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Differential expression of cathepsin K in neoplasms harboring *TFE3* gene fusions

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Cathepsin K is a protease whose expression is driven by microphthalmia transcription factor (MITF) in osteoclasts. TFE3 and TFEB are members of the same transcription factor subfamily as MITF and all three have overlapping transcriptional targets. We have shown that all t(6;11) renal cell carcinomas, which harbor an *Alpha-TFEB* gene fusion, as well as a subset of the Xp11 translocation renal carcinomas, which harbor various *TFE3* gene fusions, express cathepsin K, while no other common renal carcinoma does. We have hypothesized that overexpression of TFEB or certain TFE3 fusion proteins function like MITF in these neoplasms, and thus activate cathepsin K expression. However, the expression of cathepsin K in specific genetic subtypes of Xp11 translocation carcinomas, as well as alveolar soft part sarcoma, which harbors the same *ASPSCR1-TFE3* gene fusion as some Xp11 translocation carcinomas, has not been addressed. We performed immunohistochemistry for cathepsin K on 14 genetically confirmed t(X;1)(p11;q21) carcinomas, harboring the *PRCC-TFE3* gene fusion; eight genetically confirmed t(X;17)(p11;q25) carcinomas, harboring the *ASPSCR1-TFE3* gene fusion; and 18 alveolar soft part sarcomas (12 genetically confirmed), harboring the identical *ASPSCR1-TFE3* gene fusion. All 18 alveolar soft part sarcomas expressed cathepsin K. In contrast, all eight *ASPSCR1-TFE3* carcinomas were completely negative for cathepsin K. However, 12 of 14 *PRCC-TFE3* carcinomas expressed cathepsin K. Expression of cathepsin K distinguishes alveolar soft part sarcoma from the *ASPSCR1-TFE3* carcinoma, harboring the same gene fusion. The latter can be useful diagnostically, especially when alveolar soft part sarcoma presents in an unusual site (such as bone) or with clear cell morphology, which raises the differential diagnosis of metastatic *ASPSCR1-TFE3* renal cell carcinoma. The difference in expression of cathepsin K between the *PRCC-TFE3* and *ASPSCR1-TFE3* carcinomas, together with the observed clinical differences between these subtypes of Xp11 translocation carcinomas, suggests the possibility of functional differences between these two related fusion proteins.
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Cathepsin K is a lysosomal papain-like cysteine protease, which is selectively expressed in osteoclasts, and is responsible for bone resorption and remodeling.[1] Germline mutations in cathepsin K cause sclerosing osteochondrodysplasia pycnodysostosis, a rare autosomal recessive skeletal dysplasia characterized by abnormal bone and tooth development. Recent studies have demonstrated that microphthalmia transcription factor (MITF),[1,2] which activates expression of genes associated with melanin production in cells of melanocytic lineage, also binds to three consensus elements in the cathepsin K promoter in osteoclasts, resulting in increased cathepsin K mRNA and protein expression.[3–5]

MITF, TFE3, TFEB, and TFEC are related members of the same transcription factor subfamily, called

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MITF–TFE. All these proteins find the same specific target DNA sequences, homodimerize and heterodimerize in all combinations, and have overlapping transcriptional targets *in vitro*. Both *TFE3* and *TFEB* are implicated in gene fusions, resulting from chromosome translocations in two recently described subtypes of renal cell carcinoma.[6–8] The Xp11 translocation renal cell carcinomas harbor one of a number of possible *TFE3* gene fusions, resulting in overexpression of various TFE3 fusion proteins.[8] The renal cell carcinomas characterized by the t(6;11)(p21;q12) harbor an *Alpha-TFEB* gene fusion, resulting in overexpression of native TFEB protein.[7,9] We have hypothesized that aberrantly overexpressed TFEB or certain TFE3 fusion proteins essentially function like MITF in these renal cell carcinomas, and thus active cathepsin K expression. Indeed, we have recently shown that all t(6;11) renal cell carcinomas as well as a subset of the Xp11 translocation renal cell carcinomas express cathepsin K, whereas no other common renal cell carcinoma subtype does.[10] These results suggest that overexpressed native TFEB consistently activates cathepsin K expression like MITF does, but that only some TFE3 fusion proteins do. However, the expression of cathepsin K was not previously rigorously correlated with specific genetic subtypes of Xp11 translocation renal cell carcinoma. Moreover, cathepsin K expression has not been evaluated in alveolar soft part sarcoma, a rare soft tissue sarcoma that harbors the same *ASPSCR1-TFE3* gene fusion as a subset of Xp11 translocation renal cell carcinomas.[11–13]

The purpose of this study was to evaluate the expression of cathepsin K in a series of well-characterized tumors harboring *TFE3* gene fusions, including alveolar soft part sarcoma and genetically confirmed subtypes of Xp11 translocation renal cell carcinomas.

