RET

RET (Rearranged during Transfection) is a receptor tyrosine kinase involved in various cellular processes, including cell growth, cell differentiation, and cell survival. It is encoded by the RET proto-oncogene and plays a crucial role in the development of the nervous system and kidneys.

RET mutation

RET mutations are implicated in several diseases, including cancers and congenital syndromes.

Structure and Function of RET Structure RET consists of several key domains:

Extracellular Domain: Responsible for ligand binding, consisting of cadherin-like domains and a cysteine-rich region. Transmembrane Domain: A single alpha-helix that spans the cell membrane. Intracellular (Cytoplasmic) Domain: Contains the tyrosine kinase domain, responsible for autophosphorylation and activation of downstream signaling pathways. Function RET functions primarily as a receptor for the glial cell line-derived neurotrophic factor (GDNF) family ligands (GFLs), which include:

GDNF: Glial cell line-derived neurotrophic factor

Neurturin (NRTN)

Artemin (ARTN)

Persephin (PSPN)

These ligands bind to GDNF family receptor alpha (GFRα) co-receptors, forming a complex with RET that triggers its activation through autophosphorylation.

Signaling Pathways

Upon ligand binding and activation, RET initiates several key signaling pathways:

RAS/MAPK Pathway: Involved in cell proliferation and differentiation. PI3K/AKT Pathway: Promotes cell survival and growth. PLCγ Pathway: Leads to the activation of protein kinase C (PKC) and calcium signaling. JAK/STAT Pathway: Important for cell growth and differentiation. Clinical Significance Genetic Mutations and Associated Diseases Multiple Endocrine Neoplasia Type 2 (MEN2):

MEN2A: Characterized by medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid hyperplasia. MEN2B: Similar to MEN2A but with additional features such as mucosal neuromas, marfanoid habitus, and a more aggressive form of MTC. Familial Medullary Thyroid Carcinoma (FMTC): Variant of MEN2 with MTC as the predominant feature. Hirschsprung Disease:

A congenital condition characterized by the absence of ganglion cells in the intestines, leading to severe constipation and intestinal obstruction. Mutations in RET are one of the genetic causes of this condition. Sporadic Cancers:

Sporadic Medullary Thyroid Carcinoma: RET mutations can occur in non-familial cases of MTC.

Papillary Thyroid Carcinoma (PTC): RET/PTC rearrangements are a common genetic alteration in PTC. Targeted Therapies Given its role in various cancers, RET has become a target for therapeutic interventions:

Tyrosine Kinase Inhibitors (TKIs):

Vandetanib: Approved for the treatment of advanced MTC, it inhibits RET along with other kinases like VEGFR and EGFR. Cabozantinib: Another multi-kinase inhibitor approved for MTC. Selpercatinib (LOXO-292) and Pralsetinib (BLU-667): Highly selective RET inhibitors approved for RET-mutant and RET fusion-positive cancers, including MTC and non-small cell lung cancer (NSCLC). Monoclonal Antibodies and Other Agents:

Research is ongoing into the development of monoclonal antibodies and other agents that specifically target RET and its signaling pathways. Conclusion RET is a critical receptor tyrosine kinase with significant roles in normal cellular development and function. Mutations in RET are associated with several hereditary and sporadic diseases, particularly cancers such as medullary thyroid carcinoma. Advances in understanding RET signaling have led to the development of targeted therapies that have improved outcomes for patients with RET-associated conditions. Ongoing research continues to explore new therapeutic strategies and deepen our understanding of RET's biological functions.

Transmembrane tyrosine kinase is expressed in the central and peripheral nervous system and neural crest-derived cells and acts as a co-receptor of GDNF family neurotrophic factor in complex with GRFα family proteins.

RET expression was characterized in a cohort of patients with primary and brain metastatic tumors. RET functionality was assessed using pharmacological inhibition and gene silencing in patient-derived brain metastatic tumor explants and in vivo models, organoid models, and brain organotypic cultures. RNA sequencing was used to uncover novel brain metastatic relevant RET mechanisms of action.

Results: A statistically significant enrichment of RET in brain metastases was observed in estrogen receptor-positive breast cancer, where it played a role in promoting cancer cell adhesion, survival, and outgrowth in the brain. In vivo, RET overexpression enhanced brain metastatic competency in patient-derived models. At a mechanistic level, RET overexpression was found to enhance the activation of gene programs involved in cell adhesion, requiring EGFR cooperation to deliver a pro-brain metastatic phenotype.

The results illustrate, for the first time, the role of RET in regulating colonization and outgrowth of breast cancer intracranial metastases and provide data to support the use of RET inhibitors in the management strategy for patients with breast cancer brain metastases [1)]

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for about 85% of all lung cancers. A small subset of NSCLC cases is caused by a genetic mutation known as a rearranged during transfection (RET) gene fusion. In these cases, the RET gene becomes abnormally fused with another gene, resulting in the production of a fusion protein that promotes cancer cell growth and survival.

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Jagust P, Powell AM, Ola M, Watson L, de Pablos-Aragoneses A, García-Gómez P, Fallon R, Bane F, Heiland M, Morris G, Cavanagh B, McGrath J, Ottaviani D, Hegarty A, Cocchiglia S, Sweeney KJ, MacNally S, Brett FM, Cryan J, Beausang A, Morris P, Valiente M, Hill ADK, Varešlija D, Young LS. RET overexpression leads to increased brain metastatic competency in luminal breast cancer. J Natl Cancer Inst. 2024 Jun 10:djae091. doi: 10.1093/jnci/djae091. Epub ahead of print. PMID: 38852945.