THEMATIC REVIEW

65 YEARS OF THE DOUBLE HELIX

Exploiting insights on the RET receptor for personalized cancer medicine

Lois M Mulligan

Division of Cancer Biology and Genetics, Cancer Research Institute, Queen's University, Kingston, Ontario, Canada
Department of Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada

Correspondence should be addressed to L M Mulligan: mulligal@queensu.ca

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Abstract

The focus of precision cancer medicine is the use of patient genetic signatures to predict disease occurrence and course and tailor approaches to individualized treatment to improve patient outcomes. The rearranged during transfection (RET) receptor tyrosine kinase represents a paradigm for the power of personalized cancer management to change cancer impact and improve quality of life. Oncogenic activation of RET occurs through several mechanisms including activating mutations and increased or aberrant expression. Activating RET mutations found in the inherited cancer syndrome multiple endocrine neoplasia 2 permit early diagnosis, predict disease course and guide disease management to optimize patient survival. Rearrangements of RET found in thyroid and lung tumors provide insights on potential disease aggressiveness and offer opportunities for RET-targeted therapy. Aberrant RET expression in a subset of cases is associated with tumor dissemination, resistance to therapies and/or poorer prognosis in multiple cancers. The potential of RET targeting through repurposing of small-molecule multikinase inhibitors, selective RET inhibitors or other novel approaches provides exciting opportunities to individualize therapies across multiple pathologies where RET oncogenicity contributes to cancer outcomes.

As our appreciation of the genetic complexities underlying human pathologies increases, the imperative to precisely identify disease cause so that appropriate therapies can be applied has become the gold standard for patient care. Understanding the molecular effects of disease mutations, the mechanisms by which they cause cellular dysfunctions and the implications of these at the organismal level underlie the great strength of precision medicine to effectively target the patient’s needs and improve outcomes. The rearranged during transfection (RET) proto-oncogene represents a paradigm for the power of molecular medicine to drive changes in diagnosis and patient management that alter disease outcomes and patient quality of life. Originally identified as an oncogenic driver in thyroid cancer, RET is now recognized to have roles in familial and sporadic tumors of diverse types, where it has implications for diagnosis, prognosis and disease management. RET mutations, increased expression and functional polymorphic variants all have an impact on its oncogenic functions. As such, RET is a
novel therapeutic target with increasing importance for personalized cancer medicine.

The RET receptor

RET is a receptor tyrosine kinase essential for normal development and maturation of diverse tissues (Schuchardt et al. 1994, Mulligan 2014). RET is required for the development of the kidney and for proliferation, differentiation and survival of central and peripheral nerve lineages, particularly those of the enteric nerve plexus, and other neuroendocrine cells, notably of the thyroid, adrenal and pituitary glands (Arighi et al. 2005, Paratcha & Ledda 2008, Mulligan 2014, Lasrado et al. 2017). RET activity promotes the maturation of spermatogonia and the survival and expansion of hematopoietic stem cells, indicating its broad range of functions in developing and maturing tissues (Schuchardt et al. 1994, Meng et al. 2000, Fonseca-Pereira et al. 2014).

The mature RET receptor spans the plasma membrane, with a large extracellular domain containing cadherin-like repeats and a cysteine-rich region important for protein structure and ligand interactions (Wang 2013) (Fig. 1). The RET intracellular tyrosine kinase domain is required for autophosphorylation and phosphorylation of substrates that promote RET downstream signals through multiple pathways (Ibanez 2013, Mulligan 2014). Finally, RET has two functionally distinct protein isoforms that differ in C-terminal tail sequences due to alternative gene splicing and have differential contributions to both RET-mediated normal development and oncogenicity (de Graaff et al. 2001, Lian et al. 2017).