Materials and methods

Tissue Samples

We identified eight cases of genetically confirmed t(X;17)(p11;q25) translocation renal cell carcinomas, which bear the *ASPSCR1-TFE3* gene fusion, with available unstained slides in our files. Seven of these cases have previously been reported.[6,8,14,15] We also identified 14 cases of genetically confirmed t(X;1)(p11;q21) translocation renal cell carcinomas, which harbor the *PRCC-TFE3* gene fusion, of which 13 have previously been reported.[14,16,17] All of these displayed a strong nuclear immunoreactivity for TFE3 (Figure 2f and h). Finally, we identified 18 cases of alveolar soft part sarcoma, which consistently (100% of cases tested in the literature) harbor the *ASPSCR1-TFE3* gene fusion.[13] Of the 18 cases of alveolar soft part sarcoma in this study, all 12 that were tested (12 of 12) were confirmed to harbor the *ASPSCR1-TFE3* gene fusion. The other six demonstrated strong immunoreactivity for TFE3, which is a sensitive and specific immunohistochemical surrogate marker of neoplasms harboring *TFE3* gene fusions[18] (Figure 1e). The cases were retrieved from the Department of Pathology of The Johns Hopkins University of Baltimore, MD, USA; Memorial Sloan-Kettering Cancer Center of New York, NY, USA; and the Groupe d'Etude des Lésions Urologique of Paris. The clinicopathological findings are summarized in Table 1.

Immunohistochemical Analysis

All tissue samples had been fixed and embedded in paraffin according to the standard methods. The sections from tissue blocks of alveolar soft part sarcomas, t(X;17)(p11;q25) (*ASPSCR1-TFE3*) translocation renal cell carcinomas and t(X;1)(p11;q21) (*PRCC-TFE3*) translocation renal cell carcinomas were immunolabeled with cathepsin K antibody (clone 3F9, Abcam, Cambridge, UK) using previously described methods.[10,19,20] Heat-induced antigen retrieval was performed using a microwave oven and 0.01 mol/l of citrate buffer, pH 6.0, for 30 min. All samples were processed using a ''Bond polymer Refine'' detection system in an automated Bond immunostainer (Vision Biosystem, Menarini, Florence, Italy). Immunolabeling for cathepsin K in the osteoclasts present in 10 specimens of remodeling bone and in 10 granulomas from Crohn's disease was used as positive controls.

Results

Histological Findings

The histologic features of the neoplasms in this study have previously been reported, so they are merely summarized herein. Alveolar soft part sarcomas generally showed a dyscohesive, nested architecture (Figure 1a) composed of a population of large polygonal cells with distinct cell borders and abundant eosinophilic cytoplasm, sometimes with clear and vacuolated features. The cell borders were very well defined, conferring a distinctly epithelioid appearance. The nests were separated by fine and delicate septa containing sinusoidal vascular capillaries; individual tumor cells exhibited little variation in size and shape and contained vesicular nuclei with prominent nucleoli (Figure 1b).

The t(X;17)(p11;q25) (*ASPSCR1-TFE3*) renal cell carcinomas generally demonstrated a nested to papillary architecture composed of clear cells with voluminous cytoplasm and extensive psammomatous calcifications (Figures 1c, 2a and b).

In contrast, the t(X;1)(p11;q21) (*PRCC-TFE3*) renal cell carcinomas generally demonstrated a population of smaller clear epithelioid cells arranged in a nested to papillary manner with fewer psammoma bodies (Figure 2c and d).

