


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

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Dear Editor,

We read with great interest the commentary by Lorzadeh and Ghavami¹ 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 ccRCC development and progression.

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