Relationship of Histology of Wilms' Tumor to Growth Characteristics of Nude Mouse Heterotransplants

Herman Yeger, Reuben Baumal, Gladys Pawlin, and M. James Phillips

Department of Pathology, The Hospital for Sick Children, Toronto, Ontario, Canada M5G 1X8

ABSTRACT

Eighteen Wilms' tumors (WIT), including classical triphasic WIT (blastema, tubules, and mesenchyme) and WIT variants (blastema and tubules, monomorphous tubules, multiloculated cysts, rhabdomyomatous WIT, and clear cell sarcoma), were heterotransplanted in nude mice. Ten (56%) tumors grew and were serially passaged. With two exceptions, the histology of the surgically resected tumors and heterotransplants was found to be similar. Tumors showing a prominent blastema component grew rapidly, whereas those with tubular epithelial or mesenchymal differentiation grew more slowly. Tumors injected s.c. consisted almost entirely of blastema, while tumors injected i.p. consisted of blastema with large areas of tubular epithelium. These results demonstrate that nude mouse heterotransplants of WIT closely resemble the surgically resected tumors from which they derive, that growth rates of WIT heterotransplants depend on the identity of the tumor cells, and that differentiation of WIT heterotransplants can be modulated, depending on the route of administration of tumor cells.

INTRODUCTION

WIT or nephroblastomas account for approximately 10% of solid tumors in pediatric patients. Classically, they consist of blastema, tubules, and mesenchyme, the blastema serving as the progenitor for the other 2 elements and for structures which develop from them (2, 10). Considerable information is available concerning the histological characterization of classical WIT and WIT which have adopted a variant appearance (blastema and tubules, tubules only, rhabdomyomatous, or clear cell sarcoma) (2, 3, 8, 13). However, the factors which regulate tumor cell differentiation are largely unknown, since it has not been possible to isolate pure populations of the various cell types in this tumor by in vitro cloning methods (4, 6). Greater success has been achieved by propagating WIT in nude mice (11, 12, 14). Some authors have looked for a possible resemblance between such heterotransplants and the original surgically resected WIT. However, there are no data on the relationship between the type of tumor cells in the surgical specimens and growth of the heterotransplants or on whether growth of the different cell types in WIT heterotransplants depends on their route of administration to the nude mice. As a substitute for in vitro study of tumor cell differentiation of WIT, we characterized a group of 18 WIT that had been heterotransplanted into nude mice in terms of their morphology and growth characteristics. We found that nude mouse heterotransplants closely resembled surgically resected WIT, the degree of tumor cell differentiation was correlated with the growth characteristics of the nude mouse heterotransplants, and the morphology of nude mouse heterotransplants depended on the route of tumor cell administration.

MATERIALS AND METHODS

Morphological Studies of Surgically Resected and Heterotransplanted WIT. Tumors were obtained from 18 consecutive patients undergoing treatment of WIT by surgical resection, and samples were taken for LM, TEM, and nude mouse heterotransplantation. For LM, tissues were fixed in 10% neutral buffered formalin and embedded in paraffin. Sections were stained with hematoxylin-eosin. For TEM, tissues were fixed in phosphata-buffered 1% glutaraldehyde and 4% formaldehyde, processed, and examined on a Phillips 300 electron microscope.

Nude Mouse Heterotransplantation of WIT and Assessment of Growth Characteristics. WIT were prepared for heterotransplantation by finely mincing tumor fragments in α-medium (Flow Laboratories, Mississauga, Ontario) and injecting 100 μl of packed tissue fragments s.c. (using a 16-gauge needle) into the flanks of 4- to 6-week-old male BALB/c nude mice housed under germ-free conditions. Alternatively, tumors were gently pressed through a 100-μm nylon mesh screen (Nitex Tedco, Inc., Scarborough, Ontario), and single cells and aggregates were injected as above, using a 20-gauge needle. In addition to s.c. injection, 1 × 106 tumor cells per mouse were injected i.p., and the tumors that grew were compared with those arising after s.c. injection. Mice were examined weekly for tumor growth. Tumor nodules were measured in 2 dimensions using calipers, and tumor volumes were calculated according to Attia and Weiss (1). Latent period was defined as the time from tumor cell injection until a volume of 50 cu mm was reached. Relative growth rate (cm mm/week) was defined as the increase in tumor volume between a base volume of 50 cu mm and the final tumor volume achieved.