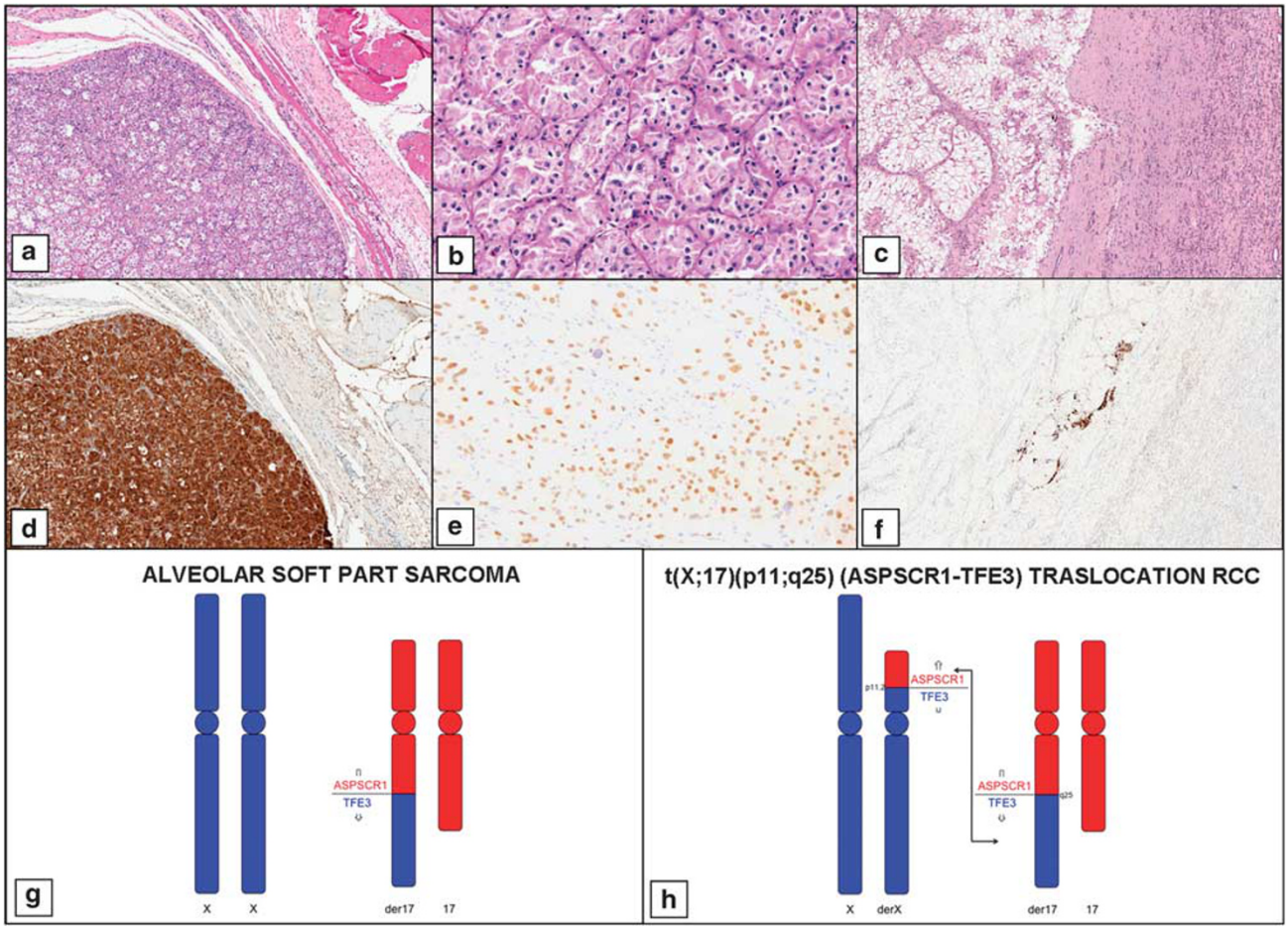


Figure 1 Alveolar soft part sarcoma (H&E) (**a**, **b**); t(X;17)(p11;q25) (*ASPSCR1-TFE3*) translocation renal cell carcinoma (**c**); cathepsin K expression in alveolar soft part sarcoma (**d**); TFE3 nuclear immunoreactivity in alveolar soft part sarcoma (**e**); absence of cathepsin K immunoexpression in t(X;17)(p11;q25) (*ASPSCR1-TFE3*) translocation renal cell carcinoma; macrophages appear positive as internal control (**f**); difference in the chromosome translocation between alveolar soft part sarcoma and the *ASPSCR1-TFE3* renal cell carcinoma (**g**, **h**); the t(X;17) chromosome translocation is consistently unbalanced in alveolar soft part sarcoma (**g**), but it is consistently balanced in *ASPSCR1-TFE3* renal cell carcinoma (**h**).

