The molecular biology of Wilms' tumour

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Keith W. Brown and Karim T.A. Malik

Wilms' tumour (WT; nephroblastoma), a kidney neoplasm, is one of the most frequently occurring solid tumours of childhood. It arises from the developing kidney by genetic and epigenetic changes that lead to the abnormal proliferation of renal stem cells (metanephric blastema). WT serves as a paradigm for understanding the relationship between loss of developmental control and gain of tumourigenic potential. In particular, loss of function of tumour suppressor genes has been implicated in the development of WT, and the Wilms' tumour suppressor gene *WT1* (at chromosome 11p13) was the second tumour suppressor gene to be cloned, after the retinoblastoma gene *RB-1*. *WT1* plays an essential role in kidney development, but is mutated in only approximately 20% of WTs, which suggests that further lesions and genetic loci are involved in Wilms' tumourigenesis. Other chromosomal regions associated with WT include 7p, 11p15, 16q and 17q. Although many of these loci probably contain tumour suppressor genes, imprinted genes (genes showing expression of only one parental allele) and oncogenes have also been implicated in WT. Some loci have been shown to be associated with particular clinical outcomes, suggesting that they might be used to determine prognosis, and especially to identify poor prognostic subgroups that can be targeted for aggressive and/or novel therapies.

Wilms' tumour (WT) is an embryonal renal neoplasm (Fig. 1) and is one of the commonest solid tumours of childhood, affecting ~1 in 10 000 children (rates vary slightly between different racial groups), typically between the ages of 2 and 4 years. It has a high cure rate (~85%), which has been achieved using a combination of surgery, chemotherapy and radiotherapy. However, 15% of affected children still die from their disease, and present therapies can have serious short- and long-term side effects. No strong environmental factors have been implicated in WT development,

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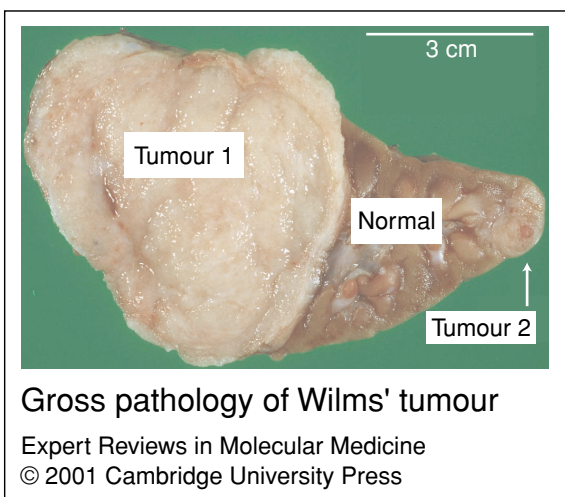
Gross pathology of Wilms' tumour

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Figure 1. Gross pathology of Wilms' tumour. A cut section of a Wilms' tumour showing remaining normal kidney, a large tumour (Tumour 1) and a smaller additional tumour (Tumour 2). This was taken from a patient with the predisposing WAGR syndrome [in which a high risk of Wilm's tumour is associated with aniridia (lack of the iris), genitourinary abnormalities and mental retardation], and is an example of multifocal disease. Image by kind permission of Professor Jem Berry (Department of Paediatric Pathology, University of Bristol, UK) **(fig001kbb)**.

but there are several predisposing syndromes that confer a greatly increased risk of developing WT, indicating a major role for genetic factors in Wilms' tumourigenesis (Ref. 1). This review briefly describes the biology of WT and then discusses recent work on the genetic and epigenetic changes underlying this disease.

Biology of WT
WT arises from the developing kidney. The definitive mammalian kidney, the metanephros, develops by an inductive interaction between the ureteric bud (which goes on to form the collecting duct system) and the metanephric blastema (which goes on to form the nephrons and connective tissue) (Fig. 2) (Ref. 2). The blastema is induced to differentiate to form both epithelial components (which will give rise to nephrons) and stromal components (which make up the connective tissue) in the kidney (Fig. 2), with cells that are not induced to differentiate undergoing programmed cell death (apoptosis) (Ref. 3). Kidney development is complete by 36 weeks of gestation in humans. WT is presumed to arise because of the failure of the metanephric blastema to undergo its normal developmental pathway. However, differentiation potential is often partly maintained in WTs, and is manifested as the classical 'triphasic histology' (Fig. 3b), in which nests of blastema are seen together with areas of epithelial tubules and stroma (Ref. 4). Other histological variants of WT occur in which one cell type predominates [e.g. blastemal-predominant (Fig. 3c) and stromal-predominant (Fig. 3d) variants].

WT is thought to develop via a premalignant stage, the 'nephrogenic rest', in which areas of undifferentiated blastema persist after 36 weeks gestation (Ref. 5). Rests are seen in less than 1% of routine autopsies of infants, but are found adjacent to ~30% of sporadic WTs and more frequently in predisposing syndromes (see below). The majority of nephrogenic rests regress, but some undergo malignant transformation, grow in size and might ultimately go on to form a WT (Fig. 2d) (Ref. 5).

Current therapies for WT
Treatment of WT usually involves removal of the whole affected kidney, comprising both the tumour and the attached remaining normal kidney (complete nephrectomy – see Fig. 1). The patient then receives adjuvant cytotoxic chemotherapy, and sometimes also radiotherapy. The exact treatment protocol depends on prognostic factors such as extent of spread of the tumour (stage) and whether the tumour has a potentially aggressive phenotype as judged by its histology (e.g. anaplasia – see Fig. 3e) (Ref. 1).

