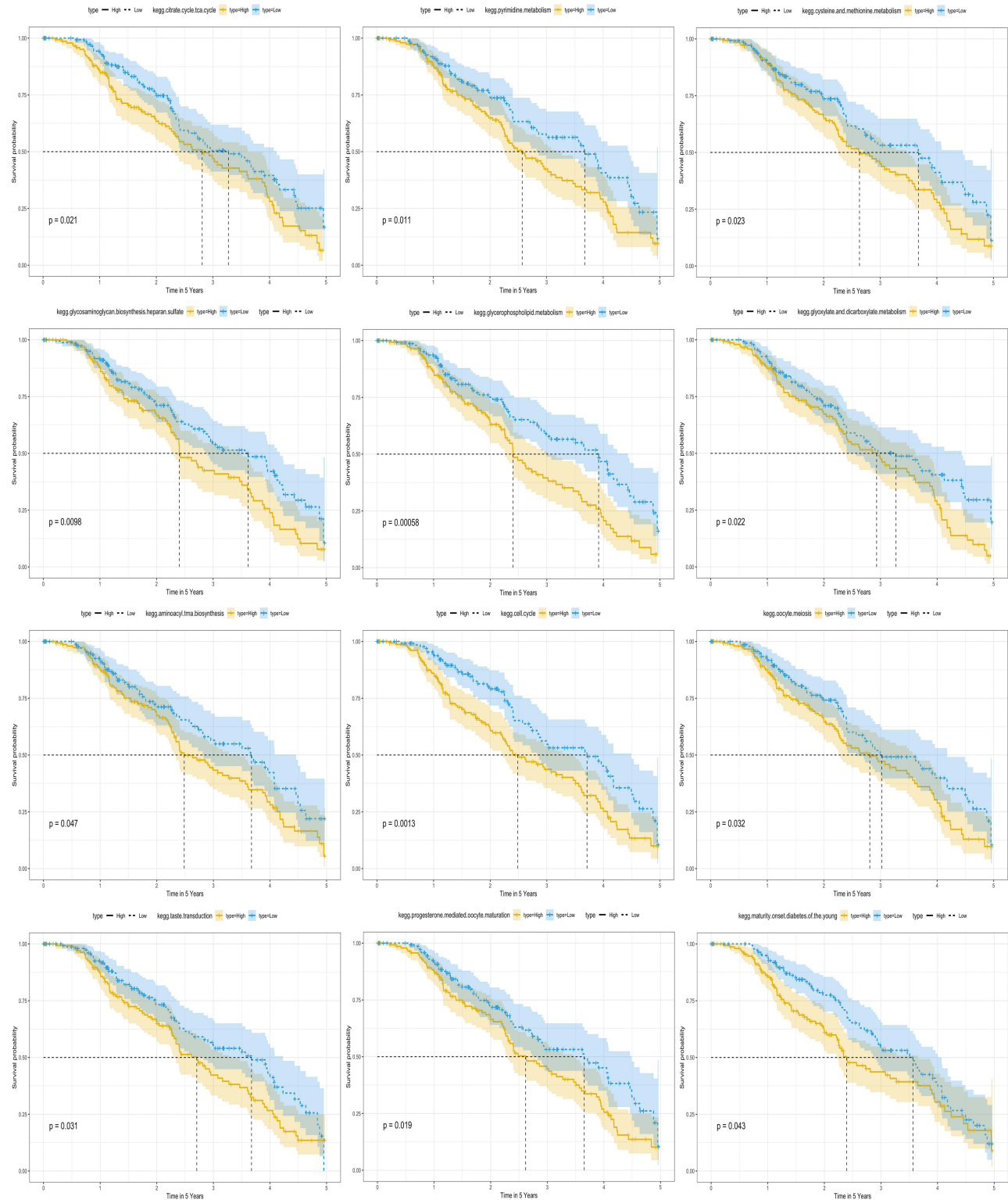


Figure 2 Kaplan-Meier survival analyses in five-years of unfavorable pathways. Yellow lines represent the high pathway activities, and blue lines represent the low pathway activities.