Immunohistochemical Findings

The immunohistochemical findings are summarized in Table 1. All 18 alveolar soft part sarcomas strongly expressed cathepsin K in a mean of 76% of neoplastic cells (range 30–100%) (Figure 1d). In contrast, all eight *ASPSCR1-TFE3* renal cell carcinomas were completely negative for cathepsin K (Figures 1f and 2e). However, 12 of 14 *PRCC-TFE3* renal cell carcinomas expressed cathepsin K in a mean of 62% of neoplastic cells (range 0–90%) (Figure 2g and h). The cytoplasm of scattered activated macrophages within the neoplastic tissue of alveolar soft part sarcomas, *PRCC-TFE3* renal cell carcinomas, and *ASPSCR1-TFE3* renal cell carcinomas served as positive internal controls (Figure 2e).

Discussion

In this study, we demonstrate that essentially all alveolar soft part sarcomas, which harbor the *ASPSCR1-TFE3* gene fusion, diffusely express cathepsin K, while the *ASPSCR1-TFE3* renal cell carcinomas, which harbor the same gene fusion, consistently do not. In contrast, almost all *PRCC-TFE3* renal cell carcinomas diffusely express cathepsin K. The reasons for these differences remain unclear at this time, though they suggest several possibilities.

One obvious possibility is that differences in cell of origin explain the differential expression of cathepsin K in alveolar soft part sarcomas *vs* the *ASPSCR1-TFE3* renal cell carcinomas.[6] As most conventional renal cell carcinomas are negative for cathepsin K, one can postulate that the renal tubular precursor cells that give rise to the *ASPSCR1-TFE3* renal cell carcinomas contain inhibitory proteins that prevent the *ASPSCR1-TFE3* fusion protein from activating cathepsin K expression, while these inhibitors are not present in the presumed mesenchymal precursor cells of alveolar soft part sarcomas.[21] The fact that we have found cathepsin K expression

in other renal mesenchymal lesions (Martignoni *et al*, submitted) suggests that cathepsin K may be more readily expressed in mesenchymal cells and supports the above hypothesis. However, the observation that cathepsin K is consistently expressed in the *PRCC-TFE3* renal cell carcinomas, which presumably derive from the same renal tubular precursors as the *ASPSCR1-TFE3* renal cell carcinomas, indicates that the presumed cell of origin cannot be the only explanation. A subtle difference in the chromosome translocation between alveolar soft part sarcoma and the *ASPSCR1-TFE3* renal cell carcinoma may explain the difference; the t(X;17) chromosome translocation is consistently unbalanced in alveolar soft part sarcoma,[13] but it is consistently balanced in *ASPSCR1-TFE3* renal cell carcinoma[6,22] (Figure 1g and h). Hence, in most cases, alveolar soft part sarcoma is associated with