Genetics of WT
Studies of patients who have syndromes that predispose to WT have been pivotal in identifying genetic factors involved in WT development. Patients with these syndromes tend to develop multiple tumours, either as tumours in both kidneys (bilateral disease) or as multiple tumours in one kidney (multifocal disease, as shown in Fig. 1). These tumours occur at an earlier age of onset than in sporadic (non-predisposed) cases, which normally present with a single tumour at a later age. The cases of genetic predisposition led Knudson to extend his 'two-hit' model of retinoblastoma to include WT, suggesting that two rate-limiting steps were essential for WT development (Ref. 6). Another aspect of the model was a prediction of large numbers of inherited cases of WT. Although this prediction turned out
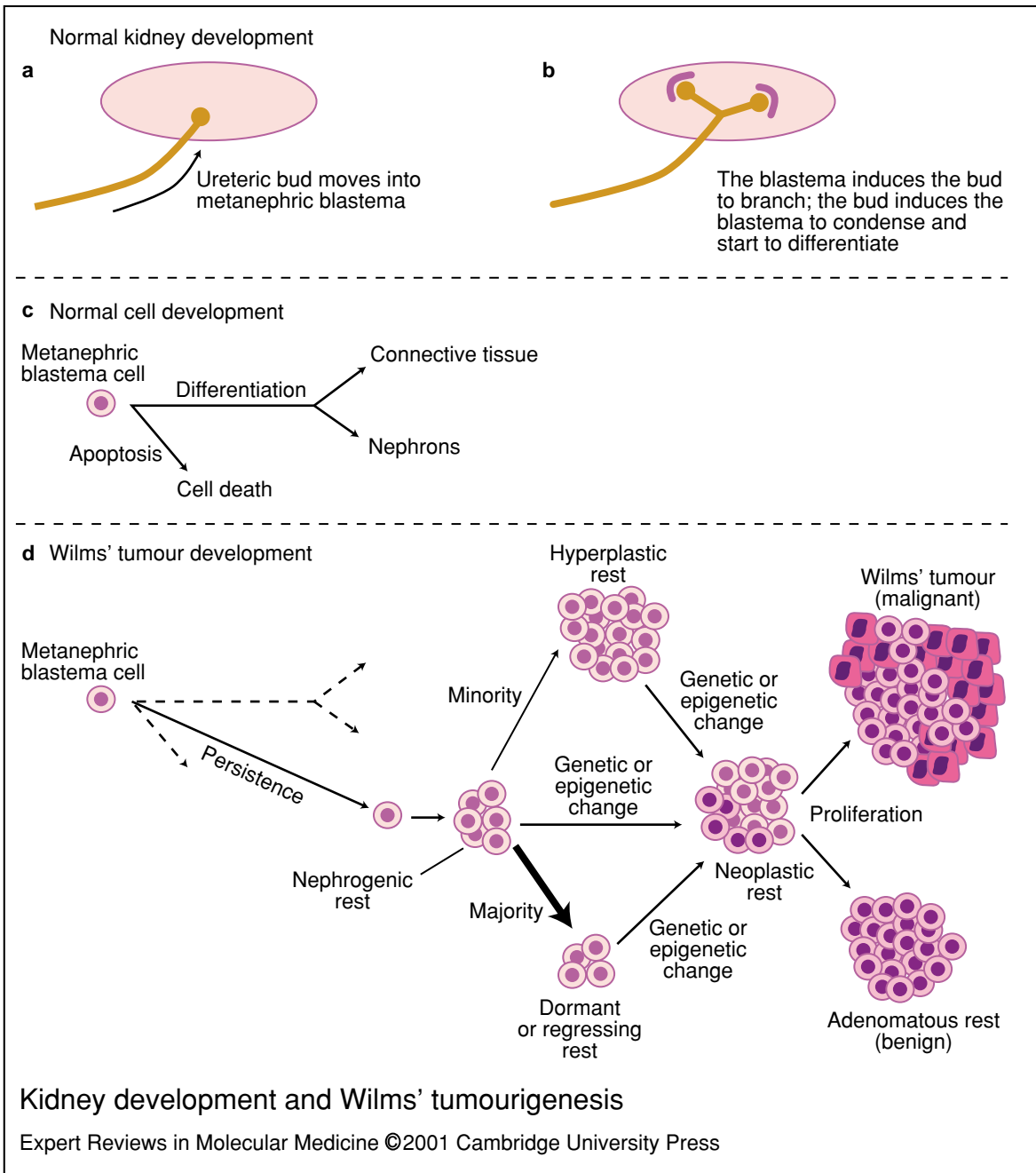
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Kidney development and Wilms' tumourigenesis

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Figure 2. Kidney development and Wilms' tumourigenesis. (a) Development of the definitive mammalian kidney begins with the ureteric bud (which develops into the ureter and collecting ducts) moving into the metanephric blastema. (b) In a two-way inductive interaction, the blastema induces the ureteric bud to branch, and the bud induces the blastema to condense around it and begin to differentiate. (c) The metanephric blastema cells are normally induced to differentiate into epithelial cells (which go on to form the mature nephrons) or stromal cells (which make up the connective tissue). Those cells that are not induced to differentiate undergo apoptosis (programmed cell death). (d) In Wilms' tumour development, some blastema cells persist to form a 'nephrogenic rest'. Most rests become dormant or regress but others proliferate to form hyperplastic rests. It is thought that any type of rest can then undergo a genetic or epigenetic change to become a neoplastic rest, which can proliferate further to produce a benign lesion (adenomatous rest) or a malignant Wilms' tumour. The diagrams in parts 'c' and 'd' are based on data in Ref. 5 **(fig002kbb)**.

