

## Wilms' Tumor and Insulin-Like Growth Factor 2

Wilms' tumor is a pediatric malignancy thought to arise when multipotential kidney blastemal cells fail to differentiate after birth and instead continue to proliferate. The occurrence of both sporadic and hereditary forms of Wilms' tumor and the early age of onset of bilateral kidney tumors suggest that Wilms' tumors result when a predisposing germ-line mutation is accompanied by a second mutation or loss of heterozygosity at the disease locus. A potential tumor suppressor gene, *wt1*, was cloned in 1990 by analyzing deletions at chromosomal locus 11p13. These are associated with Wilms' tumors. The *wt1* gene encodes a zinc finger DNA binding protein, called WT1, and this has been found to behave as a transcriptional repressor. The biologic significance of DNA binding and transcriptional regulation by WT1 is underscored by the observation that small deletions and point mutations in the WT1 Zn<sup>2+</sup> fingers that abolish this DNA binding have been detected in a number of Wilms' tumors, especially in tumors associated with the Denys-Drash syndrome.

The fetal mitogen insulin-like growth factor 2 (IGF-2) is over-expressed in Wilms' tumor. In addition, the overgrowth disorder Beckwith-Wiedemann syndrome, which is characterized by loss of the maternal copy of the IGF-2 gene, also is prone to Wilms' tumors. For these reasons, Drummond et al have examined the interaction between the suppressor protein WT1 and the IGF-2 gene. They found that WT1 binds to multiple sites in the promoter

region of the IGF-2 gene, and that it acts as a potent repressor of IGF-2 transcription in vivo. Thus, a molecular basis for the over-expression of IGF-2 in Wilms' tumor has been identified, and these experiments suggest that the *wt1* gene negatively regulates blastemal cell proliferation by limiting the production of a fetal growth factor in the developing vertebrate kidney.

Drummond IA, Madden SL, Rohwer-Nutter P, et al. Repression of the insulin-like growth factor II gene by the Wilms' tumor suppressor WT1. *Science* 1992;257:674-678.

**Editor's comment:** *This paper provides further insight into the question of specific molecular mechanisms of growth control, ie, what prevents all cells in all tissues of the body from proliferating indefinitely? In addition, there are many indications that both Wilms' tumor and Beckwith-Wiedemann syndrome are imprinted disorders, ie, they will develop when inherited from a parent of the same sex but will not when inherited from a parent of the opposite sex. The IGF-2 gene has been shown to be imprinted in mice such that only the paternally inherited gene is expressed. Thus, these experiments provide further insight into mechanisms of genomic imprinting as well as overgrowth in cancer.*

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