assigned to monthly or quarterly cyclic hormone therapy (2 mg of estradiol on days 1-78 and 1 mg of estradiol on days 79-84, with 1 mg of norethindrone on days 69-78) was stopped after 2-3 years of the planned 5 years of treatment because of an acceptably high rate of endometrial pathology (including one endometrial cancer) in the quarterly compared with the monthly cycle group (6.2% versus 0.8%; P = .004). Although this study used different hormones than those in the U.S. trial, it raises questions about the safety of quarterly cyclic therapy.

Current hormone replacement regimens might be safe, but are they optimal? For short-term treatment of menopausal symptoms, MPA appears safe and effective. However, growing evidence suggests that micronized progesterone might be a better progesterin for long-term use. Neither MPA nor progesterone added to estrogen alters the beneficial effect of estrogen in preventing loss of bone density (8), but evidence suggests that MPA negates more of the beneficial effects of estrogen on the cardiovascular system than micronized progesterone. MPA reduces the high-density lipoprotein-increasing effect of unopposed estrogen more than micronized progesterone does (9) and may reduce the beneficial effect on atherosclerosis (10) and on coronary vascular tone (11,12). The PEPI Trial found no increased risk of endometrial hyperplasia in women who were randomly assigned to cyclic therapy with daily conjugated estrogens plus micronized progesterone given at a dose of 200 mg daily for 10 days per month, but no studies of the effect of micronized progesterone on endometrial cancer risk have been published.

References


Malignant Origin of the Stromal Component of Wilms’ Tumor

K. Pritchard-Jones*

In this issue of the Journal, Zhuang et al. (1) provide molecular evidence for an important proof of principle, mainly that the various histologic components of a tumor arise from a common clone. This principle has long been accepted in the leukemic stem cell disorder chronic myeloid leukemia, where the Philadelphia chromosome can be found in morphologically normal hematopoietic elements (2). However, in solid tumors, this issue has been much more controversial. Authors talk about the “benign” stromal component of a tumor, yet this component may often make up the vastly bulk of the tumor. Is such an aberrantly proliferating stroma really benign?

By studying allelic loss in microdissected components, Zhuang et al. (1) show that, for the embryonal tumor nephroblastoma or Wilms’ tumor, the stroma is clearly part of the malignant process. Wilms’ tumor is renowned for its multipotent differentiation capabilities, sometimes bordering on teratomatous appearances. The classic triphasic Wilms’ tumor contains blastemal, epithelial, and stromal elements, all of which are believed to be differentiation products of the primitive renal stem cell; any one of these three components may dominate. The blastemal and epithelial elements usually mimic structures seen during normal nephrogenesis, whereas the stromal component can undergo heterologous differentiation along the lines of smooth or striated muscle, cartilage, bone, or adipose tissues. These diverse histologies raise the question of whether the various types of Wilms’ tumor arise from multipotent renal stem cells at various stages of commitment and how these relate to the

*Correspondence to: K. Pritchard-Jones, MRCP, Ph.D., Department of Pediatric Oncology, Institute of Cancer Research and Royal Marsden Hospital, Downs Rd., Sutton, Surrey, SM2 5PT, U.K.

© Oxford University Press
underlying molecular defect (3). Although many of the heterologous stromal components seen in Wilms’ tumor are potential differentiation products of metanephric mesenchyme, it is probable that neural elements, such as ganglion cells, represent entrapped normal structures rather than an origin in metanephric mesenchyme [discussed in (4)].

Wilms’ tumor is part of a broader family of mainly embryonal tumors that may show diverse histologic components, for example, hepatoblastoma, desmoplastic small round-cell tumor, and synovial sarcoma. Specific genetic alterations that define the tumor cell are known for each of these tumor types. However, it has not been proven formally by microdissection or in situ hybridization that both components of a biphasic synovial sarcoma, for example, contain its characteristic t(X;18). Rather, it is assumed that they have a common origin because diverse histologic subtypes contain the same chimeric messenger RNA.