Histopathology of normal fetal kidney and Wilms' tumour

a — Normal fetal kidney (16 weeks gestation)

b — Triphasic histology of typical Wilms' tumour

c — Blastema predominates

d — Stroma predominates

e — Anaplastic

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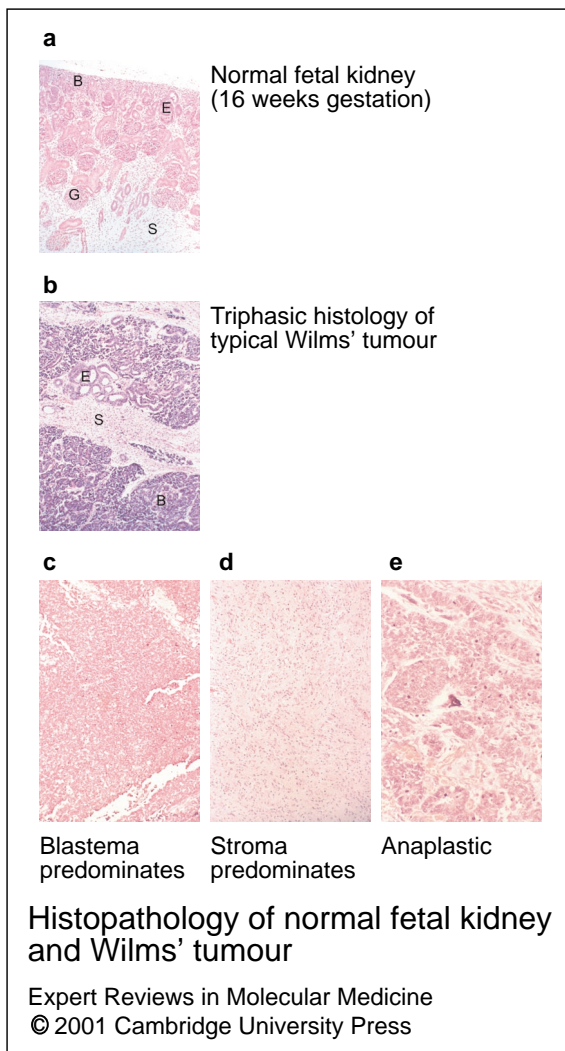© 2001 Cambridge University Press

Figure 3. Histopathology of normal fetal kidney and Wilms' tumour. (a) In normal fetal kidney at 16 weeks gestation, undifferentiated metanephric blastema cells (B) are confined to the edge of the kidney. They have been induced by the ureteric bud to differentiate to form epithelial cells (E) which go on to be part of the mature glomeruli (G). Some blastema cells are thought to differentiate into stromal cells (S). (b) In most Wilms' tumours, this pattern of differentiation is partly maintained to give the so-called 'triphasic histology' in which areas of blastema (B), epithelia (E) and stroma (S) can all be observed. Variants of the typical Wilms' tumour histology occur in which one cell type predominates, such as (c) blastema and (d) stroma. The tumour in (d) carries a *WT1* (Wilms' tumour suppressor gene) mutation. (e) A few Wilms' tumour cases show abnormal morphological features in the nuclei termed 'anaplasia'. Like some other anaplastic Wilms' tumours, the tumour shown here carries a p53 mutation **(fig003kbb)**.

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to be wrong, the two-hit model introduced the idea of recessive cancer genes, which need to have both alleles inactivated for tumourigenesis to occur (Fig. 4a). Such genes are termed tumour suppressor genes, and loss of function of these genes has been shown to be a major factor in WT development.

One of the most important predisposing syndromes is WAGR (~1% of WT cases), in which a high risk of **W**T is associated with **a**niridia (lack of the iris), **g**enitourinary abnormalities and mental **r**etardation. There are three other major syndromes that predispose to WT. First, in Denys–Drash syndrome (DDS; ~0.5% of WTs), patients have severe genitourinary abnormalities, leading to inevitable kidney failure, coupled with a very high risk of WT. Second, Beckwith–Wiedemann syndrome (BWS; about 1% of WTs) results in a fetal overgrowth that predisposes to several paediatric malignancies, including WT. Third, there is a dominantly inherited form of WT (1–2% of WT cases) that usually occurs without associated congenital abnormalities (Ref. 1).

WT genes

The discovery of cytogenetic abnormalities in syndromes predisposing to WT [e.g. 11p13 deletions in the WAGR syndrome (Ref. 7), and 11p15 partial trisomy and translocations in BWS (Ref. 8); see below] has been critical for the identification of WT genes. Studies of allele loss [which is described as loss of heterozygosity (LOH); Fig. 4] in sporadic tumours, linkage analysis in inherited tumours, and functional studies of tumour suppression have together identified several additional genetic loci as being involved in WT development. Thus, WT is genetically complex, with multiple genes involved in familial and sporadic forms (Refs 9, 10).

WT1 (chromosome 11p13)

The existence of a tumour suppressor gene on chromosome 11 was suggested by the finding of 11p13 deletions in the WAGR syndrome (Ref. 7) and 11p LOH in sporadic WTs (Fig. 4) (Refs 11, 12, 13, 14). The gene was simultaneously isolated by several groups using positional cloning methods in 1990 (Refs 15, 16, 17).

WT1 gene structure

The *WT1* gene is ~50 kb long (Refs 15, 16, 17) and encodes multiple 52–56 kDa protein isoforms

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Loss of heterozygosity (LOH) in Wilms' tumour

