Review Article

Insights into molecular aspects and targeted therapy of thymic carcinoma: a narrative review

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Background and Objective: Thymic carcinomas are rare tumors derived from thymic epithelial cells. Owing to their rarity, the search for molecular biology has been conducted in combination with thymoma as one histological subtype, and only a few studies have exclusively focused on thymic carcinoma. Currently, no therapy is more effective than complete surgical resection, and the development of novel therapies, including targeted therapies, is hampered. In this review, we summarize the knowledge regarding altered genes and pathways in thymic carcinoma with recent preclinical and clinical targeted therapies.

Methods: We conducted a narrative review of the relevant English literature available in PubMed and Google Scholar on genomic characteristics and targeted therapies for thymic carcinoma.

Key Content and Findings: Although the literature consists of a relatively small series, it suggests that the frequently involved genes or pathways associated with thymic carcinoma are tumor suppressor genes, including *TP53* and *CDKN2A/B*, and the receptor tyrosine kinase pathway. Targeted therapy demonstrated antitumor activity with encouraging results. However, potential predictive biomarkers have not been identified and the response to these therapies appears to be irrelevant to gene alterations.

Conclusions: Some studies have revealed the molecular characteristics of thymic carcinoma, although the results of these studies have shown a different pattern of gene alterations. The further accumulation of data would be helpful in revealing the genomic landscape and establishing molecular-targeted therapies.

Keywords: Thymic carcinoma; molecular profile; targeted therapies

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Introduction

Thymic carcinoma is an extremely rare thymic neoplasm, accounting for approximately 10% of thymic epithelial tumors (TETs) (1). In addition to their rarity, thymic carcinomas include various histological subtypes, with squamous cell carcinoma being the most common (2). Thymic carcinomas exhibit more aggressive behavior and a higher metastatic potential than thymomas (3). The median overall survival (OS) is 6.6 years, with 5- and 10-year OS rates of 60% and 40%, respectively. The prognosis for advanced disease, which accounts for approximately

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Table 1 Search strategy summary

Items	Specification
Date of search	15th July–10th August 2023
Databases and other sources searched	PubMed and Google Scholar
Search terms used	'thymic carcinoma', 'thymic epithelial tumor', 'gene' or 'genetic', 'mutation' or 'aberration' or 'alteration', 'molecular', 'targeted' or 'molecular targeting' and 'therapy'
Timeframe	Date unrestricted to August 2023
Inclusion and exclusion criteria	Inclusion criteria: (I) English language; (II) meta-analyses, systematic reviews, prospective studies, retrospective studies, case studies, and previous related reviews
	Exclusion criteria: studies with incomplete or irrelevant data
Selection process	One author compiled a list of eligible studies followed by review by all authors to determine suitability

70–75% of all cases, is miserable; the 5-year OS rates were 63% for stage III, 42% for stage IVa and 30% for IVb (4,5).

The factors associated with the development of TETs remain unknown; however, the understanding of the aberrant gene pathways involved in TETs has been gradually improving over the last decade, largely through the advent of next-generation sequencing (NGS) technologies. Previous studies have found that different histological subtypes of TETs exhibit different molecular profiles (6-10). In thymomas, a significant and recurrent missense mutation in the general transcription factor IIi (*GTF2I*) have been identified in type A and AB subtypes, which is reputed to drive their growth (6,8). In thymic carcinomas, owing to the rarity of these tumors and their histological heterogeneity, the results of studies show a different pattern of molecular aberrations with only a few significantly and recurrently mutated genes. Accordingly, data on their biology and clinical behavior are limited. In this review, we discuss the recent advances in the investigation of the molecular characteristics of thymic carcinoma and the development of potential targeted therapies. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-48/rc).

Methods

An extended review of the relevant literature in PubMed and Google Scholar was conducted, using different combinations of search terms, including 'thymic carcinoma', 'thymic epithelial tumor', 'gene' or 'genetic', 'mutation' or 'aberration' or 'alteration', 'molecular', 'targeted' or 'molecular targeting' and 'therapy'. The types of articles included in the search criteria were meta-analyses, systematic reviews, prospective studies, retrospective studies, case studies, and previous related reviews. Additional papers were identified by reviewing the reference lists of relevant publications. Publications with incomplete or irrelevant data, and those written in languages other than English were excluded. The search strategy is presented in *Table 1*.