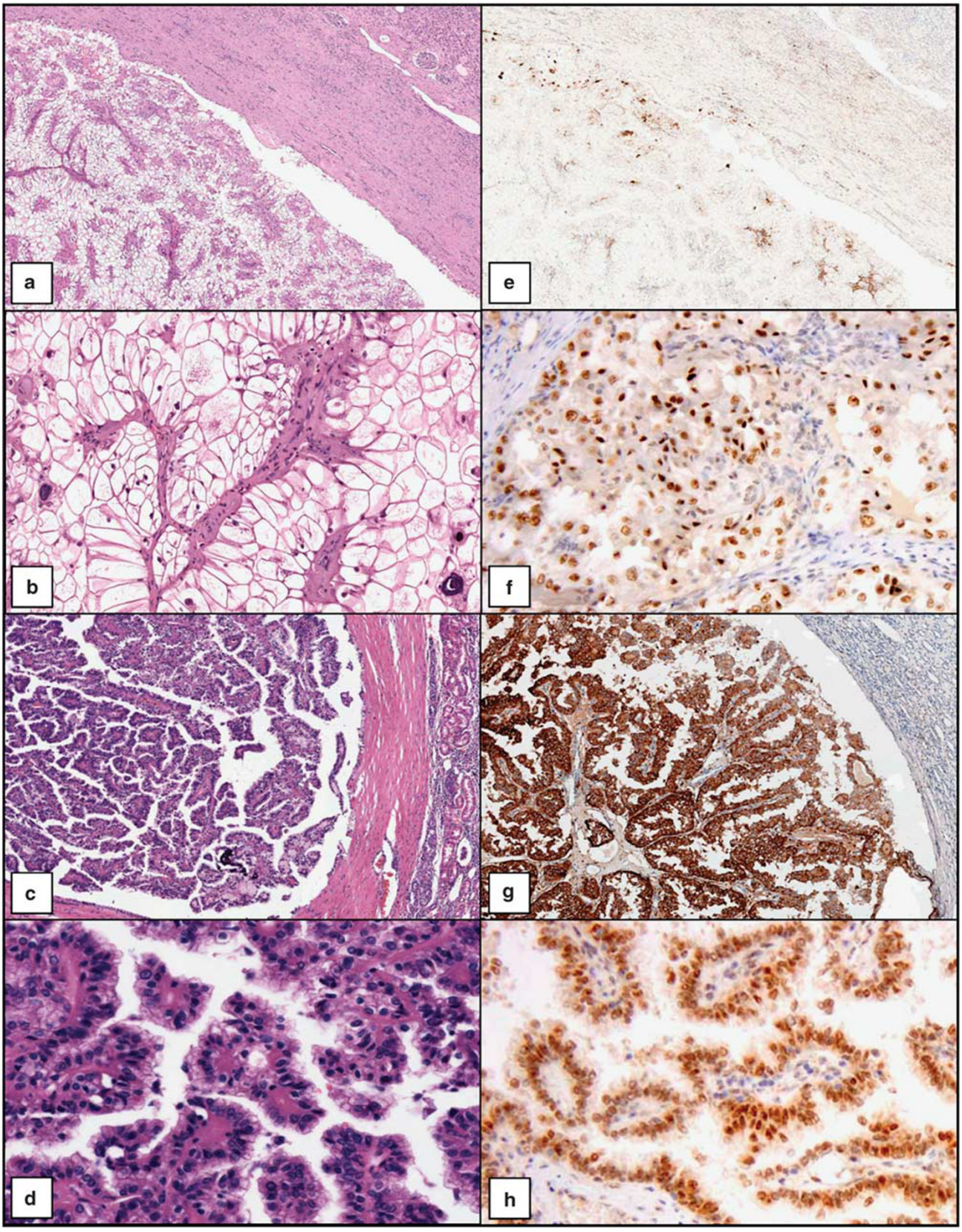
Table 1 Neoplasms with TFE3 gene fusions evaluated for cathepsin K immunoreactivity in this study

Case	*Reference*	*Age/sex*	*Location*	*Cathepsin K (% labeling)*
ASPS 1[a]	Unpublished	49/F	Left axilla	90
ASPS 2[a]	Unpublished	36/F	Right thigh	70
ASPS 3[a]	Unpublished	14/M	Left temple	50
ASPS 4[a]	Unpublished	36/M	Right arm	90
ASPS 5[a]	Unpublished	25/F	Right thigh	90
ASPS 6[a]	Case 1[13]	19/F	Right thigh	90
ASPS 7[a]	Unpublished	36/M	Left thigh	90
ASPS 8	Unpublished	52/M	Pelvis	90
ASPS 9	Unpublished	26/M	Calf	90
ASPS 10	Unpublished	39/M	Metastasis to kidney	30
ASPS 11	Unpublished	28/F	Sacrum	50
ASPS 12	Unpublished	63/F	Vaginal	80
ASPS 13	Unpublished	Unknown	Orbital	50
ASPS 14[a]	Unpublished	40/F	Thigh	90
ASPS 15[a]	Unpublished	30/F	Thigh	70
ASPS 16[a]	Unpublished	9/M	Thigh	70
ASPS 17[a]	Unpublished	30/M	Rib	90
ASPS 18[a]	Unpublished	36/M	Thigh	90
ASPSCR1-TFE3 RCC 1	Case 5[6]	17/M	Kidney	0[b]
ASPSCR1-TFE3 RCC 2	Case 1[8]	68/F	Kidney	0[b]
ASPSCR1-TFE3 RCC 3	Case 4[6]	17/F	Kidney	0[b]
ASPSCR1-TFE3 RCC 4	Case 6[6]	17/F	Kidney	0[b]
ASPSCR1-TFE3 RCC 5	Case 1[6]	8/F	Kidney	0[b]
ASPSCR1-TFE3 RCC 6	Unpublished	16/F	Kidney	0[b]
ASPSCR1-TFE3 RCC 7	[15]	9/F	Kidney	0
ASPSCR1-TFE3 RCC 8	Case 10[14]	28/M	Kidney	0[b]
PRCC-TFE3 RCC 1	Case 1[17]	15/M	Kidney	90
PRCC-TFE3 RCC 2	Case 2[17]	29/F	Kidney	90
PRCC-TFE3 RCC 3	Case 3[17]	24/F	Metastasis to bone	0
PRCC-TFE3 RCC 4	Case 4[17]	27/F	Kidney	70
PRCC-TFE3 RCC 5	Case 5[17]	9/F	Kidney	70
PRCC-TFE3 RCC 6	Case 6[17]	10/M	Abdomen recurrence	40
PRCC-TFE3 RCC 7	Case 7[17]	9/M	Kidney	90
PRCC-TFE3 RCC 8	Case 8[17]	23/F	Kidney	30
PRCC-TFE3 RCC 9	Case 9[17]	11/M	Kidney	90
PRCC-TFE3 RCC 10	Case 10[17]	64/F	Kidney	30
PRCC-TFE3 RCC 11	Case 11[17]	13/F	Kidney	90
PRCC-TFE3 RCC 12	Unpublished	14/M	Kidney	90
PRCC-TFE3 RCC 13	Case 2[16]	22/M	Kidney	0[b]
PRCC-TFE3 RCC 14	Case 2[14]	10/F	Kidney	90

