Cystine Deprivation Triggers Regulated Necrosis in VHL-Deficient Renal Cell Carcinomas

Xiaohu Tang[1,2], Jianli Wu[1,2], Chien-Kuang C. Ding[1,2], Min Lu[2,3], Melissa M. Keenan[1,2,]Chao-Chieh Lin[1,2], Chih-An Lin[1,2], Charles C. Wang[1,2], Daniel George[3], David S. Hsu[2,3], and Jen-Tsan Chi[1,2]

1. Department of Molecular Genetics and Microbiology, Duke University, Durham, North Carolina.
2. Center for Genomic and Computational Biology Duke University, Durham, North Carolina.
3. Department of Medicine, Duke University, Durham, North Carolina

Category: Molecular, Metabolic and Structural Biology

Oncogenic transformation may alter tumor metabolism and render cancer cells addicted to extracellular nutrients. Deprivation of these nutrients may therefore represent a therapeutic opportunity; therefore, understanding the mechanism behinds the dependency is essential. Here we performed a nutrigenetic screen to determine the nutrient dependency of extracellular amino acid in clear cell renal cell carcinoma (ccRCC). Although most amino acid deprivation leads to growth inhibition, only cystine deprivation triggers rapid regulated necrosis. We applied genome-wide siRNA screens to identify genetic determinants, and integrated our screen findings with the transcriptional and metabolomic profiling of ccRCC to investigate the mechanism of cystine-deprived necrosis. We identified that: 1) VHL deficiency could potentiate ccRCC to cystine-deprived cell death by preexisting elevation of TNFα-RIPK1/RIPK3-MLKL level and reciprocal amplification of Src-p38 (MAPK14)-Noxa (PMAIP1) pathway. 2) The inhibition of pro-growth pathways such as mTORC1 signaling could lead to resistance to cystine-deprivation cell death. Together, our findings reveal that cancer cells could be “addicted” to specific nutrients, which might represent alternative targets in treating drug-resistant tumors