RESULTS

Surgically Resected WIT. Classical and variant types of WIT were obtained following surgical resection (Tables 1 and 2). Eight tumors were classical WIT (WIT-1, 6, 7, 12, 13, 15, 18, and 21) consisting of blastema, tubules, and mesenchyme (Fig. 1). The blastema was made up of small, closely packed, round, ovoid, or elongated cells with scanty cytoplasm and hyperchromatic nuclei. The tubules consisted of cuboidal or columnar epithelial cells and the mesenchymal component of spindle cells, loosely arranged in a myxoid or collagenous stroma. Of the 7 variant WIT, 3 tumors (WIT-2, 17, and 19) consisted only of blastema and tubules. WIT-5 contained blastema and tubules and a prominent rhabdomyomatous component within the mesenchyme (Fig. 2). WIT-9 contained blastema, tubules which formed multiloculated cysts, and mesenchyme (Fig. 3). WIT-10 was a monomorphic tumor, consisting of cords of cuboidal to columnar epithelium, generally organized into tubule (Fig. 4). WIT-11 was...
a clear cell sarcoma and contained only scattered tubules. Specimens from 3 tumors (WIT-3, 8, and 16), which were obtained after chemotherapy, showed extensive regression with large areas of necrosis, fibrosis, and no viable tumor tissue.

TEM examination of the surgically resected WIT and nude mouse heterotransplants showed close similarities. In the heterotransplants, the blastema consisted of small, round cells which lay close together and had a high nucleocytoplasmic ratio. Nuclei were irregular with prominent nucleoli, and the cytoplasm was scanty, with few mitochondria and sparse Golgi complex, endoplasmic reticulum, ribosomes, and filaments. There were few junctional contacts between cells. Intercellular electron-dense deposits were present (Fig. 5a), and their proximity to cells suggested an origin in blastema, even though blastema did not show ultrastructural features of secretion.

In contrast to blastema, tubules and mesenchyme of WIT exhibited ultrastructural features of differentiation. By TEM, tubular epithelial cells were cuboidal to columnar and had a low nucleocytoplasmic ratio. Their cytoplasm contained a Golgi complex, prominent rough endoplasmic reticulum, and significant numbers of tonofilaments, both as separate bundles and in association with desmosomes (Figs. 5b and 6). Tubular epithelial cells, whose basal aspects were surrounded by a basement membrane, showed frequent interdigitations on their lateral margins and were arranged so that their apices circumscribed a lumen (Fig. 5b). Apical microvilli were sparse, while luminal contents consisted of proteinaceous material and scattered vesicles. In contrast, cystic epithelial cells (Fig. 7a) often exhibited numerous stubby microvilli. These cells were connected by desmosomes and rested on a thickened basement membrane. Basally located stress fibers were also seen (Fig. 7b).

By TEM, the mesenchyme of WIT contained spindle-shaped fibroblasts and a fibrillar extracellular matrix. In the rhabdomyomatous tumor (WIT-5), the spindle-shaped cells in the mesenchyme contained myofibrils which, although not as highly organized as in skeletal muscle, demonstrated Z-bands (Fig. 8).

**Heterotransplantation of WIT in Nude Mice and Histology of First-Generation WIT Heterotransplants.** Of 18 WIT which were heterotransplanted in nude mice, 10 (56%) grew (Table 2) and were serially passaged, while 8 (44%) failed to grow (Table 1). Tumors grew when implanted s.c. into the flanks of nude mice and in other s.c. sites, although in the latter instances they were not as large. In general, they were multinodded, vascularized, and enclosed by a thin connective tissue capsule. Occasionally, fat, nervous tissue, blood vessels, or muscle of host origin adhered to the heterotransplants which otherwise closely resembled the surgically resected WIT, except for differences in the relative amount of the different cell types present. The 6 classical WIT heterotransplants (WIT-1, 6, 7, 12, 13, and 21) showed a prominent blastema component and variable numbers of tubules (Fig. 9). In WIT-5 heterotransplants, there were only occasional