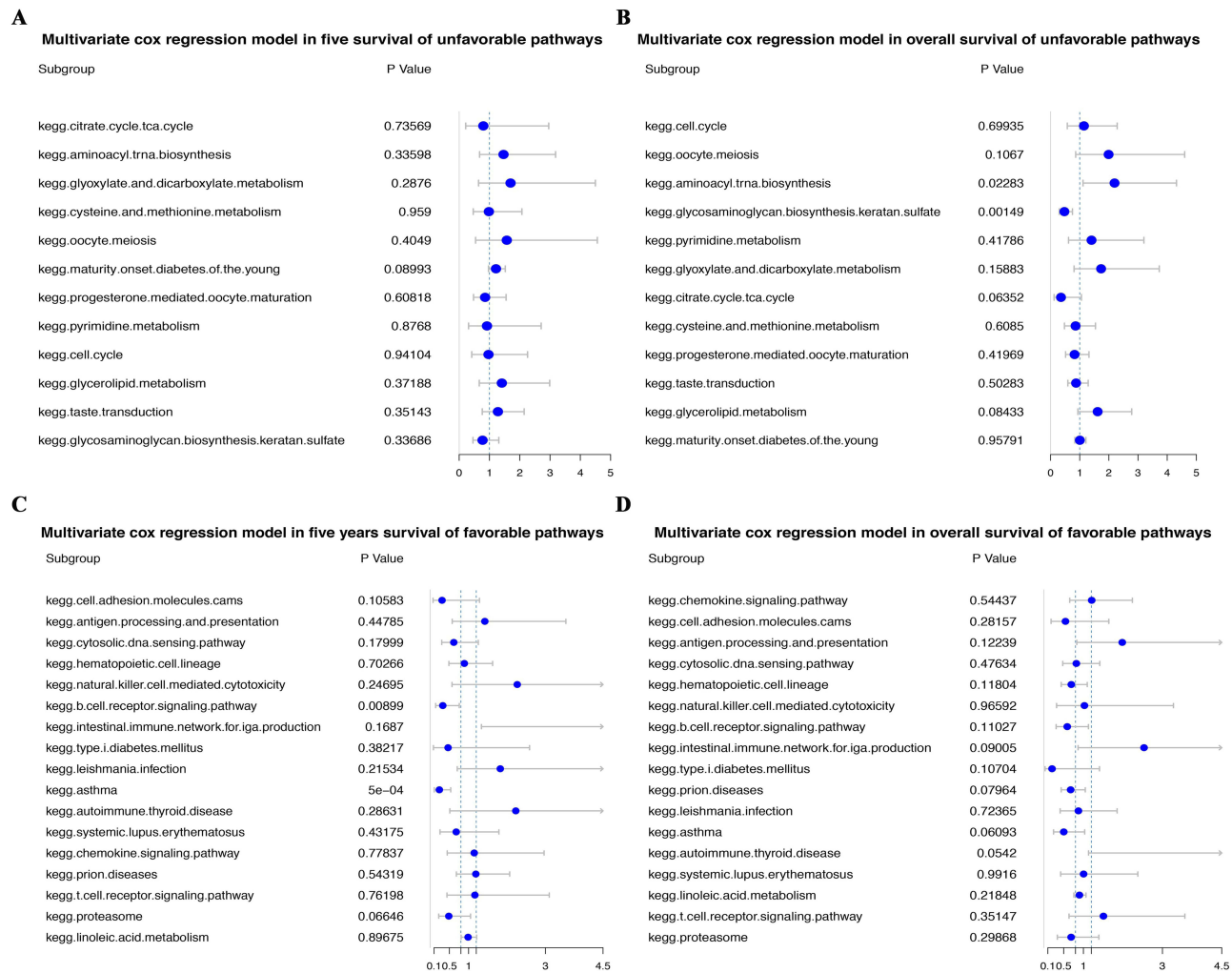


Figure 3 Forest plots of Multivariate Cox regression analyses about differential pathways. **(A)** Multivariate Cox regression analyses in five-year and overall survival **(B)** of unfavorable pathways. **(C)** Multivariate Cox regression analyses in five years and overall survival **(D)** of favorable pathways.

signaling ($r=0.45$, $p<0.0001$, **Figure 4A** and **B**). Overall, the favorable pathways were closely related to antitumor-associated pathways, while the unfavorable pathways were linked to tumor-promoting pathways.

Favorable Pathways Were Strongly Correlated with the Infiltration of Antitumor Immune Cells

The CIBERSORT algorithm was used to study the immune cell populations in TME of SKCM. Results showed that most immune cells were present in the TME (**Figure 5**). Macrophages M0, M2, resting memory CD4⁺ T cells, CD8⁺ T cells, and naive B cells made up the majority of these cells. Further analysis using Cox regression models revealed that high infiltration of activated memory CD4⁺ T cells, CD8⁺ T cells, monocytes, and macrophages M1 were associated with a favorable prognosis in five-year survival (**Figure 6A**). Activated memory CD4⁺ T cells and CD8⁺ T cells were also identified as independent factors for favorable prognosis (**Figure 6B**). Similarly, CD8⁺ T cells, activated memory CD4⁺ T cells, plasma cells, and macrophages M1 were protective factors in overall survival according to univariate Cox regression (**Figure 6C**). However, only CD8⁺ T cells were found to have independent protective effects in overall survival using multivariate Cox regression (**Figure 6D**). These results suggest that several infiltrating immune cells are associated with a favorable prognosis, indicating their protective effects.