ASPS, alveolar soft part sarcoma; RCC, renal cell carcinoma; F, female; M, male.
[a]Genetically confirmed alveolar soft part sarcomas.
[b]Macrophages positive as internal control.

Figure 2 t(X;17)(p11;q25) (*ASPSCR1-TFE3*) translocation renal cell carcinomas generally show a nested to papillary architecture composed of clear cells with voluminous cytoplasm and extensive psammomatous calcification (**a**, **b**); t(X;1)(p11;q21) (*PRCC-TFE3*) translocation renal cell carcinomas generally show a population of smaller clear epithelioid cells arranged in a nested to papillary fashion with fewer psammoma bodies (**c**, **d**); t(X;17)(p11;q25) (*ASPSCR1-TFE3*) translocation renal cell carcinomas are completely negative for cathepsin K (**e**) but show a strong and diffuse TFE3 expression in the nuclei of the neoplastic cells (**f**); t(X;1)(p11;q21) (*PRCC-TFE3*) translocation renal cell carcinomas show both a strong cytoplasmic expression of cathepsin K and a nuclear immunoreactivity for TFE3 (**g**, **h**).

allelic gain of Xp sequences telomeric to *TFE3* (which comprises most of the short arm of the X chromosome) and allelic loss of 17q25 sequences telomeric to *ASPSCR1*.[13] Perhaps the differential expression of different genes that are over or under-represented in alveolar soft part sarcoma promotes



cathepsin K expression. Another possibility is that the same fusion protein is expressed at different levels in these two neoplasms, and that the higher level in the cellular context of alveolar soft part sarcoma is permissive for cathepsin K expression. Regardless, the consistent expression of cathepsin K in alveolar soft part sarcomas can be useful diagnostically when the differential diagnosis includes the *ASPSCR1-TFE3* renal cell carcinoma. Sometimes these two neoplasms can be difficult to distinguish from each other, particularly when alveolar soft part sarcoma presents in an unusual site such as bone and/or uncommonly contains a significant component of clear cells.[8] In this setting, even if cytokeratins and renal tubular immunohistochemical markers are negative, we currently suggest imaging of the kidneys to exclude a primary renal source before a diagnosis of alveolar soft part sarcoma is rendered. Diffuse immunolabeling for cathepsin K may support the diagnosis of alveolar soft part sarcoma over *ASPSCR1-TFE3* renal cell carcinoma in such circumstances.

