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REVIEW **Open Access**

A review of neoplasms with MITF/MiT family translocations

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Summary. Microphthalmia-associated transcription factor (MITF/MiT) family is a group of basic helix-loop-helix leucine zipper (bHLH-LZ) transcription factors including TFE3 (TFEA), TFEB, TFEC and MITF. The first described neoplasms involving MITF family translocation were renal cell carcinomas with chromosome translocations involving *ASPL-TFE3*/t(X;17)(p11.23;q25) or *MALAT1-TFEB*/t(6;11)(p21.1;q12), and now it is known as MiT family translocation RCC in 2016 WHO classification. Translocations involving MITF family genes also are found in other tumor types, such as perivascular epithelioid cell neoplasm (PEComa), alveolar soft part sarcoma (ASPS), epithelioid hemangioendothelioma, ossifying fibromyxoid tumor (OFMT), and clear cell tumor with melanocytic differentiation and *ACTIN-MITF* translocation. In this review, we summarize the features of different types of neoplasms with MITF family translocations.

Key words: MITF, MiT, TFE3, TFEB, MITF, Translocation, Fusion genes, Neoplasm, Carcinoma, Sarcoma

Introduction

Microphthalmia-associated transcription factor (MITF/MiT) family is a group of basic helix-loop-helix leucine zipper (bHLH-LZ) transcription factors including TFE3 (TFEA), TFEB, TFEC and MITF (Hemesath et al., 1994; Goding and Arnheiter, 2019; Perera et al., 2019; La Spina et al., 2020; Pinto and Chetty, 2020). They can form homodimers and heterodimers and bind to the regulatory regions of the target genes (La Spina et al., 2020). They can be activated to regulate biogenesis of lysosome, autophagosome and mitochondria in response to various stress conditions. They also can be involved in cell proliferation, differentiation and tumorigenesis (La Spina et al., 2020).

The first described neoplasms involving MITF family translocation were a group of pediatric renal cell carcinomas (RCC) with chromosome translocations resulting in *ASPL-TFE3*/t(X;17)(p11.23;q25) or *MALAT1-TFEB*/t(6;11)(p21.1;q12) gene fusions (Argani et al., 2001a; Argani et al., 2002; Davis et al., 2003). MITF is critical for melanocyte development and function which is mediated by MITF family interaction and transcriptional activities (Hemesath et al., 1994; Pinto and Chetty, 2020), and neoplasms with MITF family translocations may show melanocytic differentiation, e.g., with positivity for Melan A and HMB45 and the presence of melanin pigment (Argani et al., 2001a,b, 2016a). Since then, many other fusion gene partners for *TFE3* and *TFEB* have been reported (Argani et al., 2002, 2003a; Xia et al., 2017a,b; Pei et al., 2019). Translocations involving MITF family genes also were found in other tumor types, such as perivascular epithelioid cell neoplasm (PEComa), alveolar soft part sarcoma (ASPS), epithelioid hemangioendothelioma, ossifying fibromyxoid tumor (OFMT), and clear cell tumor with melanocytic differentiation and *ACTIN-MITF* translocation (Ladanyi et al., 2001; Argani et al., 2010b; Antonescu et al., 2013; Panagopoulos et al., 2019; Suurmeijer et al., 2019; de la Fouchardiere et al., 2021a,b). In this review, we summarize the features of different types of neoplasms with MITF family translocations.

Renal cell carcinoma

Originally, *TFE3* translocation RCCs were reported in children (Argani et al., 2001a, 2002). However, they are now known to occur in adults as well, and since RCC is overall much more common in adult, *TFE3* translocation RCCs outnumber pediatric cases (Argani, 2015). The mechanism and function of the translocations

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have not been fully elucidated; however, they may be associated with exposure to DNA topoisomerase II inhibitor/platinum or alkylating chemotherapy (Argani et al., 2006, 2016a; Argani, 2015). Since this unique group of RCCs have MITF family translocations, distinct morphology and immunophenotype, it was accepted as a new RCC type as renal carcinoma associated with Xp11.2 translocations/*TFE3* gene fusions in the 2004 WHO tumor classification (Eble et al., 2004). With the discovery of t(6;11) RCC (Argani et al., 2001a; Davis et al., 2003), this entity was renamed as MiT family translocation RCC in the 2016 WHO classification (Moch and Ulbright, 2016). Recently, MITF family translocation RCCs involving the *MITF* gene have been reported; however, translocation RCC involving the *TFEC* gene has not been found (Durinck et al., 2015; Xia et al., 2018).

TFE3 (Xp11) translocation RCC

The mean age of *TFE3* (Xp11) translocation RCCs is 17 years in pediatric patients and 37 years in adult cases (Argani et al., 2007; Wu et al., 2008). It accounts for 50% of pediatric RCCs and 1-4% of RCCs in adults (Cimadamore et al., 2021). A slight female predominance (F:M=1.6:1) has been noted (Caliò et al., 2019). RCC patients who have this translocation have a similar prognosis to those with clear cell RCC (Sukov et al., 2012; Pflueger et al., 2013; Ellis et al., 2014) though adults appear to do worse than children. However, Wu and Camparo found that 50-66% of *TFE3* translocation RCCs presented at an advanced stage (Camparo et al., 2008; Wu et al., 2008), and Calio et al. reported that 47% (91/194) of such cases behaved aggressively (Caliò et al., 2019). The aggressiveness was correlated with larger tumour size and the presence of necrosis but not nucleolar grading (Caliò et al., 2020).