Genetic alterations in thymic carcinoma

Tumor suppressor genes

In addition to the two early reports by Hirabayashi *et al.* and Tateyama *et al.* that showed a high frequency *TP53* point mutations in thymic carcinoma, Wang *et al.* and Moreira *et al.* reported that *TP53* mutations were exclusively observed in thymic carcinoma and were associated with aggressive behavior (7,11-13). Petrini *et al.* also identified recurrent mutations in *TP53* in thymic carcinoma (6). Several studies have found a high frequency of *TP53* in thymic carcinoma (7.7–25.7%), some of which showed that the presence of *TP53* mutations was associated with a poor prognosis (14-22). A recent study conducted by Girard *et al.*, which included the largest cohort, identified *TP53* mutations in 25.9% of 174 thymic carcinoma cases (9).

CDKN2A and *CDKN2B*, located on chromosome 9p21, encode p16 and p15, respectively, which act by inhibiting CDK4 and CDK6, and are negative regulators of cell cycle progression (23,24). In thymic carcinoma, Aesif *et al.* examined the expression of p16 by immunohistochemistry (IHC) and cytogenetic abnormalities of *CDKN2A* by

fluorescence in situ hybridization (FISH) (25). They reported that 53.8% (14/26) of the cases showed the expression of p16 and 19.0% (4/21) had homozygous deletion of *CDKN2A*, suggesting that the loss of p16 expression and homozygous deletion of *CDKN2A* could be predictors of a poor prognosis. Another study reported that copy number aberrations of *CDKN2A* and *CDKN2B* are associated with a worse prognosis in thymic carcinoma (26). Two recent NGS analyses with large cohorts showed similar results: the mutation frequencies of *CDKN2A* and *CDKN2B* were high: approximately 40% for *CDKN2A* and approximately 25% for *CDKN2B* (9,27).

CYLD and *BAP1* are both tumor suppressor genes, and mutations in these genes have been detected in 8.5–18.8% and 8.2–12.5% of thymic carcinomas, respectively (6,7,9,13,27,28). According to the results of a phase 2 study of pembrolizumab by Giaccone *et al.*, there were five patients with a *CYLD* mutation (12.2%) among 41 patients with thymic carcinoma, and these five patients exhibited high expression of programmed death-ligand 1 (PD-L1), three of whom had a complete response (CR) or partial response (PR) (29). He *et al.* characterized the genomic profiles of ten patients with thymic carcinoma who received pembrolizumab and identified that alterations in *CYLD* were promising predictors of a response to pembrolizumab (30). Meanwhile, they found that mutations in *BAP1*, which were also correlated with the expression of PD-L1, were promising predictors of pembrolizumab resistance (30). Angirekula *et al.* demonstrated that 11.4% of thymic carcinomas had lost the nuclear expression of BAP1, and that the loss of BAP1 expression may help distinguish thymomas from thymic carcinomas (31).

Receptor tyrosine kinases

The epidermal growth factor receptor (EGFR) is frequently mutated and/or overexpressed in different types of human cancers and is a target of multiple cancer therapies (32). Several studies investigated the EGFR expression levels in thymic carcinoma using IHC and reported that EGFR was overexpressed in 20.0–100.0% of cases (33-39). However, *EGFR* mutations are rare in thymic carcinomas (18,21,35-37,40-42).

KIT plays a major role in the development and maintenance of gastrointestinal stromal tumors (GISTs). Since Pan *et al.* found that thymic carcinoma frequently overexpressed KIT, whereas thymoma was found to be consistently negative for KIT by a systematic survey using a tissue array technique, alterations or expression of KIT in thymic carcinoma have been well-demonstrated in the literature (43). Immunohistochemical KIT positivity is found in 50.0–88.2%, although *KIT* mutations are relatively rare (19,33,37,44-46). The expression of KIT has been associated with activating mutations in exons 9, 11, 13, and 17 of *KIT*. *KIT* and *PDGFRA* are highly homologous and activate similar downstream signal transduction pathways (47). *PDGFRA* mutation, which is also considered to be a major driver gene of GISTs, is reported to occur in 0.0–5.6% of thymic carcinomas (19,42,44).

HER-2/neu is a proto-oncogene, and gene amplification and the overexpression of HER-2 have been demonstrated to be targets for several cancers (48). Pan *et al.* found that 47.1% (8/17) of thymic carcinoma overexpressed HER-2 by IHC, while no evidence of gene amplification was detected by FISH (49). According to a study conducted by Weissferdt *et al.*, the significant immunohistochemical expression of HER-2 was observed in 58.3% (14/24) of cases, while 4.2% (1/24) showed *HER-2/neu* gene amplification, and 75.0% (18/24) exhibited increased *HER-2/neu* gene copy numbers (39). Genetic alterations of *HER-2/neu* are rare (9,42).