### Table 1

<table>
<thead>
<tr>
<th>WIT</th>
<th>Histology of surgical specimens</th>
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<tr>
<td>2</td>
<td>Blastema, tubules, extensive nephroblastomatosis</td>
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<tr>
<td>3</td>
<td>Treated tumor showing only fibrotic changes, no viable tumor present</td>
</tr>
<tr>
<td>8</td>
<td>Treated tumor showing only fibrotic changes, no viable tumor present</td>
</tr>
<tr>
<td>15</td>
<td>Blastema, mesenchymal; extensive nephroblastomatosis</td>
</tr>
<tr>
<td>16</td>
<td>Treated tumor showing only fibrotic changes, no viable tumor present</td>
</tr>
<tr>
<td>17</td>
<td>Blastema, focal tubular differentiation</td>
</tr>
<tr>
<td>18</td>
<td>Blastema, tubules, mesenchyme</td>
</tr>
<tr>
<td>19</td>
<td>Blastema, extensive tubular differentiation, and nephroblastomatosis</td>
</tr>
</tbody>
</table>

*WIT-4, 14, and 20 have not been included in the present study.

### Table 2

<table>
<thead>
<tr>
<th>Histology</th>
<th>WIT</th>
<th>Surgical specimen</th>
<th>Nude mouse heterotransplant</th>
<th>No. of mice developing tumors (n = 6)</th>
<th>Latent period (wk)</th>
<th>Relative growth rate (mm/wk)</th>
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</thead>
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<tr>
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<td>Few tubules, mesenchyme with marked rhabdomyosarcomatous change</td>
<td>5 (82)</td>
<td>3</td>
<td>53</td>
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<tr>
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<td>6</td>
<td>Blastema, tubules, mesenchyme</td>
<td>Blastema, tubules</td>
<td>6 (100)</td>
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<td>441</td>
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<tr>
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<td>Blastema, tubules, mesenchyme</td>
<td>Blastema, tubules</td>
<td>2 (33)</td>
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<tr>
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<td>Blastema, tubules forming multicellular cyst, mesenchyme</td>
<td>Tubules forming multicellular cysts, mesenchyme</td>
<td>5 (82)</td>
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<td>15</td>
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<tr>
<td>1</td>
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<td>Monomorphic tubules</td>
<td>Monomorphic tubular</td>
<td>6 (100)</td>
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<td>12</td>
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<tr>
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<td>11</td>
<td>Clear cell sarcoma, few tubules</td>
<td>Clear cell sarcoma, no tubules</td>
<td>2 (33)</td>
<td>24</td>
<td>78</td>
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<tr>
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<tr>
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<td>150</td>
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<tr>
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<td>289</td>
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* The values for latent period and relative growth rate shown represent means obtained from the number of nude mice that developed tumors.

a Numbers in parentheses are percentage of mice developing tumors in comparison to total number of mice.

b Only 3 mice were given injections.

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Charts 1 to 8. Growth curves of WIT nude mouse heterotransplants. Tumor volumes were measured weekly, and growth curves were plotted. Individual mice in each group are designated A to F. Heterotransplants containing a significant amount of blastema (e.g., WIT-1, 6, and 7) (Charts 1, 3, and 4) showed rapid growth rates, while heterotransplants having more differentiated features (e.g., WIT-5, 9, and 10) (Charts 2, 5, and 6) grew slowly and attained a smaller final volume. WIT-11 (Chart 7), the clear cell sarcoma, showed a low growth rate. In WIT-12 (bilateral tumor), the main tumor grew rapidly, while the contralateral nodule showed a variable growth rate (Chart 8).