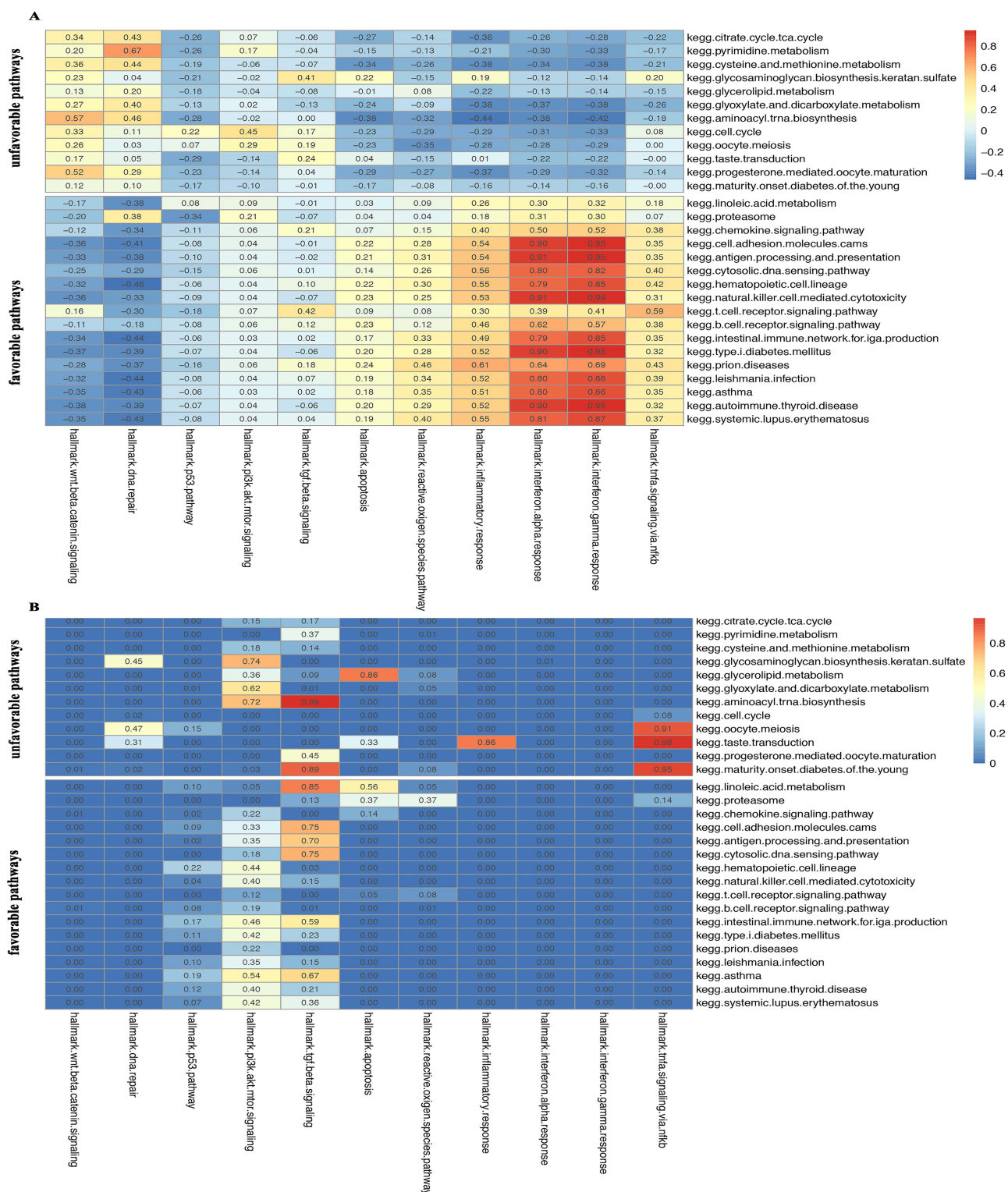


Figure 4 Pearson's correlation analyses between screened pathways and antitumor or tumor-promoting hallmark pathways. **(A)** Pearson's r values. **(B)** p values of Pearson's correlation.

We performed Pearson correlation analysis to identify the relationship between pathway activities and infiltrating immune cells in SKCM. Our results showed that favorable pathways were positively correlated with high levels of infiltrating CD8⁺ T cells, macrophages M1, and activated memory CD4⁺ T cells, which were associated with a favorable prognosis (Figure 7A and B). The favorable pathways were also positively correlated with immune score and stromal

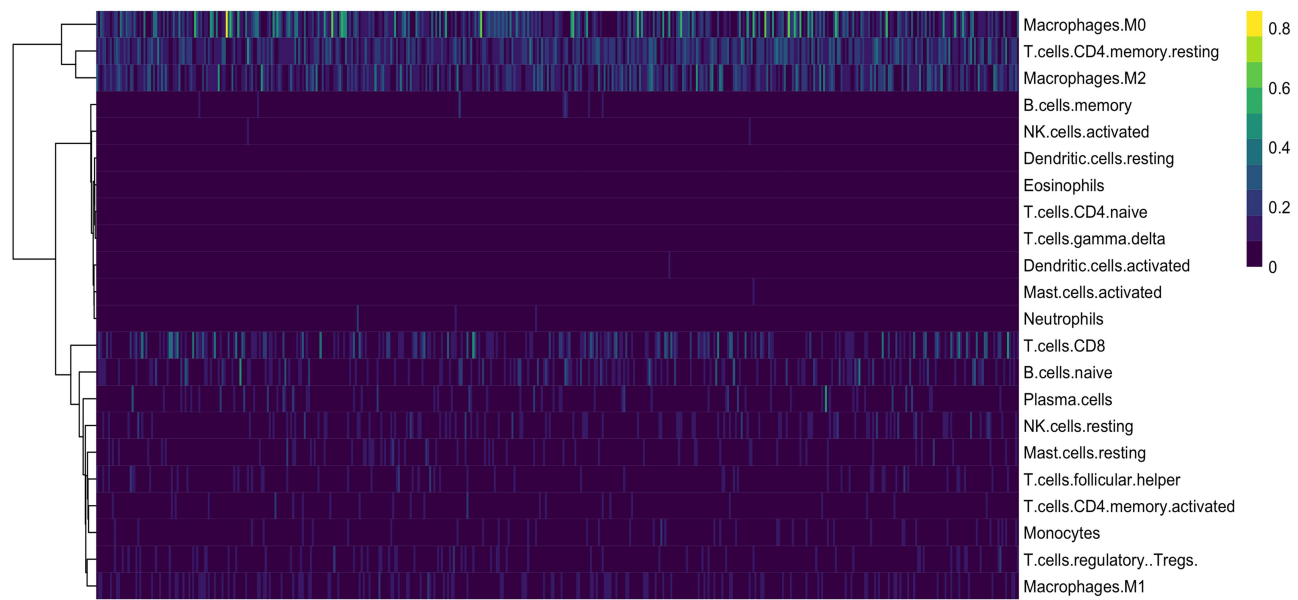


Figure 5 Heatmap showed the proportions of infiltrating immune cells. Blue represents low immune cell infiltration, while yellow indicates high immune cell infiltration.