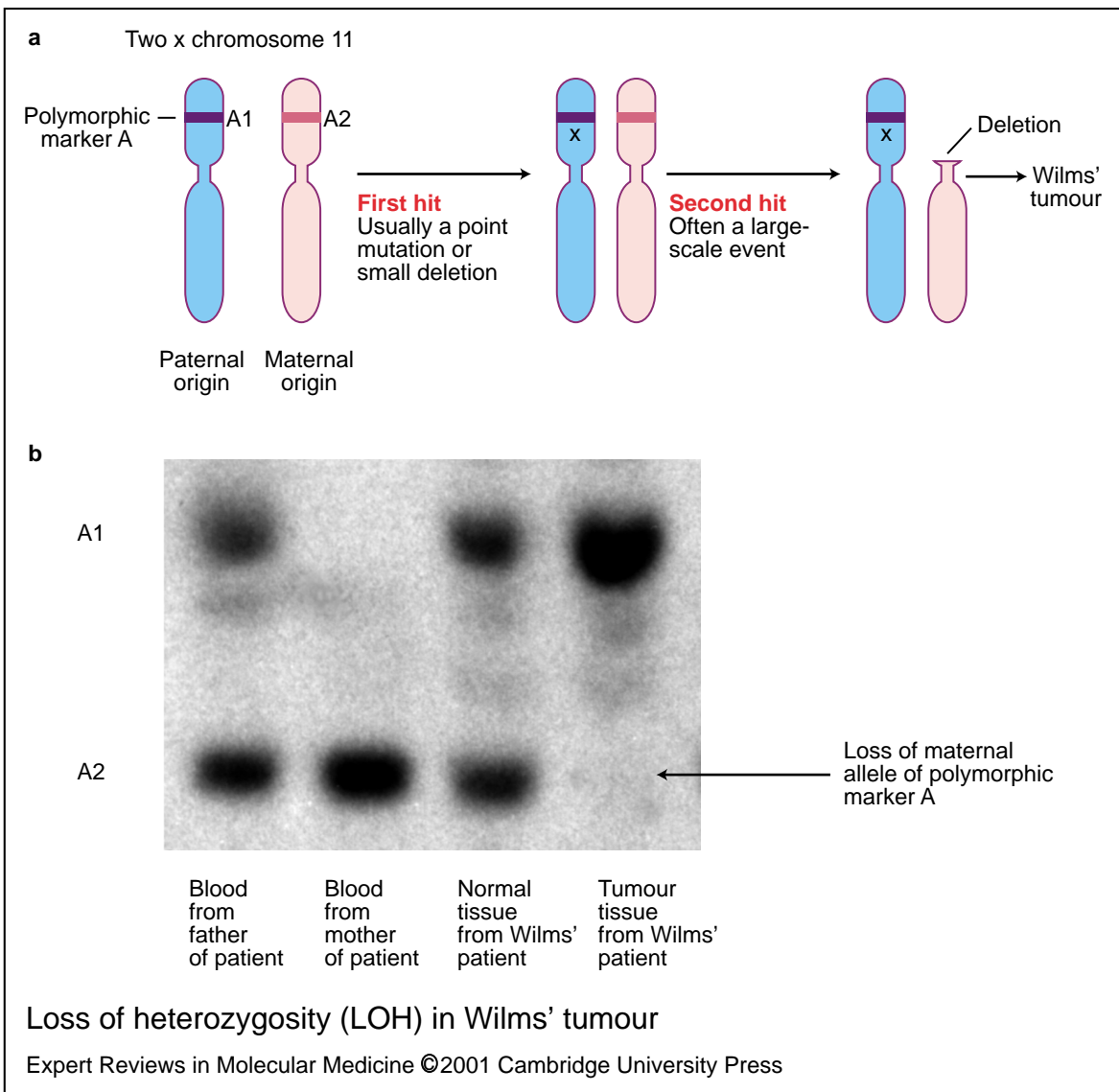Expert Reviews in Molecular Medicine ©2001 Cambridge University Press

Figure 4. Loss of heterozygosity (LOH) in Wilms' tumour. (a) An explanation of the mechanism of allele loss. Two 'hits' (mutations) that inactivate both alleles of a tumour suppressor gene on the short arm of chromosome 11 are needed for Wilms' tumour to develop. Gross genetic changes affecting this part of chromosome 11 can be monitored by examining a polymorphic marker ('A' in this figure) that lies close to the tumour suppressor gene. The first hit is usually a point mutation or small deletion, shown as a cross on the paternal chromosome. This does not affect the integrity of the chromosome, so both alleles of the polymorphic marker (conventionally named A1 and A2) are retained. The second hit often involves a large-scale chromosomal event, such as loss of a chromosome arm – in this case the loss of the short arm of the maternal chromosome. This leads to the loss of A2, which is detected as the loss of a band on the Southern blot of tumour DNA – see panel 'b'. Note that in Wilms' tumour it is always the allele on the maternal chromosome 11 that is lost. This reflects the presence of imprinted genes on this part of chromosome 11 (see text). (b) Southern blot of DNA extracted from the normal tissue and tumour of a patient with Wilms' tumour, and from the blood of the patient's father and mother. The DNA was cut with a restriction enzyme and probed with a radioactive DNA sequence that detects a polymorphism on the short arm of chromosome 11. This polymorphism has two possible alleles: A1 and A2. The patient's tumour shows loss of A2 compared with normal tissue. It can be seen that this was the allele that the patient inherited from the mother, indicating that it is the maternal allele that is lost in Wilms' tumour. [The father was heterozygous for this polymorphism (A1A2), whereas the mother was homozygous (A2A2)] **(fig004kbb)**.

generated via alternative mRNA splicing (Ref. 18), RNA editing (Ref. 19) and non-AUG translational initiation (Ref. 20). The proteins have a proline- and glutamine-rich N-terminal domain and a DNA/RNA-binding C-terminal domain containing four zinc finger motifs that are similar to those found in the EGR (early growth response) family of transcription factors (Refs 15, 16, 17). One alternative splice inserts 17 amino acids in the N-terminal domain; another inserts three amino acids (KTS) between zinc fingers 3 and 4 (Ref. 18) (Fig. 5a). The WT1 isoforms lacking KTS appear to function predominantly as transcription factors (Ref. 21), whereas the isoforms containing KTS associate with splicing complexes in the nucleus and might be involved in RNA metabolism (Refs 22, 23).