Among the four members of the MITF family (TFE3, TFEB, TFEC, and MITF), translocations involving *TFE3* are most common (Argani, 2015; Moch and Ulbright, 2016). The reported partner genes include *ASPL (ASPSCR1), EWSR1, CLTC, DVL2, FUBP1, GRIPAP1, KAT6A, KHDRBS2, KHSRP, LUC7L3, MED15, NEAT1, NONO, PARP14, PRCC, RBM10, SETD1B, SFPQ* and *ZC3H4* (Argani et al., 2001b, 2002, 2003a, 2016a, 2017; Malouf et al., 2014; Huang et al., 2015; Classe et al., 2017; Wang et al., 2018; Fukuda et al., 2019; Pei et al., 2019; Sun et al., 2021) (Table 1). The most common rearrangements involve *PRCC, ASPL* and *SFPQ* (Wang et al., 2018).

TFE3 translocation RCC has no distinct gross appearance. However, it often has an unusual morphology not typically seen in clear cell RCC, papillary RCC or chromophobe RCC (Fig. 1). This tumor shows a mixed papillary and nested pattern with mixture of cells with clear and granular/oncocytic cytoplasm. It often has psammoma bodies and hyalinized stroma (Gandhi et al., 2020; Williamson et al., 2020). The nucleolus is often large (ISUP/WHO grade 3) (Argani, 2015). *TFE3* translocation RCCs may have minor morphological differences depending on the gene fusion partners (Fig. 1), as summarized in Table 1.

The tumor is positive for Pax8 and CD10, and it is typically negative or weakly positive for keratin, EMA, vimentin and CAIX (Argani et al., 2010a; Caliò et al., 2019; Yang et al., 2019). TFE3 antibodies targeting the C-terminus of the protein can be used to confirm the diagnosis of *TFE3* translocation RCC (Argani et al., 2003b) (Fig. 1). However, it is often difficult to optimize TFE3 immunohistochemistry, which may lead to equivocal results (Zhong et al., 2010; Green et al., 2013; Rao et al., 2013; Pei et al., 2019; Sharain et al., 2019). In addition, TFE3 expression can also be found in a variety of tumor types without *TFE3* translocations, such as granular cell tumors, adrenocortical carcinomas (Argani et al., 2003b; Williams et al., 2011; Schoolmeester and Lastra, 2015; Liu et al., 2019), solid-pseudopapillary neoplasms of the pancreas (Harrison et al., 2017), ovarian sclerosing stromal tumors (Park and Kim, 2017), solitary fibrous tumors (Zhou et al., 2020), and desmoid-type fibromatoses (Zhou et al., 2019). In practice, break-apart FISH has higher sensitivity and specificity for detecting *TFE3* translocations than TFE3 immunohistochemical staining (Zhong et al., 2010; Green et al., 2013; Rao et al., 2013).

It is important to note that it may be difficult or impossible to detect certain *TFE3* inversions by FISH analysis, e.g., *NONO-TFE3* and *RBM10-TFE3* rearrangements, because *NONO, RBM10* and *TFE3* are all located on the chromosome X (Argani et al., 2016a, 2017; Xia et al., 2017b). In fact, the loci for *RBM10* (Chromosome X nucleotides 47,600,000-50,100,000) and *TFE3* (X:50,100,000-54,800,000) lie adjacent to each other, so that no separation of a probe break would be obvious visually. TFE3 immunohistochemistry is particularly useful in identifying such cases. RNA-sequencing or targeted multiplex RT-PCR can be used to confirm the fusion (Xia et al., 2017a; Pei et al., 2019).

TFEB/t(6;11) translocation RCC

TFEB translocation RCC is rare (0.02% of RCC) (Caliò et al., 2019); only ~80 cases have been reported. The affected patients generally are young, with an average age of 34 years, and no distinct gender predominance (F:M=0.75:1) (Caliò et al., 2019; Wyvekens et al., 2019; Gandhi et al., 2020). Most *TFEB* translocation RCCs follow an indolent course (Caliò et al., 2019; Gandhi et al., 2020). The reported gene fusion partners for *TFEB* are far less than for *TFE3* and include *ACTB, COL21A1, CADM2, EWSR1, KHDRBS2, MALAT1, NEAT1* and *PPP1R10*. Interestingly, *CADM2* and *KHDRBS2* are located at the 5' end of the fusion genes (Malouf et al., 2014; Linehan et al., 2016; Xia et al., 2020; Caliò et al., 2021b) (Table 1).

TFEB translocation RCC has classic biphasic morphology: larger tumor with clear or eosinophilic cytoplasm, and smaller tumor cells with condensed

Table 1. Summary of neoplasms with MITF family fusion genes/translocation.

