Mechanism of and research progress on alterations in the RET gene in thyroid cancer (Review)

MENG WEI[1], RUI WANG[2], JINCAN QIAN[3], QIANG FANG[1] and JUN TAO[4]

[1]Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230022, P.R. China; [2]Department of Oncology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui 230022, P.R. China; [3]First Clinical Medical College, Anhui Medical University, Hefei, Anhui 230022, P.R. China; [4]Department of Scientific Research, The First Hospital of Anhui University of Science and Technology, Huainan, Anhui 232007, P.R. China

Received December 10, 2025; Accepted February 19, 2026

DOI: 10.3892/mmr.2026.13874

Abstract. The global incidence of thyroid cancer (TC) has markedly increased in recent years, making it the most prevalent endocrine-related cancer worldwide. TC primarily originates from follicular and parafollicular cells of the thyroid gland, and includes four main pathological types: Papillary TC (PTC), follicular TC, medullary TC (MTC) and anaplastic TC. Notably, characteristic oncogenes and tumor suppressor genes are associated with TC, which are considered targets for the development of treatment strategies. The rearranged during transfection (RET) gene serves a pivotal role in the development of TC, and mutations and fusions of this gene are closely associated with the onset of MTC and PTC. The structure of RET includes four cadherin-like domains and 16 cysteine residues in its extracellular domain, which confer unique functionalities and contribute to its intracellular role. RET activation is a complex process involving multiple intracellular events, including calcium ion binding, glial cell line-derived neurotrophic factor family ligand binding, and RET receptor aggregation, dimerization and autophosphorylation. The present study reviews the structure and function of the RET proto-oncogene and its pathogenic roles in various TC subtypes.

Contents

Correspondence to: Dr Jun Tao, Department of Scientific Research, The First Hospital of Anhui University of Science and Technology, 203 Huaibin Road, Tianjia'an, Huainan, Anhui 232007, P.R. China
E-mail: wrwm416@126.com

Key words: thyroid cancer, RET, gene, protein structure, mechanism

1. Introduction

Thyroid cancer (TC) is currently the most common malignancy of the endocrine system and its incidence has steadily increased worldwide over the past 20 years (1,2). TC exhibits considerable heterogeneity and shares typical histopathological features with other tumors (3). The two varieties of epithelial cells that constitute the thyroid gland are follicular and parafollicular cells. Follicular cells convert iodine into T4 and T3, and the hormones T3 and T4 (tyrosine) regulate metabolism (4). By contrast, parafollicular cells are epithelial cells that produce calcitonin. Primary TC predominantly originates from thyroid follicular cells and is classified as an epithelial tumor, which can be categorized into three primary pathological types. The most prevalent type is papillary TC (PTC), followed by follicular TC (FTC), with the most aggressive form being anaplastic TC (ATC). Furthermore, medullary TC (MTC) arises from parafollicular cells (5).

Tumorigenesis is mainly driven by somatic mutations that occur during the initial stages of transformation. According to various genetic studies on TC, several oncogenes and tumor suppressor genes have been identified that can be used as diagnostic markers and therapeutic targets (6-8). For example, pathogenic loss-of-function mutations in genes responsible for tumor suppression constitute a common genetic event involved in TC. Crucial examples include phosphatase and tensin homolog and tumor protein 53, which are frequently inactivated via such mutations. These alterations are highly prevalent and well-characterized events driving the initiation and progression of TC. The use of targeted therapy in affected patients has become possible due to the development of tyrosine kinase inhibitors (TKIs) (9-11). The major driver mutations involved in TC mainly include B-Raf proto-oncogene (BRAF), RET (mutations/fusions) and RAS mutations. In addition, gene mutations related to the VEGFR and

PI3K/AKT/mTOR signaling pathways, as well as mutations in drug resistance-associated genes such as mesenchymal epithelial transition and neurofibromin 2, are also closely connected with the regulation of TKI efficacy and the mechanisms of drug resistance. TKIs function by competing with adenosine triphosphate (ATP) for binding sites, thus inhibiting phosphorylation by kinases, and ultimately preventing the signaling and proliferation of tumor cells (12). Novel and state-of-the-art genetic testing based on advanced next-generation sequencing has promoted the development of tumor-targeted therapies, in which the molecular drivers of tumorigenesis act as the therapeutic targets. Previous studies (13,14) have compared targeted therapies with non-targeted agents and immunotherapeutic agents lacking well-defined molecular targets, including chemotherapeutic drugs for advanced anaplastic thyroid carcinoma (ATC) and radioiodine-refractory differentiated thyroid carcinoma (RAIR-DTC), such as taxanes (paclitaxel, docetaxel), anthracyclines (doxorubicin), platinum-based agents (cisplatin, carboplatin, etc.), and PD-1/PD-L1 inhibitors (pembrolizumab, nivolumab). The results indicate that targeted therapies achieve superior efficacy and a lower incidence of off-target adverse events. The aim of the present study was to examine and summarize the role and organization of the rearranged during transfection (RET) proto-oncogene, along with its disease-causing mechanisms, in different variants of TC. In addition, the present revied aimed to investigate small-molecule inhibitors of tyrosine kinases that target RET mutations, and present a summary of advances in research on the management and treatment of TC linked to alterations in the RET gene.

2. Structure and physiological activation of the RET gene

The RET gene, which is located on chromosome 10q11.2 and encodes a 170 kDa transmembrane receptor tyrosine kinase, was first discovered by researchers in 1985 (15). Structurally, the RET protein comprises an extracellular region featuring four cadherin-like domains (CLD1-4), a calcium-binding site and a cysteine-rich domain (CRD), a transmembrane region, and an intracellular region containing the juxtamembrane domain and a bilobed tyrosine kinase domain (TKD). Under normal physiological conditions, RET activation is ligand-dependent. The binding of the glial cell line-derived neurotrophic factor (GDNF) family ligands, along with their co-receptor GDNF family receptor α, induces RET dimerization. This dimerization triggers the trans-autophosphorylation of specific tyrosine residues within the TKD (16-18). Subsequently, these phosphorylated residues serve as docking sites for downstream adaptor proteins, initiating crucial signaling cascades such as the RAS/MAPK and PI3K/AKT pathways, which govern essential cellular processes, including proliferation, differentiation and survival (Fig. 1) (19).

3. RET mutations and their role in MTC

The constitutive, ligand-independent activation of RET, primarily driven by specific mutations, is central to the pathogenesis of MTC (20-22). These activating mutations occur either in the germline (hereditary, 95-98%) or somatically (sporadic, 25-50%) (23-25). The 95-98% refers to germline mutations accounting for the majority of mutations in hereditary TC cases, while the 25-50% refers to somatic mutations in all TC cases (including sporadic ones); these two proportions describe different mutation subsets and are not mutually exclusive. The global age-adjusted incidence rate of germline RET mutations is estimated to be 0.06 cases per 100,000 persons/year, and the corresponding prevalence is 1.3 cases per 100,000 individuals (26,27).

Hereditary MTC and multiple endocrine neoplasia type 2 (MEN2) syndrome. Germline RET mutations are responsible for virtually all cases of hereditary MTC, which is categorized as a type of MEN2 syndrome. MEN2 is stratified into two primary clinical subtypes based on distinct genotype-phenotype associations (28,29).

MEN2A (~95% of cases): This subtype is characterized by MTC, a high frequency (~50%) of pheochromocytoma and primary hyperparathyroidism in 20-30% of patients (30). Approximately 95% of MEN2A mutations (all mutations described in the MEN2A subtype involve cysteine residues in the extracellular CRD and codon 634 in exon 11) affect cysteine residues within the extracellular CRD, with codon 634 in exon 11 being the most prevalent site (85%). The substitution of cysteine disrupts normal disulfide bonding, leading to aberrant, ligand-independent receptor dimerization and constitutive kinase activation (31-33).

MEN2B (~5% of cases): Recognized as the most aggressive form, MEN2B presents with early-onset, metastatic MTC, frequent pheochromocytoma, ganglioneuromatosis and marfanoid habitus (34,35). Over 95% of MEN2B cases are caused by a specific methionine-to-threonine substitution at codon 918 (M918T) in the TKD activation loop (36). This mutation fundamentally alters the conformation of the kinase, markedly enhancing its catalytic activity and enabling robust signaling even in a monomeric or dimerized state, independent of ligand binding (37,38). In addition, in <10% of MEN2B cases, A883F mutations or other combination mutations, such as valine-to-methionine substitution at codon 804 of RET (V804M), are involved (Fig. 2) (39,40). These mutations all occur in the RET gene.