The consistent expression of cathepsin K in *PRCC-TFE3* renal cell carcinomas, in contrast to its absence in the *ASPSCR1-TFE3* renal cell carcinomas, is also somewhat puzzling. *ASPSCR1-TFE3* renal cell carcinoma frequently metastasizes to bone,[6,8] which might suggest that it would express an osteoclastic protein such as cathepsin K, but our results do not support this hypothesis. One possibility for this difference rests in the fact that cathepsin K is located at chromosome 1q21, close to the *PRCC* gene, which is disrupted in the *PRCC-TFE3* renal cell carcinomas.[17] One could hypothesize that the chromosome translocation may disrupt the expression of cathepsin K independent of the function of the *PRCC-TFE3* fusion protein, resulting in cathepsin K overexpression. Since cathepsin K is ~6 MB away from the break point in the *PRCC-TFE3* renal cell carcinoma, this explanation seems unlikely.[2,23] It seems more likely that subtle differences in the function and/or expression level of the PRCC-TFE3 fusion protein relative to the ASPSCR1-TFE3 fusion protein may explain this difference. Perhaps the PRCC-TFE3 fusion protein is a stronger driver of cathepsin K expression than is the ASPSCR1-TFE3 fusion protein in renal tubular cells. The diffuse expression of cathepsin K in alveolar soft part sarcoma, which also harbors the ASPSCR1-TFE3 fusion protein, could be explained by the absence of expression of inhibitors that are present in renal tubular cells in the precursors of alveolar soft part sarcoma. Regardless, the differential expression of cathepsin K between the *ASPSCR1-TFE3* renal cell carcinomas and *PRCC-TFE3* renal cell carcinomas suggest that the Xp11 translocation renal cell carcinomas likely harbor subtle biological differences. Support for this concept comes from our recent clinical observations that the *ASPSCR1-TFE3* renal cell carcinomas are more likely to present at advanced stage and have lymph node metastasis than are the *PRCC-TFE3* renal cell carcinomas.[24] Perhaps the differential expression of cathepsin K between different subtypes of Xp11 translocation renal cell carcinomas contributes to some of these observed clinical differences. Given that cathepsin K immunolabeling can be measured in archival material, and Xp11 translocation renal cell carcinomas can be confirmed in archival material using either TFE3 immunohistochemistry or FISH,[14,18,25,26] it should now be possible to compare a large number of Xp11 translocation renal cell carcinomas with and without cathepsin K expression for potential clinical or pathologic differences. Such a study is underway in our laboratories. The expression of cathepsin K in other rarer subtypes of Xp11 translocation renal cell carcinomas remains to be determined. In limited material we have found diffuse cathepsin K labeling in one *PSF-TFE3* renal cell carcinoma but no labeling in a *CLTC-TFE3* renal cell carcinoma,[27] suggesting that these rarer subtypes also harbor subtle biologic differences.[10]

In summary, we demonstrate here the differential expression of cathepsin K among neoplasms harboring *TFE3* gene fusions. While alveolar soft part sarcoma is consistently immunoreactive for cathepsin K, the *ASPSCR1-TFE3* renal cell carcinomas, which harbor the same gene fusion, are consistently negative. However, the related *PRCC-TFE3* renal cell carcinomas are consistently positive for cathepsin K, suggesting significant biologic differences among subtypes of Xp11 translocation renal cell carcinomas.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

References

1 Motyckova G, Weilbaecher KN, Horstmann M, *et al.* Linking osteopetrosis and pycnodysostosis: regulation of cathepsin K expression by the microphthalmia transcription factor family. Proc Natl Acad Sci USA 2001;98:5798–5803.
2 Gelb BD, Shi GP, Heller M, *et al.* Structure and chromosomal assignment of the human cathepsin K gene. Genomics 1997;41:258–262.
3 Fisher DE, Carr CS, Parent LA, *et al.* TFEB has DNA-binding and oligomerization properties of a unique helix-loop-helix/leucine-zipper family. Genes Dev 1991;5:2342–2352.
4 Hemesath TJ, Steingrimsson E, McGill G, *et al.* Microphthalmia, a critical factor in melanocyte devel-