Fusion gene	Chromosome alteration	Neoplasm	Feature	Reference
ARID1B-TFE3	t(X;6)(p11.23;q25.3)	Melanotic translocation renal cancer	Intracytoplasmic melanin pigment	Antic et al., 2017
ASPL-TFE3	t(X;17)(p11.23;q25)	Renal cell carcinoma	Nested to papillary architecture, voluminous clear to eosinophilic cytoplasm, and abundant psammoma bodies	Argani et al., 2001a,b
ASPL-TFE3	der(17)(X;17)(p11.23;q25)	Alveolar soft part sarcoma	Alveolar pattern due to the central discohesion	Ladanyi et al., 2001
CLTC-TFE3	t(X;17)(p11.23;q23)	Renal cell carcinoma	Abundant psammoma bodies/calcification	Argani et al., 2003a,b
DVL2-TFE3	t(X;17)(p11.23;p13.1)	Renal cell carcinoma	Papillary and solid architecture with focal sarcomatoid areas	Linehan et al., 2016
DVL2-TFE3	t(X;17)(p11.23;p13.1)	PEComa	Pax8-, cathepsin K+	Argani et al., 2016a,b
EWSR1-TFE3	t(X;22)(p11.23;q12.2)	Renal cell carcinoma	Voluminous, eosinophilic, vacuolated cytoplasm, no psammoma body and melanin pigments	Fukuda et al., 2019
FUBP1-TFE3	t(X;1)(p11.23;p31.1)	Renal cell carcinoma	Trabecular, mostly eosinophilic cells	Wang et al., 2018
GRIPAP1-TFE3	inv(X)(p11.23;p11.23)	Renal cell carcinoma	n/a	Classe et al., 2017
KAT6A-TFE3	t(X;8)(p11.23; p11.21)	Renal cell carcinoma	Psammoma bodies, papillae and eosinophilic cytoplasm with clearing	Pei et al., 2019
KHSRP-TFE3	t(X;19)(p11.23;q13.3)	Renal cell carcinoma	n/a	Malouf et al., 2014
LUC7L3-TFE3	t(X;17)(p11.23;q21.33)	Renal cell carcinoma	n/a	Malouf et al., 2014
MATR3-TFE3	t(X;5)(p11.23;q31.2)	Renal cell carcinoma	Predominant eosinophilic cells	Wang et al., 2018
MED15-TFE3	t(X;22)(p11.23;q11.21)	Renal cell carcinoma	Extensively cystic architecture	Classe et al., 2017
MED15-TFE3	t(X;22)(p11.23;q11.21)	Melanotic Xp11 neoplasm	Nested, purely epithelioid cells	Wang et al., 2018
NEAT1-TFE3	t(X;11)(p11.23;q13.1)	Renal cell carcinoma	Alveolar/nested growth pattern and psammoma bodies	Pei et al., 2019
NONO-TFE3	inv(X)(p11.23;q12)	Renal cell carcinoma	Nested to papillary architecture and predominantly clear cytoplasm, psammomatous calcifications, nuclear palisading with subnuclear vacuoles	Clark, 1997
NONO-TFE3	inv(X)(p11.23;q12)	PEComa	Nested epithelioid neoplasm, with clear to finely granular eosinophilic cytoplasm and abundant melanin pigment	Argani et al., 2016a,b
PARP14-TFE3	t(X;3)(p11.23;q21)	Renal cell carcinoma	Papillary or alveolar pattern, polygonal cells with well-demarcated, predominantly clear, voluminous cytoplasm; psammoma bodies	Huang et al., 2015
PRCC-TFE3	t(X;1)(p11.23;q21)	Renal cell carcinoma	Well-demarcated, predominantly clear, voluminous cytoplasm; psammoma bodies	Argani et al., 2002
RBM10-TFE3	inv(X)(p11.23;p11.3)	Renal cell carcinoma	Clear cells and papillary architecture	Linehan et al., 2016
RBMX-TFE3	inv(X)(p11;q26)	PEComa	Epithelioid clear cells with alveolar and nested architecture	Argani et al., 2019
SETD1B-TFE3	t(X;12)(p11.23;q24.13)	Renal cell carcinoma	n/a	Sun et al., 2021
SFPQ-TFE3	t(X;1)(p11.23;q34)	Renal cell carcinoma	Clear cytoplasm with subnuclear vacuoles, psammomatous calcifications	Clark, 1997
SFPQ-TFE3	t(X;1)(p11.23;q34)	Melanotic translocation renal cancers	Solid nested architecture predominantly clear to focally eosinophilic cytoplasm	Chang, 2009
SFPQ-TFE3	t(X;1)(p11.23;q34)	PEComa	Solid nested architecture featuring epithelioid cells with predominantly clear to focally eosinophilic cytoplasm, with melanin pigment	Tanaka et al., 2009
YAP1-TFE3	t(X;11)(p11.23;q13)	Epithelioid Hemangioendothelioma	Well-formed vascular channels, variably solid growth pattern	Antonescu et al., 2013
PHF1-TFE3	t(X;6)(p11.23;p21.32)	Ossifying fibromyxoid tumour	No peripheral bony shell	Suurmeijer et al., 2019
ZC3H4-TFE3	t(X;19)(p11.23;q13.32)	Renal cell carcinoma	n/a	Sun et al., 2021
ACTB-TFEB	t(6;7)(p21.1;q22.1)	Renal cell carcinoma	Papillary and solid	Xia et al., 2020
CLTC-TFEB	t(6;17)(p21.1;q23)	Renal cell carcinoma	n/a	Durinck et al., 2015
COL21A1-TFEB	inv(6)(p21;p12)	Renal cell carcinoma	n/a	Linehan et al., 2016
EWSR1-TFEB	t(6;22)(p21.1;q12.2)	Renal cell carcinoma	Alveolar, mimicking ccRCC	Xia et al., 2020
MALAT1-TFEB	t(6;11)(p21.1;q12)	Renal cell carcinoma	Biphasic morphology: larger tumor with clear or eosinophilic cytoplasm, and smaller tumor cells with condensed chromatin arranged around basement material/eosinophilic spheres	Argani et al., 2001a,b
NEAT1-TFEB	t(6;11)(p21.1;q13.1)	Renal cell carcinoma	Solid and cystic appearance	Calio et al., 2021a,b
PPP1R10-TFEB	inv(6)(p21.1;p21.33)	Renal cell carcinoma	Alveolar architecture; cells with voluminous eosinophilic cytoplasm	Xia et al., 2020
TFEB-CADM2	t(3;6)(p12;p21)	Renal cell carcinoma	n/a	Linehan et al., 2016
TFEB-KHDRBS2	inv(6)(p21;q11)	Renal cell carcinoma	n/a	Malouf et al., 2014
PRCC-MITF	t(1;3)(q21;p13)	Renal cell carcinoma	Glandular/ tubular architecture with clear or flocculent eosinophilic cytoplasm and small cells forming pseudorosette-like architecture, psammoma bodies	Xia et al., 2018
ACTB-MITF	t(3;7)(p13;p22.1)	Clear cell tumor with melanocytic differentiation	Clear cell phenotype with abundant cytoplasm	de la Fouchardiere et al., 2021a,b
ACTG1-MITF	t(3;17)(p13;p25.3)	Renal cell carcinoma	Papillary RCC with oncocytic features	Durinck et al., 2015
ACTG1-MITF	t(3;17)(p13;p25.3)	Clear cell tumor with melanocytic differentiation	Clear cell phenotype with abundant cytoplasm	de la Fouchardiere et al., 2021a,b