Transcriptional regulation by WT1 proteins
WT1 proteins can bind to a GC-rich EGR-like DNA sequence (Ref. 24), as well as to a longer CT-rich sequence (Ref. 25). A large number of genes have been proposed as targets of WT1 transcriptional regulation, on the basis that their GC-rich promoters bind WT1 and are regulated by WT1 in transfection assays [e.g. the gene for insulin-like growth factor 2 (*IGF2*) (Ref. 26), and see genes listed in Ref. 22]. However, in only a very few cases do the endogenous genes show altered expression in cells when levels of WT1 are modulated (Ref. 27). Array techniques and other methods are now being used to attempt to define bona fide targets of the WT1 transcription factor, and some of the most recent studies suggest that genes encoding amphiregulin (a member of the epidermal growth factor family) (Ref. 28) and Bcl-2 (an anti-apoptosis protein) (Ref. 29) are regulated by WT1. The activity of WT1 is modulated by protein–protein interactions, including self-association (Ref. 30), and binding
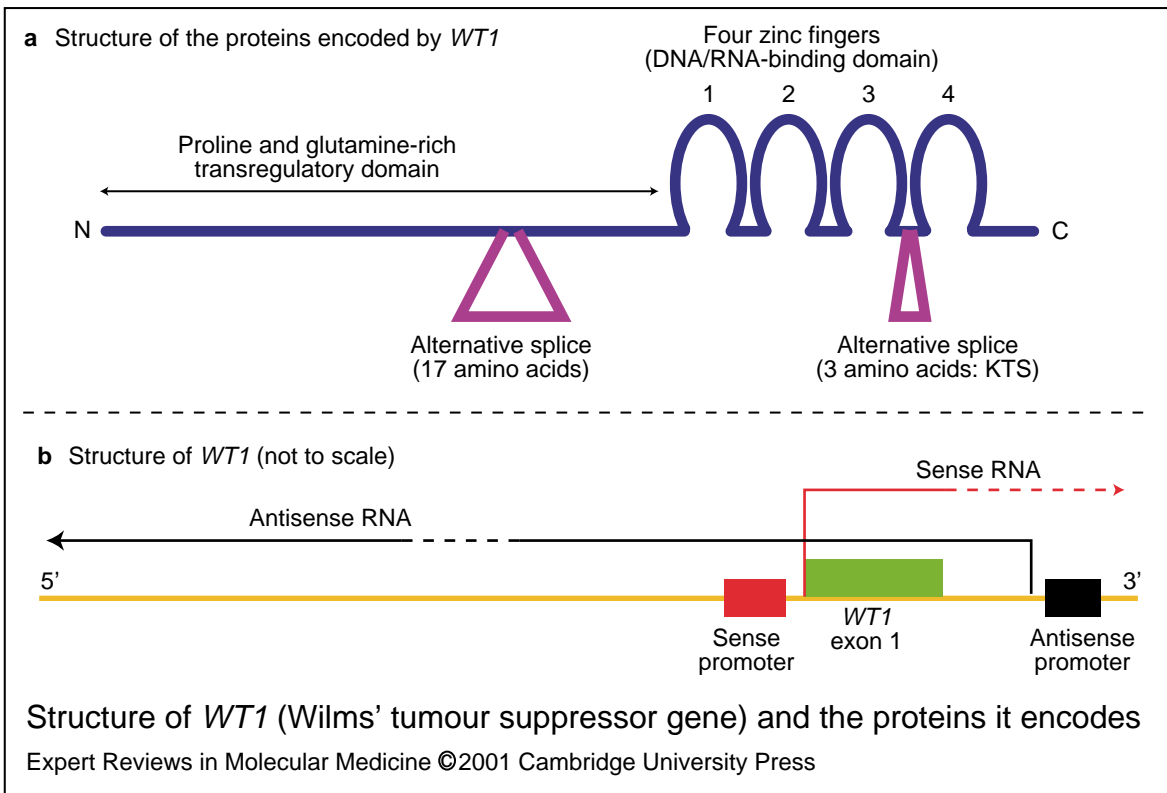

a Structure of the proteins encoded by *WT1*

Four zinc fingers
(DNA/RNA-binding domain)

Proline and glutamine-rich transregulatory domain

N   C

Alternative splice
(17 amino acids)

Alternative splice
(3 amino acids: KTS)

b Structure of *WT1* (not to scale)

Sense RNA

Antisense RNA

5'   3'

Sense promoter

WT1 exon 1

Antisense promoter

Structure of *WT1* (Wilms' tumour suppressor gene) and the proteins it encodes

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Figure 5. Structure of *WT1* (Wilms' tumour suppressor gene) and the proteins it encodes. (a) The proteins encoded by *WT1* have a proline- and glutamine-rich transregulatory domain at the N-terminal end and four zinc fingers in a C-terminal DNA/RNA-binding domain. There are two alternative splices (shown by purple triangles): one inserts 17 amino acids in the transregulatory domain and the other inserts three amino acids (KTS) between the third and fourth zinc fingers. (b) *WT1* produces overlapping sense and antisense RNAs, with the antisense promoter located in intron 1. Spliced regions of the RNAs are shown as dotted lines **(fig005kbb)**.

to the tumour suppressor p53 (Ref. 31) and to the transcriptional repressor PAR-4 (Ref. 32).

Biological effects of WT1

Investigation of the biological effects of WT1 expression is hampered by the lack of good cell-culture systems. Nonetheless, it has been shown that, in certain cells, WT1 can induce cell-cycle arrest and apoptosis (Ref. 33), although in one system it inhibited p53-mediated apoptosis (Ref. 34). Expression of WT1 in another cell type induced an epithelial phenotype, consistent with its apparent role in vivo (see below) (Ref. 35).

Expression of WT1

WT1 is normally expressed in the developing genitourinary system. Levels are low in the induced metanephric mesenchyme, increase as the cells undergo epithelial differentiation, and attenuate as they mature (Ref. 36). In *wt1*-knockout mice, the loss of function of *WT1* leads to massive apoptosis in the metanephric blastema and consequent failure of kidney development, demonstrating an essential role for *WT1* in nephrogenesis (Ref. 37).