Sporadic MTC: Somatic RET mutations are identified in ~55% of non-hereditary MTC cases (41). The prevalence of these mutations is associated with tumor burden, markedly rising in advanced or metastatic disease (42). The M918T mutation is again the most common somatic variant (~40%), underscoring its potent oncogenic potential. Other recurrent somatic mutation sites include codons 611, 618, 620, 630, 634, 768, 883 and 891 (43-47).

4. RET rearrangement/fusion and PTC

RET-activated tumors may arise from chromosomal rearrangements, which involve the fusion of the RET kinase domain with various protein partners that possess dimerization domains (48-50). This phenomenon occurs along with germline and somatic mutations that activate RET. Previous studies have proposed that the erroneous repair of DNA double-strand breaks serves a critical role in the molecular mechanisms that lead to RET fusion. Specifically, these chromosomal breaks facilitate the fusion of the 3' sequence

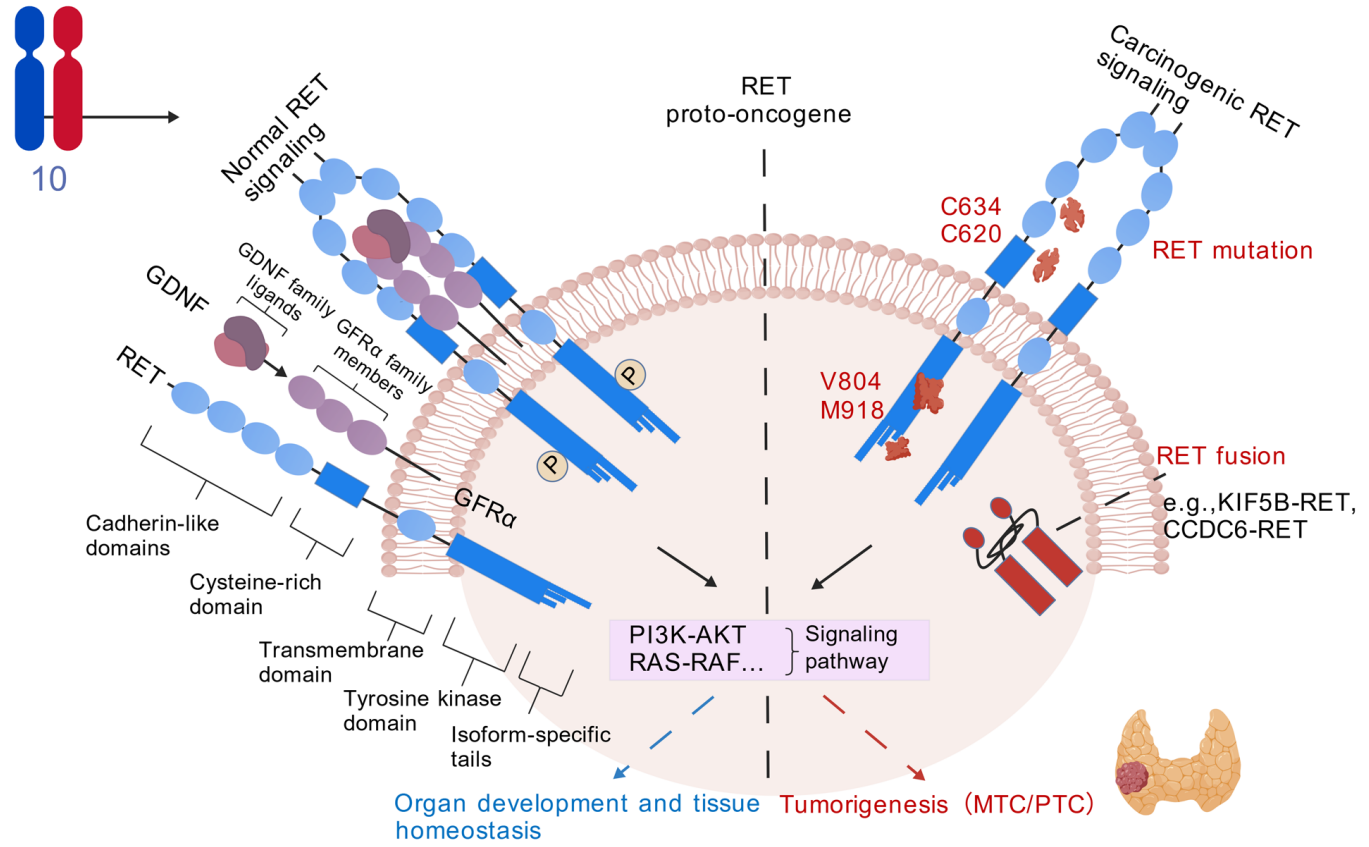

Figure 1. Structure of the RET gene and the mechanisms of its activation through mutations and fusions/rearrangements. GDNF, glial cell line-derived neurotrophic factor; GFRα, GDNF family receptor α; MTC, medullary thyroid carcinoma PTC, papillary thyroid carcinoma; RET, rearranged during transfection.

that encodes the RET mRNA kinase domain with the 5' sequence that encodes domains responsible for both the dimerization and localization of an upstream partner gene. This fusion ultimately results in the production of active RET fusion proteins, which contribute to tumorigenesis (51-53). The RET fusion protein can cause cancer through two pathways: First, by sending a message that promotes the continued proliferation of cancerous cells due to the ability to send such messages without a ligand; and secondly, due to the unique endocytosis process, which prevents RET from being inhibited by blocking the attachment of ubiquitin to the protein receptor (54).

In 1987, Grieco *et al* (55) reported the initial human chromosomal arrangement of RET in PTC, demonstrating fusion between the RET TKD and the 5' terminal segment of coiled-coil domain-containing 6 (CCDC6). Breakpoints within RET intron 11 are the most common sites for gene fusion, resulting in the binding of the RET cytoplasmic kinase domain. Additional cases have been shown to occur in introns 7 and 10, resulting in merging of the transmembrane domain of RET (56,57). According to the literature, among the several RET fusions that are associated with PTC, the most common fusions are rearrangements involving the CCDC6 gene (known as RET/PTC1) and the coiled-coil domain of the nuclear receptor coactivator gene (known as RET/PTC3) (58-60). The kinesin family member 5B/RET fusion is the most common fusion found in lung adenocarcinoma (61,62). The nuclear receptor coactivator 4-RET gene and CCDC6-RET fusions are caused by paracentric chromosomal inversion involving chromosome 10, which does not include the centromere, whereas the pericentric inversion of chromosome 10, which includes the centromere, causes the kinesin family member 5B-RET fusion (63,64). The RET gene is likely to be fused with the following additional genes: Protein kinase cAMP-dependent regulatory subunit type I-α, tripartite motif-containing 24, Golgin A5, Kinectin 1, tripartite motif-containing 33 and RET finger protein gene 9 (historical/legacy nomenclature) (65-67). Notably, the term 'RET finger protein gene 9' primarily refers to the tripartite motif-containing protein 9 gene (TRIM9), which belongs to the TRIM family of proteins characterized by typical RING finger, B-box and coiled-coil domains. The term 'RET finger protein' is a historical descriptive term for proteins harboring RING finger domains, similar to the RET-associated RFP/TRIM27, and does not indicate a direct association with the RET gene itself. The legitimate repair of double-strand breaks in DNA leads to recombination events (68). The occurrence of RET fusions in PTC is fundamentally associated with exposure to specific damaging agents such as ionizing radiation and reactive oxygen species. These two factors serve critical roles in the cellular mechanisms that lead to cancer development (69-71). Both ionizing radiation and reactive oxygen species can induce notable genomic instability by causing double-strand breaks in DNA. Such disruptions in DNA structure are pivotal in the progression of PTC as they contribute to alterations in genetic material that drive oncogenesis. RET fusions are often seen in children and young adults with TC (72-74).