chromatin arranged around basement material/eosinophilic spheres (Fig. 2A,B) (Argani et al., 2001a, 2005, 2012; Moch and Ulbright, 2016; Wyvekens et al., 2019; Gandhi et al., 2020). However, its morphology can be similar to clear cell, papillary or chromophobe RCCs or oncocytoma. It can have cystic formation, hyalinization/sclerosis and ossification (Argani et al., 2012; Inamura et al., 2012; Williamson et al., 2017). The nucleolus is graded as G2 or G3 (ISUP/WHO) (Calio et al., 2018). This tumor type has a similar immunoprofile to that of *TFE3* translocation RCC, including positivity for Pax8 and underexpressed cytokeratin (pancytokeratin and EMA). However, compared with infrequently expressed melanocytic markers in *TFE3* translocation RCC, *TFEB* translocation RCCs are always positive for Melan A and HMB45. Additionally, they consistently express cathepsin K, in contrast to its expression in 60% of *TFE3* translocation RCCs (Smith et al., 2014). Although TFEB immunohistochemistry is sensitive and specific for the diagnosis of *TFEB* translocation RCC, this is challenging to validate in the laboratory. Therefore, *TFEB* break-apart FISH or RNA sequencing are more useful (Argani et al., 2012; Gandhi et al., 2020).

RCC can also have *TFEB* amplification with or without *TFEB* translocation (Peckova et al., 2014; Argani et al., 2016b). To date, 58 cases of *TFEB*-amplified tumors have been reported, a small percentage of which harbor both *TFEB* translocation and amplification. Overall, *TFEB*-amplified tumors more often show high nuclear grade, pseudopapillary/nested/tubular structure and an aggressive clinical behavior. Notably, 50% of cases published to date have been negative for TFEB expression by immunohistochemistry (Gupta et al., 2017, 2019; Mendel et al., 2018; Skala et al., 2018; Wyvekens et al., 2019; Vormittag-Nocito and