Under normal conditions, RET is activated by binding of a group of soluble glial cell line-derived neurotrophic factor (GDNF) ligands and a cell surface glycosylphosphatidylinositol-linked GDNF family receptor α (GFRα) (Mulligan 2014, Ibanez & Andressoo 2017) (Fig. 1). Binding of this ligand–coreceptor complex recruits RET into membrane domains called lipid rafts that act as hubs for RET-mediated activation of downstream signals (Mulligan 2014, Tsui et al. 2015). However, RET can also contribute to oncogenesis, either as a result of mutations that constitutively activate the RET kinase or by increased or aberrant activity of the WT receptor. Several types of RET mutations have been recognized that contribute to RET oncogenicity, and each of these is associated with specific tumor types and disease patterns (Mulligan 2014). The activating point mutations that cause multiple endocrine neoplasia type 2 (MEN2) and RET rearrangements found in thyroid and lung cancers are to date the best characterized of these mutations and have been the primary focus of RET precision medicine strategies.

Multiple endocrine neoplasia 2

MEN2 is an autosomal dominantly inherited cancer syndrome characterized by the occurrence of early-onset medullary thyroid carcinoma (MTC). The disease is further classified as two subtypes MEN2A and MEN2B, based on disease severity and associated phenotypes (Wells et al. 2015, Wells 2018). The more common subtype, MEN2A, representing >95% of cases, may also be associated with the adrenal tumor pheochromocytoma (PCC) and parathyroid hyperplasia (HPT). A previously separate disease subtype, familial MTC, is now considered part of the MEN2A spectrum. In rare cases, MEN2A patients may have other noncancerous phenotypes, such as cutaneous lichen amyloidosis (itchy hyperpigmented epidermal plaques) or increased incidence of the congenital gut abnormality Hirschsprung disease (Wells et al. 2015). The clinically more severe MEN2B subtype has earlier disease onset and is also characterized by MTC and PCC but in addition, with developmental anomalies of several systems, including Marfanoid habitus, ganglioneuromas of the mouth and intestines and delayed puberty (Castinetti et al. 2018). Over 90% of MEN2B presents as de novo cases, making timely diagnosis challenging (Brauckhoff et al. 2014, Castinetti et al. 2018).

MEN2 is caused by gain-of-function mutations of the RET receptor (Mulligan 2014). These are primarily point mutations, creating single amino acid substitutions that lead to constitutive RET kinase activity. MEN2 mutations are found in RET exons 5–16, but the majority of the >60 pathogenic variants detected to date cluster at fewer than 15 residues (Margraf et al. 2009). There are strong associations of disease phenotype and RET mutation genotype. Risks of developing PCC and HPT are mutation dependent, which has been extremely valuable in guiding recommendations for disease management (Mulligan et al. 1994, Eng et al. 1996, Wells et al. 2015). Over 95% of MEN2A cases arise from substitutions of cysteine residues in the RET extracellular domain (C609, C611, C618, C620, C634) that allow receptor dimerization and constitutive activity in the absence of ligand (Mulligan et al. 1994, Eng et al. 1996) (Figs 1 and 2). Other less common MEN2A mutations in the RET extracellular domain (e.g. G533C) or intracellular domain (residues E768, L790, V804, S891) are generally associated with more indolent disease or later disease onset or with MTC as the only disease feature (Machens & Dralle 2008, Mulligan 2014, Wells 2018).
Figure 1
The RET receptor tyrosine kinase and its oncogenic mutations. (A) Activation of WT RET occurs by binding of a GDNF ligand to GFRα. This complex binds and promotes RET activity. (B) Schematic diagram showing locations of the common RET mutations identified in MEN2 patients (left) and RET rearrangements found in multiple cancers (right). The locations of RET mutations that give rise to MEN2 and the associated disease phenotypes are indicated. Two sequence variants suggested to act as modifiers, either affecting severity of other RET mutations or as risk-associated alleles in other cancers, are indicated in red. RET fusion proteins are located in the cytosol. RET kinase domain and partner genes that provide dimerization domains that permit constitutive activation, are indicated. GDNF, glial cell line-derived neurotrophic factor; GFRα, GDNF receptor α; MEN2, multiple endocrine neoplasia type 2; RET, rearranged during transfection.
MEN2B is uniquely associated with a substitution of a methionine at codon 918 for threonine, within the RET catalytic domain, close to the activation loop of the kinase (Gujral et al. 2006, Knowles et al. 2006). These mutants have altered phosphorylation kinetics, and ten-fold increased ATP-binding and kinase activity, allowing robust activation of downstream signals (Gujral et al. 2006, Plaza-Menacho 2018). In some cases, an alanine-to-phenylalanine change at codon 883 in the RET kinase domain, also proximal to the activation loop, has been linked to MEN2B, but may be associated with a less aggressive form of the disease (Jasim et al. 2011, Mathiesen et al. 2017). In rare instances, an MEN2B variant has been reported associated with dual mutations in cis lying close to the ATP-binding pocket of the RET kinase (e.g. V804M, Y806C). The two variants act synergistically to enhance RET activity; however, the phenotypes of these patients are not fully consistent with MEN2B but are generally more indolent than M918T mutants (Cranston et al. 2006, Nakao et al. 2013). Interestingly, MEN2B-type RET mutations occur somatically in approximately 65% of sporadic MTCs where they are associated with more aggressive disease (Elisei et al. 2008, Moura et al. 2009).

