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Perivascular Epithelioid Cell Tumors (PEComas) Harboring *TFE3* Gene Rearrangements Lack the *TSC2* Alterations Characteristic of Conventional PEComas: Further Evidence for a Biologic Distinction

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Perivascular epithelioid cell neoplasms (PEComas) are a group of lesions composed of distinctive perivascular epithelioid cells which typically demonstrate both melanocytic and muscular differentiation. This family includes the common renal angiomyolipoma, pulmonary clear cell sugar tumor, lymphangioleiomyomatosis, and less common neoplasms of the soft tissue, gynecologic and gastrointestinal tracts (7, 8, 9, 14, 16, 19). The cells comprising these lesions may be variably epithelioid or spindled in shape, and have variable cytoplasm ranging from clear to eosinophilic. By immunohistochemistry (IHC), PEComas typically express the melanocytic markers HMB45 and Melan-A and the protease Cathepsin K (18), but also typically label for smooth muscle actin and may express desmin. Some members of the PEComa family (specifically angiomyolipoma and lymphangioleiomyomatosis) are seen with high frequency in the genetic syndrome Tuberous Sclerosis Complex (TSC) (16), and a high frequency of syndromic and sporadic PEComas have demonstrated inactivation of the *TSC1* or *TSC2* genes (12, 20, 21) with subsequent activation of the mammalian target of rapamycin (mTOR) pathway (15). Specifically, mutation in and loss of heterozygosity (LOH) of *TSC2* with loss of expression of the protein tuberlin, the protein encoded by *TSC2*, is consistently found in conventional PEComas.

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TFE3 is a member of the MiT family of transcription factors, which includes MiTF, TFEB, TFEC, and TFE3 (11). *TFE3* gene fusions are known to occur in several types of neoplasia. Alveolar soft part sarcoma (ASPS), a rare epithelioid cell soft tissue sarcoma of uncertain histogenesis, characteristically demonstrates a der (17) t(X;17)(p11;q25) resulting in an *ASPL-TFE3* gene fusion (17). In addition, a group of recently-described renal cell carcinomas (RCCs) which often occur in children bear various *TFE3* gene fusions; these are designated the Xp11 translocation RCC (1, 2, 5, 6). Moreover, a distinctive subgroup of renal cancers in young patients with overlapping features of melanoma, RCC and PEComas have also proven to harbor *TFE3* gene fusions (3). Finally, we have recently identified a subgroup of lesions currently characterized as PEComas which, in contrast to conventional PEComas, harbor *TFE3* gene fusions (4). Although the number of cases identified are small, distinctive features of these *TFE3*-rearranged PEComas include a tendency to young age, absence of the association with tuberous sclerosis, predominant alveolar architecture and epithelioid cytology, minimal immunoreactivity for muscle markers, and strong (3+) TFE3 immunoreactivity. In contrast, conventional PEComas frequently have a spindle cell component, typically label for muscle markers, lack strong TFE3 immunoreactivity, and in young patients are frequently associated with tuberous sclerosis.

Since conventional PEComas frequently demonstrate *TSC2* LOH, and loss of expression of the tuberin protein which this gene encodes (13), we evaluated *TFE3*-rearranged PEComas for *TSC2* LOH and for tuberin expression by IHC. The study cohort consisted of four PEComas previously shown to harbor *TFE3* gene fusions (4), and four conventional PEComas which lacked *TFE3* alterations. To assess LOH or allelic loss we performed analysis of three microsatellite markers, STR3, KG8 and STR7 in the region of the *TSC2* gene, on paraffin-extracted DNA from tumor and normal tissue as described elsewhere (21). IHC was performed by standard techniques using Target Retrieval Solution pH 6.1 (Dako), incubation with anti-tuberin antibody (1:200 dilution, Cell Signaling, #4308), and development with horseradish peroxidase (HRP)-conjugated secondary antibody and DAB (Dako Envision System). Slides were counterstained with hematoxylin.

By IHC, all four of the conventional non-TFE3 PEComas demonstrated loss of tuberin protein labeling by immunohistochemistry, with the surrounding normal tissue serving as an internal control (Figure 1, top row). In contrast, all four of the PEComas previously shown to harbor *TFE3* gene fusions demonstrated intact, robust tuberin protein labeling (Figure 1, bottom row). In addition, two of the four conventional PEComas showed LOH or allelic loss for one or more *TSC2* microsatellite markers (Figure 1, top right), as we and others have seen previously (12, 15, 20). In contrast, none of the four PEComas previously shown to harbor *TFE3* gene fusions demonstrated *TSC2* LOH (Figure 1, bottom right).

Thus, these observations, while limited in scope due to the limited number of cases available to us, are consistent with our hypothesis that there is a different pathogenetic mechanism in *TFE3*-rearranged PEComas which does not involve the *TSC2* gene through mutation or allelic loss, or other mechanisms of loss of expression. Thus, they suggest that *TFE3*-rearranged PEComas represent an entity which morphologically overlaps with conventional PEComas, but is biologically distinctive. This concept has clinical translational importance in that mTORC1 inhibitors, such as rapamycin and everolimus, have been shown to be effective in some cases of PEComas (22). If there is no *TSC2* gene involvement in *TFE3*-rearranged PEComas, then these patients may not respond to mTORC1 inhibitors.

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Figure1. Hematoxylin and Eosin staining, IHC for tuberin, and *TSC2* microsatellite marker analysis is shown for a conventional PEComa (top row), and a *TFE3*-rearranged PEComa (bottom row). The insets show regions of normal tissue stained for *TSC2* from each tumor section. LOH with reduction in signal intensity for the *TSC2* marker STR7 is shown at right for the conventional PEComa but not the *TFE3*-rearranged PEComa.