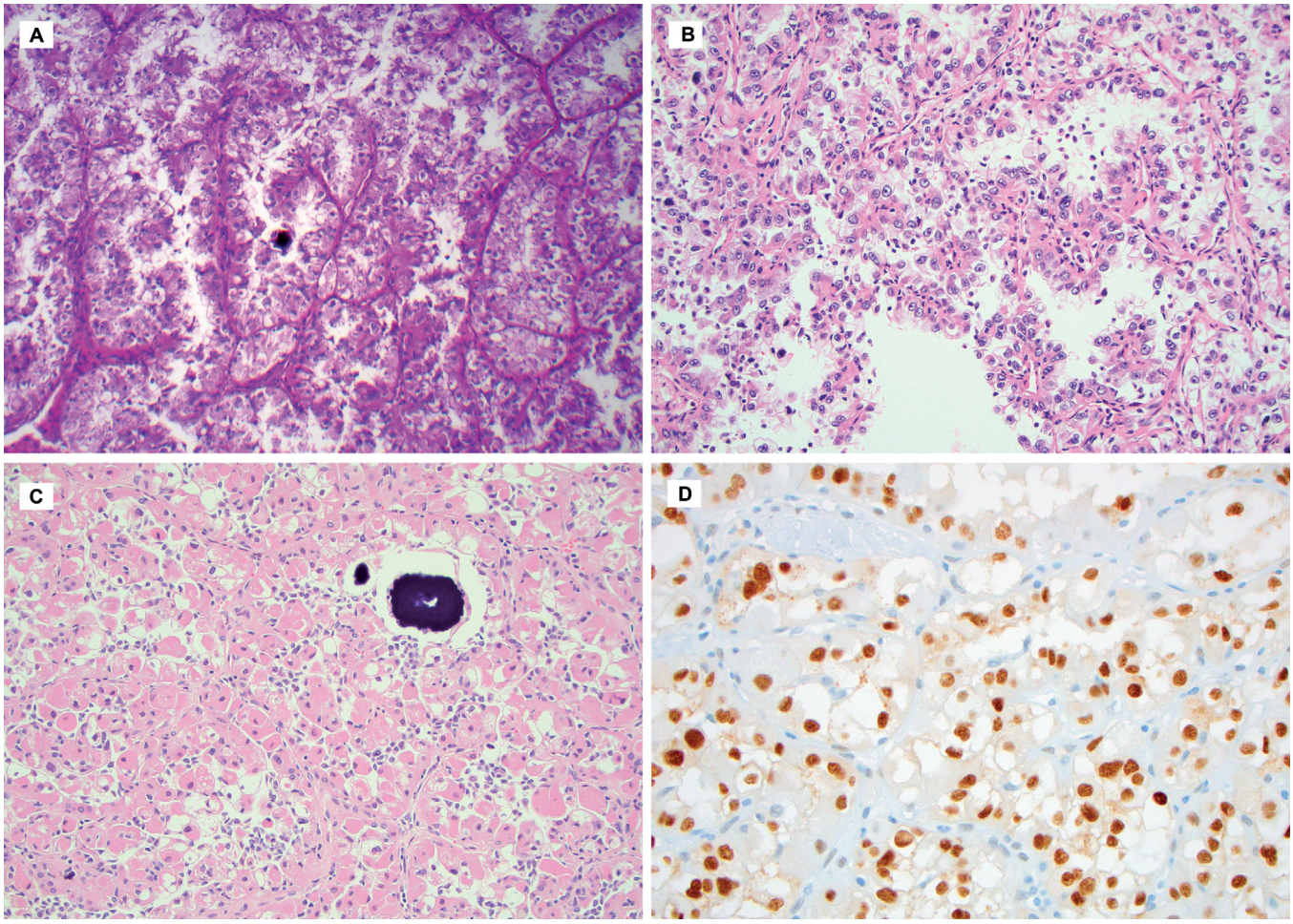

Fig. 1. A. *ASPL-TFE3* translocation RCC shows a papillary architecture with psammoma body. The tumor cells have a granular and clear cytoplasm. **B.** *RBM10-TFE3* translocation RCC demonstrates papillae with clear and granular cytoplasm. **C.** *NEAT1-TFE3* translocation RCC has a nested structure with psammoma bodies. It has biphasic tumor cells: cells with voluminous eosinophilic cytoplasm and cells with scant cytoplasm. **D.** TFE3 immunohistochemistry is positive in the *NEAT1-TFE3* RCC.

Matrova, 2020).

MITF translocation RCC

Durinck et al. reported a RCC exhibiting oncocytic and papillary feature had *ACTG1-MITF* translocation (Durinck et al., 2015). Recently, Xia et al. reported a RCC with *PRCC-MITF* translocation. The tumor showed glandular/tubular architecture with small cells forming a pseudorosette-like pattern. The tumor cells had abundant clear or eosinophilic cytoplasm with psammoma bodies and basement membrane. It is positive for cathepsin K but negative for TFE3, TFEB, HMB45, Melan A and MITF (Xia et al., 2018).

In summary, MITF family translocation RCC should be considered when a RCC demonstrates a papillary and nested architecture with voluminous clear and/or eosinophilic cytoplasm, psammoma bodies and hyalinized stroma, especially in a young patient (Williamson et al., 2020).

PEComa / Melanotic *TFE3* translocation renal cancers

PEComas are composed of distinctive perivascular epithelioid cells (Board, 2020; Utpatel et al., 2020; Caliò et al., 2021a). This tumor has a wide anatomical distribution, including previously known angiomyolipoma of the kidney, lymphangiomyomatosis, and clear cell sugar tumor of the lung. Most of PEComas show loss of heterozygosity (LOH) for the *TSC2* tumor suppressor gene at chromosome band 16p13.3. About 15% of PEComas have strong TFE3 nuclear staining; however, only a small portion of these harbor a *TFE3* translocation (Argani et al., 2010b; Ohe et al., 2012; Utpatel et al., 2020; Bennett et al., 2021). The fusion genes include *SFPQ-TFE3* (Tanaka et al., 2009; Agaram et al., 2015; Rao et al., 2015), *DVL2-TFE3, NONO-TFE3* (Argani et al., 2016a) and *RBMX-TFE3* (Argani et al., 2019) (Fig. 2C,D) (Table 1). *SFPQ-TFE3* is the most common fusion gene (Caliò et al., 2021a). *TEF3* translocation PEComas lack *TSC2*