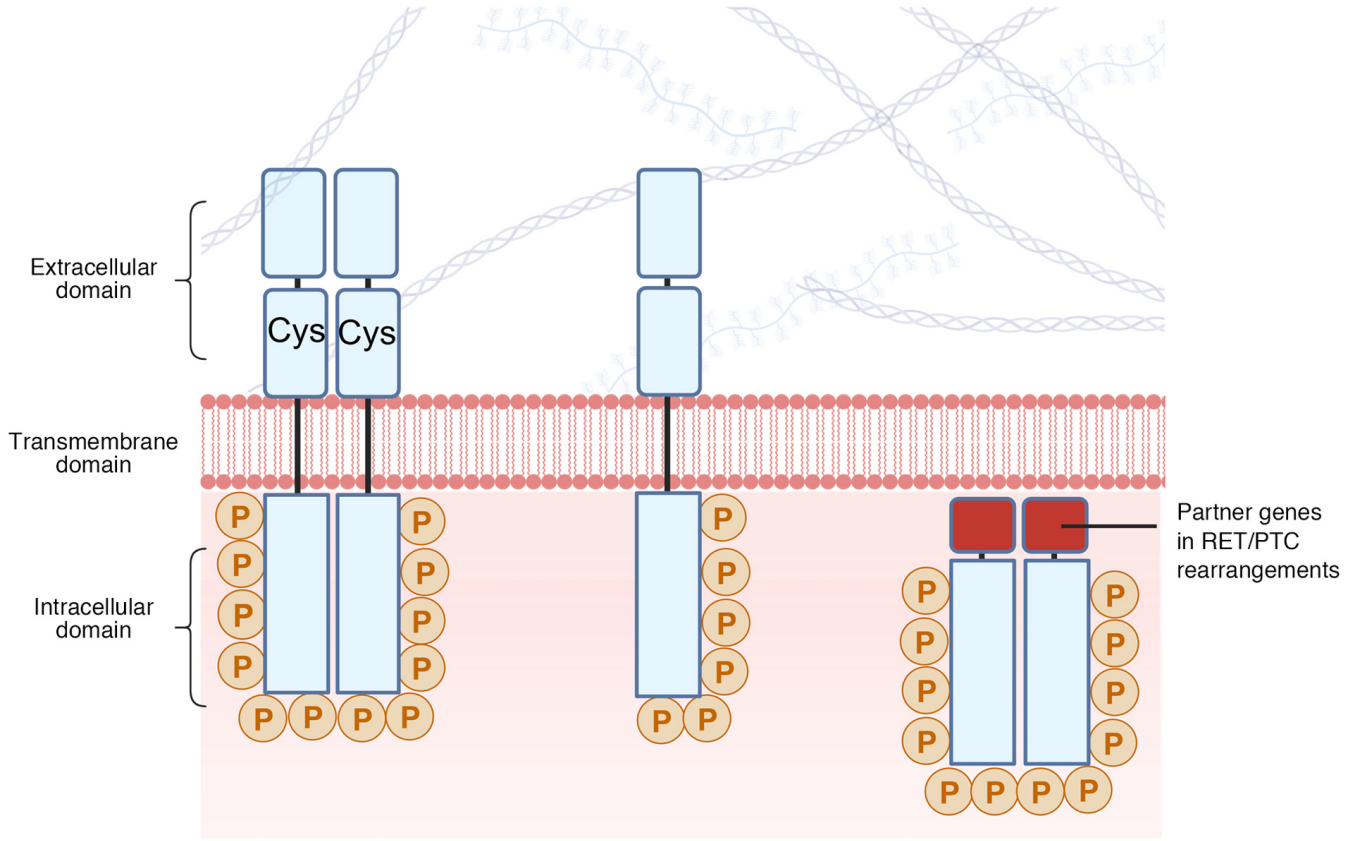

Figure 2. RET gene alterations and associated types of thyroid cancer (MEN2A/MEN2B and RET/PTC). MEN2, multiple endocrine neoplasia type 2; PTC, papillary thyroid cancer; RET, rearranged during transfection.

The rate at which RET fusion occurs is even higher in radiation-induced TC. A previous study was performed to analyze molecular genetic aberrations and associated phenotypes in the pathological tissues of 191 patients with PTC who were exposed to radioactive iodine from the Chernobyl reactor as young children. The results revealed that the frequency of RET gene rearrangements increased to 62.3% in the first decade following exposure to radiation. In addition, ELE1/RET (PTC3) rearrangements were markedly more common than H4/RET (PTC1) rearrangements (75). Note that NCOA4 is the official symbol for the nuclear receptor coactivator gene involved in this rearrangement, which is also widely known by the aliases ELE1 and ARA70. RET/PTC1 is defined as the CCDC6 (formerly H4)-RET gene fusion, whereas RET/PTC3 corresponds to the NCOA4 (ELE1/ARA70)-RET gene fusion. An additional investigation of the survivors of the atomic bombings that took place in Hiroshima and Nagasaki (Japan), revealed that among 50 patients with PTC who were exposed to nuclear radiation, 11 (22%) exhibited RET rearrangements, whereas only 5% of the 21 unexposed patients exhibited the same RET rearrangements. To the best of our knowledge, this study is the first to clearly demonstrate a statistically significant positive association between radiation exposure dose and the incidence rate of RET/PTC rearrangement in a large-scale human sample (analyzing 249 PTC tumor samples from atomic bomb survivors). Specifically, the higher the radiation dose received by the survivors, the higher the proportion of RET/PTC rearrangement in the PTC tumors they later developed (76).

5. Mechanisms of RET tyrosine kinase signaling and oncogenic activation in cancer

The specific phosphotyrosine residues on the activated RET intracellular tail recruit distinct adaptor and effector proteins, thereby activating multiple downstream signaling pathways critical for both normal development and oncogenesis (77-79). The RAS/RAF/MEK/ERK pathway (80-84) is primarily initiated through phosphorylated-Y1062 and -Y1096 (these phosphorylated tyrosine residues are located on the RET protein. Specifically, phosphorylated-Y1062 and phosphorylated-Y1096 are tyrosine phosphorylation sites on the intracellular domain of the activated RET receptor tyrosine kinase), and this pathway is a key driver of cellular proliferation and differentiation. The PI3K/AKT pathway (85-87) is a pro-survival pathway that is activated through several mechanisms, including the recruitment of SHP2 to phosphorylated-Y687 (phosphorylated-Y687 is also a tyrosine phosphorylation site on the intracellular domain of the activated RET receptor tyrosine kinase). The JAK2/STAT3 pathway (88,89) is activated following the binding of STAT3 to phosphorylated-Y752 and -Y928 (phosphorylated-Y752 and -Y928 are tyrosine phosphorylation sites of the RET protein), leading to nuclear translocation and the regulation of target gene expression. The phospholipase (PLC) γ/protein kinase C pathway (90) is triggered by PLCγ binding to phosphorylated-Y1015 (phosphorylated-Y1015 is a tyrosine phosphorylation site on the intracellular domain of the activated RET receptor tyrosine kinase); this pathway contributes to various cellular responses.

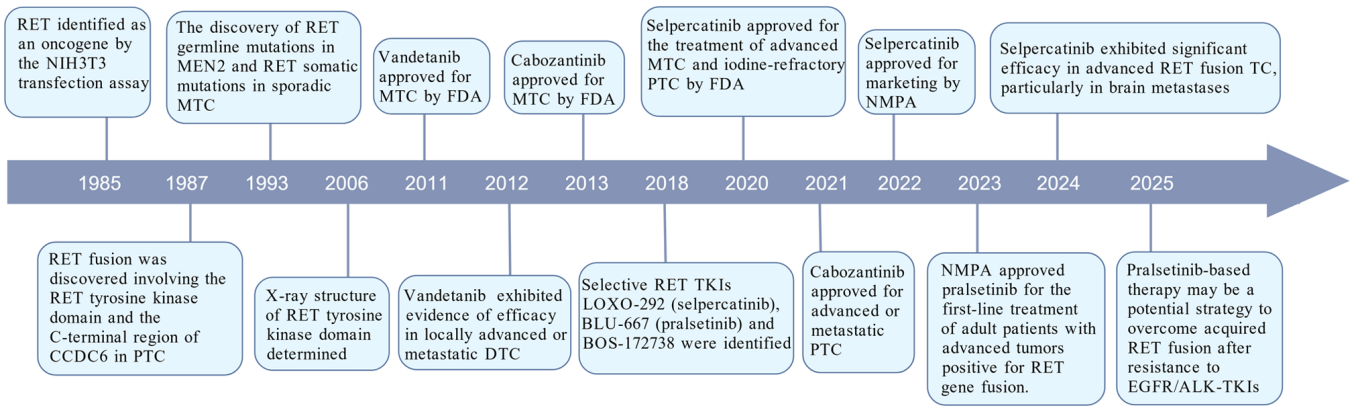

Figure 3. Timeline of key discoveries related to the role of RET as a driver oncogene and its use as a therapeutic target in TC. CCDC6, coiled-coil domain-containing 6; DTC, differentiated TC; FDA, Food and Drug Administration; MEN2, multiple endocrine neoplasia type 2; NMPA, National Medical Products Administration; MTC, medullary TC; PTC, papillary TC; RET, rearranged during transfection; TC, thyroid cancer; TKIs, tyrosine kinase inhibitors.

