Abnormal hyperactivation of Akt/mTOR signaling in Chordoma

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Tuberous Sclerosis Complex

- Autosomal dominant multisystem disorder with an incidence of 1 in 6,000-10,000 individuals.

- Sporadic cases are common.

- Characterized by the widespread development of growths known as hamartomas in many tissues and organs including brain, kidney, heart, skin, lung, and skeleton.

- Incidence of chordoma has been reported in a few cases of TSC.

- The TSC1 and TSC2 proteins, hamartin and tuberin function together as a complex to inhibit mTOR signaling.
mTOR signaling is activated in both TSC-associated chordomas & sporadic chordomas

TSC-associated Chordoma

2 Cases of Sporadic Chordoma

P-S6 staining (read-out for mTOR activation):
- positive staining in tumor appears brown, while negative in non-tumor regions appears blue

PTEN deficiency and hyperactivation of Akt signaling in sporadic chordomas

PTEN staining:
- negative staining in tumor appears blue, while positive staining in non-tumor regions appears brown

Summary of immunohistochemical staining in 10 sporadic chordomas

Table 1. Summary of immunohistochemical staining in chordomas

<table>
<thead>
<tr>
<th>Case #</th>
<th>P-S6 (10/10)</th>
<th>PTEN (6/10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>+++</td>
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<td>4</td>
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<td>7</td>
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<td>9</td>
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<tr>
<td>10</td>
<td>++</td>
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</tr>
</tbody>
</table>

Note: Two independent observers blindly scored staining semi-quantitatively:
- = negative; + = weak; ++ = medium; +++ = strong
Rapamycin and wortmannin reverse the abnormal activation of mTOR signaling in the U-CH1 chordoma cell line

Rapamycin suppresses proliferation of the U-CH1 chordoma cell line
Summary

• Abnormal hyperactivation of mTOR signaling in sporadic chordomas resembles TSC-associated chordomas.

• Chordoma-derived cell lines also display hyperactivated mTOR signaling

• Approximately 60% of the tumors examined exhibit loss of PTEN.

• The abnormally activated mTOR signaling is sensitive to mTOR inhibitor rapamycin and PI3K inhibitor wortmannin.

• Rapamycin in combination with PI3K inhibitors may be effective in treating chordoma.

• In collaboration with Brian Harfe, we are generating chordoma mouse models by deleting Tsc1 or Pten specifically in the developing notochord (tissue from which chordomas arise).

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