Peer Review File

Article information: https://dx.doi.org/10.21037/tcr-23-1765

Reviewer A

Comment1: The "INTRODUCTION" section is difficult to follow, and the first paragraph should be more concise.

Reply 1: Thank you very much for your suggestion. We have made changes to the first paragraph.

Changes in the text: Lines 47 to 63

Comment2: The "INTRODUCTION" should include more background information about mitophagy and its mechanisms related to cancers. Prior studies on mitophagy in the context of kidney cancer should be cited.

Reply 2: Thank you very much for your suggestion. We have made changes to the second paragraph.

Changes in the text: Lines 64 to 84

Comment3: Keywords should conform to standardized terms that can be found in the Medical Subject Headings (MeSH) database.

Reply 3: Thank you very much for your suggestion. The keywords have been modified as you requested.

Changes in the text: Line 27

Comment4: The "Materials and methods" section should be written in the past tense and reorganized for better reader comprehension.

Reply 4: Thank you very much for your suggestion. In order to improve the reading experience of reviewers and readers, we have invited professional institutions to edit the manuscript. The polished manuscript and the relevant certificates have been uploaded to the official website.

Comment5: Provide more detailed information on the number of samples, parameters, and criteria used for each analysis.

Reply 5: Thank you very much for your suggestion, which we have added to the manuscript.

Changes in the text: Lines 109 to 122

Comment6: Include proper citations for bioinformatic databases used in the study, such as "UALCAN," "HPA," "TISCH," and others.

Reply 6: Thank you very much for your suggestion, we have cited these databases.

Changes in the text: Lines 102 to 107

HPA(1, 2)

UALCAN(3, 4)

TISCH(5)
1. Thul PJ, Lindskog C. The human protein atlas: A spatial map of the human proteome. Protein Sci. 2018;27(1):233-44.
2. Digre A, Lindskog C. The Human Protein Atlas-Spatial localization of the human proteome in health and disease. Protein Sci. 2021;30(1):218-33.
3. Chandrashekar DS, Bashel B, Balasubramanya SAH, et al. UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses. Neoplasia. 2017;19(8):649-58.
4. Chandrashekar DS, Karthikeyan SK, Korla PK, et al. UALCAN: An update to the integrated cancer data analysis platform. Neoplasia. 2022;25:18-27.
5. Sun D, Wang J, Han Y, et al. TISCH: a comprehensive web resource enabling interactive single-cell transcriptome visualization of tumor microenvironment. Nucleic Acids Res. 2021;49(D1):D1420-D30.

Comment7: Clearly define terms like "M cohort," "T cohort," "H group," and "L group" for better understanding.

Reply 7: Thank you very much for your suggestion. We have defined the abbreviation that first appears in the manuscript and in the legend.

UALCAN,The University of ALabama at Birmingham CANcer data analysis Portal;
HPA, Human Protein Atlas;
TCGA, The Cancer Genome Atlas;
GEO, Gene Expression Omnibus;
GSE, Gene Series;
ICGC, International Cancer Genome Consortium;
TISCH, Tumor Immune Single-cell Hub;
IHC,Immunohistochemistry;
M, Model;
T, Test;
Lasso, Least absolute shrinkage and selection operator;
COX, Cox regression model.
PC1, Principal Component1;
PC2, Principal Component2;
AUC, Area Under Curve.
ccRCC, Clear cell renal cell carcinoma
MRGMS, Mitophagy-Related Gene Model Signature
MRGM, Mitophagy-Related Gene Model
H group, high risk group
T cohort, Test cohort
PCA, principal component analysis
ROC, Receiver Operating Characteristic
DCA, Decision Curve Analysis
GSVA, Gene Set Variation Analysis
KEGG, Kyoto Encyclopedia of Genes and Genomes

GO, Gene Ontology
ssGSEA, single sample gene set enrichment analysis

Comment8: The flowchart presented in Figure 1A shows "Drug susceptibility analysis" and "Subtype identification" in the boxes, but these experiments are not discussed in the "Materials and methods" and "Results" sections.