In cancer, genetic alterations subvert this tightly regulated system. In MTC, extracellular cysteine mutations (C609, C611, C618, C620, C630 and C634) cause constitutive dimerization (91,92), whereas intracellular kinase domain mutations (for example, M918T and V804M) stabilize the active conformation, enhance ATP binding or impair autoinhibitory mechanisms. In PTC, chromosomal rearrangements create RET fusion genes (93-96). These chimeric proteins, often lacking the transmembrane domain and fused to dimerization partners, exhibit ligand-independent, constitutive kinase activity localized in the cytoplasm. Collectively, these diverse genetic events lead to the persistent and unregulated activation of RET-driven oncogenic signaling, fueling tumor initiation, growth and progression.

6. TKIs focused on RET mutations

Numerous TKI medications have advanced to the stages of preclinical and clinical development (97-99). For example, the 2025 National Comprehensive Cancer Network Guidelines recommendations on TKI inhibitors for TC are as follows (100): For iodine-refractory PTC and FTC, both lenvatinib and sorafenib are Category 1 recommendations, with lenvatinib as the preferred first-line option for locally recurrent/metastatic, progressive radioactive iodine-refractory PTC and FTC. For MTC, first-line agents include vandetanib and cabozantinib (Category 1 recommendations). For MTC with RET mutations, selpercatinib and pralsetinib (highly selective RET inhibitors) are preferred. For ATC, treatment is mainly chemotherapy combined with immunotherapy, whereas TKIs may be used in the setting of positive specific targets. For example, dabrafenib plus trametinib can be used for tumors with the BRAF V600E mutation.

The recommendations on TKI inhibitors for TC in the 2025 American Thyroid Association Guidelines (101) include: For TC with RET fusions, highly selective TKIs, such as selpercatinib (for RET) and larotrectinib (for neurotrophic tyrosine receptor kinase), are preferred first-line treatments. These agents demonstrate superior efficacy and safety compared with conventional multikinase inhibitors, such as lenvatinib and sorafenib. In the absence of specific targets, lenvatinib is the first-line choice, and sorafenib is an alternative. For TC with the BRAF V600E mutation, dabrafenib plus trametinib may be used as first-line in patients intolerant to multi-target TKIs; in those who are tolerant, this combination is reserved for later-line therapy. These kinase inhibitors are organic compounds with small molecular structures that interact with the nucleotide-binding site within the kinase domain, either entirely or in part, and block kinase function (102,103). Depending on the orientation of the activation loop, kinases can adopt either an active or an inactive conformation. A kinase achieves its active state when the aspartate-phenylalanine-glycine (DFG) motif is located at the N-terminus of the activation loop; this configuration is referred to as DFG-in. By contrast, when the DFG motif is found at the C-terminus of the activation loop, the kinase is considered to be in an inactive conformation, referred to as DFG-out (104-106). TKIs are divided into two primary categories based on their preference for DFG-in (Type I) or DFG-out (Type II) conformations. Type I TKIs function by competing with ATP at the active site. By contrast, Type II inhibitors promote the inactive state of kinases by binding both to the ATP-binding pocket and the nearby allosteric site, which can only be accessed in the DFG-out conformation (107,108).

Several multikinase inhibitors (MKIs) exhibit anti-RET activity and are approved for the treatment of TC, including vandetanib (MTC), cabozantinib (MTC), regorafenib and sorafenib (differentiated TC). A variety of highly selective RET inhibitors have been developed. These agents target specific RET mutations and are associated with lower toxicity, lower required doses, and lower discontinuation rates compared with MKIs, such as vandetanib, cabozantinib, regorafenib and sorafenib (109-112).

The LIBRETTO-001 (NCT03157128) trial was an international, multicenter, open-label, phase I/II trial assessing the safety and efficacy of selpercatinib (49). A total of 531 patients aged 12 years were enrolled in the study. All of the patients had locally advanced or metastatic solid tumors of various types. This occurs with the activation of RET alterations. Of the 531 patients, 162 had RET-altered TC. In the TC subgroup, 55 patients had RET-mutated medullary TC (MTC) previously treated with cabozantinib and vandetanib, 88 patients had

RET-mutated MTC without prior cabozantinib or vandetanib treatment, and 19 patients had RET fusion-positive non-MTC. Notably, these 19 patients had been previously treated for fusion-positive non-MTC, not for RET-altered MTC. Based on the findings from the clinical trial, RET-mutant patients with MTC who were not previously treated with cabozantinib and vandetanib exhibited an overall response rate (ORR) of 69% and progression-free survival (PFS) rate of 82% after 1 year. By contrast, patients with RET-mutant MTC who had not previously received these treatments had a 73% ORR and a 1-year PFS rate of 92%. For patients with RET fusion-positive non-MTC, the ORR reached 79%, with treatment effectiveness noted across various histological subtypes and a corresponding 1-year progression-free survival (PFS) rate. Furthermore, selpercatinib demonstrated overall treatment effectiveness in all patients with MTC. All patients enrolled in the LIBRETTO-001 trial, including the 162 patients with RET-altered TC described in the text, were treated with selpercatinib, regardless of their previous exposure to MKIs, radioactive iodine, or the specific type of RET mutation or fusion.

Pralsetinib specifically inhibits RET and is an ATP-competitive inhibitor (113). According to the imaging results of the ARROW trial, a single-arm phase I/II clinical study, pralsetinib led to a 90% reduction in tumors among patients with PTC and MTC (114,115). In patients with RET mutations in MTC, the ORR was 63% and the disease control rate was 94%. Furthermore, nine individuals with MTC who experienced brain metastases had an intracranial response rate of 56% (116). Pralsetinib has broad applicability, independent of the RET fusion partner (117). Consequently, owing to these results, the Food and Drug Administration approved pralsetinib for use in treating RET-mutated MTC in 2020, and in March 2021, the National Medical Products Administration approved this drug for use in patients with MTC in China (Fig. 3).

Based on the current research status and clinical practice, it is proposed that future studies on TKIs targeting RET alterations should focus on the following aspects: i) The development of more efficient selective RET inhibitors to overcome existing resistance mechanisms; ii) the exploration of combinations of RET inhibitors with other targeted therapies or immunotherapies to enhance treatment efficacy; and iii) the utilization of technologies such as liquid biopsy to monitor RET mutations and resistance in real time, thereby providing a foundation for personalized treatment.

7. Conclusion

In conclusion, TC is an increasingly common endocrine malignancy with genetic drivers, particularly RET mutations and rearrangements, which serve key roles in MTC and PTC subtypes, respectively. While targeted RET inhibitors represent a promising therapeutic advance, future research should prioritize deeper molecular studies of RET signaling, the interplay between genetic and environmental risk factors such as radiation, and the development of improved strategies for early detection and precision treatment. Advancing these areas will be critical to enhancing patient outcomes and understanding TC pathogenesis.

Acknowledgements

Not applicable.

Funding

This research was funded by the Anhui Provincial New Era Education Quality Engineering Project (Graduate Education) (grant no. 2024qyw/sysfkc017) and the Anhui Medical University Quality Engineering Project (grant no. 2024xjxm72).

Availability of data and materials

Not applicable.