Insulin-like growth factor 1 receptor (IGF-1R) is a transmembrane receptor involved in cancer development, metastasis, and therapeutic resistance (50). Zucali *et al.* analyzed the IGF-1R expression in eight cases of thymic carcinoma by IHC, and seven cases (87.5%) were positive for IGF-1R (51). They also found that the expression of IGF-1R was significantly more common in aggressive histological subtypes than in indolent ones. Meanwhile, *IGF-1R* mutations have been reported to be rare, with a frequency of less than 8.3% (9,14,21).

FGFR3 encodes a member of the FGFR family (52). Aberrant FGFR signaling has been reported in many cancers, including breast cancer and colorectal cancer, and contributes to oncogenesis, tumor progression, and resistance to anticancer therapies (53,54). Asselta *et al.* performed an NGS analysis targeting the hotspot regions of 50 oncogenes and tumor suppressor genes and found five *FGFR3* mutations in four (26.7%) out of 15 patients with thymic carcinoma (46). In this study, *FGFR3* was the most frequently mutated gene, and patients carrying *FGFR3* mutations showed significantly better survival. Enkner *et al.* reported, based on NGS with a gene panel, that 5.7% (2/35) of cases of thymic carcinoma harbored *FGFR3*

mutations; other NGS studies did not identify any *FGFR3* mutations (7,15-17,19).

Rat sarcoma virus (RAS)/mitogen-activated protein kinase (MAPK) cascade

EGFR-mediated activation of the canonical RAS/MAPK signaling cascade is responsible for cell proliferation and death. Gene mutations in this cascade are rare in thymic carcinoma. To date, only a few studies have identified low mutation rates of genes of the RAS family, including *HRAS*, *KRAS*, *NRAS*, as well as RAF genes, including *ARAF* and *BRAF* (9,18-20,42,46).

PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway

The frequency of gene alterations in this signaling pathway in thymic carcinoma is low. Alberobello *et al.* first reported mutations in the subunits of *PI3K* using thymic carcinoma cell lines (55). Several studies that used NGS have reported that mutations of *PI3K*, *Akt*, *mTOR*, and *TSC1/2* were detected in 0.0–5.0% of thymic carcinoma (6,8,9,14,17,27,46).

PTEN

PTEN is a tumor suppressor gene that plays a role in growth and survival and is a negative regulator of the PI3K/Akt signaling pathway (56). There have only been a few reports on PTEN expression or *PTEN* mutations. Masunaga *et al.* analyzed TET samples, including four cases of thymic carcinoma, for the expression of PTEN, *PTEN* exon mutations, and PTEN promoter methylation (57). They found that the PTEN protein was immunohistochemically expressed in all thymic carcinoma cases; however, they did not detect *PTEN* mutations. Enkner *et al.* reported that the expression of PTEN was found in 30 of 31 thymic carcinoma cases (96.8%), 14 (45.2%) of which showed high expression levels (15).

GTF2I

Previous reports have revealed that the *GTF2I* point mutation (L424H) was the most frequent mutation in thymomas, especially in indolent type A and AB thymomas (6,8). However, *GTF2I* mutations have not been identified in thymic carcinoma (6,8,58).

Tumor mutation burden (TMB) and microsatellite instability (MSI) in thymic carcinoma

Multiple biomarkers related to immune checkpoint inhibitors (ICIs), as well as the immunohistochemical detection of PD-L1 in tumor cells, have been identified. The TMB and MSI have been clinically used in several oncologic cases.

