Gene of the month: TFE 3

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ABSTRACT

Transcription factor enhancer 3 (TFE3), on the short arm of chromosome Xp11.23 and its protein, belongs to the microphthalmia transcription family (MiTF) of transcription factors. It shares close homology with another member of the family, MiTF which is involved in melanocyte development. When a cell is stressed and/or starved, TFE3 protein translocates into the nucleus. TFE3 gene fusions with multiple different partner genes occur in several tumours with resultant nuclear expression of TFE3 protein. The main tumours associated with TFE3 gene fusions are: renal cell carcinoma, alveolar soft part sarcoma, a subset of epithelioid haemangioendotheliomas (EHE), some perivascular epithelioid cell tumours and rare examples of ossifying fibromyxoid tumour and malignant chondroid syringoma. TFE3 immunohistochemistry is of use in routine diagnostic practice with the aforementioned tumours harbouring TFE3 fusions leading to nuclear staining. In addition, there are tumours lacking TFE3 fusions but also display TFE3 nuclear immunolabeling, and these include: granular cell tumour, solid pseudopapillary neoplasm of the pancreas and ovarian sclerosing stromal tumour.

INTRODUCTION

The TFE3 gene belongs to the MIcrophthalmia/Transcription Family (MiTF) or Transcription Factor Enhancer family (TFE) that are characterised by a basic helix-loop-helix (bHLH) leucine zipper dimerisation motif, a transactivation domain and a common basic region required for DNA binding.[1–3] The MiTF/TFE family encode for four genes: MiTF, TFEB, TFE3 and TFEC.[4]

As the role of autophagy and lysosomes in cancer became apparent and evolved, the MiTF/TFE family of genes were noted to play a pivotal role in this process.[4] In the presence of cell hypoxia or starvation, these proteins relocate from the cytoplasm to the nucleus.[3] Under normal circumstances, MiTF/TFE proteins are regulated by several pathways: Mechanistic Target of Rapamycin C1, Mitogen-Activated Protein Kinase, Extracellular signal-Regulated Kinase and Glycogen Synthase Kinase 3. These pathways also play a role in MiTF/TFE nuclear localisation.[3]

MiTF is principally responsible for melanocyte development and function, but TFE3 and TFEB both have a strong homology with MiTF.

Transcription factor binding to IGHM enhancer 3

Gene and protein

The TFE3 (sometimes called TFEA) gene is located at chromosome Xp11.23, which is the short (p) arm of the X chromosome at position 11.23 (see figure 1). It encodes a bHLH domain-containing transcription factor that binds MUE3-type E-box sequences in the promoter of genes. The encoded protein promotes the expression of genes downstream of transforming growth factor beta signalling.

Physiological role

TFE3 is present in many tissues and plays a major role in activation of the immune system (thought to be involved in T-cell antibody response),[5 6] control of allergic diseases,[7 8] development of osteoclasts[9] and regulation of the expression of critical metabolic regulators.[10]

TFE3 has a close relationship with TFEB and both are part of the cellular response to endoplasmic reticulum stress which results in their translocation to the nucleus of the cell.[11] When normal cellular homoeostasis exists, mTOR phosphorylation prevents TFE3/TFEB activation and translocation into the nucleus. In conditions of cellular stress/starvation mTOR phosphorylation is diminished leading to their nuclear translocation.

In the nucleus, they upregulate other important regulators involved in the cellular stress response resulting in initiation of autophagy, promotion of lysosomal activity and expression of critical metabolic regulators.[11]

Nuclear TFE3 protein is demonstrated immunohistochemically in a range of tumours (some displaying morphological similarity/homology), with and without TFE3 gene fusions. Figure 2 depicts, highlights and summarises these tumours.

In many instances, immunohistochemistry for TFE3, when combined with other antibodies, is of diagnostic value.

