L-2-Hydroxyglutarate: An Epigenetic Modifier and Putative Oncometabolite in Renal Cancer

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Oncometabolites: Small Molecules with Putative Transforming Properties

![Diagram of oncometabolites and their interactions](image)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Oncometabolite</th>
<th>Tumor Types</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>FH</em></td>
<td>Fumarate</td>
<td>Renal, Uterine, Sarcoma</td>
</tr>
<tr>
<td><em>SDHA</em></td>
<td>Succinate</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td><em>SDHB</em></td>
<td>Succinate</td>
<td>Paraganglioma, Renal</td>
</tr>
<tr>
<td><em>SDHC</em></td>
<td>Succinate</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td><em>SDHD</em></td>
<td>Succinate</td>
<td>Paraganglioma</td>
</tr>
<tr>
<td><em>IDH1</em></td>
<td>2-Hydroxyglutarate</td>
<td>Glioma, GBM, AML</td>
</tr>
<tr>
<td><em>IDH2</em></td>
<td>2-Hydroxyglutarate</td>
<td>Glioma, GBM, AML</td>
</tr>
</tbody>
</table>

Figure 1. Oncometabolites in cancer
Figure 6. 2OG oxygenases probably regulate gene expression at multiple points. 2OG oxygenase-catalyzed modifications include those to nucleic acids (DNA and RNA), histones, transcription factors, and splicing related and other proteins. Note that the same 2OG oxygenases might act on different ‘forms’ of their substrates (e.g. free protein or complexes) and/or at different stages of the expression process. It is not yet clear whether, in addition to oxygen sensing via the HIF hydroxylases, the activity of other 2OG oxygenases is regulated by oxygen availability within physiologically relevant ranges.
Figure 3. 2-HG levels from normal adjacent and tumor renal tissues obtained from metabolomic profiling.
The L(S) Enantiomer of 2-HG is Elevated in ccRCC
TET Enzymes: 2-OG Dioxygenases Involved in DNA Demethylation

TET2 Mutated RCC !!!

Sato et al, Nat Genet 2013
TCGA Nature 2013
L more potent than D and inhibiting TET function!

Xu et al. Cancer Cell 2011
High L-2HG Tumors Demonstrate 5hmC Loss
Reduced 5hmC Levels in High L-2HG Tumors
Formation and degradation of L-2-HG

Adapted from Journal of Inherited Metabolic Disease, 2007.
L2HGDH Expression is Lost in High L-2HG Tumors

![Image of Western Blot and Immunohistochemistry](image-url)

**Western Blot Analysis:**
- **L2HGDH**
  - Normal (N) vs. Tumor (T)
  - Loss of L2HGDH expression in tumors

**Immunohistochemistry:**
- Normal tissue vs. High L2HG Tumor
  - Reduced L2HGDH staining in tumors
L2HGDH: Located at 14q

- **L2HGDH RNA-seq**
  - Z-score
  - LOH
  - Diploid

- **ΔC_{\text{i},L2HGDH}**
  - High-L2HG tumor
  - Normal
  - Low-L2HG tumor
L2HGDH Reconstitution in RCC Cells Reverses DNA/Histone Marks
L-2-HG and L-2-hydroxygultaric aciduria

- L-2-hydroxygultaric aciduria is a neurometabolic disorder characterized by the presence of elevated level of L-2-HG in plasma, cerebrospinal fluid, and urine.
- L-2-hydroxygultaric aciduria is caused by a defect in mitochondrial enzyme L2HGDH.
- High L-2-HG level causes leukoencephalopathy and increased prevalence of brain tumors.
L2HGDH Suppresses *In Vitro* Tumor Phenotypes

**A498**

- **CV**
- **L2HGDH**

**RXF393**

- **CV**
- **L2HGDH**

Cell count (cells/6 well)

Days
Conclusions

- L-2HG is Elevated in ccRCC
- Loss of *L2HGDH* promotes L-2HG Elevation
- L-2HG is an Epigenetic Modifier
  - promotes 5hmC loss
  - promotes DNA hypermethylator phenotype
- L2HGDH has tumor suppressor activity in RCC
- L-2HG is a putative oncometabolite
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