The Genetic Modifications in Wilms Tumour

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Abstract

The most common renal cancers of childhood is Wilms tumour. However, majority of the cases can be treated and curable. The genetic changes related Wilms tumour have been illustrated from the various studies of clinical case studies and undifferentiated dna sequencing of tumour genomes all these approaches together defined the overview of the genes that are active in Wilms tumour, in which many of the genes are indirectly linked to the fetal neophrogenesis. Improvement in the understanding of germ line and somatic genetic changes that are linked to the Wilms tumour may help in better patient outcomes. Recognizing the favoured mutations that led to the potential new targets with some new compounds undergoing testing in early phase trials.

Keywords: Wilms tumour; Neophrogenesis; MiRNAPGs; Aneuploidy

Introduction

Based on the histological history of stages in neophrogenesis and age of onset, Wilms tumour is considered to be embryonic childhood tumour. 90% of childhood renal tumours and constitutes 7% of all childhood cancers account for Wilms tumour. The understanding of Wilms tumour came from the information given by the patients with Wilms tumour. Whole sequencing has recognised unique mutations in micro RNA processing genes (miRNAPGs) and in the transcription factor homeo box genes SIX1 and SIX2. In 2017,a mixed whole-genome and whole-exome sequencing study of 117 Wilms tumours identified novel mutations in genes encoding proteins involved in histone modification during nephrogenesis (BCOR and MAP3K4), proteins that interact with N-MYC proto-oncogene protein(MYCN; that is, NONO and MAX) and proteins that act as transcriptional co-repressors (such as BCORL1),among others12. This study identified germ line mutations in cancer risk genes (REST, CHEK2 and PALB2) in children with non-syndromic Wilms tumour.

In this Review article we give brief information in Epidemiology, Stages of Wilms tumour, Management and Risk Stratification, Relapse, Bilateral Tumours, Anaplasia, Wilms Tumorigenesis and Nephrogenesis, Germ line mutations, Syndromic and Familial Wilms Tumour, Non-Syndromic Wilms Tumour, Novel Therapeutic Targets.

Epidemiology

Out of 10,000 children, one child is affected by Wilms tumour world wide before the age of 15 years. Incidence rates appear to be slightly elevated for U.S. and African Blacks when compared to Whites, but are only half as great among Asians. Several casecontrol studies have revealed that paternal occupational or maternal hormonal exposures during pregnancy period may increase the risk of Wilms tumour, but small numbers of subjects and inconsistencies in the patterns of exposures do not permit firm conclusions to be drawn. It is unlikely that such environmental exposures play a major role in the aetiology of Wilms tumour. The median age at onset of Wilms tumour is 38 months in the U.S. National Wilms Tumour Study series, with cases in girls occurring on average 6 months later than in boys. Patients with bilateral tumours, aniridia, cryptorchism / hypospadias, BeckwithWiedemann syndrome, or intralobar nephrogenic rests tend to be diagnosed much younger than average (median 17 – 27 months).

Stages of Wilms tumour

Stage I: Tumour limited to the kidney and completely excised. The renal capsule is intact and the tumour was not ruptured before removal. There is no residual tumour.

Stage II: Tumour extends through the perirenal capsule but is completely excised. Extra renal vessels may contain tumour thrombus or may be infiltrated by the tumour.

Stage III: Residual nonhematogenous tumour confined to the abdomen; lymph-node involvement, diffuse peritoneal spillage, peritoneal implants, either gross or microscopic tumour beyond the surgical margin, or tumour not completely removed.
Stage IV: Hematogenous metastases to lung, liver, bone, brain or other organ.

Stage V: Bilateral renal involvement at diagnosis.