Tumours with *TFE3* gene abnormalities

Renal cell carcinoma with Xp11 translocation

Xp11 translocation renal cell carcinoma (RCC) is one of the most commonly encountered paediatric RCC and is distinguished by chromosome translocations involving the Xp11.2 breakpoint. These tumours demonstrate various *TFE3* gene fusions including: ASPSCR1(ASPL), PRCC, NONO, CLTC, SFPQ1, LUC7L3, KHSRP, PARP14, DVL2, RBM10, NEAT1, KAT6A and, unknown genes on chromosomes 10.[12–14] A potential pitfall in these gene fusions is that they may be missed if only the conventional TFE3 break-apart FISH assay is performed. Most of these RCC, do however, exhibit strong nuclear positivity for TFE3 immunostain, which can be used as a screening tool.

Each of these fusions with *TFE3* can result in consistent, unique RCC morphologies.

- NONO-TFE3 and SFPQ-TFE3 fusions: suprabasal nuclear alignment of tumour nuclei.

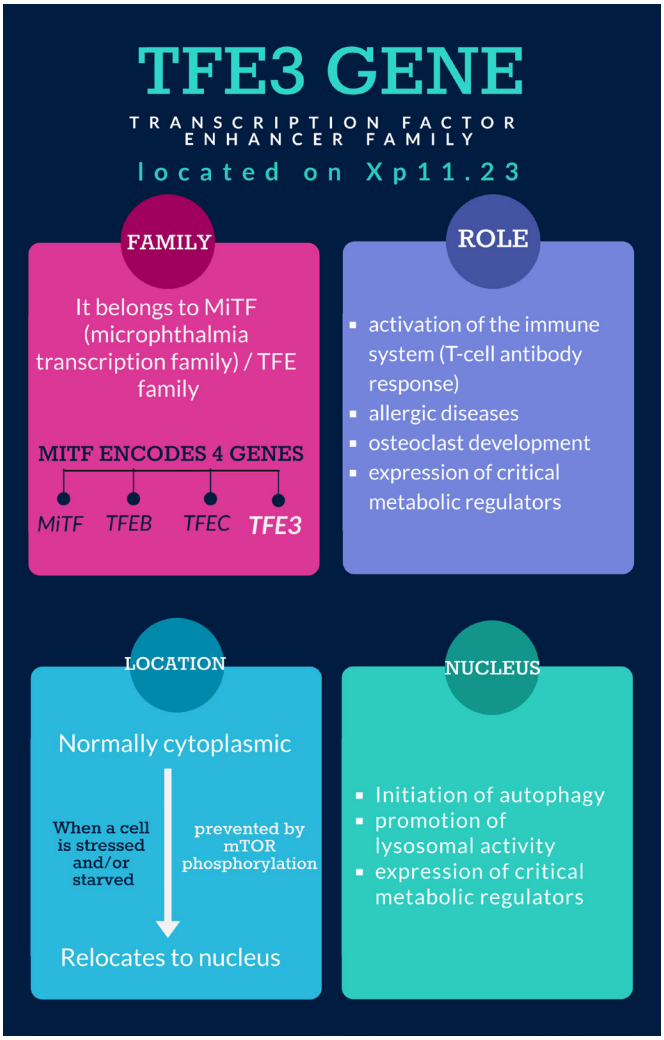

Figure 1 Schematic representation of the TFE3 gene and its physiological functions. MiTF, microphthalmia transcription family; mTOR, mechanistic target of rapamycin; TFE, transcription factor enhancer 3.

- MED15-TFE3: prominent cystic architecture within the tumour.
- SFPQ-TFE3: shows a biphasic morphology with pseudorosette formation and clusters of small grouped cells surrounding hyaline material.
- *S*ETD1B and PRCC: predominantly papillary architecture.
- ASPSCR1 and LUC7L3: mainly show a nested/alveolar pattern.[15]

An interesting feature is that these gene fusions are shared among other tumours of the *TFE3* family despite the morphology and sites of occurrence varying and being different. For instance, the ASPSCR1/TFE3 gene fusion has been identified in some alveolar soft part sarcomas (ASPS).[16]

Alveolar soft part sarcoma

ASPS is a malignant mesenchymal tumour with an ASPSCR1-TFE3 fusion molecular signature: (der(17)t(X;17)(p11.2;q25) translocation. This results in the fusion of TFE3 transcription factor gene at Xp11.2 with ASPSCR1 (also known as ASPL) at 17q25. As mentioned earlier, the same gene signature is also present in a subset of RCCs, which have a nested and pseudopapillary architecture and are composed of clear, epithelioid tumour cells.