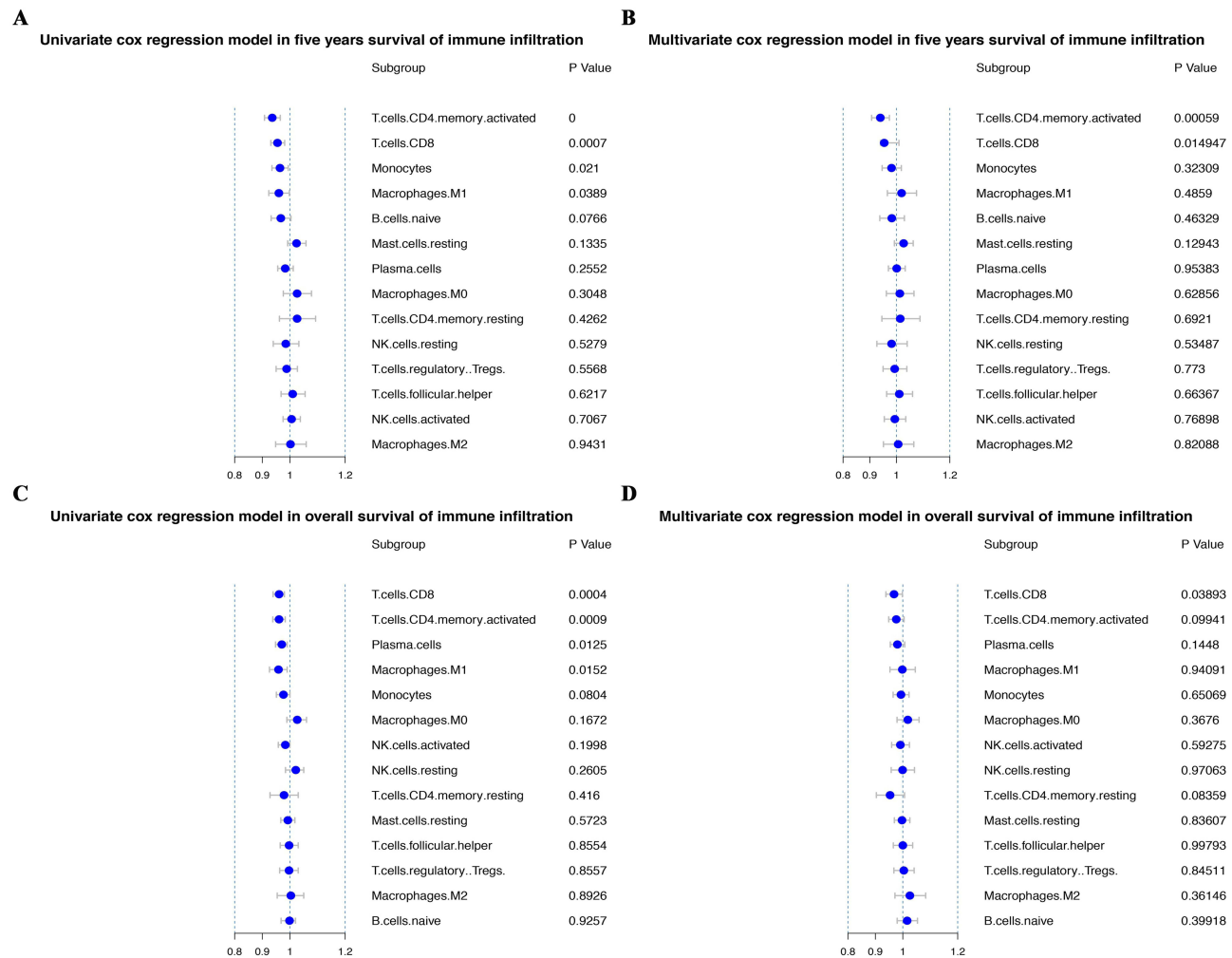


Figure 6 Forest plots of Univariate and Multivariate Cox regression analyses about infiltrating immune cells. **(A)** Univariate and Multivariate **(B)** Cox regression analyses in five years of infiltrating immune cells. **(C)** Univariate and Multivariate **(D)** Cox regression analyses in overall survival of infiltrating immune cells.

