GTF2I gene mutation—a driver of thymoma pathogenesis

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Thymic epithelial tumors (TETs) are a rare malignancy overall, but are the most common anterior mediastinal tumors in adults. They are divided into thymomas (A, AB, B1, B2, B3 subtypes) and thymic carcinomas (1). Type A and AB thymomas are relatively indolent neoplasms (2). The B1, B2 and B3 thymomas however exhibit a propensity for local infiltrative growth and intrathoracic dissemination. Thymic carcinomas are the most aggressive TETs with frequent invasion of mediastinal structures as well as lymphatic and hematogenous spread (3).

Resection is the main treatment of TETs (4), chemoradiotherapy are used for advanced tumors (5). Targeted therapy has been limited to tyrosine kinase inhibitor treatment of the rare thymic carcinomas with a KIT mutation (6). The development of additional targeted therapies has been hindered by insufficient knowledge of the genetic alterations of TETs. Within the last few years next generation sequencing approaches however identified genetic alterations that drive the pathogenesis of TETs and revealed novel targets for therapy (7-12).

Petrini et al. applied whole exome sequencing to TETs and identified a unique missense mutation in the GTF2I gene (7). All the mutated tumors harboured the same single T>A nucleotide change at the same position on chromosome 7, which results in an amino acid change from leucine to histidine (p.Leu404His) in the GTF2I protein. The mutation was present in 82% of type A, 74% of type AB, 32% of B1, 22% of B2 and 21% of B3 thymomas but only 8% of thymic carcinomas.

The GTF2I gene encodes the transcription factor TFII-I, which is involved in the transcriptional regulation of several genes that control cell proliferation, cell cycle and developmental processes (13). TFII-I is activated in response to a variety of extracellular signaling pathways, including B and T cell receptor stimulation as well as growth factor signaling. TFII-I may have additional cytoplasmic functions that are independent of its nuclear transcription function (13). GTF2I is an essential gene, the ablation of GTF2I in mice causes early embryonic lethality (14).

The p.(Leu404His) mutation affects the second of six helix-loop-helix–like domains of TFII-I in proximity to its DNA binding site (7) and alters a residue within the amino acid sequence RILLAKE that may represent a noncanonical destruction box (7). The mutation may render TFII-I undetectable by the protein degradation system (7,13). This hypothesis is supported by the observation that mutant tumors exhibit higher TFII-I protein but not mRNA expression than wild-type tumors (7).

The GTF2I p.(Leu404His) mutation seems to be unique to TETs. However GTF2I missense mutations at other positions have been described in 6% of angioimmunoblastic T cell lymphomas (15). Furthermore, a gene fusion involving GTF2I and NCOA2 has been reported recently in a case of angiofibroma (16) and a
fusion of GTF2I and the retinoic acid receptor alpha has been recognised in a case of acute promyelocytic leukemia resistant to retinoic acid (17). The deletion of a region on chromosome 7 that contains the GTF2I locus is associated with Williams-Beuren syndrome (18) and the duplication of this region with the 7q11.23 microduplication syndrome, also known as Somerville—van der Aa syndrome (19). Both syndromes encompass malformations, mild to moderate mental retardation and abnormal social behaviour. Recent genome wide association studies revealed that GTF2I variants are involved in at least three autoimmune diseases: primary Sjögren's syndrome, systemic lupus erythematoses, and rheumatoid arthritis (20-22).

In the study by Petrini et al. patients with TETs bearing GTF2I mutations had a better prognosis than those bearing wild-type GTF2I (96% compared to 70% 10-year survival, respectively), reflecting the higher mutation frequency in less aggressive tumors (7). A recent study by Feng et al. determined the frequency of GTF2I mutations in a large cohort of 296 Chinese patients with TETs (23). One hundred and twenty-four (41.9%) patients harbored the GTF2I mutation. The mutation was present in 20 (87.0%) type A thymoma, 70 (78.7%) AB thymomas, 17 (29.3%) B1 thymomas, 8 (20.0%) B2 thymomas, 3 (10.0%) B3 thymomas, and 3 (7.7%) thymic carcinomas. These mutation frequencies are similar to the results of Petrini et al. (7), although obtained with an ethnically different patient cohort.

The GTF2I mutation was found more frequently in patients with early Masaoka stage (I–II, n=112, 90.3%) than in those with advanced stage (III–IV , n=12, 9.6%) (23). The presence of the GTF2I mutation correlated with better prognosis, 90.0% compared to 72.0% 5-year survival, and 86% compared to 56% 10-year survival, respectively. The only factor that predicted the presence of the GTF2I mutation was histological subtype. The GTF2I mutation did not correlate with age, gender and myasthenia gravis. Survival analysis stratified by stage revealed that, in every stage, patients carrying the GTF2I mutation had better prognosis than those carrying wild-type GTF2I. Multivariate analysis demonstrated that GTF2I mutation and Masaoka stage were independent prognostic factors in patients with TETs. In summary, the studies of Petrini et al. and Feng et al. demonstrate that GTF2I mutation is associated with better prognosis. This is mostly a consequence of its strong association with the more indolent A and AB thymomas. It remains to be determined whether a GTF2I mutation within the B1-B3 thymoma subtypes and in particular thymic carcinomas differentiates tumors with a good prognosis from tumors with a worse outcome.

The discovery of the GTF2I mutation in TETs is important for a better understanding of the pathogenesis of TETs. At present however GTF2I is not a target for therapy. Nevertheless a current clinical application might be the detection of the GTF2I mutation in small biopsy samples that are difficult to diagnose by histology alone, because the p.(Leu404His) mutation seems to be specific for TETs. Furthermore the development of a liquid biopsy assay for the detection of the GTF2I mutation may be envisaged. Such an assay might, provided that TETs release tumor DNA into blood, aid in the pre-operative diagnosis of mediastinal tumors and facilitate the therapy monitoring of GTF2I mutated tumors.

In general thymomas harbor a low number of mutations in comparison to thymic carcinomas (7,8,11,12). In thymic carcinomas the tumor suppressors TP53, CDKN2A, CYLD and PBRM1 and the oncogene KIT are amongst the most frequently mutated genes (7-12). Wang et al. furthermore revealed that mutations of genes involved in chromatin remodeling (SMARCA4), histone modification (BAP1, SETD2, ASXL1) and DNA methylation (DNMT3A, TET2, WT1) are frequent in thymic carcinomas, but not in thymomas (8).

In summary, next generation sequencing has revealed GTF2I as a master gene in the pathogenesis of TETs and identified many more genetic alterations that contribute to the development of TETs. The translation of these findings into the clinic will require the invention of more targeted drugs and multi-institutional trials, because of the rarity of TETs and the heterogeneity of mutated genes, with most mutations present only in the one digit percent range or below.

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Footnote
Conflicts of Interest: The author has no conflicts of interest to declare.

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