Mutations in WT1

In humans, deletion of one allele of *WT1* causes genitourinary abnormalities in the WAGR syndrome, whereas heterozygous germline missense mutations lead to the more severe defects observed in DDS, probably because of a dominant-negative effect of the mutant protein (Ref. 38). Of sporadic WTs, only about 20% have a *WT1* mutation (Ref. 39). In these tumours, *WT1* appears to act as a classic loss-of-function tumour suppressor gene (Ref. 39). *WT1* mutation represents an early event (Ref. 40), because mutations have also been found in 'nephrogenic rests', which are premalignant precursors of WT (Refs 41, 42).

Control of WT1 expression

Although mutations in *WT1* underlie a significant fraction of WTs, significant quantitative changes in *WT1* expression might also play a role in tumourigenesis. Possible factors controlling expression levels of this gene include an autoregulatable 5' promoter (Refs 43, 44), 5' and 3' enhancer elements (Ref. 45), a silencer in intron 3 (Ref. 46), other long-range-acting sequences (Ref. 47), and antisense RNAs (see below).

The *WT1* promoter is a TATA-less GC-rich promoter that is autorepressed by *WT1* in transfection assays (Refs 43, 44). Initially, it was proposed that this promoter was bidirectional, such that another gene, termed *WIT-1*, was transcribed in a similar temporal and spatial pattern to *WT1*, but in the opposite direction (Ref. 17). The putative *WIT-1* transcript contained no large open reading frames, and was therefore proposed to function as an RNA (Ref. 17). Longer transcripts have subsequently been isolated; these contain the *WIT-1* sequences, but are much larger, continuing back into *WT1*, where they overlap with exon 1 and are thus partly antisense *WT1* transcripts (Refs 48, 49). An antisense *WT1* promoter located in intron 1 has been identified, which is transactivated by WT1 (Ref. 50) and is regulated by epigenetic modifications (see below) (Ref. 51). It therefore appears that the *WIT-1* gene is in fact part of long antisense RNA(s) that originate from a promoter in intron 1 (Fig. 5b). These transcripts affect levels of WT1 protein when overexpressed in cultured cells, suggesting a role for them in the control of WT1 expression (Ref. 52).

Other loci

To date, *WT1* is the only cloned WT gene. Since it is mutated in only 20% of tumours, other loci have been investigated to attempt to account for the development of the remainder of WT cases.

Chromosome 11p15

LOH at 11p occurs in 40–50% of WTs (Ref. 4), and, in some of these, the loss is limited to the 11p15 region (Refs 53, 54), implicating a further tumour suppressor gene, *WT2*, on 11p. In addition, the gene(s) associated with the WT-predisposing disease BWS map to 11p15 (Ref. 55). 11p15 contains a cluster of imprinted genes that have been shown to be involved in WT both by LOH and by epigenetic changes (see below) (Ref. 56).

Chromosomes 16q and 1p

Chromosome 16q LOH occurs in about 20% of WTs and is associated with a poor prognosis. 1p LOH occurs less often and the evidence for prognostic significance is marginal (Ref. 57). LOH at 16q does not normally occur in nephrogenic rests, implying that it is a relatively late event in Wilms' tumourigenesis (Ref. 42). These results suggest additional WT suppressor genes at 16q and 1p, but neither has yet been identified.

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Chromosome 11q

LOH at 11q has been reported in over 30% of WTs (Ref. 58), implicating another putative tumour suppressor gene on chromosome 11.

Chromosome 7p

This locus was implicated in WT by investigations of a patient with WT who also had an unusual set of congenital abnormalities and a constitutional balanced translocation (in which parts of chromosomes are swapped around, with no visible loss of genetic material) between chromosomes 1 and 7: t(1;7)(q42;p15) (Ref. 59). Subsequent LOH studies suggested that there is a tumour suppressor gene on 7p that is involved in at least 10% of WTs (Refs 60, 61, 62).

Inherited WT

In rare cases, WT is inherited as an autosomal dominant trait and linkage has been reported in these families to chromosomes 17q (Ref. 63) and 19q (Ref. 64). Interestingly, LOH studies suggest that the 17q gene is not a tumour suppressor gene (Ref. 65), although it is not yet cloned.

p53

Mutations in the p53 tumour suppressor gene are frequently associated with adult-onset tumours of the colon, lung, brain and breast. They also occur in WTs, but very rarely, where they are associated with an anaplastic histology (Fig. 3e) and poor prognosis (Refs 66, 67). p53 mutations might be associated with advanced disease in WT (Ref. 66).

Other genetic abnormalities

Mutations in the gene encoding β-catenin have recently been reported in 15% of WTs, implicating the Wnt signalling pathway in Wilms' tumourigenesis (Ref. 68). Wnt-4 is a secreted glycoprotein that functions as an autoinducer of mesenchymal to epithelial transition in normal nephron development, and activation of β-catenin-mediated transcription is the nuclear end-point of this pathway (Ref. 68). Thus, deregulation of this process appears to be involved in WT development.

High telomerase reverse transcriptase (hTERT) mRNA levels have been detected in WT, and high levels appear to correlate with tumour recurrence (Ref. 69). Indeed, high telomerase enzyme activity (which maintains chromosome ends) is known to be an unfavourable prognostic factor in several malignancies (Ref. 69). Interestingly, WT1 has been shown to repress hTERT expression in some cells (Ref. 70), although the presence of WT1 mutations has not so far been implicated in tumour recurrence.

Epigenetics

The genetic loci listed above are involved in WT via classical mutational and cytogenetic mechanisms. However, it has recently become apparent that epigenetic changes, particularly alterations in DNA methylation, also occur on chromosome 11, both at 11p13 and at 11p15. These changes mainly involve imprinted genes.