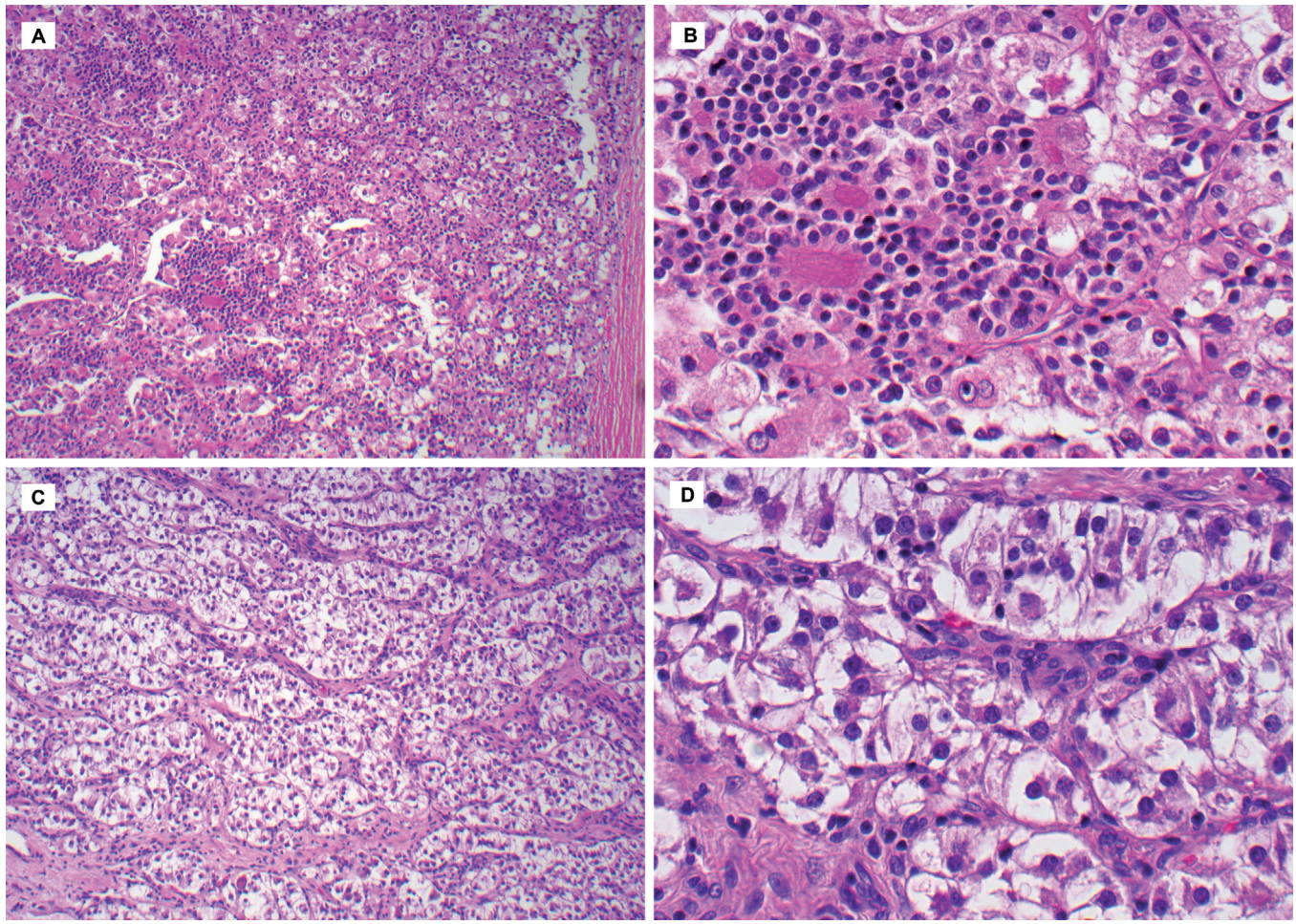

Fig. 2. A. *TFEB* translocation RCC shows a nested architecture and two cell populations. **B.** High-power of Fig A show a characteristic biphasic pattern: larger cells with clear and granular cytoplasm and smaller cells clustered around hyaline material. **C.** PEComa with *SFPQ-TFE3* translocation demonstrates nested tumor cells with clear cytoplasm. **D.** High-power of Fig C shows the clear tumor cells have focal granular/eosinophilic cytoplasm.

mutation/LOH which suggests it is a pathogenetically distinct entity (Malinowska et al., 2012; Agaram et al., 2015; Board, 2020).

Melanotic *TFE3* translocation renal cancers are now thought to represent pigmented *TFE3* translocation PEComas. (Argani et al., 2009, 2010b; Rao et al., 2015; Antic et al., 2017).