opment, defines a discrete transcription factor family. Genes Dev 1994;8:2770–2780.
5 Kuiper RP, Schepens M, Thijssen J, *et al.* Regulation of the MiTF/TFE bHLH-LZ transcription factors through restricted spatial expression and alternative splicing of functional domains. Nucleic Acids Res 2004;32: 2315–2322.
6 Argani P, Antonescu CR, Illei PB, *et al.* Primary renal neoplasms with the ASPL-TFE3 gene fusion of alveolar soft part sarcoma: a distinctive tumor entity previously included among renal cell carcinomas of children and adolescents. Am J Pathol 2001;159:179–192.
7 Argani P, Hawkins A, Griffin CA, *et al.* A distinctive pediatric renal neoplasm characterized by epithelioid morphology, basement membrane production, focal HMB45 immunoreactivity, and t(6;11)(p21.1;q12) chromosome translocation. Am J Pathol 2001;158: 2089–2096.
8 Argani P, Olgac S, Tickoo SK, *et al.* Xp11 translocation renal cell carcinoma in adults: expanded clinical, pathologic, and genetic spectrum. Am J Surg Pathol 2007;31:1149–1160.
9 Davis IJ, Hsi BL, Arroyo JD, *et al.* Cloning of an Alpha-TFEB fusion in renal tumors harboring the t(6;11)(p21;q13) chromosome translocation. Proc Natl Acad Sci USA 2003;100:6051–6056.
10 Martignoni G, Pea M, Gobbo S, *et al.* Cathepsin-K immunoreactivity distinguishes MiTF/TFE family renal translocation carcinomas from other renal carcinomas. Mod Pathol 2009;22:1016–1022.
11 Auerbach HE, Brooks JJ. Alveolar soft part sarcoma. A clinicopathologic and immunohistochemical study. Cancer 1987;60:66–73.
12 Christopherson WM, Foote Jr FW, Stewart FW. Alveolar soft-part sarcomas; structurally characteristic tumors of uncertain histogenesis. Cancer 1952;5: 100–111.
13 Ladanyi M, Lui MY, Antonescu CR, *et al.* The der(17)t(X;17)(p11;q25) of human alveolar soft part sarcoma fuses the TFE3 transcription factor gene to ASPL, a novel gene at 17q25. Oncogene 2001;20:48–57.
14 Camparo P, Vasiliu V, Molinie V, *et al.* Renal translocation carcinomas: clinicopathologic, immunohistochemical, and gene expression profiling analysis of 31 cases with a review of the literature. Am J Surg Pathol 2008;32:656–670.
15 Zambrano E, Reyes-Mugica M. Renal cell carcinoma with t(X;17): singular pediatric neoplasm with specific phenotype/genotype features. Pediatr Dev Pathol 2003;6:84–87.
16 Argani P, Lae M, Ballard ET, *et al.* Translocation carcinomas of the kidney after chemotherapy in childhood. J Clin Oncol 2006;24:1529–1534.
17 Argani P, Antonescu CR, Couturier J, *et al.* PRCC-TFE3 renal carcinomas: morphologic, immunohistochemical, ultrastructural, and molecular analysis of an entity associated with the t(X;1)(p11.2;q21). Am J Surg Pathol 2002;26:1553–1566.
18 Argani P, Lal P, Hutchinson B, *et al.* Aberrant nuclear immunoreactivity for TFE3 in neoplasms with TFE3 gene fusions: a sensitive and specific immunohistochemical assay. Am J Surg Pathol 2003;27:750–761.
19 Pedica F, Pecori S, Vergine M, *et al.* Cathepsin-k as a diagnostic marker in the identification of microgranulomas in Crohn's disease. Pathologica 2009;101: 109–111.
20 Chilosi M, Pea M, Martignoni G, *et al.* Cathepsin-k expression in pulmonary lymphangioleiomyomatosis. Mod Pathol 2009;22:161–166.
21 Argani P, Hicks J, De Marzo AM, *et al.* Xp11 translocation renal cell carcinoma (RCC): extended immunohistochemical profile emphasizing novel RCC markers. Am J Surg Pathol 2010;34:1295–1303.
22 Huang HY, Lui MY, Ladanyi M. Nonrandom cell-cycle timing of a somatic chromosomal translocation: the t(X;17) of alveolar soft-part sarcoma occurs in G2. Genes Chromosomes Cancer 2005;44:170–176.
23 Rood JA, Van Horn S, Drake FH, *et al.* Genomic organization and chromosome localization of the human cathepsin K gene (CTSK). Genomics 1997;41: 169–176.
24 Ellis CL, Eble JN, Subhawong AP, *et al.* Not all Xp11 translocation renal cell carcinomas (RCC) are the same: ASPL-TFE3 RCC are more likely to present at advanced stage than are PRCC-TFE3 RCCs. Mod Pathol 2011;24(S1):190A.
25 Aulmann S, Longerich T, Schirmacher P, *et al.* Detection of the ASPSCR1-TFE3 gene fusion in paraffin-embedded alveolar soft part sarcomas. Histopathology 2007;50:881–886.
26 Zhong M, Habermann J, Andraws N. Xp11.2 translocation renal cell carcinoma (RCC) in adults - a TMA study of 120 RCC cases. Mod Pathol 2009;22(S1):203A.
27 Argani P, Lui MY, Couturier J, *et al.* A novel CLTC-TFE3 gene fusion in pediatric renal adenocarcinoma with t(X;17)(p11.2;q23). Oncogene 2003;22:5374–5378.