Prior to identification of RET mutations in 1993 (Donis-Keller et al. 1993, Mulligan et al. 1993), MEN2 diagnosis was based on family history and the inheritance of linked markers (Calmettes et al. 1992). As MTC responds poorly to standard chemotherapy and radiotherapy, the primary treatment is surgical intervention. Repeated biochemical screening in at-risk individuals for the MTC precursor lesion C-cell hyperplasia or early-stage disease was used to identify those family members carrying the MEN2 mutation and to plan the timing of thyroidectomy. Unfortunately, these assays had relatively frequent false positives leading to unnecessary surgeries (Marsh et al. 1996). Further, even with regular screening, it was not always possible to detect nascent MTC before it spread, reducing long-term survival and quality of life in these patients. The identification of the underlying genetic cause of MEN2 has profoundly changed disease management (Wells et al. 1994, 2015, Leary et al. 1997, Dralle et al. 1998, Machens & Dralle 2018, Wells 2018). Genetic testing for MEN2 RET mutations as early as possible is now standard of care for all at-risk individuals (Wells et al. 2015). Confirmation of RET mutation status eliminates the need for repeated biochemical screening for those who have not inherited the disease allele and can focus resources on those who will develop MEN2. Presymptomatic genetic testing allows for prophylactic or very early interventions in these individuals, before disease has a chance to spread outside the thyroid (Wells et al. 2015, Machens & Dralle 2018, Wells 2018). Testing is also valuable in apparently sporadic MTC cases as 7–15% of these have germline RET mutations and represent de novo MEN2 cases (Eng et al. 1995, Romei et al. 2011).

Importantly, the association of specific disease phenotypes with RET mutation genotype in MEN2 has offered the opportunity to tailor management recommendations optimally based on the identified disease mutation. For individuals with the highest risk MEN2B RET mutation (M918T), which is associated with earliest onset and most aggressive phenotypes,
prophylactic thyroidectomy is recommended in the first year of life (Wells et al. 2015), since MTC micrometastases have been recognized as early as 3 months of age (Sanso et al. 2002, Zenaty et al. 2009). In individuals with other mutations considered high risk, including the most common MEN2A mutation, C634R and the MEN2B A883F mutations, surgery should be performed before age 5 years. The remaining, so-called ‘moderate risk’ RET mutations, may be associated with later or more variable age of onset, and an individualized combination of biochemical monitoring and thyroidectomy based on age of onset in family members is recommended (Wells et al. 2015, Voss et al. 2017). Importantly, despite these differences, recent analyses have found very little difference in overall survival and distant metastasis for patients with high- or moderate-risk RET mutations when age at diagnosis is taken into account highlighting the need for the earliest possible genetic testing (Voss et al. 2017). Monitoring for PCC and HPT can also be prioritized based on RET mutation, as PCC is much more common in patients with C634 (~90% by age 80 years) or M918 (~100%) mutations, while parathyroid involvement occurs primarily with C634R mutations (Mulligan et al. 1994, Eng et al. 1996, Imai et al. 2013).

