Mps1 Mediated Phosphorylation of Hsp90 Confers RCC Sensitivity and Selectivity to Hsp90-Drugs

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NORMAL CELLS

- Cell Signaling
- Cell Cycle
- Cell Proliferation
- Gene Expression
- Intracellular Transport
- Protein Folding
- Protein Degradation

CANCER CELLS

- Evading Immune Destruction
- Limitless Replicative Potential
- Sustained Angiogenesis
- Tissue Invasion & Metastasis
- Insensitivity to anti-growth signals
- Evading Apoptosis
- Self-Sufficiency in Growth Signals
- Reprogramming of Energy Metabolism

HSP90
Hsp90 plays a Janus-like role in the cell
**Hsp90 Inhibitors Prevent the Stabilization and Activation of Client Proteins Critical to Malignant Growth**

Hsp90 binds to client protein → Proper folding → Activated client; cell survival, proliferation

Client proteins, including:
ALK, AKT, BCR-ABL, BRAF, CDK4, CHK1, EGFR, ERK5, FLT3, HER2, HIF1α, KIT, MET, PDGFRα, CRAF, SRC, VEGFR, AR, ER...

Drugs prevent Hsp90 binding to client (competitively binds the ATP pocket of Hsp90) → Inactive client, degraded through proteasome
Hsp90 Inhibitors in Clinical Trials - 2015

- Phase 1
- Phase 2
- Phase 3

Woodford MR, et al. (2016). *Advances in Cancer Research*
Phosphorylation and dephosphorylation of Hsp90 is essential for the mitotic checkpoint

Human Renal Epithelial Neoplasms

Type: Clear Cell
Gene: VHL

Type: Papillary Type 1
Gene: MET

Type: Papillary Type 2
Gene: FH

Type: Chromophobe

Type: Oncocytoma

Type: Hybrid
Gene: BHD (FLCN)

Type: TFE3 Angiomyolipoma Oncocytic Clear/Chromophobe
Gene: TFE2, TFEB, TSC1, TSC2, SDHB, SDHC, SDHD, PTEN

73-year-old male
Left Kidney, Radical Nephrectomy
Diagnosis: Clear Cell Renal Cell Carcinoma
Stage: T3N0M0 Tumor, Node, Metastasis (T3N0M0)
Grade: G3 (Poorly differentiated cancer with bad prognosis)
Kidney Cancers Sensitivity and Selectivity to Hsp90 inhibitors

Hsp90 Inhibitors
Accumulation & Sensitivity

Mps1

P

P-T101

T101

Hsp90

Contributions of Co-chaperones and Post-translational Modifications Towards Hsp90 Drug Sensitivity & Selectivity

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