Wilms’ Tumor

“The most common renal tumor in children”
Overview

- What is Wilms’ Tumor?
- History.
- Cause and proposed mechanisms of tumor development.
- Identification of Wilms’ tumor.
- Staging and Cellular classification.
- Treatments.
- Future outlook.
What is Wilms’ tumor?

- It is the most common kidney tumor of children.
- Originates within the kidney during early childhood development.
- Occurs with a frequency of 1 in 10,000 live births.
- Average age of diagnosis—3 yrs.
- Average size—0.5 lbs.
- Two types:
  1. Favorable histology.
  2. Unfavorable histology
     --anaplastic and diffuse anaplastic
History

- Discovered in 1899 by Max Wilms.
- Establishment of the National Wilms Tumor Study Group (NWTSG).
  *Goals: --increase the survival rate of children.
    --identify adverse effects of treatments.
    --study long-term effects of treatments.
    --study epidemiology and biology of the Wilms tumor.
Cause and proposed mechanisms of tumor development.

- Caused by one or more changes in several genes.
- Two mutations recognized are on chromosome 11p; 11p13 & 11p15.
- Other loci possibly affected: 1p, 7p, 16p, 17p (the p53 suppressor gene), and 19p.
- Possible causes I will look at are:
  1. Mutations in gene WT1
  2. Mutations in gene WT2
  3. Mutations in p53
  4. Mutations in the beta-catenin pathway
Chromosome 11
**WT1 mutation**

- WT1 functions as a zinc finger transcription factor.
  -- Amino terminus is rich in proline and glutamine
  -- Carboxyl terminus contains four C2H2 zinc finger DNA-binding motifs and a NLS sequence.
- In vivo there are 4 major isoforms that are generated by alternative splicing at two sites. These 4 isoforms are at a constant ratio, which suggest that there functions are independent of each other.
- DNA binding is isoform-dependent.
- WT1 has been shown to be a transcriptional activator or repressor.
Zinc Finger
Zinc Finger
Alternative Splicing of WT1

Figure 1. The four patterns of alternative splicing of the WT1 gene. The details are explained in the text.
Other mutations found:

- Mutations at 11p15 has now been identified and designated as WT2.
- *B-catenin* mutations were also found associated with Wilms’ tumor. 

*p53* identified as a cyclin-dependent kinase (CDK) inhibitor.
Regulation of the cell cycle

Figure 2. The relation between the proteins that regulate cell cycle progression.
Identification of Wilms’ tumor.

- 1st sign is a large lump or swelling in the abdomen.
- 25% also have other symptoms:
  - stomach pain
  - fever
  - blood in the urine
  - high blood pressure
- Medical history, examination, and imaging testing.
- Surgical removal of the tumor is performed in 95% of the cases.
Staging and Cellular classification.

- Staging of the tumor.
  - Stages 1, 2, 3, 4, & 5.
- 2 prognostic groups on the basis of histology:
  - Favorable histology
  - Unfavorable histology
    - Anaplastic
    - Diffuse anaplastic
Treatments.

- Surgery—complete removal of the tumor and surrounding tissue without tumor rupture.
- Treatments range from:
  -- 18 weeks of chemotherapy /no radiation
  -- 24 weeks of chemotherapy plus abdominal and whole lung radiation
- Relapse treatment depends on these factors:
  - Site of recurrence
  - Tumor histology
  - Length of remission
  - Initial chemotherapy regimen
Future outlook.

- Amount of chemotherapy and radiation used has decreased over the years.
- Further studies associated with WT1, WT2, b-catenins, etc…
- Discoveries of new mutations that lead to Wilms’ tumor.
- Therapies that might use anti-telomerase.
- Study #5 will be finished in 2003.
References

- P. Stanhope-Baker, B. Williams, “Identification of Connective Tissue Growth Factor as a Target of WT1 Transcriptional Regulation.” *JBC online*. http://www.jbc.org/cgi/content/full/275/49/38139.


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