Management and Risk Stratification

With modern surgery, chemotherapy, and radiation therapy procedures, the overall survival rate for patients with Wilms tumour has reached 90%. Extraordinarily, the increase in survival has been accomplished with a reduction in therapy for most patient subgroups, leading not only to more survivors, but also to healthier survivors. A key contributor to upgraded outcomes has been the development of clinical and biologic prognostic markers that have entitled risk-directed therapy. Whereas the early cooperative group studies used only tumour stage for risk stratification, current Children's Oncology Group (COG) and International Society of Pediatric Oncology (SIOP) protocols employ a multitude of prognostic factors to guide therapy. Prognostic factors used in the current generation of COG studies include stage, histology, patient age, tumour weight, completeness of lung nodule response, and loss of heterozygosity at chromosomes 1p and 16q. Future COG studies seek to incorporate gain of chromosome 1q and methylation pattern of chromosome 11p15 into the risk classification schema [1-5].

Relapse

Factors for relapsed Wilms’ tumour include an initial diagnosis of stage I or II, initial two-agent treatment, no radiotherapy, favourable histology and longer time from diagnosis to relapse.

Bilateral Tumours

At present, bilateral disease is treated with pre-operative chemotherapy at time of diagnosis followed by surgery. A major clinical challenge is to decide the best time for nephron-sparing surgery (NSS) and if and when there may be value in intensifying or prolonging pre-operative chemotherapy. Thus far, response assessment is based purely on tumour shrinkage. However, it is recognised that the stromal subtype of WT, common in children with WT1 mutant tumours, may not shrink and may even show a paradoxical increase in tumour size owing to rhabdo myoblastic differentiation, even though it is a favourable histological subtype. Hence, having a technique that could monitor histological response during pre-operative chemotherapy would be useful in planning NSS.

Unilateral Tumours (Anaplasia)

Anaplasia, defined by the presence of extreme nuclear and mitotic atypia, is a potent marker of adverse prognosis in Wilms tumour (WT). Anaplastic WT cells apparently have increased resistance to therapy rather than increased aggressiveness. The distribution of anaplasia should therefore have critical prognostic relevance. The original definitions for focal anaplasia (FA) and diffuse anaplasia (DA) were based on quantitative rather than topographical criteria and lacked prognostic significance. A new definition was developed based on the distribution of anaplastic changes within the tumour: FA applies only to tumours with anaplasia confined to one or a few discrete loci within the primary tumour, with no anaplasia or marked nuclear atypia elsewhere [6-10].

Wilms Tumorigenesis and Nephrogenesis

In Wilms tumour, the differentiation arrest of renal progenitor cells is incomplete, and all three lineages of the developing kidney (blastema, epithelia and stroma) can be identified in classic triphasic Wilms tumour histology. A microarray analysis of over 300 Wilms tumours reported that the gene expression forms a triangular continuum with vertices corresponding to blastemal, stromal and epithelial cell types, which correlate with cap mesenchyme, uninduced metanephric mesenchyme and renal epithelium, respectively.

Familial Wilms Tumour

Only 1-2% of Wilms tumour cases cluster within families, but the underlying causes of these rare pedigrees are heterogeneous and complex. A minority of families with more than one individual with Wilms tumour are associated with syndromes described elsewhere in this review: WT1 mutations/deletions (four families), Mosaic variegated aneuploidy syndrome (two families), biallelic BRCA2 mutations (one family), and 11p15 defects (one family).33 However, the underlying cause of most familial Wilms tumour is currently unknown.

Novel Therapeutic Targets

Several targeted treatments, each directed at a specific cancer trait, have been approved for clinical use. A few examples are outlined: targeting of specific cell signaling pathways such as the epidermal growth factor inhibitors—cetuximab (Erbitux), a chimeric (mouse/human) monoclonal antibody (mAb), used in the treatment of colorectal cancer and head and neck carcinoma, trastuzumab (Herceptin), an anti-HER2 mAb, used against breast tumours and metastatic gastric cancer—expressing HER2 interference with tumour angiogenesis—bevacizumab (Avastin), an anti-VEGFA humanized mAb, used against colorectal, lung, breast, glioblastoma, kidney, and ovarian tumours targeting of specific tumour antigens—rituximab (MabThera), an antiCD20 mAb, used against non Hodgkin’s lymphoma. A growing number of targeted treatments have reached the clinical setting; some replacing the conventional systemic treatments and others are used in conjunction with them to allow application of lower doses of the later, more toxic, drugs [11-14].

Conclusion

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References


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