The TMB refers to the total number of somatic non-synonymous mutations in a particular region of the tumor genome. A TMB of ≥10 mutations per megabase was reported to predict a better response to ICIs in non-small cell lung cancer (NSCLC) (59). According to the comprehensive genomic analysis of TET in The Cancer Genome Atlas (TCGA) Project, the TMB of thymic carcinoma was high (21.29 mutations per megabase), while TETs had the lowest average TMB (0.48 mutations per megabase) among adult cancers (8). Hou *et al.* also found a similar trend, in that the TMB of thymic carcinoma was significantly higher than that of thymoma (58). In contrast, two studies from China reported that the average TMB value of patients with thymic carcinoma was 0.72 and 0.66 mutations per megabase (10,60). According to a recent study by Kurokawa *et al.*, who examined data from a cohort of TET cases in the United States using the Foundation Medicine Inc. research database, the prevalence of TMB-high cases was 7.0% (27). Conforti *et al.* conducted a phase 2 study of the combination of the anti-PD-L1 inhibitor avelumab with the anti-angiogenesis drug axitinib in patients with advanced thymic carcinoma (n=27), B3 thymoma (n=3), and mixed-type thymic carcinoma and B3 thymoma (n=2) (61). Although this population was not limited to patients with thymic carcinoma, there was a positive association between a higher TMB and the response rate.

Microsatellites are short tandem repeats scattered throughout the genome and are prone to a high mutation rate. MSI is defined as a hypermutable phenotype that occurs in genomic microsatellites in the presence of a deficient DNA mismatch repair machinery (62). Several clinical trials have revealed that patients with MSI-high colorectal cancer benefit from ICI treatment (63). The data on MSI in thymic carcinoma are limited. According to a study by Kurokawa *et al.*, MSI-high cases accounted for 2.3% of thymic carcinoma cases, and Girard *et al.* reported that no MSI-high cases were found in 174 thymic carcinoma cases (9,27).

Targeted therapy in thymic carcinoma

Despite significant research efforts, the development of new drugs for thymic carcinoma is slow. Lenvatinib was approved in 2021 on the basis of a phase 2 trial, the REMORA study (64). Lenvatinib is a multitargeted kinase inhibitor of VEGFR, FGFR, KIT, and other kinases (64). The REMORA study assessed the activity of lenvatinib as a second-line treatment in 42 patients with advanced or metastatic thymic carcinoma and showed that 38.1% of patients had PR and 57.1% had stable disease (SD) with a median progression-free survival (PFS) of 9.3 months, which could be considered as the most promising results for previously advanced or metastatic thymic carcinoma. Currently, predictive biomarkers for lenvatinib activity have not been identified. Tsukaguchi *et al.* reported a lenvatinib-refractory thymic mucinous adenocarcinoma, whose *PIK3CA* mutation could be associated with resistance to lenvatinib (65).

Activating mutations in *KIT* and *PDGFRA* in GISTs are related to the response to the KIT inhibitor imatinib (66). Despite the rare *KIT* mutations in thymic carcinoma, several studies found that *KIT*-mutated thymic carcinoma showed a significant clinical response to imatinib (67,68). Sunitinib and sorafenib are multitarget tyrosine kinase inhibitors (TKIs) of *KIT* and other kinases. Thomas *et al.* observed a PR to sunitinib in 26.1% (6/23) of patients with thymic carcinoma and a SD in 65.2% (15/23); disease control was achieved in 91.3% (21/23) (69). Recently, Proto *et al.* conducted a phase 2 trial of sunitinib in patients with thymic carcinoma and found that 3.6% of the patients had CR, 17.9% had PR and 67.9% had SD; the objective response rate (ORR) was 21.4% and the disease control rate was 89.3% (70). At present, the correlations between the response to sunitinib and *KIT* mutation status are uncertain. Pagano *et al.* retrospectively evaluated sorafenib activity in five patients with metastatic thymic carcinoma, and reported that two patients (40.0%) achieved PR and two (40.0%) achieved SD (44). They also reported that sorafenib activity seemed independent from the *KIT* and *PDGFRA* mutation status. Perrino *et al.* reported the results of the Resound Trial, which examined the efficacy of regorafenib in seven patients with thymic carcinoma (71). Regorafenib potentially inhibits angiogenic and stromal receptor tyrosine kinases, VEGFR1-3, tyrosine kinase with immunoglobulin-like and EGF-like domains 2, and PDGFRB, which have been approved by the Food and Drug Administration for the treatment of colorectal cancer and GIST. SD was observed in six patients (85.7%) and progressive disease (PD) was observed in one patient (14.3%); the response was not satisfactory (71). Anlotinib is a new oral multitarget TKI targeting VEGFR1-3, FGFR1-4, PDGF-A and -B, and KIT (72). Several retrospective studies have examined the efficacy and safety of anlotinib in patients with relapsed or refractory TET (73,74). Wang *et al.* reported an ORR of 41.1% and a median PFS of 6 months (74).