Authors' contributions

MW and RW wrote the manuscript. JQ made substantial contributions to the conception and design of the review's visual data presentation, created the figures and verified that the visual content accurately reflected the core research findings and academic conclusions of the review. JT and QF supervised the research, revised the manuscript, obtained financial support, conceptualized the review and performed the literature search. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Seib CD and Sosa JA: Evolving understanding of the epidemiology of thyroid cancer. Endocrinol Metab Clin North Am 48: 23-35, 2019.
2. Miranda-Filho A, Lortet-Tieulent J, Bray F, Cao B, Franceschi S, Vaccarella S and Dal Maso L: Thyroid cancer incidence trends by histology in 25 countries: A population-based study. Lancet Diabetes Endocrinol 9: 225-234, 2021.
3. Ni Z, Cong S, Li H, Liu J, Zhang Q, Wei C, Pan G, He H, Liu W and Mao A: Integration of scRNA and bulk RNA-sequence to construct the 5-gene molecular prognostic model based on the heterogeneity of thyroid carcinoma endothelial cell: Five-gene TC prognostic model. Acta Biochim Biophys Sin (Shanghai) 56: 255-269, 2024.
4. Dahiya V, Vasudeva N, Sharma S and Kumar A: Role of dietary supplements in thyroid diseases. Endocr Metab Immune Disord Drug Targets 22: 985-996, 2022.
5. Elisei R and Romei C: Looking for RET alterations in thyroid cancer: Clinical relevance, methodology and timing. Endocrine 81: 206-215, 2023.
6. Agrawal N, Akbani R, Aksoy BA, Ally A, Arachchi H, Asa SL, Auman JT, Balasundaram M, Balu S, Baylin SB, *et al*: Integrated genomic characterization of papillary thyroid carcinoma. Cell 159: 676-690, 2014.

7. Simbolo M, Mian C, Barollo S, Fassan M, Mafficini A, Neves D, Scardoni M, Pennelli G, Rugge M, Pelizzo MR, *et al*: High-throughput mutation profiling improves diagnostic stratification of sporadic medullary thyroid carcinomas. Virchows Arch 465: 73-78, 2014.
8. Xiao X, Chen M, Sang Y, Xue J, Jiang K, Chen Y, Zhang L, Yu S, Lv W, Li Y, *et al*: Methylation-mediated silencing of ATF3 promotes thyroid cancer progression by regulating prognostic genes in the MAPK and PI3K/AKT pathways. Thyroid 33: 1441-1454, 2023.
9. Fallahi P, Ferrari SM, Galdiero MR, Varricchi G, Elia G, Ragusa F, Paparo SR, Benvenga S and Antonelli A: Molecular targets of tyrosine kinase inhibitors in thyroid cancer. Semin Cancer Biol 79: 180-196, 2022.
10. Zago E, Galluzzo A, Pradella S, Antonuzzo L, Maggi M, Petrone L and Sparano C: Cabozantinib for different endocrine tumours: Killing two birds with one stone. A systematic review of the literature. Endocrine 83: 26-40, 2024.
11. Saltiki K, Simeakis G, Karapanou O, Paschou SA and Alevizaki M: Metastatic medullary thyroid carcinoma (MTC): Disease course, treatment modalities and factors predisposing for drug resistance. Endocrine 80: 570-579, 2023.
12. Jiao Q, Bi L, Ren Y, Song S, Wang Q and Wang YS: Advances in studies of tyrosine kinase inhibitors and their acquired resistance. Mol Cancer 17: 36, 2018.
13. Cabanillas ME, Ryder M and Jimenez C: Targeted Therapy for Advanced Thyroid Cancer: Kinase Inhibitors and Beyond. Endocr Rev 40: 1573-1604, 2019.
14. De Leo S, Trevisan M and Fugazzola L: Recent advances in the management of anaplastic thyroid cancer. Thyroid Res 13: 17, 2020.
15. Takahashi M, Ritz J and Cooper GM: Activation of a novel human transforming gene, ret, by DNA rearrangement. Cell 42: 581-588, 1985.
16. Takahashi M: RET receptor signaling: Function in development, metabolic disease, and cancer. Proc Jpn Acad Ser B Phys Biol Sci 98: 112-125, 2022.
17. Knowles PP, Murray-Rust J, Kjaer S, Scott RP, Hanrahan S, Santoro M, Ibáñez CF and McDonald NQ: Structure and chemical inhibition of the RET tyrosine kinase domain. J Biol Chem 281: 33577-33587, 2006.
18. Treanor JJ, Goodman L, de Sauvage F, Stone DM, Poulsen KT, Beck CD, Gray C, Armanini MP, Pollock RA, Hefti F, *et al*: Characterization of a multicomponent receptor for GDNF. *Nature* 382: 80-83, 1996.
19. Arighi E, Borrello MG and Sariola H: RET tyrosine kinase signaling in development and cancer. Cytokine Growth Factor Rev 16: 441-467, 2005.
20. Melillo RM, Cirafici AM, De Falco V, Bellantoni M, Chiappetta G, Fusco A, Carlomagno F, Picascia A, Tramontano D, Tallini G and Santoro M: The oncogenic activity of RET point mutants for follicular thyroid cells may account for the occurrence of papillary thyroid carcinoma in patients affected by familial medullary thyroid carcinoma. Am J Pathol 165: 511-521, 2004.
21. Ciampi R, Romei C, Pieruzzi L, Tacito A, Molinaro E, Agate L, Bottici V, Casella F, Ugolini C, Materazzi G, *et al*: Classical point mutations of RET, BRAF and RAS oncogenes are not shared in papillary and medullary thyroid cancer occurring simultaneously in the same gland. J Endocrinol Invest 40: 55-62, 2017.
22. Pham VH, Pham QT, Nguyen M, Ngo HN, Luu TTT, Minh NDT, Đặng T, Thai AT, Vu HA and Ngo DQ: Characteristics of RET gene mutations in Vietnamese medullary thyroid carcinoma patients: A single-center analysis. J Pathol Transl Med 59: 125-132, 2025.