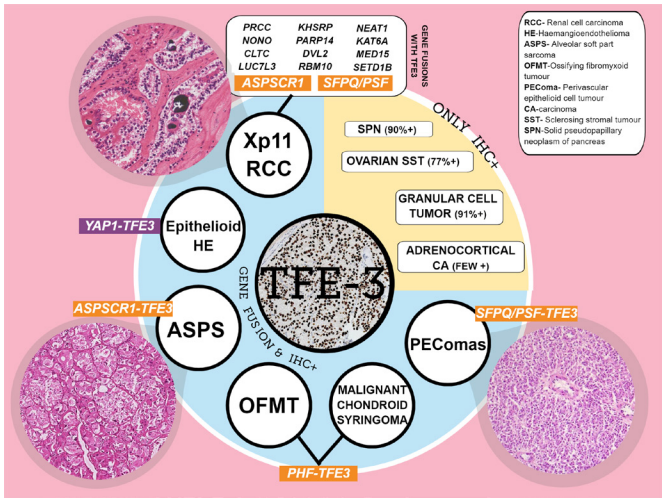

Figure 2 This composite illustration demonstrates the tumours bearing TFE3 fusions and, those tumours that express nuclear TFE3 protein demonstrated immunohistochemically in the absence of TFE3 fusions. TFE, transcription factor enhancer 3.

However, in RCC there appears to be a preferentially balanced translocation, while in ASPS the translocation is unbalanced. Considering this molecular overlap, difficulties may arise when assessing a metastatic lesion or limited material containing this morphology.[17]

The vast majority of ASPS show nuclear immunoreactivity for TFE3 protein.

Perivascular epithelioid cell tumour

Perivascular epithelioid cell tumours (PEComas) are now a well-recognised tumour constellation thought to arise from perivascular epithelioid cells and manifest a characteristic immunohistochemical profile. They show positivity with melanocytic and muscle markers. Within the family of PEComas both angiomyolipoma and lymphangioleiomyomatosis have been associated with Tuberous SClerosis 1 and *2* genes.

In a detailed study of soft tissue and gynaecological tract PEComa, Folpe *et al* described five cases which were TFE3 positive by immunohistochemistry.[18] Subsequently, Righi *et al* described two PEComas with nuclear immunoreactivity.[19] Both tumours were characterised by epithelioid cell morphology and cytoplasmic eosinophilia with granularity. Cho *et al* recapitulated these findings and concurred that these TFE3 positive-PEComas had a distinctly nested or packeted architecture and were composed of epithelioid cells with abundant clear or eosinophilic cytoplasm and distinct cell borders.[20] Indeed, these features were shared with translocation RCC and ASPS.

A molecular basis for nuclear TFE3 staining in PEComa was established by Tanaka *et al* who demonstrated a SFPQ/PSF-TFE3 gene fusion in a sigmoid colon PEComa.[21] It should be noted that this gene rearrangement is found in RCC. The tumour was composed of epithelioid cells arranged in an alveolar or pseudoglandular pattern and demonstrated nuclear immunoreactivity for TFE3.[21]

In view of the growing evidence displaying TFE3 immunostaining of PEComas, Argani *et al* undertook a study exploring TFE3 fusions in PEComas.[22] They showed that TFE3 gene fusions only occur in a small subset of PEComas and the immunohistochemical expression of TFE3 protein is not necessarily correlated with TFE3 fusions.[22] They ascribed the increased

immunoreactivity to automated immunohistochemical assays. The study delineated this subset of TFE3 fusion-PEComa as being characterised by: non-renal location, young patients, no history of tuberous sclerosis, epithelioid cells in an alveolar arrangement, paucity of muscle marker positivity and strong TFE3 immunoreactivity.[22] This was corroborated by a study on gynaecological tract PEComas which displayed TFE3 rearrangements, immunohistochemical expression of TFE3 protein and clear cell epithelioid cell morphology.[23] Melanoma and clear cell sarcoma of soft tissue may also show TFE3 nuclear immunoexpression which is focal and less intense that PEComas.[24]