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Incidence of Tumors and Growth Characteristics of First-Generation WIT Heterotransplants. The 6 classical WIT (WIT-1, 6, 7, 12, 13, and 21) were each implanted s.c. into 6 mice and took in 2 to 6 of the mice (Table 2). The heterotransplants demonstrated variable latent periods (2 to 16 weeks) and rapid growth rates (150 to 476 cu mm/week) (Charts 1 to 8). WIT-12 heterotransplants, derived from a case of bilateral WIT, showed a relatively short latent period (7 weeks); there was a high growth rate (350 cu mm/week) in the right tumor and a highly variable growth pattern in the left (Chart 8). Of the variant WIT, WIT-5 showed a short latent period (3 weeks) and an intermediate growth rate (53 cu mm/week) (Chart 2). WIT-9 had an intermediate latent period (9 weeks) and an extremely low growth rate (15 cu mm/week) (Chart 5). WIT-10 showed a very short latent period (3 weeks) and a slow growth rate (12 cu mm/week) which leveled off after 12 weeks (Chart 6). WIT-11 showed a very long latent period (24 weeks) and an intermediate growth rate (78 cu mm/week) (Chart 7).

Growth and Histology of Second-Generation WIT-1 Heterotransplants. Second-generation WIT-1 heterotransplants demonstrated a decrease in their latent periods and more similar growth rates. However, differences were found in the growth and histology of second-generation heterotransplants of WIT-1C and 1E. WIT-1C, a to d, showed little variation in their latent periods (2 to 5 weeks), while WIT-1E, a to f, showed slower and more variable latent periods (8 to 32 weeks). The growth rate of
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WIT-9

WIT-10

WIT-11

WIT-12

WIT-1C, a to d (588 cu mm/week), was almost twice that of WIT-1E, a to f (259 cu mm/week) (Charts 9 and 10). By LM, WIT-1C, a to d, consisted of blastema with few tubules, and this persisted in further passages. In contrast, WIT-1E, a to f, showed a prominent tubular epithelial differentiation pattern (Figs. 13 and 14). Thus, the presence of extensive tubular differentiation correlated with a variable latent period and a significantly decreased growth rate.

Effect of Route of Tumor Cell Administration on Histology and Growth of WIT Heterotransplants. The effect of route of tumor cell administration on histology was assessed using the third-generation WIT-1Ca heterotransplant. One × 10⁶ tumor cells were injected s.c. and i.p. By LM, s.c. tumors contained blastema and no tubules (Fig. 15). In contrast, i.p. tumors showed blastema and zones of tubular epithelial differentiation, especially in a subcapsular position (Fig. 16). The latent period for the i.p. tumors could not be determined; however, measurement of tumor volumes as an index of growth showed that these tumors increased in volume as fast as the s.c. tumors.

DISCUSSION

We succeeded in heterotransplanting 10 of 18 surgically resected WIT in nude mice and achieved growth of both classical WIT and several types of variant tumors. Why growth failed to occur in 8 cases was not readily apparent but could be partially explained by the histology of the surgically resected tumors. For example, WIT-2, 15, and 19 either contained an extensive nephroblastomatosis component of a benign nature or were highly differentiated along epithelial lines. These features may have led to growth retardation. On the other hand, WIT-17 and 18 were classical tumors. Since 6 other classical WIT (1, 6, 7, 12, 13, and 21) grew in nude mice, insufficient inoculum or host influences may be responsible for the failure of WIT-17 and WIT-18 to grow. In the remaining 3 cases which failed to grow (WIT-3, 8, and 16), the tumors were surgically resected after chemotherapy. This may account for the extensive fibrosis and absence of viable tissue seen in these tumors and the fact that heterotransplantation in nude mice was unsuccessful. In one of the WIT variants which did grow (WIT-11, the clear cell sarcoma), only a few
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tubules were seen in the original tumor. Since nude mouse heterotransplants of WIT-11 did not contain tubules, these were considered to be trapped normal elements rather than part of the tumor. WIT-12 and 21 were from patients with bilateral tumors, both of which grew in nude mice and showed the classical features of blastema, tubules, and mesenchyme.

