Editorial

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), chemo- and radiotherapy 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). In gene transfection assays the mutated GTFI increased cell proliferation. However, there was no difference in soft-agar colony formation, a cell culture assay that assesses the transforming capacity of genes, between mutant or wild-type *GTF2I* transfected cells (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 erythematodes, 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 GFT2I 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

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References

1. Marx A, Chan JK, Coindre JM, et al. The 2015 WHO Classification of Tumors of the Thymus: Continuity and Changes. J Thorac Oncol 2015;10:1383-95.
2. Weis CA, Yao X, Deng Y, et al. The impact of thymoma histotype on prognosis in a worldwide database. J Thorac Oncol 2015;10:367-72.
3. Travis WD, Brambilla E, Burke AP, et al. Editors. WHO classification of tumours of the lung, pleura, thymus and heart. Fourth edition. Lyon: IARC Press, 2015.
4. Ahmad U, Huang J. Current readings: The most influential and recent studies involving surgical management of thymoma. Semin Thorac Cardiovasc Surg 2013;25:144-9.
5. Merveilleux du Vignaux C, Maury JM, Girard N. Novel Agents in the Treatment of Thymic Malignancies. Curr Treat Options Oncol 2017;18:52.
6. Schirosi L, Nannini N, Nicoli D, et al. Activating c-KIT mutations in a subset of thymic carcinoma and response to different c-KIT inhibitors. Ann Oncol 2012;23:2409-14.
7. Petrini I, Meltzer PS, Kim IK, et al. A specific missense mutation in GTF2I occurs at high frequency in thymic epithelial tumors. Nat Genet 2014;46:844-9.
8. Wang Y, Thomas A, Lau C, et al. Mutations of epigenetic regulatory genes are common in thymic carcinomas. Sci Rep 2014;4:7336.
9. Shitara M, Okuda K, Suzuki A, et al. Genetic profiling of thymic carcinoma using targeted next-generation sequencing. Lung Cancer 2014;86:174-9.
10. Moreira AL, Won HH, McMillan R, et al. Massively parallel sequencing identifies recurrent mutations in TP53 in thymic carcinoma associated with poor prognosis. J Thorac Oncol 2015;10:373-80.
11. Enkner F, Pichlhöfer B, Zaharie AT, et al. Molecular Profiling of Thymoma and Thymic Carcinoma: Genetic Differences and Potential Novel Therapeutic Targets. Pathol Oncol Res 2017;23:551-64.
12. Lee HS, Jang HJ, Shah R, et al. Genomic Analysis of Thymic Epithelial Tumors Identifies Novel Subtypes Associated with Distinct Clinical Features. Clin Cancer Res 2017;23:4855-64.
13. Roy AL. Pathophysiology of TFII-I: Old Guard Wearing New Hats. Trends Mol Med 2017;23:501-11.
14. Enkhmandakh B, Makeyev AV, Erdenechimeg L, et al. Essential functions of the Williams-Beuren syndrome-associated TFII-I genes in embryonic development. Proc Natl Acad Sci U S A 2009;106:181-6.
15. Vallois D, Dobay MP, Morin RD, et al. Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell-derived lymphomas. Blood 2016;128:1490-502.
16. Arbajian E, Magnusson L, Mertens F, et al. A novel GTF2I/NCOA2 fusion gene emphasizes the role of NCOA2 in soft tissue angiofibroma development. Genes Chromosomes Cancer 2013;52:330-1.
17. Li J, Zhong HY, Zhang Y, et al. GTF2I-RARA is a novel fusion transcript in a t(7;17) variant of acute promyelocytic leukaemia with clinical resistance to retinoic acid. Br J Haematol 2015;168:904-8.
18. Pober BR. Williams-Beuren syndrome. N Engl J Med 2010;362:239-52.
19. Van der Aa N, Rooms L, Vandeweyer G, et al. Fourteen new cases contribute to the characterization of the 7q11.23 microduplication syndrome. Eur J Med Genet 2009;52:94-100.
20. Li Y, Zhang K, Chen H, et al. A genome-wide association study in Han Chinese identifies a susceptibility locus for primary Sjogren's syndrome at 7q11.23. Nat Genet 2013;45:1361-5.
21. Sun C, Molineros JE, Looger LL, et al. High-density genotyping of immune-related loci identifies new SLE risk variants in individuals with Asian ancestry. Nat Genet 2016;48:323-30.
22. Kim K, Bang SY, Ikari K, et al. Association-heterogeneity mapping identifies an Asian-specific association of the GTF2I locus with rheumatoid arthritis. Sci Rep 2016;6:27563.
23. Feng Y, Lei Y, Wu X, et al. GTF2I mutation frequently occurs in more indolent thymic epithelial tumors and predicts better prognosis. Lung Cancer 2017;110:48-52.

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