Imprinted genes

Imprinted genes are those that have an epigenetic mark applied during gametogenesis, resulting in the expression of only one parental allele (monoallelic expression) (Ref. 71). Only a minority of genes are imprinted, but many play important roles in development and carcinogenesis (Ref. 72). Imprinting is controlled by epigenetic modification, with DNA methylation acting as an essential epigenetic signal (Ref. 73). In imprinted genes there is differential methylation of one parental allele at specific sites [known as differentially methylated regions (DMRs)], which correlates with expression or non-expression of that allele, depending on the mechanisms of transcriptional control in that particular gene (Ref. 74).

Epigenetic changes at 11p15

Involvement of imprinted genes in WT was first indicated by the discovery that LOH at 11p almost always involved the loss of the maternal allele (Fig. 4) (Refs 75, 76, 77, 78). This could be driven by the necessity either to lose a maternally expressed growth inhibitory gene or to retain a paternally expressed growth factor (Ref. 79). A cluster of imprinted genes has now been described at 11p15, containing both the paternally expressed growth factor IGF2, and the maternally expressed growth-inhibitory genes H19 and CDKNIC (p57^{KIP-2}) (Ref. 56).

WTs that lacked 11p15 LOH revealed consistent biallelic expression of IGF2, which has been termed 'relaxation' or 'loss' of imprinting (Refs 80, 81). Biallelic IGF2 expression is normally accompanied both by loss of expression of the tightly linked H19 gene and by hypermethylation of a 5' DMR on the normally unmethylated

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maternal allele (Refs 82, 83). Methylation of the DMR 5' of *H19* inactivates a chromatin boundary, allowing access of *IGF2* to a common set of enhancers, which leads to *IGF2* expression from that allele (Refs 84, 85). *H19*-independent control of *IGF2* expression has also been suggested by the discovery of an antisense RNA from *IGF2* that is overexpressed in WT (Ref. 86); however, the function of *IGF2* antisense RNA is unclear at present. These results suggest that LOH at 11p15 (which usually involves duplication of the retained paternal copy of chromosome 11p15) and relaxation of imprinting both lead to the overexpression of a growth-promoting gene (*IGF2*) and the loss of expression of growth-inhibitory genes (*H19* and *CDKNIC*). Such aberrant expression of growth-promoting and growth-inhibitory genes could give fetal kidney cells a growth advantage, resulting in tumourigenesis. Epigenetic lesions in *H19* are detectable in normal kidney tissue adjacent to WTs, and in premalignant lesions (nephrogenic rests). This suggests that imprinting changes are a relatively early event in tumourigenesis (Refs 82, 87, 88).

Altered imprinting of the 11p15 region is also involved in the fetal overgrowth syndrome BWS, where patients exhibit organomegaly and increased risk of childhood cancer, especially WT (Ref. 55). Familial cases of BWS map to 11p15, and some sporadic cases have chromosomal abnormalities involving the same region. Parent-of-origin effects are seen in each of the genetic abnormalities associated with BWS: preferential maternal transmission of inherited BWS and, in sporadic cases, paternal uniparental disomy (i.e. both copies of 11p15 are derived from the father's chromosomes), paternally derived chromosome duplications, and maternally derived chromosome translocations (Ref. 55). These data have all implicated imprinting defects in BWS. Furthermore, constitutional relaxation of imprinting of *IGF2* has been found in several BWS patients (Ref. 89). The precise molecular lesions causing BWS are complex, and involve two DMRs at 11p15, centred around *H19* (Refs 84, 85) and *KvLQT1* (Refs 90, 91). Chromosomal isodisomy, duplications, translocations and imprinting defects affecting 11p15 can all lead to increased *IGF2* expression, which presumably leads to the increased growth in certain fetal tissues that is seen in BWS. However, some familial cases have inactivating germline mutations in *CDKNIC*, a gene encoding an inhibitor of cyclin-dependent kinases (Ref. 55). Loss of function of this gene would deregulate cell-cycle control, which might cause the overgrowth observed in certain fetal tissues in BWS. The exact relationship between changes in *IGF2* expression in some patients and *CDKNIC* expression in others is not yet explained, but clearly this demonstrates genetic heterogeneity in BWS.

Epigenetic changes at 11p13

The human *WT1* antisense promoter region, on chromosome 11p13, was shown to be aberrantly hypermethylated in some cases of breast cancer (Ref. 92), suggesting that epigenetic control of this region might play an important role in some cancers. Recently, it was demonstrated that the antisense regulatory region was a DMR: the maternal allele was methylated and the paternal allele was unmethylated in normal kidney (Ref. 51). Consistent with this, *WT1* antisense RNA is imprinted in normal kidney, with only the paternal allele being expressed (Ref. 51). In WTs with no LOH, two hypomethylated alleles were observed instead of one methylated and one unmethylated allele, and both alleles were expressed, demonstrating relaxation of imprinting. By contrast, non-Wilms' renal tumours did not exhibit hypomethylation of both alleles, but exhibited a degree of hypermethylation, indicating that tumour-specific epigenetic variations occur at the *WT1* locus (Ref. 51).

Outstanding research questions: the molecular pathogenesis of WT

Analysis of *WT1* mutations in WTs, together with the data discussed above, indicate that multiple loci are involved in WT development. This is in marked contrast to retinoblastoma, which involves just one rate-limiting genetic alteration: inactivation of the retinoblastoma gene *RB-1* (Ref. 93). The early age of onset of WT shows that there are likely to be few rate-limiting genetic steps, in contrast to the multiple steps required for the development of adult tumours. Thus, many of the loci implicated in WT development are probably alternative loci, and inactivation of any one might be sufficient to initiate tumourigenesis, with further genetic and epigenetic changes being involved in tumour progression. Identifying subsets of WTs containing specific genetic or epigenetic changes

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and correlating these with biological properties is one obvious avenue of research to pursue. Thus far, only a few such correlations have been proposed, such as the presence of *WT1* mutations in stromal-predominant WTs (Fig. 3d) (Ref. 94), and the presence of p53 mutations in anaplastic WTs (Fig. 3e) (Refs 44, 67).

