Abnormal hyperactivation of Akt/mTOR signaling in Chordoma

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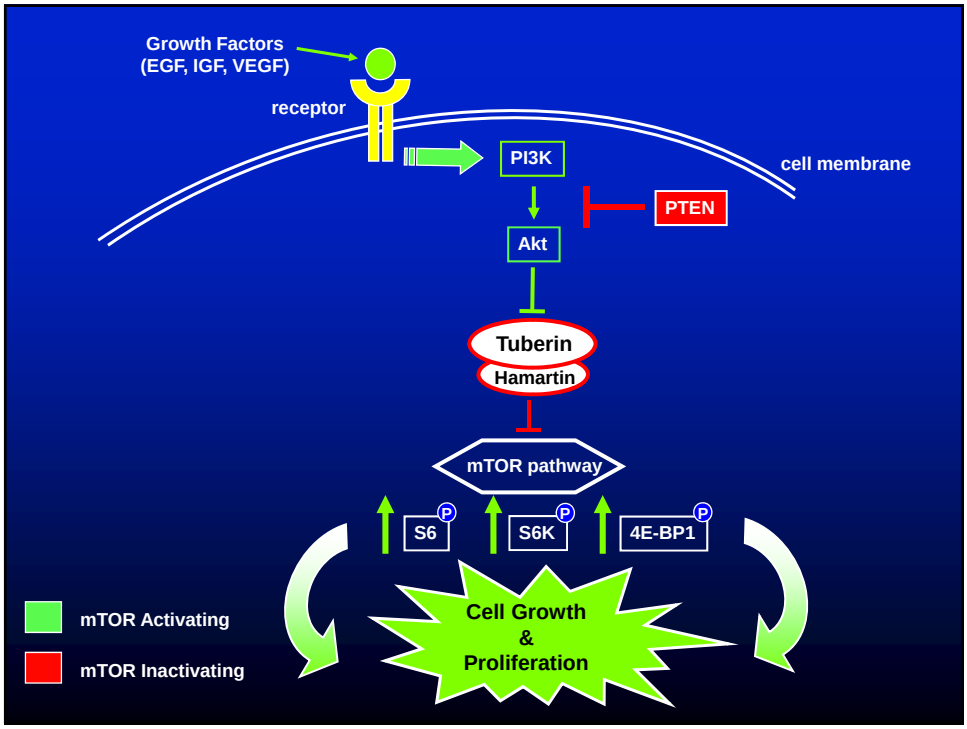
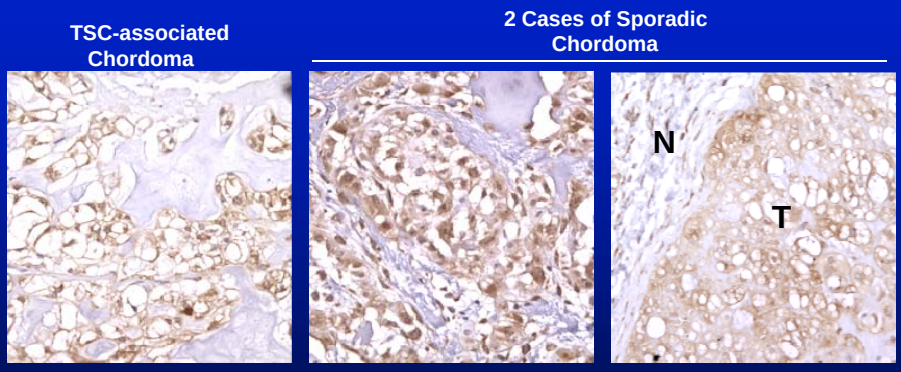
Tuberous Sclerosis Complex