23. Hofstra RM, Landsvater RM, Ceccherini I, Stulp RP, Stelwagen T, Luo Y, Pasini B, Höppener JW, van Amstel HK, Romeo G, *et al*: A mutation in the RET proto-oncogene associated with multiple endocrine neoplasia type 2B and sporadic medullary thyroid carcinoma. *Nature* 367: 375-376, 1994.
24. Barletta JA, Nosé V and Sadow PM: Genomics and epigenomics of medullary thyroid carcinoma: From sporadic disease to familial manifestations. Endocr Pathol 32: 35-43, 2021.
25. Prinzi A, Vella V, Bosco A, Mirone A, Russo M, Piticchio T, Di Benedetto G, Bartoloni G, Frasca F and Malandrino P: Sporadic and familial medullary thyroid carcinoma: A retrospective single center study on presentation and outcome. Endocr Res 49: 179-185, 2024.
26. Mathiesen JS, Kroustrup JP, Vestergaard P, Stochholm K, Poulsen PL, Rasmussen ÅK, Feldt-Rasmussen U, Schytte S, Londero SC, Pedersen HB, *et al*: Incidence and prevalence of sporadic and hereditary MTC in Denmark 1960-2014: A nationwide study. Endocr Connect 7: 829-839, 2018.
27. Machens A and Dralle H: Long-term outcome after DNA-based prophylactic neck surgery in children at risk of hereditary medullary thyroid cancer. Best Pract Res Clin Endocrinol Metab 33: 101274, 2019.
28. Yasir M, Mulji NJ and Kasi A: Multiple endocrine neoplasia type 2. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2025.
29. Greenberg LA: Multiple endocrine neoplasia type 1, type 2A, and type 2B. Prim Care 51: 483-494, 2024.
30. Wells SA Jr: Advances in the management of MEN2: From improved surgical and medical treatment to novel kinase inhibitors. Endocr Relat Cancer 25: T1-T13, 2018.
31. Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel RF, van Amstel HK, Lips CJ, Nishisho I, Takai SI, *et al*: The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2: International RET mutation consortium analysis. JAMA 276: 1575-1579, 1996.
32. Santoro M, Carlomagno F, Romano A, Bottaro DP, Dathan NA, Grieco M, Fusco A, Vecchio G, Matoskova B, Kraus MH, *et al*: Activation of RET as a dominant transforming gene by germline mutations of MEN2A and MEN2B. Science 267: 381-383, 1995.
33. Asai N, Iwashita T, Matsuyama M and Takahashi M: Mechanism of activation of the ret protooncogene by multiple endocrine neoplasia type 2A mutations. Mol Cell Biol 15: 1613-1619, 1995.
34. Castinetti F, Moley J, Mulligan L and Waguespack SG: A comprehensive review on MEN2B. Endocr Relat Cancer 25: T29-T39, 2018.
35. Frank-Raue K and Raue F: Hereditary Medullary Thyroid Cancer: Genotype-Phenotype Correlation. Recent Results Cancer Res 223: 183-209, 2025.
36. Zhang ZW, Guo X and Qi XP: Molecular diagnosis and treatment of multiple endocrine neoplasia type 2b in ethnic Han Chinese. Endocr Metab Immune Disord Drug Targets 21: 534-543, 2021.
37. Plaza-Menacho I, Barnouin K, Goodman K, Martínez-Torres RJ, Borg A, Murray-Rust J, Mouilleron S, Knowles P and McDonald NQ: Oncogenic RET kinase domain mutations perturb the autophosphorylation trajectory by enhancing substrate presentation in trans. Mol Cell 53: 738-751, 2014.
38. Gujral TS, Singh VK, Jia Z and Mulligan LM: Molecular mechanisms of RET receptor-mediated oncogenesis in multiple endocrine neoplasia 2B. Cancer Res 66: 10741-10749, 2006.
39. Menko FH, van der Luijt RB, de Valk IA, Toorians AW, Sepers JM, van Diest PJ and Lips CJ: Atypical MEN type 2B associated with two germline RET mutations on the same allele not involving codon 918. J Clin Endocrinol Metab 87: 393-397, 2002.
40. Cranston AN, Carniti C, Oakhill K, Radzio-Andzelm E, Stone EA, McCallion AS, Hodgson S, Clarke S, Mondellini P, Leyland J, *et al*: RET is constitutively activated by novel tandem mutations that alter the active site resulting in multiple endocrine neoplasia type 2B. Cancer Res 66: 10179-10187, 2006.
41. Censi S, Galuppini F, Clausi C, Battheu F, Manso J, Piva I, Corvaglia S, Pedron MC, Mondin A, Iacobone M, *et al*: Tumor grade and molecular characteristics associated with survival in sporadic medullary thyroid carcinoma. Thyroid 34: 177-185, 2024.
42. Heilmann AM, Subbiah V, Wang K, Sun JX, Elvin JA, Chmielecki J, Sherman SI, Murthy R, Busaidy NL, Subbiah I, *et al*: Comprehensive genomic profiling of clinically advanced medullary thyroid carcinoma. Oncology 90: 339-346, 2016.
43. Keskin Ç, Canpolat AG, Canlar Ş, Bahçecioğlu Mutlu AB and Erdoğan MF: Men 2B cases with atypical presentation, unusual clinical course and a literature review. Acta Endocrinol (Buchar) 19: 260-266, 2023.
44. Erickson TA, Shih YP, Fass J, Jang M and Tran E: T cells engineered to express immunoreceptors targeting the frequently expressed medullary thyroid cancer antigens calcitonin, CEA, and RET M918T. Thyroid 32: 789-798, 2022.
45. Qi XP, Lin GB, Chen B, Li F, Cao ZL, Zheng WH and Zhao JQ: Multiple endocrine neoplasia type 2B associated mixed medullary and follicular thyroid carcinoma in a Chinese patient with RET M918T germline mutation. Endocr Metab Immune Disord Drug Targets 21: 554-560, 2021.
46. Ciampi R, Romei C, Ramone T, Prete A, Tacito A, Cappagli V, Bottici V, Viola D, Torregrossa L, Ugolini C, *et al*: Genetic landscape of somatic mutations in a large cohort of sporadic medullary thyroid carcinomas studied by next-generation targeted sequencing. iScience 20: 324-336, 2019.