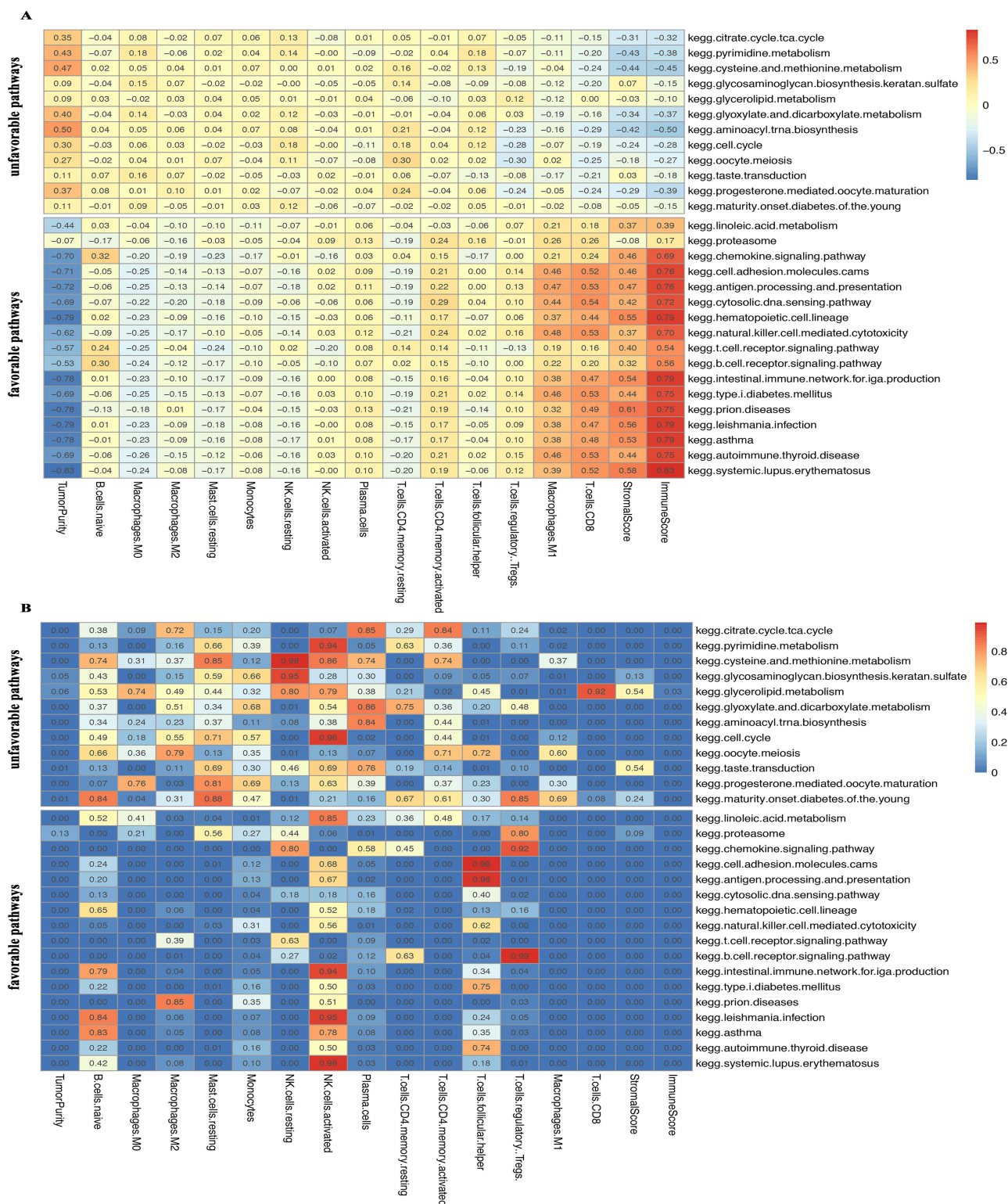


Figure 7 Pearson's correlation analyses between screened pathways and infiltrating immune cells. **(A)** Pearson's *r* values. **(B)** *p* values of Pearson's correlation.

score, which may be protective factors in SKCM. Kaplan-Meier survival analysis revealed that high immune score was linked to a favorable prognosis (Figure S3A). However, the results of the analysis of the stromal score were not statistically significant ($p=0.051$, Figure S3B). Although not significant, the Kaplan-Meier curve showed a higher

survival probability with high stromal score compared to low stromal score after 2 years (Figure S3B). On the other hand, unfavorable pathways were negatively correlated with infiltrating CD8⁺ T cells, macrophages M1, immune score, stromal score, and activated memory CD4⁺ T cells (Figure 7A and B). Furthermore, several metabolic pathways were strongly positively correlated with tumor purity (Figure 7A and B), which was linked to a worse prognosis in SKCM (Figure S3C). Our results indicate that both favorable and unfavorable pathways play a role in regulating immune cell infiltration and have either antitumor or tumor-promoting functions in SKCM.

Discussion

Mounting evidence indicates that multiple factors contribute to the development of tumors.^{22–24} Immune infiltration, metabolic pathways, and antitumor immune pathways are considered key factors in this process.^{25–30} To better understand these relationships, we conducted a series of bioinformatics analyses to evaluate the role of several pathways in immune infiltration and clinical outcomes in SKCM.

We first evaluated 186 pathways in SKCM and eventually identified 12 unfavorable and 17 favorable pathways. After conducting a five-year survival analysis using multivariate Cox regression, the B cell receptor signaling pathway and asthma were found to be independent factors with a favorable prognosis in SKCM. Furthermore, we investigated the relationships between the screened pathways and hallmark pathways of antitumor or tumor-promoting functions. The favorable pathways were generally positively correlated with the antitumor pathways and negatively correlated with the tumor-promoting pathways. For instance, the interferon-gamma response is a pleiotropic antitumor response that serves as an antiproliferative and pro-apoptotic factor.³¹ Similarly, the interferon-alpha response can also induce antiproliferative and apoptotic cellular responses.³² There is a growing body of evidence that reactive oxygen species can trigger autophagy, apoptosis, and DNA damage.^{33–35} The Wnt pathway has also been recognized as playing a crucial role in tumor progression and metastasis in various cancers.^{36–38} These results indicated that favorable pathways may be also involved in antitumor process. Likewise, favorable pathways were also positively correlated with antitumor associated immune cells in SKCM TME. CD8⁺ T cells, the most prominent anti-tumor cells, can recognize and clear immunogenic cancer cells in early cancer.²⁶ Importantly, our results demonstrated that high CD8⁺ T cells infiltration would also serve as an independent factor and contribute to a favorable prognosis in SKCM. M1-polarized macrophages mediate antitumoral response through secretion of high amounts of proinflammatory cytokines, direct cytostatic and cytotoxic effect on tumor cells, and the stimulatory effect on T cells.^{39–41} Our results suggest that favorable pathways in SKCM may also contribute to the antitumor process. Additionally, these favorable pathways were positively correlated with antitumor-associated immune cells in the SKCM tumor microenvironment. High infiltration of CD8⁺ T cells, a key player in anti-tumor immunity, was found to be an independent factor for a favorable prognosis in SKCM. M1-polarized macrophages, which mediate anti-tumoral responses through the secretion of proinflammatory cytokines and direct cytostatic and cytotoxic effects on tumor cells, were also shown to have a protective effect in SKCM, though they were not independent factors. Furthermore, high infiltration of activated memory CD4⁺ T cells was found to result in a better prognosis and was an independent factor according to our multivariate Cox regression analysis of five-year survival. Immune and stromal scores, which were positively correlated with favorable pathways and also had a favorable prognosis, further highlighted the protective effects of favorable pathways and their potential to promote immune infiltration.