Of the 10 WIT (6 classical and 4 variant) which grew successfully in nude mice, there was no apparent relationship between tumor histology and latent period. However, the classical WIT showed more rapid growth rates (150 to 476 cu mm/week; mean, 317.5 cu mm/week) than did the variant WIT (12 to 78 cu mm/week; mean, 39.5 cu mm/week). For both classical and variant WIT, there was a close resemblance between surgically resected tumors and nude mouse heterotransplants. Nevertheless, in 2 of the tumors, a single tissue component predominated in the nude mouse heterotransplants (i.e., skeletal muscle in WIT-5 and cystic tubular epithelium in WIT-9). This predominance may be explained in 4 ways. (a) Most surgically resected specimens of WIT are large and consist of several hundred cu cm of tissue. Such tumors may show unequal distribution of the different cell types which are present, so that a tumor sample of the size used for heterotransplantation may not contain all of the tumor cell types. Consequently, the tissue used for injection of nude mice may not be representative of the entire tumor. (b) Different blastema cell populations may show heterogeneity in terms of growth rates, with the result that certain subpopulations of blastema may undergo rapid proliferation when hetero-transplanted. (c) Microenvironmental influences in the s.c. injection site may have favored growth of one cell type over another. (d) Selection may have occurred during tissue preparation, so that some cell types were eliminated and others enriched.

The histogenesis of WIT is not clear, although an origin from metanephric mesenchyme is most likely (2, 10). It is also probable that blastema cells give rise to tubular epithelial and mesenchymal elements (2, 10). Since none of the nude mouse heterotransplants consisted only of blastema and mesenchyme, it is reasonable to speculate that blastema, or at least a subtraction of it, is involved in tubule formation. However, the possibility exists that, in the case of the monomorphic tubular variant (WIT-10), the progenitor cell was a more differentiated type, distinct from blastema.

The presence of anaplasia in the blastema of WIT has been correlated with a high degree of malignancy and a poor prognosis (3). Anaplasia may also indicate that blastema cells contain genomic changes which might favor tumor growth in nude mice. WIT-7 exhibited anaplasia in blastema cells within the original tumor and grew well in nude mice. However, WIT-1 and WIT-6, which did not display anaplasia, were found to take frequently and have fast growth rates in nude mice. Therefore, there is no evidence that anaplasia is necessary for successful growth of WIT in nude mice. The fact that tumors with a prominent blastema component (WIT-1, 6, 7, 12, 13, and 21) produced larger masses and had faster growth rates in nude mice than did the monomorphic tubular variant (WIT-10) emphasizes the potential aggressive and malignant nature of blastema.

It is apparent from work reported previously (12) that in WIT there is progressive loss of differentiated tubules with subsequent passage of tumors in nude mice. However, the degree of differentiation in first-generation nude mouse heterotransplants (e.g., WIT-IC versus WIT-IE) in our study was retained in second-generation heterotransplants. This finding suggests that WIT contain subpopulations of blastema which differ in their differentiation capacities. An inverse correlation between growth rate and the degree of tubular differentiation was found with the second-generation WIT heterotransplants. A considerably longer cell cycle and population doubling time in tubular epithelium may account for this finding.

It has also been proposed that a favorable clinical prognosis in WIT is correlated with greater tubular differentiation (5) or with the presence of increased numbers of differentiated cells (3). The pattern of slow growth and small size of the tubular types of tumor (WIT-9, WIT-10) in nude mice supports this suggestion. Moreover, the data of Neely et al. (11) indicate that tumor growth in nude mice implies an unfavorable clinical prognosis. Of 9 WIT heterotransplanted in nude mice, 3 took and were carried from 6 to 11 passages (11). Although not discussed, these were most likely blastematous histologically and had the worst outcome.

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In transplantation of human tumor cells in nude mice, the route of administration influences the degree of acceptance of the heterografts (9) and the latent period (7). However, little is known about the effect of different implantation sites on tumor cell differentiation. It would appear from our studies that the peritoneal environment supplies factors which either promote tubular differentiation of WIT or allow selection of a subpopulation of cells committed to tubular differentiation. Whether all blastemal tumors can be modulated in this manner is unknown.

Our study differs from previous studies in which human tumors have been heterotransplanted in nude mice because it compares a wide spectrum of classical and variant types of WIT with respect to their histology and growth rates in nude mice. Of importance was the finding of tubular differentiation in i.p. heterotransplants of WIT, a route of tumor implantation which is rarely used. Moreover, the absence of any mesenchymal differentiation in i.p. heterotransplants supports the view that it is the blastema which gives rise to tubular epithelium. In this connection, it would be important to determine whether the i.p. environment would support the growth and differentiation of mesenchymal variants of WIT.