47. Romei C, Ciampi R and Elisei R: A comprehensive overview of the role of the RET proto-oncogene in thyroid carcinoma. Nat Rev Endocrinol 12: 192-202, 2016.
48. Thomas GA, Bunnell H, Cook HA, Williams ED, Nerovnya A, Cherstvoy ED, Tronko ND, Bogdanova TI, Chiappetta G, Viglietto G, *et al*: High prevalence of RET/PTC rearrangements in Ukrainian and Belarussian post-Chernobyl thyroid papillary carcinomas: A strong correlation between RET/PTC3 and the solid-follicular variant. *J Clin Endocrinol Metab* 84: 4232-4238, 1999.
49. Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, Worden F, Brose M, Patel J, Leboulleux S, *et al*: Efficacy of selpercatinib in RET-altered thyroid cancers. *N Engl J Med* 383: 825-835, 2020.
50. Nacchio M, Pisapia P, Pepe F, Russo G, Vigliar E, Porcelli T, Luongo C, Iaccarino A, Pagni F, Salvatore D, *et al*: Predictive molecular pathology in metastatic thyroid cancer: The role of RET fusions. Expert Rev Endocrinol Metab 17: 167-178, 2022.
51. Subbiah V, Yang D, Velcheti V, Drilon A and Meric-Bernstam F: State-of-the-art strategies for targeting RET-dependent cancers. J Clin Oncol 38: 1209-1221, 2020.
52. Yao Y, Yu Z, Ma Y, Ou Q, Wu X, Lu D and Li X: Characterizing kinase intergenic-breakpoint rearrangements in a large-scale lung cancer population and real-world clinical outcomes. *ESMO Open* 7: 100405, 2022.
53. Sorokin M, Rabushko E, Rozenberg JM, Mohammad T, Seryakov A, Sekacheva M and Buzdin A: Clinically relevant fusion oncogenes: Detection and practical implications. *Ther Adv Med Oncol* 14: 17588359221144108, 2022.
54. Mahato AK and Sidorova YA: RET receptor tyrosine kinase: Role in neurodegeneration, obesity, and cancer. *Int J Mol Sci 21: 7108*, 2020.
55. Grieco M, Santoro M, Berlingieri MT, Melillo RM, Donghi R, Bongarzone I, Pierotti MA, Della Porta G, Fusco A and Vecchio G: PTC is a novel rearranged form of the ret proto-oncogene and is frequently detected in vivo in human thyroid papillary carcinomas. *Cell* 60: 557-563, 1990.
56. Saenko V, Rogounovitch T, Shimizu-Yoshida Y, Abrosimov A, Lushnikov E, Roumiantsev P, Matsumoto N, Nakashima M, Meirmanov S, Ohtsuru A, *et al*: Novel tumorigenic rearrangement, delta rfp/ret, in a papillary thyroid carcinoma from externally irradiated patient. Mutat Res 527: 81-90, 2003.
57. Zhao Y, Du R, Chen M and Chen Z: The fusion characteristics of RET fusion in pan-cancer among the Chinese population: A comprehensive genomic analysis. Transl Oncol 55: 102384, 2025.
58. Nakazawa T, Kondo T, Kobayashi Y, Takamura N, Murata S, Kameyama K, Muramatsu A, Ito K, Kobayashi M and Katoh R: RET gene rearrangements (RET/PTC1 and RET/PTC3) in papillary thyroid carcinomas from an iodine-rich country (Japan). Cancer 104: 943-951, 2005.
59. Demin DE, Murashko MM, Uvarova AN, Stasevich EM, Shyrokova EY, Gorlachev GE, Zaretsky AR, Korneev KV, Ustiugova AS, Tkachenko EA, *et al*: Adversary of DNA integrity: A long non-coding RNA stimulates driver oncogenic chromosomal rearrangement in human thyroid cells. Int J Cancer 152: 1452-1462, 2023.
60. Alswailem M, Alghamdi B, Alotaibi A, Aljomiah A, Al-Hindi H, Murugan AK, Abouelhoda M, Shi Y and Alzahrani AS: Molecular genetics of diffuse sclerosing papillary thyroid cancer. J Clin Endocrinol Metab 108: e704-e711, 2023.
61. Yokota K, Sasaki H, Okuda K, Shimizu S, Shitara M, Hikosaka Y, Moriyama S, Yano M and Fujii Y: KIF5B/RET fusion gene in surgically-treated adenocarcinoma of the lung. Oncol Rep 28: 1187-1192, 2012.
62. Lee MR, Shin JY, Kim MY, Kim JO, Jung CK and Kang J: FOXA2 and STAT5A regulate oncogenic activity of KIF5B-RET fusion. Am J Cancer Res 13: 638-653, 2023.
63. Santoro M, Moccia M, Federico G and Carlomagno F: RET gene fusions in malignancies of the thyroid and other tissues. Genes (Basel) 11: 424, 2020.
64. Ju YS, Lee WC, Shin JY, Lee S, Bleazard T, Won JK, Kim YT, Kim JI, Kang JH and Seo JS: A transforming KIF5B and RET gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing. Genome Res 22: 436-445, 2012.
65. Tanaka A, Okita R, Morishige T, Okada M, Inokawa H, Hirazawa K, Kameyama K, Ikeda A and Ikeda E: A case of primary lung adenocarcinoma mimicking metastatic papillary thyroid carcinoma. Thorac Cancer 15: 353-357, 2024.
66. Zhao M, Yin X, He H, Xia Q and Ru G: Recurrent RET fusions in fibrosarcoma-like neoplasms in adult viscera: Expanding the clinicopathological and genetic spectrum. Histopathology 82: 633-645, 2023.
67. Salassidis K, Bruch J, Zitzelsberger H, Lengfelder E, Kellerer AM and Bauchinger M: Translocation t(10;14)(q11.2:q22.1) fusing the kinetin to the RET gene creates a novel rearranged form (PTC8) of the RET proto-oncogene in radiation-induced childhood papillary thyroid carcinoma. Cancer Res 60: 2786-2789, 2000.
68. Mizukami T, Shiraishi K, Shimada Y, Ogiwara H, Tsuta K, Ichikawa H, Sakamoto H, Kato M, Shibata T, Nakano T and Kohno T: Molecular mechanisms underlying oncogenic RET fusion in lung adenocarcinoma. J Thorac Oncol 9: 622-630, 2014.
69. Duque CS, Vélez A, Cuartas J, Jaimes F, Dueñas JP, Agudelo M, Nikiforova MN, Nikiforov YE and Condello V: Molecular profiling of papillary thyroid carcinomas in healthcare workers exposed to low dose radiation at the workplace. Endocrine 76: 95-100, 2022.
70. Ameziane-El-Hassani R, Boufraqech M, Lagente-Chevallier O, Weyemi U, Talbot M, Métivier D, Courtin F, Bidart JM, El Mzibri M, Schlumberger M and Dupuy C: Role of H2O2 in RET/PTC1 chromosomal rearrangement produced by ionizing radiation in human thyroid cells. Cancer Res 70: 4123-4132, 2010.
71. Djerir B and Maréchal A: Detection of γ-H2A.X for rapid assessment of genotoxic agent-induced double-strand DNA breaks by immunofluorescence. Methods Mol Biol 2019: 83-89, 2025.
72. Su X, Li Z, He C, Chen W, Fu X and Yang A: Radiation exposure, young age, and female gender are associated with high prevalence of RET/PTC1 and RET/PTC3 in papillary thyroid cancer: A meta-analysis. Oncotarget 7: 16716-16730, 2016.
73. Vanden Borre P, Schrock AB, Anderson PM, Morris JC III, Heilmann AM, Holmes O, Wang K, Johnson A, Waguespack SG, Ou SI, *et al*: Pediatric, adolescent, and young adult thyroid carcinoma harbors frequent and diverse targetable genomic alterations, including kinase fusions. Oncologist 22: 255-263, 2017.
74. Tian T, Huang S, Dai H, Qi M, Liu B and Huang R: Radioactive iodine-refractory pulmonary metastases of papillary thyroid cancer in children, adolescents, and young adults. J Clin Endocrinol Metab 108: 306-314, 2023.
75. Rabes HM, Demidchik EP, Sidorow JD, Lengfelder E, Beimfohr C, Hoelzel D and Klugbauer S: Pattern of radiation-induced RET and NTRK1 rearrangements in 191 post-chernobyl papillary thyroid carcinomas: Biological, phenotypic, and clinical implications. Clin Cancer Res 6: 1093-1103, 2000.
76. Hamatani K, Eguchi H, Ito R, Mukai M, Takahashi K, Taga M, Imai K, Cologne J, Soda M, Arihiro K, *et al*: RET/PTC rearrangements preferentially occurred in papillary thyroid cancer among atomic bomb survivors exposed to high radiation dose. Cancer Res 68: 7176-7182, 2008.
77. Ibáñez CF: Structure and physiology of the RET receptor tyrosine kinase. Cold Spring Harb Perspect Biol 5: a009134, 2013.
78. Krampitz GW and Norton JA: RET gene mutations (genotype and phenotype) of multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma. Cancer 120: 1920-1931, 2014.
79. Li J, Shang G, Chen YJ, Brautigam CA, Liou J, Zhang X and Bai XC: Cryo-EM analyses reveal the common mechanism and diversification in the activation of RET by different ligands. Elife 8: e47650, 2019.
80. Zhang Y, Liu H, Wang K, Zheng J, Luan H and Xin M: RET inhibitor SPP86 triggers apoptosis and activates the DNA damage response through the suppression of autophagy and the PI3K/AKT signaling pathway in melanoma cells. Drug Des Devel Ther 19: 67-82, 2025.
81. Asai N, Murakami H, Iwashita T and Takahashi M: A mutation at tyrosine 1062 in MEN2A-Ret and MEN2B-Ret impairs their transforming activity and association with shc adaptor proteins. J Biol Chem 271: 17644-17649, 1996.
82. Alberti L, Borrello MG, Ghizzoni S, Torriti F, Rizzetti MG and Pierotti MA: Grb2 binding to the different isoforms of Ret tyrosine kinase. Oncogene 17: 1079-1087, 1998.
83. Srivastava A, Tommasi C, Sessions D, Mah A, Bencomo T, Garcia JM, Jiang T, Lee M, Shen JY, Seow LW, *et al*: MAB21L4 deficiency drives squamous cell carcinoma via activation of RET. Cancer Res 82: 3143-3157, 2022.
84. Pu X, Xu C, Wang Q, Wang W, Wu F, Cai X, Song Z, Yu J, Zhong W, Wang Z, *et al*: Expert consensus on the diagnosis and treatment of RET gene fusion non-small cell lung cancer in China. Thorac Cancer 14: 3166-3177, 2023.

