Comprehensive Molecular Characterization of Thymic Epithelial Tumors

Chul Kim[1], Tolulope Adeyelu[2], Rohan Maniar[3], Alex Farrell[2], Jacob Zaemes[1], Jeffrey Solzak[2], Bradley Hancock[2], Andrew Elliott[2], Ida Micaily[5], Misako Nagasaka[6], Jorge Nieva[7], Hossein Borghaei[8], Balazs Halmos[9], Patrick Ma[10], Milan Radovich[2], Sunil Badve[4], Patrick Loehrer[3].

[1]Georgetown University, [2]Caris Life Sciences, Phoenix, AZ, [3]Indiana University, [4]Emory University, [5]Sidney Kimmel Cancer Center at Thomas Jefferson University, [6]UCI Health, [7]University of South California, [8]Fox Chase Cancer Center, [9]Montefiore Medical Center, [10]Penn State Cancer Institute.

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Background

- Thymic epithelial tumors (TETs), which include thymomas (TMM) and thymic carcinomas (TC), are rare, yet they are the most common neoplasms in the anterior mediastinum.
- TETs can lead to significant morbidity and mortality.
- Thymomas are categorized into subtypes based on histological features (WHO subtypes - A, AB, B1, B2, B3)
- To develop more effective therapeutics for TETs, it is necessary to better understand their molecular underpinnings.
- Herein, we present the findings from an in-depth molecular characterization of TETs.

Methods

- TETs samples (n = 138; 55 from thymus and 81 from metastatic sites) were profiled using next generation sequencing (NGS) of DNA (592-genes/WES) and RNA (WTS) at Caris Life Sciences (Phoenix, AZ).
- Histological review was carried out to confirm the WHO subtypes for TETs.
- PD-L1+ expression was tested by IHC (SP142; ≥2+, ≥5%).
- Tumor Mutational Burden (TMB)-High was defined as ≥10 Mut/Mb.
- Cell infiltration in the tumor microenvironment was estimated by quanTIseq.
- Gene expression profiles were analyzed for transcriptomic signatures (T-cell-inflamed score) predictive of IO response.
- The relative expression (transcript per million -TPM) of surface antigens (surfaceome) were evaluated.
- Pathway enrichment was obtained using Gene Set Enrichment Analysis (GSEA).

Results

Table 1: Patient Demographics

Characteristic	Thymic Epithelial Tumor	Primary Tumor Sites	Metastatic Tumor Sites
Total, N cases	138	55	81
Age, Median [Range], years	60.5 [17-88]	60 [17-82]	60 [23-81]
Sex, n(%)			
Male	75 (54.3%)	35 (63.6%)	39 (48.1%)
Female	63 (45.7%)	20 (36.4%)	42 (51.9%)

Table 2: Alterations in Thymic Epithelial Tumors.

Molecular Alterations (%)	A (n=10)	AB (n=13)	B1 (n=6)	B2 (n=15)	B3 (n=46)	Thymic carcinoma (n=48)
TP53	0.0	0.0	0.0	6.7	10.9	29.2
GTF2I	30.0	23.1	0.0	6.7	2.2	0.0
KIT	0.0	0.0	0.0	0.0	15.2	6.3
KRAS	0.0	0.0	0.0	0.0	4.3	0.0
HRAS	10	0.0	0.0	0.0	0.0	6.3
PIK3CA	0.0	7.7	0.0	0.0	2.2	2.1
TMB-H	0.0	0.0	0.0	0.0	6.8	8.3
dMMR/MSI-H	0.0	0.0	0.0	0.0	2.2	8.3
High PD-L1 (≥ 50%)	37.5	60	20	87.5	51.2	28.3

Genomic Landscape of Thymic Epithelial Tumor

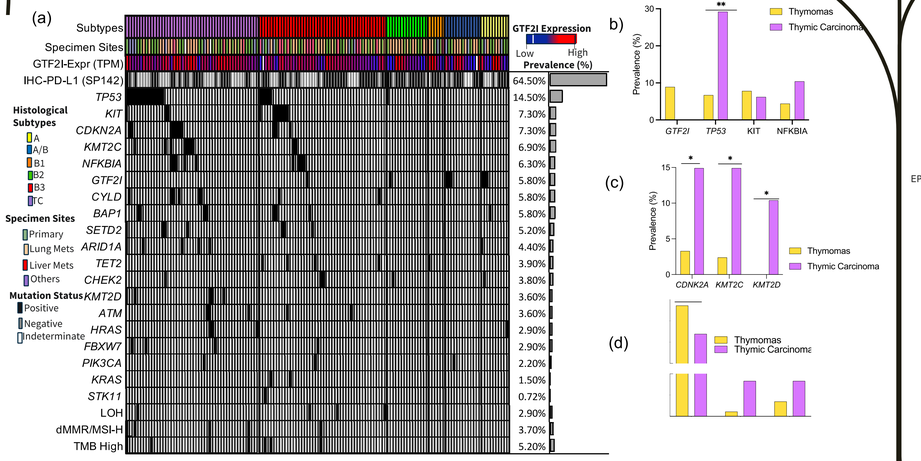


Figure 1: Genomic Landscape of Thymic Epithelial Tumor. Mutation in *GTF2I* exclusively observed in thymomas while alteration in dMMR/MSI-H was predominant in thymic carcinoma.