RET mutation-guided management has significantly improved disease outcomes and quality of life for MEN2A patients (Grey & Winter 2018, Machens & Dralle 2018, Machens et al. 2018). Early genetic screening in these patients provides the earliest possible opportunity for prophylactic thyroidectomy or surgical intervention before MTC has spread outside the thyroid, thereby reducing the need for extensive lymph node dissections, reducing morbidity from surgical complications (Machens & Dralle 2018, Machens et al. 2018). Effective cure for MEN2A patients detected by presymptomatic mutation screening approaches 100%, compared to 10-year survival rates as low as 40% for MTC patients with extensive metastasis at diagnosis (Lodish & Stratakis 2008). In contrast, MEN2B predominantly results from de novo RET mutations and therefore genetic screening is not generally guided by family history. Further, MEN2B is clinically more aggressive, with earlier metastasis, narrowing the window where early thyroidectomy will provide effective cure (Brauckhoff et al. 2014, Castinetti et al. 2018). Thus, early recognition of nonendocrine signs of MEN2B, detailed earlier (Brauckhoff et al. 2014, Castinetti et al. 2018), by pediatricians, dentists and other health care providers is critical to minimizing delays in diagnosis and improving outcomes. Despite advances, surgical cure for MEN2B-MTC operated after age 4 years is rare (Brauckhoff et al. 2014, Machens & Dralle 2018). Since MEN2B de novo cases are often diagnosed much later than this, prophylactic thyroidectomy is not the norm and morbidity for this disease subtype is much higher. Thus, MEN2B patients in particular benefit from more recent advances in RET-targeted therapies, discussed below (Fox et al. 2013, Schlumberger et al. 2017). Nonetheless, RET mutation detection as early as possible in these cases also permits an appropriate regimen of follow-up testing and screening for PCC.

RET polymorphic variants and cancer risk

In addition to MEN2-RET pathogenic mutations, there are several polymorphic sequence variants that act as modifiers of RET mutation genotype. Combinations of polymorphic RET coding or intronic sequence variants have been suggested to increase MTC or MEN2A-PCC risk (McWhinney et al. 2003, Ceolin et al. 2012, Siqueira et al. 2014, Lebeault et al. 2017). The Y791F non-synonymous variant lies within the RET kinase domain and was originally thought to be a pathogenic mutation, while the G691S variant lies in the juxtamembrane region of RET (Fig. 1). In families, co-occurrence of either of these variants with other MEN2A mutations enhances disease severity and promotes earlier onset of some, or all, disease phenotypes (Robledo et al. 2003, Toledo et al. 2010, 2015, Lantier et al. 2013, Colombo et al. 2015), making assessment of these variants a valuable contribution to improve disease management. Interestingly, the G691S variant is also over represented in patients with sporadic MTC, pancreatic ductal adenocarcinoma and cutaneous or desmoplastic melanoma (Fig. 2), and may be correlated with increased tumor growth or invasion (Elisei et al. 2004, Sawai et al. 2005, Narita et al. 2009) suggesting this variant may act as a modifier or low penetrance risk allele in these cancers also.

RET rearrangements

A distinct group of oncogenic mutations are the somatically occurring rearrangements of the RET gene (Fig. 2). As a result of chromosomal rearrangement or inversion, gene sequences encoding the intracellular kinase domain of RET become juxtaposed to 5’ sequences from a partner gene containing protein dimerization domains (Fig. 1). The resultant chimeric proteins are constitutively dimerized and localized in the cytosol, where they escape regulation by the mechanisms controlling the WT RET protein at the cell membrane and enhance signaling,
particular through MAP kinase pathways (Richardson et al. 2009, Xing 2013). RET rearrangements are identified in 20–40% of papillary thyroid carcinomas (PTCs) and incidence varies geographically (Hamatani et al. 2008, Leeman-Neill et al. 2013, Liang et al. 2018). Although close to 20 different partner genes have been recognized to date, the most frequent rearrangements involve the genes for coiled-coil domain containing 6 (CCDC6) termed RET-PTC1 and the nuclear receptor co-activator 4 (NCOA4; RET-PTC3) (Romei et al. 2016). RET rearrangements, and particularly RET-PTC3, are associated with more aggressive PTC histology (Romei et al. 2016) and promote tumor cell migration and invasion in vitro (Lian et al. 2017).