85. Hong DS, Cabanillas ME, Wheler J, Naing A, Tsimberidou AM, Ye L, Busaidy NL, Waguespack SG, Hernandez M, El Naggar AK, *et al*: Inhibition of the Ras/Raf/MEK/ERK and RET kinase pathways with the combination of the multikinase inhibitor sorafenib and the farnesyltransferase inhibitor tipifarnib in medullary and differentiated thyroid malignancies. J Clin Endocrinol Metab 96: 997-1005, 2011.
86. Perrinjaquet M, Vilar M and Ibáñez CF: Protein-tyrosine phosphatase SHP2 contributes to GDNF neurotrophic activity through direct binding to phospho-Tyr687 in the RET receptor tyrosine kinase. J Biol Chem 285: 31867-31875, 2010.
87. Wang Z, Chen Y, Zhang S, *et al*: SHP2 is required for the oncogenic activity of the EML4-ALK fusion protein in non-small cell lung cancer. Oncogene 39: 3281-3295, 2020.
88. Plaza Menacho I, Koster R, van der Sloot AM, Quax WJ, Osinga J, van der Sluis T, Hollema H, Burzynski GM, Gimm O, Buys CH, *et al*: RET-familial medullary thyroid carcinoma mutants Y791F and S891A activate a Src/JAK/STAT3 pathway, independent of glial cell line-derived neurotrophic factor. Cancer Res 65: 1729-1737, 2005.
89. Schuringa JJ, Wojtachnio K, Hagens W, Vellenga E, Buys CH, Hofstra R and Kruijer W: MEN2A-RET-induced cellular transformation by activation of STAT3. Oncogene 20: 5350-5358, 2001.
90. Borrello MG, Alberti L, Arighi E, Bongarzone I, Battistini C, Bardelli A, Pasini B, Piutti C, Rizzetti MG, Mondellini P, *et al*: The full oncogenic activity of Ret/ptc2 depends on tyrosine 539, a docking site for phospholipase Cgamma. Mol Cell Biol 16: 2151-2163, 1996.
91. Arlt D, Baur B, Wagner B and Höppner W: A novel type of mutation in the cysteine rich domain of the RET receptor causes ligand independent activation. Oncogene 19: 3445-3448, 2000.
92. Tabata J, Nakaoku T, Araki M, Yoshino R, Kohsaka S, Otsuka A, Ikegami M, Ui A, Kanno SI, Miyoshi K, *et al*: Novel calcium-binding ablating mutations induce constitutive RET activity and drive tumorigenesis. Cancer Res 82: 3751-3762, 2022.
93. Carlomagno F, Guida T, Anaganti S, Provitera L, Kjaer S, McDonald NQ, Ryan AJ and Santoro M: Identification of tyrosine 806 as a molecular determinant of RET kinase sensitivity to ZD6474. Endocr Relat Cancer 16: 233-241, 2009.
94. Carlomagno F, Guida T, Anaganti S, Vecchio G, Fusco A, Ryan AJ, Billaud M and Santoro M: Disease associated mutations at valine 804 in the RET receptor tyrosine kinase confer resistance to selective kinase inhibitors. Oncogene 23: 6056-6063, 2004.
95. Gimm O, Marsh DJ, Andrew SD, Frilling A, Dahia PL, Mulligan LM, Zajac JD, Robinson BG and Eng C: Germline dinucleotide mutation in codon 883 of the RET proto-oncogene in multiple endocrine neoplasia type 2B without codon 918 mutation. J Clin Endocrinol Metab 82: 3902-3904, 1997.
96. Carlson KM, Dou S, Chi D, Scavarda N, Toshima K, Jackson CE, Wells SA Jr, Goodfellow PJ and Donis-Keller H: Single missense mutation in the tyrosine kinase catalytic domain of the RET protooncogene is associated with multiple endocrine neoplasia type 2B. Proc Natl Acad Sci USA 91: 1579-1583, 1994.
97. Zhang J, Yang PL and Gray NS: Targeting cancer with small molecule kinase inhibitors. Nat Rev Cancer 9: 28-39, 2009.
98. Gross S, Rahal R, Stransky N, Lengauer C and Hoeflich KP: Targeting cancer with kinase inhibitors. J Clin Invest 125: 1780-1789, 2015.
99. Mok T, Jänne PA, Nishio M, Novello S, Reck M, Steuer C, Wu YL, Fougeray R, Fan PD, Meng J, *et al*: HERTHENA-Lung02: Phase III study of patritumab deruxtecan in advanced EGFR-mutated NSCLC after a third-generation EGFR TKI. Future Oncol 20: 969-980, 2024.
100. National Comprehensive Cancer Network (NCCN): NCCN clinical practice guidelines in oncology: Thyroid carcinoma. Version 1.2025. NCCN, Washington, PA, 2025.
101. Haugen BR, Alexander EK, Doherty GM, *et al*: 2025 American Thyroid Association (ATA) Guidelines for Adult Patients with Differentiated Thyroid Cancer. American Thyroid Association; 2025.
102. Wang Z, Wang H, Bu C, Meng B, Mu Y, Gao S, Chen W and Tao X: Tyrosine kinase inhibitor-induced hypothyroidism: Mechanism and clinical implications. Eur J Clin Pharmacol 80: 827-838, 2024.
103. Fu M, Zhao J, Zhang L, Sheng Z, Li X, Qiu F, Feng Y, You M, Xu H, Zhang J, *et al*: Overcoming tyrosine kinase inhibitor resistance in lung cancer brain metastasis with CTLA4 blockade. Cancer Cell 42: 1882-1897.e7, 2024.
104. Zhao Z, Wu H, Wang L, Liu Y, Knapp S, Liu Q and Gray NS: Exploration of type II binding mode: A privileged approach for kinase inhibitor focused drug discovery? ACS Chem Biol 9: 1230-1241, 2014.
105. Modi SJ and Kulkarni VM: Exploration of structural requirements for the inhibition of VEGFR-2 tyrosine kinase: Binding site analysis of type II, 'DFG-out' inhibitors. J Biomol Struct Dyn 40: 5712-5727, 2022.
106. Xu G, Zhang W, Du J, Cong J, Wang P, Li X, Si X and Wei B: Binding mechanism of inhibitors to DFG-in and DFG-out P38α deciphered using multiple independent Gaussian accelerated molecular dynamics simulations and deep learning. SAR QSAR Environ Res 36: 101-126, 2025.
107. Vijayan R, He P, Modi V, Duong-Ly KC, Ma H, Peterson JR, Dunbrack RL Jr and Levy RM: Conformational analysis of the DFG-out kinase motif and biochemical profiling of structurally validated type II inhibitors. J Med Chem 58: 466-479, 2015.
108. Peng YH, Shiao HY, Tu CH, Liu PM, Hsu JT, Amancha PK, Wu JS, Coumar MS, Chen CH, Wang SY, *et al*: Protein kinase inhibitor design by targeting the Asp-Phe-Gly (DFG) motif: The role of the DFG motif in the design of epidermal growth factor receptor inhibitors. J Med Chem 56: 3889-3903, 2013.
109. Buffet C, Leboulleux S, Kraeber-Bodéré F, Bodet-Milin C, Cabanes L, Dohan A, Leprince P, Schlumberger M, Huillard O and Groussin L: Cardiac metastasis from medullary thyroid cancers with long-term survival under vandetanib. Eur Thyroid J 10: 517-522, 2021.
110. Ly NS, Li J, Faggioni R, Roskos LK and Brose MS: Population pharmacokinetics and exposure-response analysis for the phase 3 COSMIC-311 trial of cabozantinib for radioiodine-refractory differentiated thyroid cancer. Clin Pharmacokinet 62: 587-598, 2023.
111. Sherman EJ, Dunn LA, Ho AL, Baxi SS, Ghossein RA, Fury MG, Haque S, Sima CS, Cullen G, Fagin JA and Pfister DG: Phase 2 study evaluating the combination of sorafenib and temsirolimus in the treatment of radioactive iodine-refractory thyroid cancer. Cancer 123: 4114-4121, 2017.
112. Hadoux J, Elisei R, Brose MS, Hoff AO, Robinson BG, Gao M, Jarzab B, Isaev P, Kopeckova K, Wadsley J, *et al*: Phase 3 trial of selpercatinib in advanced RET-mutant medullary thyroid cancer. N Engl J Med 389: 1851-1861, 2023.
113. Kassir N, McDougall D, Kuruvilla D, Kim S, Kumar S, Rahman A, Ruf T, Cheeti S and Ankrom W: Exposure-response relationships for pralsetinib in patients with RET-altered thyroid cancer or RET fusion-positive nonsmall cell lung cancer. J Clin Pharmacol 64: 685-696, 2024.
114. Subbiah V, Hu MI, Wirth LJ, Schuler M, Mansfield AS, Curigliano G, Brose MS, Zhu VW, Leboulleux S, Bowles DW, *et al*: Pralsetinib for patients with advanced or metastatic RET-altered thyroid cancer (ARROW): A multi-cohort, open-label, registrational, phase 1/2 study. Lancet Diabetes Endocrinol 9: 491-501, 2021.
115. Subbiah V, Hu MI, Mansfield AS, Taylor MH, Schuler M, Zhu VW, Hadoux J, Curigliano G, Wirth L, Gainor JF, *et al*: Pralsetinib in patients with advanced/metastatic rearranged during transfection (RET)-altered thyroid cancer: Updated efficacy and safety data from the ARROW study. Thyroid 34: 26-40, 2024.
116. Subbiah V, Cassier PA, Siena S, Garralda E, Paz-Ares L, Garrido P, Nadal E, Vuky J, Lopes G, Kalemkerian GP, *et al*: Pan-cancer efficacy of pralsetinib in patients with RET fusion-positive solid tumors from the phase 1/2 ARROW trial. Nat Med 28: 1640-1645, 2022.
117. Griesinger F, Curigliano G, Thomas M, Subbiah V, Baik CS, Tan DSW, Lee DH, Misch D, Garralda E, Kim DW, *et al*: Safety and efficacy of pralsetinib in RET fusion-positive non-small-cell lung cancer including as first-line therapy: update from the ARROW trial. Ann Oncol 33: 1168-1178, 2022.