By contrast, unfavorable pathways have a positive correlation with tumor-promoting pathways and a negative correlation with antitumor-associated pathways. The majority of unfavorable metabolism pathways showed a negative correlation with infiltrating antitumor immune cells. There is increasing evidence that deregulated metabolism is associated with more aggressive tumors and higher degrees of malignancy.^{42–44} Thus, the strong correlations of unfavorable metabolism pathways with a poor prognosis and high tumor purity are understandable.

Incorporating the combination of local treatments, such as radiotherapy, with molecular pathway targeting and immune response modulation is particularly relevant in the context of melanoma metastases to “sanctuary” sites like the brain. Melanoma brain metastasis presents significant treatment challenges due to the blood-brain barrier and the immunosuppressive microenvironment. Recent studies, highlight the potential of combining radiotherapy with immune checkpoint inhibitors and targeted therapies to enhance both local tumor control and systemic immune activation.⁴⁵ Radiotherapy can increase tumor immunogenicity, making it more responsive to immune therapy. This combination

approach offers a promising strategy to overcome the unique barriers of sanctuary sites, potentially improving outcomes in patients with advanced melanoma metastases. Future research should focus on optimizing these combinatory therapies to enhance efficacy and broaden their clinical application.

The results of this study provide significant insights into the differential pathway activities and immune interactions in SKCM. However, one limitation of this analysis is the potential batch effects that may influence the reproducibility and interpretation of results when comparing different tumor types. Specifically, when analyzing RNA-seq data from multiple cohorts or across different cancer types, batch effects—such as differences in sequencing platforms, sample collection methods, and data processing pipelines—can introduce significant variability. This can obscure true biological differences and lead to challenges in comparing pathway activities between SKCM and other cancers.

One notable limitation is the reliance on bulk RNA-seq data, which, while providing valuable insights into overall gene expression, is inherently limited in its ability to capture single-cell heterogeneity. Tumors are highly heterogeneous, with distinct subpopulations of cells that may exhibit different gene expression profiles, response to treatment, and tumor microenvironment interactions. Bulk RNA-seq data, therefore, aggregates these differences and cannot fully account for the spatial or cellular diversity within the tumor, potentially masking important variations in pathway activity that are critical for tumor progression and response to therapy.

Additionally, sample preparation biases may introduce confounding factors that could affect the accuracy of our pathway activity assessments. Variability in tissue collection, RNA extraction methods, and sequencing protocols can influence gene expression measurements, which in turn might affect the interpretation of differential pathway activities between SKCM and normal tissues. To minimize such biases, we performed stringent quality control and normalization, but some residual effects may still impact the results, particularly when comparing samples across different cohorts or when integrating datasets from various sources. Another critical consideration is the potential influence of confounding factors such as tumor stage and patient treatment history, which may alter the tumor microenvironment and pathway activities. For example, advanced stages of SKCM may exhibit different metabolic reprogramming or immune infiltration compared to early-stage tumors. Similarly, patients who have undergone prior treatments, such as chemotherapy or immunotherapy, may have altered immune cell populations or pathway activity profiles, which could skew our findings. Future studies should account for these factors by stratifying patient data based on tumor stage, treatment history, and other relevant clinical variables to ensure a more accurate representation of pathway activities and their implications for prognosis and therapy.

Regarding the clinical implications of our findings, we have identified several pathways that could serve as therapeutic targets or biomarkers in SKCM. For example, immune-related pathways such as those involved in immune cell recruitment and activation could be targeted to enhance anti-tumor immunity. Additionally, metabolic pathways may offer new avenues for targeted therapies aimed at reprogramming the metabolic landscape of SKCM cells. However, practical challenges exist in targeting these pathways. For instance, the complexity of metabolic reprogramming and the potential for off-target effects in immune modulation therapies could pose significant hurdles in clinical translation. Therefore, careful validation of these pathways through preclinical models and clinical trials is necessary before they can be implemented as viable therapeutic options.

Conclusion

Our findings reveal several favorable and unfavorable pathways in SKCM that are associated with clinical outcomes, tumor progression, and immune infiltration. These insights provide a deeper understanding of the roles these pathways play in SKCM and highlight potential therapeutic targets. Specifically, immune-modulating treatments and pathway inhibitors targeting metabolic reprogramming or immune checkpoints could be further developed based on our findings. However, the clinical translation of these targets will require careful consideration of pathway heterogeneity, tumor stage, and patient treatment history. Future research should focus on validating these pathways as potential biomarkers and therapeutic targets in clinical settings.

Funding

This work was supported by the National Natural Science Foundation of China (82404157).

Disclosure

The authors report no conflicts of interest in this work.