- 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

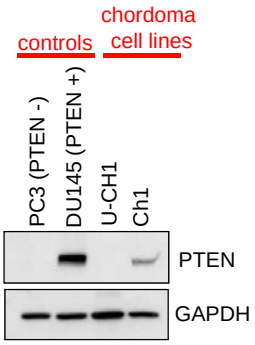


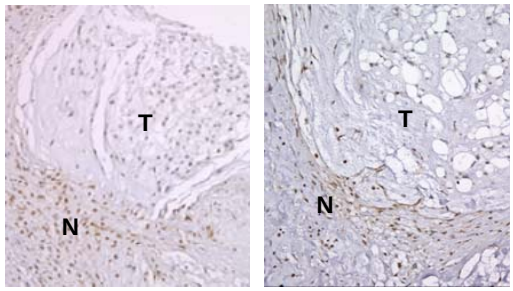
P-S6 staining (read-out for mTOR activation):

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

Han, *et al. Clinical Cancer Research* (2009).

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**

Han, *et al. Clinical Cancer Research* (2009).

Summary of immunohistochemical staining in 10 sporadic chordomas

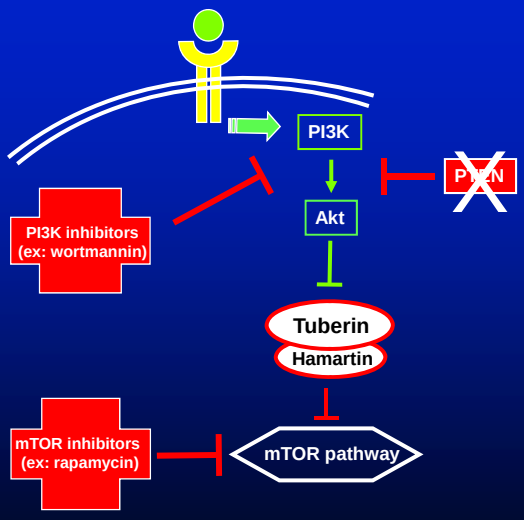
Table 1. Summary of immunohistochemical staining in chordomas

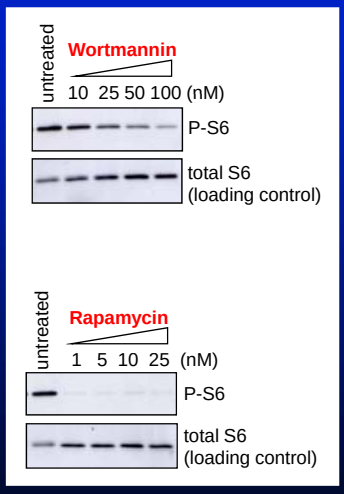
Case #	P-S6 (10/10)	PTEN (6/10)
1	++	-
2	+++	-
3	+++	+
4	+++	+
5	++	+
6	+++	-
7	+++	-
8	+++	+
9	+++	-
10	++	-

Note: Two independent observers blindly scored staining semi-quantitatively:
- = negative; + = weak; ++ = medium; +++ = strong

Han, *et al. Clinical Cancer Research* (2009).

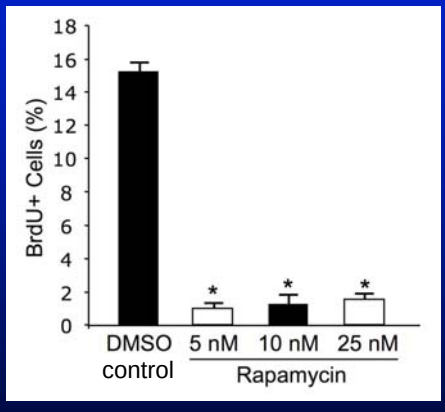
Rapamycin and wortmannin reverse the abnormal activation of mTOR signaling in the U-CH1 chordoma cell line





Han, *et al. Clinical Cancer Research* (2009).

Rapamycin suppresses proliferation of the U-CH1 chordoma cell line



Han, *et al. Clinical Cancer Research* (2009).

Summary

- Abnormal hyperactivation of mTOR signaling in sporadic chordomas resembles TSC-associated chordomas.
- Chordoma-derived cell lines also display hyperactivated mTOR signaling
- Approximaely 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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