Tumor Microenvironment and IO Response Markers

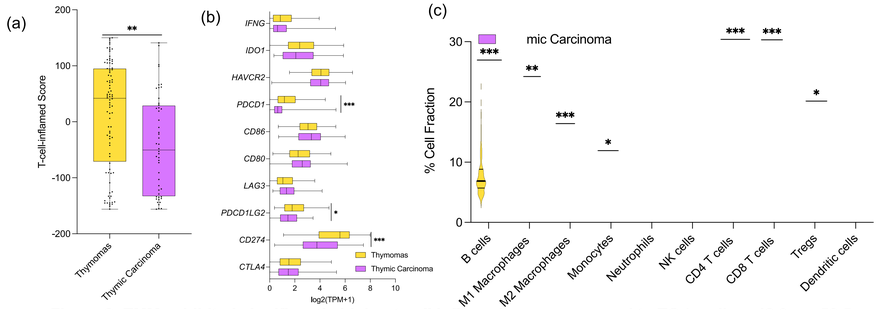
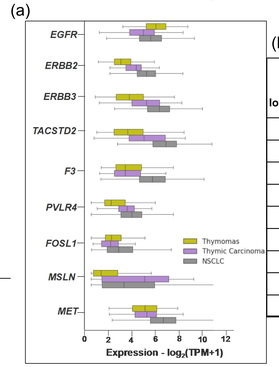


Figure 2: TMM exhibited significantly higher t-cell inflamed score compared to TC (median: 42.0 vs -50.5 a.u, $p<0.001$). Expression of immune checkpoint genes (PDCD1, PD-L2 and PD-L1) were significantly higher in TMM compared to TC. TMM exhibited significantly higher T cells (CD4+/8+), macrophages (M2) while TC had significantly higher B-cells and Tregs.

Expression of Surfaceome (SF) Genes in TETs



(b)

SF Genes (Median log2(TPM+1))	Thymomas	Thymic Carcinoma	NSCLC
TACSTD2	3.13*	4.52*	6.38
ERBB2	2.55*	3.85*	4.74
ERBB3	3.28*	4.73*	5.83
FOSL1	1.73*	1.67*	2.36
EGFR	5.53*	4.47*	5.08
PVRL4	1.73*	3.07	3.48
F3	2.91*	2.92*	5.24
MET	4.60*	4.77*	6.18
MSLN	0.87*	4.57	2.82

Gene Expression: Low Med High

*q<0.05 in comparison to NSCLC

Figure 3: Surfaceome genes (*ERBB2*: fold change (FC) = 1.51, *ERBB3*: FC = 1.45, *TROP2*: FC = 1.45, *NECTIN-4*: FC = 1.77 and *MESOTHELIN*: FC = 5.25) were significantly highly expressed in TC compared to T. Relative the NSCLC, TETs had a lower expression of surfaceome genes.

Gene Set Enrichment Analysis in TETs

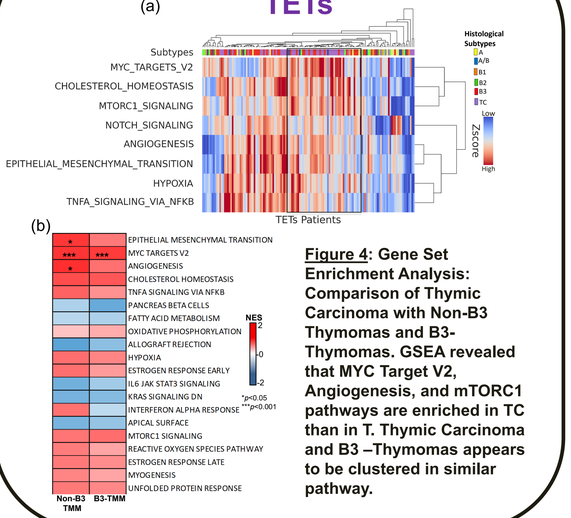


Figure 4: Gene Set Enrichment Analysis: Comparison of Thymic Carcinoma with Non-B3 Thymomas and B3-Thymomas. GSEA revealed that MYC Target V2, Angiogenesis, and mTORC1 pathways are enriched in TC than in T. Thymic Carcinoma and B3 –Thymomas appears to be clustered in similar pathway.

Conclusions

- **Our findings offer insights into the molecular characteristics of TETs and identify potential therapeutic targets, contributing valuable information for drug development.**
- **Specifically, the relatively high prevalence of dMMR/MSI-H status in TC underscores the potential utility of assessing dMMR/MSI-H in patients with TC.**

Contact

Dr. Chul Kim (chul.kim@gunet.georgetown.edu)
Georgetown University