Wilms’ tumor is one of a small group of tumors showing direct transition of mesenchyme into epithelium. The results reported by Zhuang et al. (1) cannot, therefore, be directly applied to most common adult epithelial cancers, where the stromal and epithelial components have different developmental origins. Here, the dogma is that the stromal component represents the remnants of the normal mesenchyme, which may show aberrant proliferation in response to the adjacent malignant epithelium (5). Indeed, in these tumors, immunohistochemical analyses of oncprotein expression, particularly p53, would support the viewpoint that stromal and epithelial components are of distinct origins. However, one could argue that this phenotype simply reflects the arrested differentiation status of the cell, as is seen for WT1 expression in Wilms’ tumors (4,6). Direct molecular evidence that the stroma is truly nonmalignant comes from in situ studies of c-erbB-2 gene amplification in breast cancer, where it is restricted to malignant epithelium (7).

Although Zhuang et al. show a common 11p allelic loss, they have not addressed the issue of whether this loss is sufficient for Wilms’ tumorigenesis. It is possible that the different histologic components have undergone further different genetic changes allowing evolution to malignancy. One could argue that the stromal component, although sharing the same allelic loss, is relatively benign, whereas the epithelial component is malignant. Certainly this has been seen for relaxation of imprinting (the functional equivalent of allelic loss and reduplication) of the IGF2 gene, which can be detected both in normal tissues of children with overgrowth syndromes and in sporadic Wilms’ tumors (8). A similar question has been addressed as to whether nephrogenic rests are true precursor lesions for Wilms’ tumor. One study (9) has questioned whether two “hits” at the WT1 locus are either sufficient or always necessary for Wilms’ tumorigenesis. In two cases, both the nephrogenic rest and the associated Wilms’ tumor shared the same underlying molecular abnormality, in one case homozygous and in the other heterozygous WT1 mutation. These findings emphasize that the molecular genetics of Wilms’ tumor is more complex than was first suggested by the two-hit hypothesis of Knudson (10), even though some cases involving the WT1 gene have been shown to conform to this model.

The findings of Zhuang et al. do not add to current knowledge about the genetic complexity of Wilms’ tumor, with at least seven genes now implicated in its development (11). It is well established that, although 30%-50% of Wilms’ tumor show 11p allelic loss, the vast majority of this loss does not implicate mutation of the WT1 gene at 11p13. More likely, such allelic loss reflects alterations in genes at 11p15, known to contain a second Wilms’ tumor locus. Although only 5%-10% of sporadic Wilms’ tumors have WT1 gene mutations, the contribution of WT1 to tumorigenesis through its disregulated expression may be much greater than this (6). Zhuang et al. confirm many previous reports that cell types expressing the WT1 gene in Wilms’ tumors mimic the pattern seen during normal nephrogenesis; that is, WT1 expression is high in epithelial and blastemal components but extremely low or absent in the stroma (4). To date, no ectopic WT1 expression has been described in the various histologic components of Wilms’ tumors. This situation implies that the factors regulating WT1 expression relative to morphologic differentiation are relatively preserved. However, such differentiation can occur in the absence of WT1, inasmuch as Wilms’ tumors with complete deletion of the WT1 gene are reported to have classic triphasic histology. The continued high expression of WT1 in primitive components of Wilms’ tumors may contribute to the uncontrolled proliferation of these cells. WT1 has been suggested to have roles in apoptosis and cell cycle control (12). Whatever the molecular mechanism causing the differentiation block of the metanephric mesenchymal cell is, whether it be a mutation in WT1 or other genes, the overexpression of WT1 may be contributing to tumorigenesis, even if the gene is wild type. In some cases, very high levels of WT1 expression may reflect an underlying WT1 gene mutation with failure of the postulated autoregulation of WT1, as has been suggested for acute leukemias (13).

Analyses of the histology of Wilms’ tumors occurring in patients with the Denys-Drash syndrome (caused by germline WT1 mutation) and of sporadic tumors with WT1 mutation have shown that stromal differentiation, particularly along muscle lines, tends to predominate (14). This observation suggests that the normal role of WT1 may be to suppress muscle differentiation in the primitive metanephric mesenchymal cell; when WT1 is mutant, this suppression is released, allowing aberrant myogenic differentiation to proceed. In the classic triphasic Wilms’ tumor, however, the continued high expression of WT1 will usually be wild type and probably represents an arrested differentiation stage. Identifying the mutant genes that are responsible for this developmental arrest and how they fit into the nephrogenic pathway and have an impact on WT1 control are the key issues for a further understanding of Wilms’ tumorigenesis.

References

(4) Pritchard-Jones K, Fleming S. Cell types expressing the Wilms’ tumor gene