Similar forms of RET rearrangements are identified in ~1–2% non-small-cell lung carcinomas (NSCLCs), where they are more prevalent in younger patients and represent 6–19% of tumors in never smokers without any other genetic cause (Ferrara et al. 2018). At least 12 different RET fusions have been recognized, but interestingly, these chimeras involve a different distribution of RET partner genes than in PTC, with rearrangements involving kinesin family 5B (KIF5B) and CCDC6 being the most prevalent events (Gautschi et al. 2017, Ferrara et al. 2018). In particular, the KIF5B-RET rearrangement results in a 2- to 30-fold increase in expression of the RET kinase, suggesting that the fusion protein is responsible for transformation in these tumors (Kohno et al. 2012) and highlighting it as an actionable therapeutic target (Gautschi et al. 2017).

As deep sequencing methods are applied more broadly to human cancers, RET fusions are beginning to be discovered as rare events in other cancers as well. RET rearrangements with several partners (GOLGA5, KIF5B) are found in ~3% of Spitzoid tumors (Wiesner et al. 2014). RET fusion with the breakpoint cluster region protein (BCR) or fibroblast growth factor receptor 1 oncogene partner (FGFR1OP) genes have been identified infrequently in chronic myelomonocytic leukemia (Ballerini et al. 2012). Rare examples of RET fusions have also been found in breast, colon, ovarian, salivary gland and inflammatory myofibroblastic tumors (Stransky et al. 2014, Antonescu et al. 2015, Kato et al. 2017), suggesting potential value of customized strategies for targeting of patients with RET anomalies.

RET expression in other tumors

In addition to oncogenic mutations, altered RET expression is also detected in diverse tumor types where it may provide an actionable therapeutic target. Increased expression and activation of RET receptors is detected in approximately 30–70% of breast cancers, and expression is somewhat more common in estrogen receptor-positive tumors (Morandi et al. 2011, 2013, Gattelli et al. 2013). RET has been linked to larger tumors, higher stage and decreased metastasis-free and overall survival in these patients (Plaza-Menacho et al. 2010, Wang et al. 2012, Morandi et al. 2013). Increased RET levels are also associated with resistance to multiple endocrine therapy modalities (tamoxifen, aromatase inhibitors, fulvestrant), which are key tools in targeting hormone receptor-positive breast cancers (Plaza-Menacho et al. 2010, Gattelli et al. 2013, Morandi et al. 2013). Preclinical models have suggested benefit in targeting RET in breast cancer where it might act as an adjuvant to block tumor growth and increase response to endocrine therapies (Nguyen et al. 2015, Andreucci et al. 2016, Hatem et al. 2016, Gattelli et al. 2018).

Elevated RET expression is detected in 50–65% of pancreatic ductal adenocarcinomas, particularly in higher grade tumors, where it promotes metastasis and perineural invasion, the spread of tumor cells along nerve fibers, which is associated with poor prognosis and tumor-related pain (Zeng et al. 2008, Gil et al. 2010, Amit et al. 2017). In prostate adenocarcinomas, increased RET expression may increase proliferation and is also linked to perineural invasion (Dawson et al. 1998, Ban et al. 2017). Some level of RET expression is detected in a number of other cancers including melanoma, head and neck tumors, neuroblastoma, and lung, colon and renal cell carcinomas (Fig. 2) (Narita et al. 2009, Flavin et al. 2012, Luo et al. 2013, Kosari et al. 2014, Lin et al. 2016). The oncogenic importance of RET in tumor growth and spread in these diseases and its value as a therapeutic target is yet to be fully characterized.