References

- DeBerardinis RJ, Chandel NS. Fundamentals of cancer metabolism. *Sci Adv*. 2016;2(5):e1600200. doi:10.1126/sciadv.1600200
- Mo Y, Wang Y, Zhang L, et al. The role of Wnt signaling pathway in tumor metabolic reprogramming. *J Cancer*. 2019;10(16):3789. doi:10.7150/jca.31166
- Tang L, Wei F, Wu Y, et al. Role of metabolism in cancer cell radioresistance and radiosensitization methods. *J Exp Clin Cancer Res*. 2018;37(1):87. doi:10.1186/s13046-018-0758-7
- Reina-Campos M, Moscat J, Diaz-Meco M. Metabolism shapes the tumor microenvironment. *Curr Opin Cell Biol*. 2017;48:47–53. doi:10.1016/j.ceb.2017.05.006
- Boroughs LK, DeBerardinis RJ. Metabolic pathways promoting cancer cell survival and growth. *Nat Cell Biol*. 2015;17(4):351–359. doi:10.1038/ncb3124
- Vander Heiden MG, DeBerardinis RJ. Understanding the intersections between metabolism and cancer biology. *Cell*. 2017;168(4):657–669. doi:10.1016/j.cell.2016.12.039
- Palm W, Thompson CB. Nutrient acquisition strategies of mammalian cells. *Nature*. 2017;546(7657):234–242. doi:10.1038/nature22379
- Chang C-H, Qiu J, O'Sullivan D, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell*. 2015;162(6):1229–1241. doi:10.1016/j.cell.2015.08.016
- Mocellin S, Nitti D. Therapeutics targeting tumor immune escape: towards the development of new generation anticancer vaccines. *Med Res Rev*. 2008;28(3):413–444. doi:10.1002/med.20110
- Woo S-R, Corrales L, Gajewski TF. Innate immune recognition of cancer. *Ann Rev Immunol*. 2015;33:445–474. doi:10.1146/annurev-immunol-032414-112043
- Marcus A, Gowen BG, Thompson TW, et al. Recognition of tumors by the innate immune system and natural killer cells. In: *Advances in Immunology*. Vol. 122. Elsevier; 2014:91–128.
- Cao Y, Feng Y, Zhang Y, Zhu X, Jin F. L-Arginine supplementation inhibits the growth of breast cancer by enhancing innate and adaptive immune responses mediated by suppression of MDSCs in vivo. *BMC Cancer*. 2016;16(1):343. doi:10.1186/s12885-016-2376-0
- Shi L, Chen L, Wu C, et al. PD-1 blockade boosts radiofrequency ablation-elicited adaptive immune responses against tumor. *Clin Cancer Res*. 2016;22(5):1173–1184. doi:10.1158/1078-0432.CCR-15-1352
- Schmidt L, Eskiocek B, Kohn R, et al. Enhanced adaptive immune responses in lung adenocarcinoma through natural killer cell stimulation. *Proc Natl Acad Sci*. 2019;116(35):17460–17469. doi:10.1073/pnas.1904253116
- Becht E, Giraldo NA, Lacroix L, et al. Estimating the population abundance of tissue-infiltrating immune and stromal cell populations using gene expression. *Genome Biol*. 2016;17(1):218. doi:10.1186/s13059-016-1070-5
- Newman AM, Liu CL, Green MR, et al. Robust enumeration of cell subsets from tissue expression profiles. *Nature Methods*. 2015;12(5):453–457. doi:10.1038/nmeth.3337
- Yadav VK, De S. An assessment of computational methods for estimating purity and clonality using genomic data derived from heterogeneous tumor tissue samples. *Briefings Bioinf*. 2015;16(2):232–241. doi:10.1093/bib/bbu002
- Yoshihara K, Shahmoradgoli M, Martinez E, et al. Inferring tumour purity and stromal and immune cell admixture from expression data. *Nat Commun*. 2013;4(1):1–11. doi:10.1038/ncomms3612
- Deng W, Su Z, Liang P, et al. Single-cell immune checkpoint landscape of PBMCs stimulated with *Candida albicans*. *Emerging Microbes Infect*. 2021;10(1):1272–1283. doi:10.1080/22221751.2021.1942228
- Deng W, Ma Y, Su Z, et al. Single-cell RNA-sequencing analyses identify heterogeneity of CD8+ T cell subpopulations and novel therapy targets in melanoma. *Mol Ther Oncol*. 2021;20:105–118. doi:10.1016/j.omto.2020.12.003
- Xiao Z, Dai Z, Locasale JW. Metabolic landscape of the tumor microenvironment at single cell resolution. *Nat Commun*. 2019;10(1):1–12. doi:10.1038/s41467-019-11738-0
- Tu C, Zeng Z, Qi P, et al. Identification of genomic alterations in nasopharyngeal carcinoma and nasopharyngeal carcinoma-derived Epstein-Barr virus by whole-genome sequencing. *Carcinogenesis*. 2018;39(12):1517–1528. doi:10.1093/carcin/bgy108
- Wu C, Li M, Meng H, et al. Analysis of status and countermeasures of cancer incidence and mortality in China. *Sci China Life Sci*. 2019;62(5):640–647. doi:10.1007/s11427-018-9461-5
- Miao Y, Yang H, Levorse J, et al. Adaptive immune resistance emerges from tumor-initiating stem cells. *Cell*. 2019;177(5):1172–1186.e1114. doi:10.1016/j.cell.2019.03.025
- Thang NNT, Derouazi M, Philippin G, et al. Immune infiltration of spontaneous mouse astrocytomas is dominated by immunosuppressive cells from early stages of tumor development. *Cancer Res*. 2010;70(12):4829–4839. doi:10.1158/0008-5472.CAN-09-3074
- Gonzalez H, Hagerling C, Werb Z. Roles of the immune system in cancer: from tumor initiation to metastatic progression. *Genes Dev*. 2018;32(19–20):1267–1284. doi:10.1101/gad.314617.118
- Ericksen RE, Lim SL, McDonnell E, et al. Loss of BCAA catabolism during carcinogenesis enhances mTORC1 activity and promotes tumor development and progression. *Cell Metab*. 2019;29(5):1151–1165.e1156. doi:10.1016/j.cmet.2018.12.020
- Beloribi-Djefailia S, Vasseur S, Guillaumond F. Lipid metabolic reprogramming in cancer cells. *Oncogenesis*. 2016;5(1):e189–e189. doi:10.1038/oncsis.2015.49
- Bayyurt B, Tincer G, Almacioglu K, Alpdundar E, Gursel M, Gursel I. Encapsulation of two different TLR ligands into liposomes confer protective immunity and prevent tumor development. *J Control Release*. 2017;247:134–144. doi:10.1016/j.jconrel.2017.01.004
- Smyth MJ, Dunn GP, Schreiber RD. Cancer immunosurveillance and immunoediting: the roles of immunity in suppressing tumor development and shaping tumor immunogenicity. *Adv Immunol*. 2006;90:1–50.
- Castro F, Cardoso AP, Gonçalves RM, Serre K, Oliveira MJ. Interferon-gamma at the crossroads of tumor immune surveillance or evasion. *Front Immunol*. 2018;9:847. doi:10.3389/fimmu.2018.00847

