Response to: Correspondence on 'Role of AMPK/mTOR-independent autophagy in clear cell renal cell carcinoma' by Lorzadeh *et al*

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Accepted 3 August 2021
Published Online First 7 September 2021

► http://dx.doi.org/10.1136/jim-2021-002015
► http://dx.doi.org/10.1136/jim-2020-001524

To cite: Radovanovic M, Vidicevic S, Tasic J, *et al*. *J Investig Med* 2021;**69**:1485.

Dear Editor,

We read with great interest the commentary by Lorzadeh and Ghavami[1] on our article that reported AMP-activated protein kinase (AMPK)/mechanistic target of rapamycin (mTOR)-independent upregulation of autophagy in the tumor tissue of clear cell renal cell carcinoma (ccRCC) patients.[2] We agree with their observation that the somewhat surprising absence of a link between AMPK/mTOR signaling and autophagy induction in ccRCC might be due to the fact that we studied whole tumor tissue, containing a heterogeneous population of cancer cells, fibroblasts, vascular cells, and infiltrated immune cells.[3] Moreover, intratumor heterogeneity with diverse genetic subclones within a single tumor has been increasingly recognized as an important factor influencing clinical and therapeutic outcome in ccRCC.[4] On the other hand, genetic mutations associated with ccRCC often result in reduced AMPK and/or increased mTOR activity,[5] and a subset of ccRCC patients responds to mTOR inhibitors,[6] which is consistent with our findings. Also, our data that the decrease in AMPK activation was accompanied by enhanced phosphorylation of autophagy initiator Unc 51-like kinase 1 (ULK1) at the AMPK site Ser317, indicates that the latter was at least partly independent of AMPK. Possible candidates for AMPK-independent ULK1 activation and subsequent initiation of autophagy include protein kinase C and p38 mitogen-activated protein kinase, which have been found to directly phosphorylate ULK1 at AMPK sites.[7 8] Nevertheless, exploring the AMPK/mTOR-autophagy connection at the level of specific cell types within the tumor tissue, as proposed by Lorzadeh and Ghavami, could provide important insights into the mechanisms of cRCC development and progression.

Contributors VT wrote the manuscript; MR, SV, JT, NT, ZS, PN, AV, ZD, UB, and AI provided critical feedback and contributed to the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

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REFERENCES

1 Lorzadeh S, Ghavami S. Correspondence on 'Role of AMPK/mTORindependent autophagy in clear cell renal cell carcinoma' by Radovanovic et al. *J Investig Med* 2021;69:1483–4.
2 Radovanovic M, Vidicevic S, Tasic J, *et al*. Role of AMPK/mTOR-independent autophagy in clear cell renal cell carcinoma. *J Investig Med* 2020;68:1386–93.
3 Mier JW. The tumor microenvironment in renal cell cancer. *Curr Opin Oncol* 2019;31:194–9.
4 López JI, Angulo JC. Pathological bases and clinical impact of intratumor heterogeneity in clear cell renal cell carcinoma. *Curr Urol Rep* 2018;19:3.
5 Massari F, Ciccarese C, Santoni M, *et al*. Metabolic alterations in renal cell carcinoma. *Cancer Treat Rev* 2015;41:767–76.
6 Faes S, Demartines N, Dormond O. Mechanistic target of rapamycin inhibitors in renal cell carcinoma: potential, limitations, and perspectives. *Front Cell Dev Biol* 2021;9:636037.
7 Miao H, Qiu F, Huang B, *et al*. PKCα replaces AMPK to regulate mitophagy: another PEDF role on ischaemic cardioprotection. *J Cell Mol Med* 2018;22:5732–42.
8 Liu Z, Sin KWT, Ding H, *et al*. p38β MAPK mediates ULK1-dependent induction of autophagy in skeletal muscle of tumor-bearing mice. *Cell Stress* 2018;2:311–24.