Exploiting synthetic lethality in kidney cancer to target the loss of VHL for targeted therapy

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Kidney Cancer

<table>
<thead>
<tr>
<th></th>
<th># of people diagnosed</th>
<th># of people dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide</td>
<td>200,000</td>
<td>100,000</td>
</tr>
<tr>
<td>Canada</td>
<td>6,100</td>
<td>1,800</td>
</tr>
<tr>
<td>USA</td>
<td>63,920</td>
<td>13,860</td>
</tr>
</tbody>
</table>

Type of kidney cancer

<table>
<thead>
<tr>
<th>Type</th>
<th>Clear Cell</th>
<th>Papillary Type 1</th>
<th>Papillary Type 2</th>
<th>Chromophobe</th>
<th>Oncocytoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>VHL</td>
<td>Met</td>
<td>FH</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Linehard et al., 2003

Treatment used in clinic to treat RCC

JCO, 2009
Genetic interaction between two genes. When either gene is mutated, the cell remains alive. However, when both genes are mutated the cell will die. (Chan and Giaccia, 2011)

Targeting VHL-deficient cells through synthetic lethality
To develop a targeted therapy that kills cancer cells and spare normal tissue

VHL + unknown gene = ☹️ VHL + gène inconnu = ☹️

High Throughput Screen Schema

STF-62247 induces selective cytotoxicity in multiple VHL-deficient RCC
What do we know about the STF-62247?

- HIF-independent (shHIF-1a, shHIF-2a)
- Modulates autophagy and increases autophagosome formation
- Autophagy is important for selective cytotoxicity
- Autophagic flux is not block
- Target lysosome???

What is autophagy?

- Auto «self» phagy «eat»
- Lysosomal degradation process to remove misfolded proteins, aggregate or organelle
- Important for balancing sources of energy
Autophagosomes increase in VHL-deficient cells exposed to STF-62247

Degradation of long-lived proteins increased in STF-62247-treated VHL-expressing cells

Lysosomal membrane permeabilization is observed in VHL-deficient cells

Release of cathepsin D into the cytosol
To study the transcriptomic of RCC in response to STF-62247
To understand the STF-62247 signalling
To identify targets of the small molecule
To evaluate the contribution of glutamate/glutamine in RCC

Genomic
Transcriptomic
Proteomic
Metabolomic

VHL mutation
Next-generation sequencing
microRNA
Next-generation Sequencing
Autophagy
Target of STF-62247
Glutamate/glutamine
NMR

EBSS
BafA1
CQ
Rapamycine

Concanamycine A (nM)

Survie (%)

RCC4
RCC4/VHL

0 0, 10, 30, 51248 1 6

RCC4
RCC4-VHL

STF-62247 localized into lysosomes
Summary

- We demonstrated the possibility of targeting VHL-deficient cells specifically using small molecule
- Mechanistically, STF-62247 modulates autophagy
- Lysosome behavior is an important step in the decision between cell death or survival in response to STF-62247
- This work identified a function for VHL at a late stage of autophagy

The use of synthetic lethality in cancer therapeutics is very promising. This research offers an attractive opportunity insofar as our fundamental research lead to the development of VHL targeted treatment for RCC

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