The Evolving Story of Renal Translocation Carcinomas

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The majority of renal cell carcinomas (RCCs) in adults are readily classified into one of several well-defined categories under the 2004 World Health Organization classification, a classification based on morphologic features and genetics.1 The types of RCC include clear cell (conventional), papillary, chromophobe, collecting duct, and the recently described mucinous tubular and spindle cell carcinoma. Many of these morphologically defined entities are associated with specific genetic alterations (ie, chromosome 3p deletion in clear cell RCC and trisomy of chromosome 7 and 17 in papillary RCC), further validating the classification. Only approximately 5% of adult RCCs remain unclassifiable. In contrast, pediatric RCCs have been more difficult to categorize. Early studies recognized that pediatric RCCs were more frequently papillary than their adult counterparts, and subtle morphologic differences were noted.2 Dr J. Bruce Beckwith (personal communication) often noted that pediatric RCCs were more frequently negative for cytokeratins by immunohistochemical analysis compared with adult RCCs. However, the biologic basis for these distinctions remained unclear.

In the past 5 years, it has become apparent that approximately one third of pediatric RCCs belong to the newly recognized family of Xp11 translocation RCCs.3 These RCCs are characterized by various chromosome translocations, all of which involve a breakpoint at Xp11.2 and all of which result in fusions involving the TFE3 transcription factor gene that maps to this locus. Five distinct gene fusions involving TFE3 have been characterized (Table I).4-6 These include an ASPL-TFE3 gene fusion identical to the gene fusion first identified in alveolar soft part sarcoma (ASPS),7 resulting from a t(X;17)(p11.2;q25) chromosome translocation. Xp11 translocation RCCs typically have a nested to papillary architecture and are composed of clear cells with frequent associated psammomatous calcifications. Tumors with different specific gene fusions may have slightly different clinical manifestations and morphologic features. For example, the RCCs associated with the ASPL-TFE3 gene fusion (so-called ASPL-TFE3 RCC) frequently present at an advanced stage and have voluminous cytoplasm with extensive psammomatous calcifications. In contrast with clear cell and papillary RCCs usually seen in adults, the Xp11 translocation RCCs underexpress vimentin and cytokeratins on immunohistochemical analysis, the latter fact providing at least part of the explanation for Dr Beckwith’s astute observations more than a decade ago. Occasional Xp11 translocation RCCs express melanocytic markers by immunohistochemical analysis. Ultrastructurally, despite the unusual immunophenotype, these neoplasms show predominantly epithelial features.

Aside from molecular genetic analysis, the most sensitive and specific assay for the Xp11 translocation RCCs is nuclear labeling with antibodies to the retained C-terminal portion of the TFE3 protein.8 TFE3 protein is expressed ubiquitously, but, like most transcription factors, its levels are tightly regulated so that it is undetectable by routine immunohistochemical analysis in normal tissues and almost all other neoplasms. All TFE3 fusion proteins retain the C-terminal portion of TFE3, including its leucine zipper dimerization domain, nuclear localization signal, and DNA binding domain. It is likely that the genes fused 5’ to TFE3 contribute strong promoters that cause overexpression of the TFE3 fusion protein such that it now becomes detectable by immunohistochemical analysis. Therefore, TFE3 immunohistochemical analysis allows these tumors to be delineated in archival paraffin-embedded material when frozen tissue samples for molecular analysis are not available.
Another variant of RCC harboring a t(6;11)(p21;q12) translocation was described in 2001.9 Morphologically, these neoplasms frequently have nested architecture and are composed of a biphasic population of larger and smaller epithelioid cells, the latter typically clustered around hyaline basement membrane material. However, individual cases may be indistinguishable morphologically from the Xp11 translocation RCC. It is interesting that although these neoplasms show predominantly epithelial features ultrastructurally, they usually are negative for cytokeratin but consistently express melanocytic markers HMB-45 and MelanA on immunohistochemical analysis.

Recently, the gene fusion that results from the t(6;11) translocation has been characterized. The translocation fuses the Alpha gene, an intronless gene of unknown function at 11q12, with the first intron of the TFEB transcription factor gene at 6p21.10,11 Importantly, TFEB is a member of the same MITFTFE family of transcription factors as TFE3; the other 2 members of the subfamily are MITF and TFE3. All of the members of this transcription factor family share a common DNA binding domain, bind the same DNA sequences, homodimerize and heterodimerize in all combinations, and activate transcription of similar downstream target genes. The breakpoint on TFEB is just upstream of its initiation ATG codon, which results in retention of the entire TFEB coding region in the gene fusion. Although the Alpha promoter drives expression of the fusion gene, the Alpha gene does not contribute to the open reading frame. Therefore, the consequence of the Alpha-TFEB fusion is dysregulated expression of the normal full-length TFEB protein. Along these lines, we have found that the t(6;11) RCCs demonstrate specific nuclear labeling for TFEB protein by immunohistochemical analysis, whereas other neoplasms and normal tissues do not.12 Hence, nuclear labeling for TFEB is a sensitive and specific diagnostic marker for this neoplasm with a TFEB gene fusion, just as nuclear labeling for TFE3 is a sensitive and specific diagnostic marker for neoplasms bearing TFE3 gene fusions, namely ASPS and Xp11 translocation RCCs. Because the Xp11 translocation RCCs and the t(6;11) RCCs share clinical, morphologic, immunohistochemical, and genetic features, we have proposed that these neoplasms be linked together as part of a larger family of MITF/TFE renal translocation carcinomas.