The sequence of genetic events in Wilms' tumourigenesis has begun to be unravelled by studying the alterations present in premalignant nephrogenic rests. For instance, genetic and epigenetic changes at 11p (LOH, *WT1* mutation, loss of imprinting) are found in nephrogenic rests, whereas LOH at 16q is not (Refs 41, 42, 86, 87). This implies that genetic and epigenetic events at 11p are initiating events in WT development, whereas 16q alterations are involved in later progression to a more aggressive phenotype. This is consistent with 16q LOH being associated with a poor prognosis in WT (Ref. 57). Similarly, p53 mutation is associated with a poor prognosis and might therefore be predicted to be a late event (Ref. 66).

The various genes implicated in WT development could be involved in separate pathways (e.g. control of proliferation versus differentiation or apoptosis). Alternatively, they could all be inter-related, for example as targets for WT1, or as controllers of *WT1* expression, or as proteins that interact with the WT1 protein. For 16q and *WT1*, some indication of which of these theories applies comes from the data on tumour progression. Thus, the 16q loci/ genes are unlikely to be part of the same pathway as *WT1*, because they are involved at different stages of tumourigenesis. Recent data on β-catenin mutations have shown that they are frequently associated with *WT1* mutations in WTs (Ref. 95), suggesting that *WT1* and β-catenin mutations affect two different biochemical pathways.

The only way to be certain about the biochemical pathways these genes are involved in is to study their biological functions. This means that to gain a full understanding of WT development we must accomplish the following objectives: (1) clone all the genes involved; (2) determine how frequently they are mutated in WTs and at what progression stage; and (3) find out their biological and biochemical functions. With the near completion of the human genome project, the first two objectives should be attainable in the next few years. The third objective

is much more difficult, and it is instructive to consider that although *WT1* was cloned ten years ago, there is still controversy as to its essential biochemical function.

Knockout and transgenic mice will be very useful for studying the biology of WT genes but, for many studies, cell culture systems would be advantageous. In contrast to our advanced knowledge of WT genetics, we know little or nothing about the cell biology of WT. The only true WT cell lines in existence are derived from anaplastic tumours (an aggressive WT subtype) that represent a tiny fraction of WTs (Ref. 96, and K. Brown, unpublished). Thus, it has not even been possible to test the tumour suppressor activity of WT1 in a cell line containing a *WT1* mutation. It is therefore essential not only to isolate the critical WT genes, but also to develop systems with which to study the biological role of WT genes in normal nephrogenesis and how this is altered in WT development.

Conclusions and future prospects

It is now clear that WT development involves several, probably alternative, genetic pathways, but there is still an incomplete picture as to the identity of most of these genes, or the mechanisms by which they are controlled. However, the recent advances in human molecular genetics should soon enable a complete description of molecular defects in individual WTs. This should allow the stratification of WTs into good and poor prognosis groups, so that treatment can be targeted more effectively. It is especially important to be able to identify those patients who appear to have a good prognosis by conventional criteria, but who relapse and die when treated by what seemed the most appropriate regimen at the time of diagnosis.

The ultimate aim of all this work must be to develop effective, specific therapies that avoid the harmful side effects of present-day treatments. In view of the existing high cure rate for WT, any novel therapies will have to be demonstrably superior in all respects. A detailed knowledge of the molecular pathogenesis of WT is essential if we are to identify the biochemical targets for new methods of treatment.

Acknowledgements

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Further reading, resources and contacts

The American Cancer Society's Wilms' Tumor Resource Center provides information for patients and their families.

> http://www3.cancer.org/cancerinfo/load_cont.asp?ct=46

The Atlas of Genetics and Cytogenetics in Oncology and Haematology has searchable indices of genes, chromosomes and cancers.

> http://www.infobiogen.fr/services/chromcancer/

CancerWEB provides information on many cancers, including Wilms' tumour, for patients, health care professionals and researchers.

> http://www.graylab.ac.uk/cancerweb.html

The Children's Cancer Web includes information on Wilms' tumour and links to other resources.

> http://www.cancerindex.org/ccw/guide2w.htm

The Genetics of Cancer website has general interest sections as well as detailed discussion of inherited cancers, with case studies.

> http://www.cancergenetics.org/

The Genomic Imprinting Website provides information for researchers and students, including reviews and commentaries, and reports of conferences.

> http://www.geneimprint.com/

The Kidney Development Database describes genes involved in kidney development.

> http://golgi.ana.ed.ac.uk/kidhome.html

The Lancet supplement on cancer (Vol. 351, Supplement 2) contains several interesting articles on modern cancer research.

> http://www.thelancet.com

OncoLink has disease-specific pages and links for many types of cancer, aimed at patients and their families, health care professionals and the general public.

> http://oncolink.upenn.edu/cancernet/

The Pediatric Oncology Resource Center includes information on Wilms' tumour, provided by parents of children with cancer.

> http://www.acor.org/ped-onc

The Universal Mutation Database includes the *WT1* mutation database.

> http://www.umd.necker.fr/

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Features associated with this article

Figures

Figure 1. Gross pathology of Wilms' tumour (fig001kbb).
Figure 2. Kidney development and Wilms' tumourigenesis (fig002fbb).
Figure 3. Histopathology of normal fetal kidney and Wilms' tumour (fig003kbb).
Figure 4. Loss of heterozygosity (LOH) in Wilms' tumour (fig004kbb).
Figure 5. Structure of *WT1* (Wilms' tumour suppressor gene) and the proteins it encodes (fig005kbb).

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