Alveolar soft part sarcoma (ASPS)

ASPS is a rare sarcoma of uncertain histogenesis characterized by an unbalanced recurrent X;17 translocation, which leads to a *ASPL-TFE3* fusion gene (Ladanyi et al., 2001; Paoluzzi and Maki, 2019). The *ASPL-TFE3* in ASPS is typically a non-reciprocal rearrangement, der(17)t(X;17)(p11;q25), unlike the balanced t(X;17)(p11;q25) observed in *ASPL-TFE3* translocation RCC (Ladanyi et al., 2001; Argani, 2015). This sarcoma predominantly involves the deep soft tissue of the extremities. It shows nested epithelioid tumor cells forming a distinct alveolar appearance due to the central discohesion (Fig. 3A). The tumor cells have eosinophilic cytoplasm with prominent nucleoli (Board, 2020). It is positive for TFE3 and cathepsin K, and it is negative for keratin, EMA, Pax8 and HMB45 (Williams et al., 2011; Jaber and Kirby, 2015; Board, 2020). Some of the translocation RCCs may have similar morphology and immunoprofile, except for their positivity for Pax8 and negativity for cathepsin K (Argani et al., 2016a; Pei et al., 2019).

Ossifying fibromyxoid tumor (OFMT)

OFMT is a rare mesenchymal tumor of uncertain

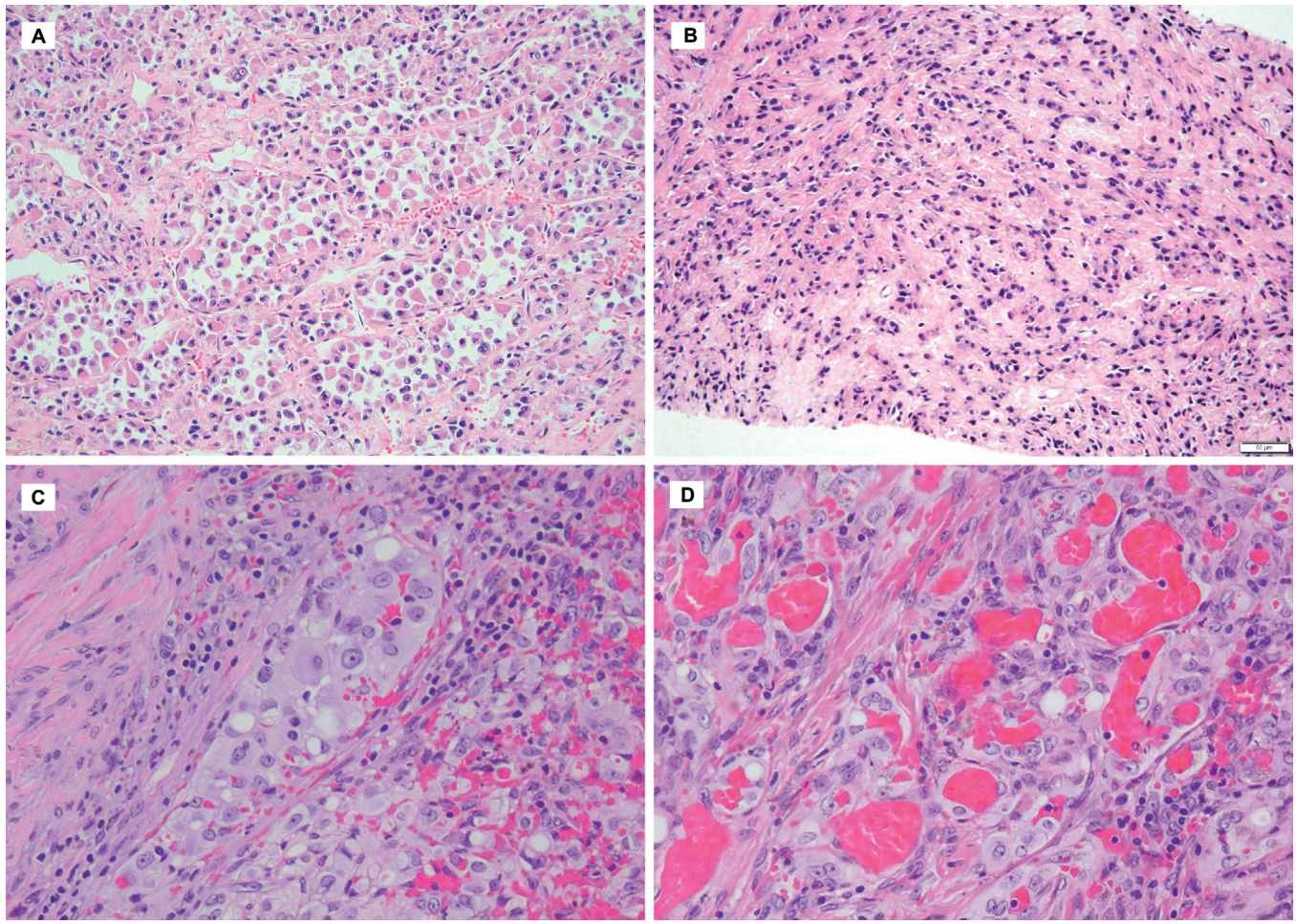

Fig. 3. A. Alveolar soft part sarcoma has typical nested epithelioid tumor cells forming a distinct alveolar appearance due to the central discohesion. The tumor cells have eosinophilic cytoplasm with prominent nucleoli. **B.** Ossifying fibromyxoid tumor with *PHF1-TFE3* translocation shows bland monotonous round to spindle tumor cells forming cords or nests in a fibromyxoid stroma. **C.** Epithelioid hemangioendothelioma with *YAP1-TFE3* has epithelioid endothelial cells with cytoplasmic vacuoles representing incomplete vascular space formation. **D.** Epithelioid hemangioendothelioma with *YAP1-TFE3* shows focal well-formed vascular channels (Figs. 3B-D, courtesy of Dr. Cristina R. Antonescu, Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York).