In this issue of the Journal, the study by Ramphal et al13 adds to the body of knowledge on these unusual neoplasms. The authors studied 13 consecutive pediatric RCCs from their institution, 11 of which had predominantly papillary morphologic features. Of the 13 RCCs, 7 (54%) demonstrated nuclear labeling for TFE3 protein and, hence, can be assumed to belong to the Xp11 translocation RCC family. Of the 7 cases, 4 were confirmed by cytogenetics to have the ASPL-TFE3 gene fusion. None of the neoplasms demonstrated labeling for TFEB protein. It is interesting that 5 neoplasms demonstrated nuclear labeling for MITF, 3 of which were Xp11 translocation RCCs. The authors suggest that some of these 5 neoplasms may harbor genetic alterations involving MITF.

The study by Ramphal et al13 raises several interesting points about this family of neoplasms. First, the high proportion of pediatric RCCs that harbor Xp11 translocations is reaffirmed; although the percentage in the study is higher than the 33% reported in the literature, the small patient population may account for this discrepancy. Second, an important clinical history is provided: 1 patient in the series (case 10) received chemotherapy for ganglioneuroblastoma 5 years before developing her genetically confirmed ASPL-TFE3 RCC. We have recently identified an association of previous chemotherapy with the development of translocation RCC; in our files, approximately 10% to 15% of translocation RCCs are associated with previous exposure to cytotoxic chemotherapy.14 Hence, we believe that translocation RCCs should be added to the list of chemotherapy-associated secondary neoplasms in children (along with acute leukemias, soft tissue sarcomas, and malignant gliomas), and the study by Ramphal et al13 adds data to support this assertion. Third, the absence of TFEB immunoreactivity in any of the neoplasms suggests that t(6;11) RCCs are less common than the Xp11 translocation RCCs, although Ramphal et al13 do not specify the control tissue used for this assay. To our knowledge, only a cytogenetically or molecularly verified t(6;11) RCC is a suitable control, a fact that limits the number of laboratories that can perform this assay. Finally, the possibility of MITF alterations in pediatric RCCs is suggested and is intriguing.

Because members of the MITF/TFE family of transcription factors have overlapping transcriptional targets and homodimerize and heterodimerize in all combinations, dysregulation of MITF in the proper cellular context could be expected to potentially generate a neoplasm similar to the RCC resulting from TFE3 or TFEB gene fusions. MITF dysregulation in pediatric RCCs potentially could be another

Table 11 Xp11 Translocation Neoplasms

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<thead>
<tr>
<th>Gene Fusion</th>
<th>Chromosome Translocation</th>
<th>Neoplasm</th>
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<tbody>
<tr>
<td>ASPL-TFE3</td>
<td>der(17)t(X;17)(p11.2;q25)</td>
<td>ASPS</td>
</tr>
<tr>
<td>ASPL-TFE3</td>
<td>t(X;17)(p11.2;q25)</td>
<td>RCC</td>
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<tr>
<td>PRCC-TFE3</td>
<td>t(X;1)(p11.2;q21)</td>
<td>RCC</td>
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<td>PSSTFE3</td>
<td>t(X;1)(p11.2;p34)</td>
<td>RCC</td>
</tr>
<tr>
<td>NonO-TFE3</td>
<td>inv(X)(p11;q12)</td>
<td>RCC</td>
</tr>
<tr>
<td>CLTCTFE3</td>
<td>t(X;17)(p11.2;q23)</td>
<td>RCC</td>
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ASPS, alveolar soft part sarcoma; RCC, renal cell carcinoma.

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example of the molecular genetic principle that alterations in related genes activating a common downstream signaling pathway may lead to a similar neoplastic phenotype. Examples of this paradigm abound in pathology, exemplified by the KIT-mutation–negative gastrointestinal stromal tumors that harbor mutations in the related platelet-derived growth factor receptor α. The latter activates downstream targets similar to those activated in the KIT-mutant gastrointestinal stromal tumors. However, as Ramphal et al acknowledge, the MITF data in the article should be viewed with caution; there are several explanations for the MITF labeling aside from the potential presence of MITF genetic alterations. First, it is possible that MITF is up-regulated secondarily in some of the neoplasms by the TFE3 fusion proteins; because it is known that all members of the MITF/TFE transcription factor subfamily bind to each other, overexpressed TFE3 fusion proteins, in theory, could compensatorily increase the levels of the MITF to which they bind. It should be noted, however, that up-regulation of TFE3, TFEC, or MITF has not been demonstrated in the t(6;11) RCC with TFE3 gene fusions, so this mechanism lacks a precedent.11 Second, a greater concern is caused by specific immunohistochemical analysis.15 A further search for genetic alterations with MITF in this family of neoplasms is warranted. Finally, the study raises further questions about the prognosis for Xp11 translocation RCC. Ramphal et al note that one of their patients (case 12) with a genetically confirmed ASPL-TFE3 RCC had hematogenous metastases at initial examination and died of cancer within 1 year. We have noted heterogeneity in the clinical behavior of these neoplasms. Although several of the cases in our initial study had indolent clinical courses and we subsequently have seen other cases with indolent clinical behavior, we and others16 have noted aggressive behavior in some Xp11 translocation RCCs, particularly those with the ASPL-TFE3 gene fusion that manifest at an advanced stage. Further work is required to elucidate the biologic basis for this clinical heterogeneity.

References


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