Epithelioid haemangioendothelioma

Antonescu *et al* described a cohort of TFE3 immunopositive epithelioid haemangioendotheliomas (EHE) characterised by more obvious vessel formation than the conventional EHE, composed of epithelioid cells with abundant eosinophilic cytoplasm displaying mild to moderate cytological atypia.[25] The partner gene with TFE3 in this subset of EHE is *YAP1*. Flucke *et al* found only 2 of 33 EHE cases with a YAP1-TFE3 fusion but 21 of 24 cases showed nuclear staining for TFE3 protein, irrespective of TFE3 gene fusion status.[26] This study also confirmed that the two cases with *YAP1-TFE3* fusion showed more obvious vascular formation than those without this fusion.[26]

Ossifying fibromyxoid tumour

Ossifying fibromyxoid tumour (OFMT) display gene fusions most frequently involving the PHF1 gene, although the molecular profile has been expanding. PHF1-TFE3 fusions have been seen in a subset of OFMT and are important because these are associated with aggressive clinical behaviour.[27] These OFMT harbouring PHF1-TFE3 fusions also display strong nuclear staining for TFE3 antibodies.[27]

Malignant chondroid syringoma

A single case of malignant chondroid syringoma displaying a t(X;6)(p11;p21) resulting in fusion of the PHF1 gene from 6p21 with TFE3 on chromosome Xp11, has been described.[28]

Tumours with TFE3 immunoexpression but no gene abnormalities

Granular cell tumour

Argani *et al* first showed aberrant TFE3 nuclear staining in granular cell tumour (GCT).[29] Chamberlain *et al* compared the staining characteristics of ASPS with that of GCT.[30] In addition to 100% of ASPS being TFE3 positive, 91% of GCTs were also positive. Schoolmeester and Lastra confirmed nuclear staining in GCT for TFE3 and furthermore demonstrated that this aberrant expression occurred in the absence of TFE3 gene fusions.[31]

Solid pseudopapillary neoplasm of pancreas

Harrison *et al* demonstrated nuclear positivity for TFE3 in 30 of 31 solid pseudopapillary neoplasm (SPN) with 90% being moderate to strong intensity.[32] These authors also confirmed the absence of TFE3 gene fusions in SPN.[32]

Another study conducted by Jiang *et al* showed that 71 of 75 SPN showed moderate to intense nuclear labelling for TFE3.[33] They suggested that TFE3 immunohistochemistry is a useful marker in helping distinguishing SPN from other pancreatic look-alikes such as neuroendocrine tumours, which showed a lower rate of immunopositivity.[33]

Ovarian sclerosing stromal tumour

Seven of nine ovarian sclerosing stromal tumour were noted to be strongly immunopositive, while luteinzed thecomas and fibromas of the ovary were negative or weakly positive.[34]

Adrenocortical carcinoma

Very rare cases (3 of 60) were described with variable intensity staining by Argani *et al*.[29]

Take home messages

- Transcription factor enhancer 3 *(TFE3)* on Xp11.23, belongs to the microphthalmia transcription family of transcription factors and is involved in autophagy and lysosomal generation.
- When there is cellular stress and starvation TFE3 protein is translocated to the nucleus.
- TFE3 gene fusions are found in several tumours and with a number of partner genes.
- The principal tumours manifesting TFE3 fusions and nuclear TFE3 protein expression are: renal cell carcinoma, alveolar soft part sarcoma, a subset of epithelioid haemangioendotheliomas, some perivascular epithelioid cell tumours and rare examples of ossifying fibromyxoid tumour and malignant chondroid syringoma.
- Tumours lacking TFE3 fusions but showing nuclear immunolabeling that are of diagnostic value include: granular cell tumour, solid pseudopapillary neoplasm of the pancreas and ovarian sclerosing stromal tumour.

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