The Wilms tumour gene, WT1, has been shown to play an important role in normal development of the kidney and gonad. Constitutional mutations predispose to both malformation and childhood tumours of these organs. There is a genotype-phenotype correlation, with missense mutations producing more severe abnormalities than complete absence of one allele. Two syndromes with early-onset protein-losing nephropathy can be distinguished according to the type of WT1 mutation. Children with apparently isolated diffuse mesangial sclerosis may also be WT1 mutation carriers. WT1 is not the major gene mutated in Wilms tumour, but has given important insights into the molecular genetics of this childhood embryonal kidney cancer. Recommendations for management of children suspected of having a WT1 mutation are discussed.

Key words Nephrotic syndrome · Diffuse mesangial sclerosis · Frasier syndrome · Denys-Drash syndrome · Nephrogenic rests

Introduction

WT1 was first identified as a tumour suppressor gene involved in Wilms tumour, an embryonal kidney cancer occurring mainly in early childhood. The development of Wilms tumour was originally postulated to follow a two-mutation model, whereby the first mutation could be either inherited or somatic, but the second mutation was always somatic and involved the same gene [1]. Subsequently, this model has been shown to be inadequate to fully explain the complex genetics of Wilms tumour, although it may be applicable in individual cases involving the WT1 gene [2, 3]. WT1 is one of the few cancer predisposition genes to have a highly tissue-specific expression pattern, and has become the paradigm illustrating that tumorigenesis and malformation of the same organ can be pleiotropic effects of mutation in a single gene. Although WT1 mutations account for only a minority of sporadic Wilms tumours, study of this fascinating protein and its associated malformation syndromes has led to important insights into the molecular basis of nephrogenesis.

WT1 in nephrogenesis

WT1 expression is at its highest during embryogenesis, mainly in the developing genitourinary system, but persists in the podocytes of adult kidney. A common feature of cell types that express WT1 is that they undergo a mesenchymal-epithelial transition (metanephric blastema, sex cord stromal cells and mesothelium), although there are exceptions, such as spinal cord [4]. WT1 expression is detectable at low levels in uncondensed metanephric mesenchyme, but increases dramatically in the condensates induced by interaction with the ureteric bud. Once differentiation of the nephron is apparent, WT1 expression becomes confined to the future podocyte layer of the renal glomerulus (Fig. 1). WT1 is essential for survival and proper differentiation of the metanephric mesenchyme, as shown by analysis of mice engineered to lack both copies of the WT1 gene (“knock out” mouse model) [5, 6]. These animals fail to develop either kidneys or gonads and there is massive apoptosis in the rudimentary metanephric mesenchyme, which also cannot be stimulated to differentiate in vitro in the presence of its normal inducers. WT1 is also expressed in the mesonephric glomeruli (Fig. 1) and analysis of wt1 null embryos shows that the caudal tubules fail to develop, but the more-rostral tubules are unaffected [6]. Since persistent mesonephric structures play a greater role in the development of male than female internal genitalia, this may explain the greater severity of genital phenotype in individuals with an XY genotype and WT1 mutation.
WT1 expression is at very low levels in the adult kidney and in situ hybridisation experiments suggest it is confined to the glomerulus. In a rat model of compensatory renal hypertrophy, WT1 expression increased in the remaining kidney, suggesting it may have a role in this process [7]. The immediate and short-lived nature of the increase suggests WT1 may be involved in signalling a need for renal growth. Since such growth is thought to occur via hypertrophy of existing nephrons rather than de novo nephron formation, it would be interesting to examine in which cell types WT1 is expressed during this process. Assuming it remains confined to the podocytes, this would confirm the importance of WT1 in maintenance of glomerular function of the mature kidney, as suggested by its involvement in Denys-Drash syndrome (DDS).

**The WT1 protein**

*WT1* encodes a zinc finger protein that can function as a transcription factor, but that is also capable of binding RNA [8]. WT1 mRNA is subject to alternative splicing at two sites, the whole of exon 5 and an additional three amino acids (KTS) in the linker separating zinc fingers 3 and 4. The use of an alternative initiation codon and the possibility of RNA editing increases the number of potential protein isoforms to 16; however, it is the functional effects of the KTS splice that are the best understood. Both WT1+KTS and WT1–KTS are capable of binding DNA, but with differing sequence specificities and affinities [9]. WT1–KTS isoforms are found in diffuse domains of transcriptional activity in the nucleus, whereas WT1+KTS isoforms are found in discrete speckles whose integrity depends on the presence of RNA and that contain some elements of the splicing machinery [10]. One possible mechanism for the functional effects of the KTS splice is to reduce DNA binding activity and favour other interactions of WT1, either with other proteins, through its N-terminal domain, or with RNA, through the altered zinc finger structure. However, a recent analysis suggests that the DNA- and RNA-binding domains of WT1 overlap and are mutually competitive, and that WT1–KTS binds both nucleic acids with a greater affinity than +KTS isoforms [11]. The ratio of +/– KTS splicing is almost constant between tissue types, whereas splicing of exon 5 varies and may account for tissue-specific functions of WT1 [12].

The regulatory pathways involving WT1 are as yet unclear, although several target genes have been suggested, including insulin-like growth factor 2 and some of its interacting proteins [2]. novH, a gene overexpressed in avian nephroblastoma and which may be involved in podo-

---

**Fig. 1** WT1 expression shown by in situ mRNA hybridisation during human embryogenesis. *Upper panels* are bright-field and *lower panels* dark-field illumination to emphasise the position of the silver grains. WT1 expression is seen in the developing podocyte layer of an 18-week gestation fetal kidney (*left-hand panel*) and in the gonadal ridge, mesonephric glomeruli, mesothelium and condensed metanephric mesenchyme around the branching ureteric bud tips in a 7-week gestation embryo (*right-hand panel*).