β-Catenin and K-ras synergize to form Wilm's tumor with concurrent p53 pathway activation.

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Wilm's Tumor- A childhood cancer.

Humans can get pediatric kidney tumors called Wilm's tumors

If one identifies the specific genes that cause Wilm's tumor, or that concomitantly change expression levels in the tumor tissue, then diagnosis and eventually drug targets for therapy are expedited.

Characterizing genetic determinants in the mouse model can help actualize these future therapies...

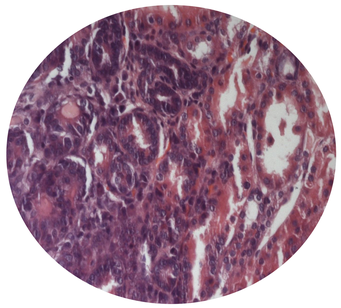
So mutations drive Wilm's tumor, but how?

Microarray analysis on mouse tumor tissue showed modulated expression levels of gene targets in the p53 tumor suppressor pathway.

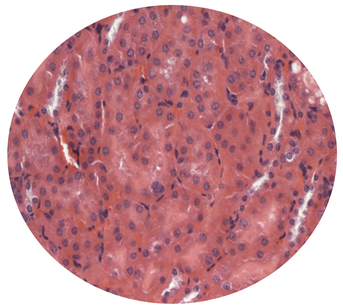
This pathway is possibly the route through which K-ras and β-catenin together drive tumor growth...

Mice with Wilm's tumor.

When the genes K-ras and β-Catenin are overexpressed in a mouse, it develops a renal tumor histologically identical to a human Wilm's tumor.



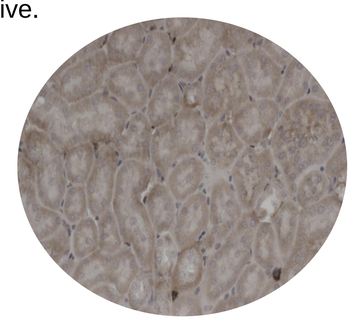
When the genes K-ras or β-Catenin are overexpressed individually, the mouse does not develop Wilm's tumor.



p53 in Wilm's tumor tissue.

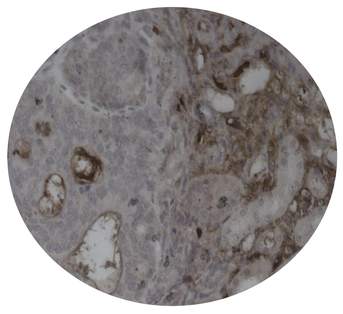
Immunohistochemistry stained mice tissue specifically for p53.

In tissue without both K-ras and β-catenin overexpression, p53 staining is negative.



In tissue with K-ras and β-catenin overexpression, p53 staining is positive surrounding the tumor.

p53 is activated, but through what specific genes?

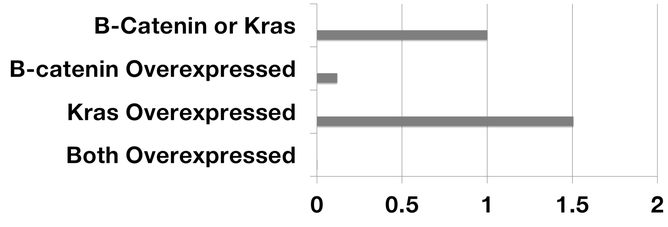


Identifying candidate genes.

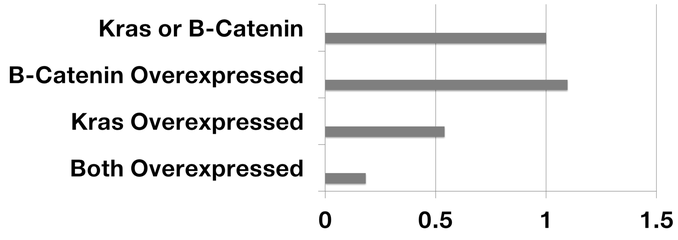
RT qPCR measured levels of gene expression of p53 pathway associated genes. Combination mutants β-Catenin and Kras were compared with controls...

Some genes, such as for C-jun and Dapk1, were downregulated.

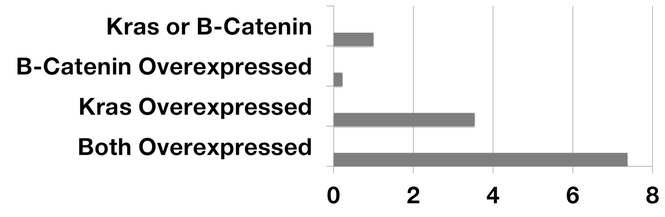
Many genes, such as Traf1 and Cdkn2a, were upregulated.



Fold change of Death associated protein kinase 1



Fold change of **C-Jun**



Fold change of Tnf receptor-associated factor 1

From candidate genes to therapy.

PCR array analysis identified genes with significant expression changes in the combination mutant when compared to either mutant individually.

The expression is modulated in a non-additive fashion in K-ras + β-catenin mutant tissues, which can explain the phenotype of Wilm's tumor in only double mutant mice.

These genes individually represent targets for therapy in the future, and together represent an identifying fingerprint for diagnosis and prediction.

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