32. Medrano RF, Hunger A, Mendonça SA, Barbuto JAM, Strauss BE. Immunomodulatory and antitumor effects of type I interferons and their application in cancer therapy. *Oncotarget*. 2017;8(41):71249. doi:10.18632/oncotarget.19531
33. Panda PK, Mukhopadhyay S, Behera B, et al. Antitumor effect of soybean lectin mediated through reactive oxygen species-dependent pathway. *Life Sci*. 2014;111(1–2):27–35. doi:10.1016/j.lfs.2014.07.004
34. Filomeni G, De Zio D, Cecconi F. Oxidative stress and autophagy: the clash between damage and metabolic needs. *Cell Death Differ*. 2015;22(3):377–388. doi:10.1038/cdd.2014.150
35. Scherz-Shouval R, Shvets E, Elazar Z. Oxidation as a post-translational modification that regulates autophagy. *Autophagy*. 2007;3(4):371–373. doi:10.4161/auto.4214
36. Watson AL, Rahrmann EP, Moriarty BS, et al. Canonical Wnt/ β -catenin signaling drives human Schwann cell transformation, progression, and tumor maintenance. *Cancer Discovery*. 2013;3(6):674–689. doi:10.1158/2159-8290.CD-13-0081
37. Yardy G, Brewster S. Wnt signalling and prostate cancer. *Prostate Cancer Prostatic Dis*. 2005;8(2):119–126. doi:10.1038/sj.pcan.4500794
38. Zhang Y, Morris JP, Yan W, et al. Canonical wnt signaling is required for pancreatic carcinogenesis. *Cancer Res*. 2013;73(15):4909–4922. doi:10.1158/0008-5472.CAN-12-4384
39. Corthay A, Skovseth DK, Lundin KU, et al. Primary antitumor immune response mediated by CD4⁺ T cells. *Immunity*. 2005;22(3):371–383. doi:10.1016/j.immuni.2005.02.003
40. Haabeth OAW, Lørvik KB, Hammarström C, et al. Inflammation driven by tumour-specific Th1 cells protects against B-cell cancer. *Nat Commun*. 2011;2(1):1–12. doi:10.1038/ncomms1239
41. Porta C, Riboldi E, Ippolito A, Sica A. Molecular and epigenetic basis of macrophage polarized activation. In: *Seminars in Immunology*. Elsevier; 2015:237–248.
42. vdH AP, J J, W RF, B KE. Analysis of glutamine dependency in non-small cell lung cancer: GLS1 splice variant GAC is essential for cancer cell growth. *Cancer Biol Ther*. 2012;13(12):1185–1194. doi:10.4161/cbt.21348
43. G F, S A, N J. Systematic analysis reveals that cancer mutations converge on deregulated metabolism of arachidonate and xenobiotics. *Cell Rep*. 2016;16(3):878–895. doi:10.1016/j.celrep.2016.06.038
44. Cassago A, Ferreira APS, Ferreira IM. Mitochondrial localization and structure-based phosphate activation mechanism of Glutaminase C with implications for cancer metabolism. *Proc Natl Acad Sci USA*. 2012;109(4):1092–1097. doi:10.1073/pnas.1112495109
45. Lancellotta V, Del Regno L, Di Stefani A, et al. The role of stereotactic radiotherapy in addition to immunotherapy in the management of melanoma brain metastases: results of a systematic review. *La Radiologia Medica*. 2022;127(7):773–783. doi:10.1007/s11547-022-01503-7

Clinical, Cosmetic and Investigational Dermatology

Publish your work in this journal

Clinical, Cosmetic and Investigational Dermatology is an international, peer-reviewed, open access, online journal that focuses on the latest clinical and experimental research in all aspects of skin disease and cosmetic interventions. This journal is indexed on CAS. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/clinical-cosmetic-and-investigational-dermatology-journal>

Dovepress
Taylor & Francis Group