differentiation. This tumor often (81%) has a capsule and an incomplete peripheral mature bony shell (Zou and Billings, 2016). The bland monotonous round to spindle tumor cells usually form cords or nests in a fibromyxoid stroma (Fig. 3B) (Board, 2020). The tumor is often positive for S100 and desmin and negative for keratin and EMA. The majority of OFMTs display gene fusions, most frequently involving the *PHF1* gene, including *EP400-PHF1, MEAF6-PHF1* and *EPC1-PHF1* (Board, 2020). Recently Suurmeijer et al. reported *PHF1-TFE3* fusions in five OFMTs with strong nuclear TFE3 staining. However, these OFMTs did not have a peripheral bony shell. Three of the five cases developed metastases (Suurmeijer et al., 2019).

A single case of malignant chondroid syringoma displaying a *PHF1-TFE3*/t(X;6)(p11;p21) fusion has been described (Panagopoulos et al., 2019). Malignant chrondroid syringoma is a very rare tumor also known as malignant mixed tumor (Elder et al., 2018). Myoepithelial cell predominant mixed tumor may be difficult to distinguish from OFMT (Zou and Billings, 2016). In retrospect, this case may represent OFMT with *PHF1-TFE3*. Since PHF1 resides at the N-terminus of the *PHF1-TFE3* fusion gene compared to C-terminus in other fusion genes in OFMT, *PHF1-TFE3*-positive OFMT may have a distinctive molecular pathogenesis.

Epithelioid hemangioendothelioma

Epithelioid hemangioendothelioma is typically a low/intermediate grade malignant vascular neoplasm consisting of epithelioid endothelial cells with cytoplasmic vacuoles representing incomplete vascular space formation and fibromyxoid stroma. A *WWTR1-CAMTA1*/t(1;3)(p36;q23-25) can be found in more than 90% of epithelioid hemangioendotheliomas (Board, 2020; Rosenbaum et al., 2020). Antonescu et al. reported a *YAP1-TFE3*/t(X;11)(p11;q22) in 10 epithelioid hemangioendotheliomas without a *WWTR1-CAMTA1* (Antonescu et al., 2013). These tumors show distinct morphology including well-formed vascular channels, in addition to a variably solid growth pattern (Fig. 3C,D). The tumors express endothelial markers as well as strong nuclear TFE3. However, *WWTR1-CAMTA1*-positive epithelioid hemangioendotheliomas may also show positive staining for TFE3 (Flucke et al., 2014; Doyle et al., 2016). Patients with *YAP1-TFE3*-positive epithelioid hemangioendothelioma had a favorable clinical outcome compared to patients with *WWTR1-CAMTA1*-positive tumor (Rosenbaum et al., 2020).

Clear cell tumor with melanocytic differentiation and *ACTIN-MITF* translocation

Fouchardiere et al. recently reported a group of clear cell cutaneous tumors with melanocytic differentiation that had either *ACTB-MITF* or *ACTG1-MITF* translocations. The fusion genes preserve the *MITF* bHLH-LZ domain for dimerization and transcriptional activation (de la Fouchardiere et al., 2021b), which is also preserved in *TFE3* and *TFEB* related fusion genes (Perera et al., 2019). MITF is the regulator of melanin synthesis, which explains the expression of Melan A and HMB-45. This tumor type may represent a new variant of PEComa; however, 5 of 7 reported tumors also had S100 expression, which is not common in PEComa (de la Fouchardiere et al., 2021b). The differential diagnosis includes melanoma, clear cell sarcoma, and cutaneous metastasis of RCC with melanocytic differentiation. The limited follow up data are suggestive of an aggressive or malignant course (de la Fouchardiere et al., 2021b). Fouchardiere et al. recently also reported a tumor with clear cell features and melanocytic differentiation with a *MITF-CREM* translocation that showed morphologic, immunohistochemical, and molecular similarity to clear cell sarcoma. CREM is a member of the ATF1/CREB1/CREM family. The most common translocations in clear cell sarcoma are *EWSR1-ATF1* and *EWSR1-CREB1*. The *MITF-CREM* gene fusion may be analogous to these fusions (de la Fouchardiere et al., 2021a).

Summary

Our knowledge on neoplasms with MITF family translocations has rapidly expanded recently. Activation of MITF family members by a wide assortment of translocation fusion partners contributes to the pathogenesis of a variety of tumors. They may play a different role in the carcinogenesis of distinct neoplasms. Further investigation on the mechanism and function of these molecular oncogenic events is warranted to advance our understanding of the biology of these associated neoplasms and to identify novel approaches for therapeutic intervention.

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