Zucali *et al.* conducted a phase 2 study of everolimus, a potent oral mTOR inhibitor, in 18 patients with thymic carcinoma (75). Disease control was achieved in 77.8% of the patients (CR, n=1; PR, n=2; SD, n=11); the median PFS was 5.6 months and the median OS was 14.7 months. Hellyer *et al.* performed NGS with a 130-gene targeted panel on samples from 12 TET patients, including three with thymic carcinoma; however, they failed to identify correlations between detectable tumor mutations and everolimus activity (76). Predictive biomarkers for everolimus remain unclear.

Aesif *et al.* reported that CDK4/6 inhibitors may be considered for targeted therapy (25). Recently, Jung *et al.* conducted a phase 2 trial of palbociclib, an oral inhibitor of CDK4/6, in patients with recurrent or refractory advanced TETs, including 23 cases of thymic carcinoma (77). The PFS at 6 months was 52.2% and the median PFS and OS were 9.2 and 25.6 months, respectively. Two patients (8.7%) achieved PR, 16 (69.8%) achieved SD, and 18 (78.3%) achieved disease control.

Rajan *et al.* investigated the efficacy of cixutumumab, a fully human IgG1 monoclonal antibody that targets IGF-1R, in patients with TETs (78). The thymic carcinoma cohort was closed after enrolling 12 patients due to lack of activity. Five (41.7%) of 12 patients had SD and seven (58.3%) patients had PD; there were no objective responses and the disease control rate was 41.7%, with a median time to progression of 1.7 months and a median survival of 8.4 months. The tumor expression of IGF-1R did not appear as a good biomarker predictive response to anti-IGF treatment, as well as the raise of serum IGF-1 level.

EGFR-TKIs, a standard treatment modality for *EGFR*-mutated NSCLC, have not been proven to be effective in thymic carcinoma, although only a few case reports have described the clinical activity of EGFR-TKIs (79,80). In 2005, Kurup *et al.* conducted a phase 2 study of gefitinib and failed to demonstrate any activity in seven cases of thymic carcinoma (81). In 2008, Bedano *et al.* performed a phase 2 study of erlotinib plus bevacizumab in seven cases

with thymic carcinoma, and reported that it was associated with a limited response (82).

Somatostatin (SST) is a naturally occurring peptide composed of 14 amino acids. Among the five SST receptors identified, the most common SST receptor expressed in human tumors is the SST2 subtype, which is visualized using radionuclide octreotide scintigraphy. The octapeptide SST analog has a high affinity for a selective SST subtype receptor (SST2). Palmieri *et al.* and Loehrer *et al.* have conducted phase 2 trials of octreotide alone or with prednisone in patients with refractory or unresectable, advanced TETs who were positive in an octreotide scan (83,84). In these studies, the ORRs of the entire TET cohort were 37.5% and 30.3%, respectively; however, thymic carcinoma treatment did not produce an objective response. Kirzinger *et al.* conducted another phase 2 trial of octreotide in combination with prednisone in 17 patients with primary or locally recurrent unresectable TETs, including two patients with thymic carcinoma (85). In this trial, one patient had SD and one had PD.

The wild-type Wilms tumor gene, *WT1* is expressed in various types of neoplasms and has been considered to be a tumor suppressor (86,87). In recent years, WT1 has been identified as a target antigen for tumor-specific immunotherapy. Oji *et al.* conducted a phase 2 study of cancer immunotherapy with the WT1 peptide vaccine in patients with advanced TET, including nine patients with thymic carcinoma, which overexpressed the WT1 protein in tumor cells (88). Unfortunately, no patients achieved a CR or PR; 75.0% of patients with thymic carcinoma had SD and the remaining 25.0% of patients had PD without serious adverse events. Autoimmune complications related to thymoma, pure red cell aplasia, and myasthenia gravis occurred in two of four patients with thymoma.

Conclusions

Thymic carcinomas have a distinct genomic landscape characterized by a high prevalence of specific genes and a high TMB. Despite the rarity and histological heterogeneity of these tumors, several studies have revealed significant molecular alterations. However, there have been few suitable alterations for targeted therapy and the identified alterations seem to have little correlation with activity. Most clinical trials for thymic carcinomas have been conducted in combination with thymoma, although thymic carcinomas exhibit different biological behavior from thymoma in genetic, clinical, and immunological aspects. Continued data sharing and international collaborations would be helpful in better understanding the genomic landscape, leading to molecular targeted therapies.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-23-48/coif). The authors have no conflicts of interest to declare.

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