Targeting acquired resistance to HIF2α inhibition in ccRCC

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Mechanism of inhibition and the development of resistance after prolonged treatment of PT2399 in renal cancer

Hasanov et al., 2021; Chen et al., 2016

Belzutifan

RCC tumourgraft-bearing mice

Hasanov et al., 2021; Chen et al., 2016
Establishment of PT2399 resistant ccRCC cell lines

Soft agar quantification

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Multi-omics characterization of resistant cell lines

94 genes with differential signals from all sequencing data

Pathway enrichment for all upregulated genes

- HDACs deacetylate histones
- Formation of the beta-catenin:TCF ...
- Sialic acid metabolism
- Immunoregulatory interactions between a ...
- Antiviral mechanism by IFN-stimulated genes
  - ISG15 antiviral mechanism
  - ERCC6 (CSB) and EHMT2 ...
  - Signaling by Nuclear Receptors
  - Condensation of Prophase Chromosomes
  - SIRT1 negatively regulates rRNA expression
  - PRC2 methylates histones and DNA
  - Activated PKN1 stimulates transcription ...
  - Packaging Of Telomere Ends
  - DNA methylation
  - RNA Polymerase I Promoter Opening
  - Amyloid fiber formation
  - Endosomal/Vacuolar pathway
  - Interferon gamma signaling
  - Interferon Signaling
  - Interferon alpha/beta signaling

Jeremy Simon
Both mRNA and protein levels of p72 are upregulated in PT2399 resistant cell lines.
p72 overexpression induces partial resistance to HIF2α inhibition

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Conclusions

• We have established HIF2α inhibitor adaptive resistant ccRCC cell lines

• Multi-omics approaches identifies signaling pathways that may be important mediating HIF2α inhibitor resistance

• P72 was identified to be important partially mediating HIF2α inhibitor resistance in ccRCC