In summary, 10 classical and variant WIT were successfully heterotransplanted in nude mice, and the relationship between the histology and growth rates of the heterotransplants was determined. The nude mouse heterotransplants showed close morphological similarities to the surgically resected tumors, although some variation occurred in the relative amounts of the different cell types present. One of the nude mouse heterotransplants (WIT-1) was studied in greater detail, in terms of the histology and growth characteristics of second-generation heterotransplants and the influence of the route of tumor cell administration on histology and growth of third-generation heterotransplants. Our results suggest that the system of heterotransplanting WIT in nude mice may be a satisfactory in vivo model for studying the regulation of tumor cell differentiation. Such a study would require markers for delineating the various cell types in WIT. This subject forms the basis of the next paper.

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REFERENCES
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Figs. 1 to 4. Histology of surgically resected WIT. Fig. 1. WIT-1, consisting of a mixture of blastema (B), tubules (T), and mesenchyme (M). H & E, × 100. Fig. 2. WIT-5, consisting of blastema, tubules, and mesenchyme containing striated muscle cells (arrows). H & E, × 100. Inset, cross striations in one of these muscle cells. H & E, × 400. Fig. 3. WIT-9 consisting of blastema (B), and mesenchyme (M), and tubules (T) lined by cuboidal epithelium and forming multiloculated cysts. H & E, × 100. Fig. 4. WIT-10, consisting of sheets of tubules (T). There is sparse mesenchyme and blastema. H & E, × 100.
Figs. 5 to 8. Ultrastructural characteristics of WIT heterotransplants. Fig. 5. WIT-1, showing a blastema cell connected by primitive junctions (arrowhead) and containing few cytoplasmic organelles, with intercellular dense deposits seen occasionally (arrow) (a) and tubular cells with a low nucleocytoplasmic ratio, ovoid nuclei, and large numbers of cytoplasmic organelles (b). Desmosomes and intermediate filaments are prominent features in these cells (arrow). Tubular cells rest on a basement membrane (arrowheads) and are connected by complex junctions. × 3,600. Fig. 6. WIT-10, showing columnar epithelial cells forming tubules. In a, intermediate filaments (arrow) are present in the cytoplasm. × 7,750. In b, a basement membrane (arrowheads) subtends these cells. × 11,500. Fig. 7. WIT-9, showing that the epithelial cells lining the multiloculated cysts have stubby, apical microvilli. × 11,500. Inset, thick basement membrane (arrowheads). × 7,750. The intervening stroma consists of fibroblasts. Fig. 8. WIT-5, showing spindle cells embedded in a collagenous matrix. Many of the cells show striated muscle features, such as Z bands (arrow) and basal laminae (arrowhead). × 11,500.
Figs. 9 to 12. Histology of WIT nude mouse heterotransplants. Fig. 9. WIT-1, showing tightly packed blastema cells (B), tubules (T), and a small mesenchymal component (M) of mouse origin. H & E, x 100. Fig. 10. WIT-5, showing rhabdomyomatous cells having a sarcomatous appearance (arrows) in the mesenchyme. A few tubules (T) can be seen. H & E, x 100. Fig. 11. WIT-9, showing multiloculated cysts embedded in a fibrous stroma. The cysts are lined by cuboidal epithelium resting on a basement membrane (arrow). H & E, x 100. Fig. 12. WIT-10, showing sheets of columnar epithelial cells arranged into tubules (T). Few blastema cells (B) and a small mesenchymal component (M) are also present. H & E, x 100.

Figs. 13 and 14. Histology of WIT-1 second-generation nude mouse heterotransplants. Fig. 13. WIT-1C second-generation heterotransplant (WIT-1Cc), showing only blastema cells (B) and no tubular component. H & E, x 200. Fig. 14. WIT-1E second-generation heterotransplant (WIT-1Ea), showing a marked amount of tubular epithelial differentiation (T). H & E, x 200.
Figs. 15 and 16. Histology of WIT-1Ca third-generation heterotransplant grown s.c. and i.p. Fig. 15. Tumor s.c. consisting only of blastema cells (B), interspersed with host mesenchyme (M). H & E, × 200. Fig. 16. Tumor i.p. consisting of large zones of tubular epithelial cells (T) located peripherally, with blastema in the central part of the tumor. H & E, × 200.
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