Reply 8: Thank you very much for your suggestion. We've fixed that error. The revised illustrations, as well as the manuscript, will be uploaded for your review.

Changes in the text: **Figure 1: Lines 179 to 184**

Comment9: Extensively discuss the prognostic roles of the eight MRGs and their potential involvement in mitophagy and ccRCC to provide a more comprehensive understanding of these MRGs.

Reply 9: Thank you very much for your suggestion. This section has been modified as per your requirements.

Changes in the text: Lines 334 to 350

Comment10: Expand the discussion on the following topics: (1) the relationship between significantly enriched pathways of MRGs and mitophagy mechanisms related to ccRCC, and (2) the connection between immune cell infiltration and mitophagy in ccRCC.

Reply 10: Thank you very much for your suggestion. This section has been modified as per your requirements.

Changes in the text: Lines 350 to 354

Comment11: Discuss limitations and the necessity for further experimental and clinical validations.

Reply 11: Thank you very much for your suggestion. We've added that section as per your request.

Changes in the text: Lines 355 to 359

Reviewer B

Comment1: In the abstract ccRCC should be spelt out.

Reply 1: Thank you very much for your suggestion. We have defined the abbreviations that appear for the first time in the manuscript and in the legend.

UALCAN,The University of ALabama at Birmingham CANcer data analysis Portal;
HPA, Human Protein Atlas;
TCGA, The Cancer Genome Atlas;
GEO, Gene Expression Omnibus;
GSE, Gene Series;
ICGC, International Cancer Genome Consortium;
TISCH, Tumor Immune Single-cell Hub;

IHC,Immunohistochemistry;
M, Model;
T, Test;
Lasso, Least absolute shrinkage and selection operator;
COX, Cox regression model.
PC1, Principal Component1;
PC2, Principal Component2;
AUC, Area Under Curve.
ccRCC, Clear cell renal cell carcinoma
MRGMS, Mitophagy-Related Gene Model Signature
MRGM, Mitophagy-Related Gene Model
H group, high risk group
T cohort, Test cohort
PCA, principal component analysis
ROC, Receiver Operating Characteristic
DCA, Decision Curve Analysis
GSVA, Gene Set Variation Analysis
KEGG, Kyoto Encyclopedia of Genes and Genomes
GO, Gene Ontology
ssGSEA, single sample gene set enrichment analysis

Comment2: Renal cell carcinoma (RCC) is essentially a metabolic disease characterized by a reprogramming of energetic metabolism (PMID: 36960789; PMID: 30983433, PMID: 36430837,PMID: 36310399, PMID: 37685983). In particular the metabolic flux through glycolysis is partitioned (PMID: 29371925, PMID: 28933387, PMID: 25945836), and mitochondrial bioenergetics and OxPhox are impaired , as well as lipid metabolism (PMID: 30538212; PMID: 32861643, PMID: 29371925, PMID: 36430448). In this scenario it has been shown that mitophagy is an important regulator of cell metabolism. These findings should be referenced and discussed.

Reply 2: Thank you very much for your suggestion. This section has been modified as per your requirements. Your recommended references are helpful for the reader to understand the study.

Changes in the text: Lines 64 to 84

Comment3: In addition, renal cell carcinoma is one of the most immune-infiltrated tumors (PMID: 31527133, PMID: 30738745; PMID: 27063186). Emerging evidence suggests that the activation of specific metabolic pathway have a role in regulating angiogenesis and inflammatory signatures (PMID: 32345771, PMID: 28359744). Features of the tumor microenvironment heavily affect disease biology and may affect responses to systemic therapy (PMID: 37189689; PMID: 33265926; PMID: 36902242; PMID: 37373581). Mitophagy can modulate immune cell infiltration and regulate immunoflogosis. These processes should be explored and discussed.

Reply 3: Thank you very much for your suggestion. This section has been modified as

per your requirements.
Changes in the text: Lines 350 to 354