**RET-targeted therapies**

The holy grail of precision medicine is to establish the patient-specific disease mechanisms that allow us to ‘personalize’ cancer therapy to improve individual care outcomes. As summarized here, RET is an important driver of both familial and sporadic cancers (Fig. 2), and RET-targeted therapies have potential applications in diverse cancers. There are currently no RET-specific agents approved for clinical use; however, multikinase inhibitors originally developed to target conserved regions of other kinases have also shown efficacy against RET (Redaelli et al. 2018). The ATP-competitive multikinase inhibitors vandetanib and cabozantinib effectively block activity and
signaling of both full-length and fusion RET proteins and have been approved for use in patients with progressive unresectable MTC or treatment-resistant FTC (Wells et al. 2012, Elisei et al. 2013, Redaelli et al. 2018). These drugs have significantly improved progression-free survival (PFS), leading to stable disease or increased duration of response in patients with advanced or metastatic MTC (Wells et al. 2012, Karras et al. 2013, Schlumberger et al. 2015, Viola et al. 2016). Importantly, treatment provides significant improvements in PFS and overall survival for MTC patients with RET M918T mutations, which respond very poorly to other chemotherapies, although some initial studies with cabozantinib suggest that benefits for other RET mutations may be more modest (Fox et al. 2013, Schlumberger et al. 2015, 2017). Notably, some specific MEN2 RET mutations that affect the ‘gate keeper’ residue (V804) adjacent to the RET ATP-binding pocket, block binding of inhibitors to RET and confer resistance to these agents (Carlomagno et al. 2004), making RET mutation genotype an important determinant of treatment success. Recent clinical trials have also shown vandetanib and cabozantinib increase PFS for lung adenocarcinoma expressing RET fusion genes, and this is more pronounced for KIF5B-RET than CCDC6-RET fusions (Subbiah et al. 2016), making cabozantinib increase PFS for lung adenocarcinoma expressing RET fusion genes, and this is more pronounced for KIF5B-RET than CCDC6-RET fusions (Subbiah et al. 2016). Two of these inhibitors, BLU-667 and LOXO-292, have >100-fold greater selectivity for RET compared to other kinases in cell-based and preclinical animal models (Drilon et al. 2018, Subbiah et al. 2018a,b). Phase I trials for both of these agents are currently underway but early results are promising, showing low toxicity and significantly improved inhibition of the range of RET mutants (Subbiah et al. 2018a,b). Trials of additional RET-targeted agents are likely to follow soon. Interestingly, early data suggest that LOXO-292 crosses the blood–brain barrier and may be effective for management of brain metastases, particularly in NSCLC (Subbiah et al. 2018b).

Alternative strategies for targeting RET, such as antibody–drug conjugates, provide additional modalities that may complement existing ATP-competitive inhibitors and avoid the potential for acquired resistance (Nguyen et al. 2015). Combination therapies, using RET inhibitors in conjunction with agents to block downstream pathways, are also showing promising effects. The combination of RET and mTOR inhibitors induces synergistic growth inhibition in MTC cells and may enhance RET inhibitor delivery to the central nervous system, essential to target NSCLC brain metastasis (Gild et al. 2013, Subbiah et al. 2015).

The future: from cause to cure

The RET receptor is a ‘poster child’ for the potential of precision medicine strategies to change the ways we understand and manage cancer risks, but there are still many avenues to improve patient care. The identification of individual RET mutations allows accurate presymptomatic diagnosis and prediction of disease course in MEN2, which permits personalized disease management. Sensitive liquid biopsy approaches are being developed to identify RET mutations in circulating tumor cells or cell-free DNA, which will speed the recognition of primary or recurrent RET-driven cancers, identify candidates for RET-targeted therapies and provide accurate monitoring of response to therapy, disease recurrence or acquired drug resistance (Cote et al. 2017, Reckamp et al. 2018). Exciting developments of highly selective small-molecule RET inhibitors and combination therapies are changing the way we manage RET-associated cancers today, but new approaches to complement these are needed. Novel strategies using
agents to block RET expression (e.g. ellipticine analogs (Kumarasamy & Sun 2017)) or enhance RET degradation (e.g. heat shock protein inhibitors (Alfano et al. 2010)) are already being explored in preclinical models. Studies identifying direct modulators of RET expression (e.g. estrogen receptor α, ATF4, TFA2C), and RET-negative regulators (e.g. HSP90, CBL and NEDD4 ubiquitin ligases), suggest additional potential actionable processes to limit RET function that could be used in combination with RET inhibitors to improve their therapeutic efficacy and limit the development of drug resistance (Alfano et al. 2010, Bagheri-Yarmand et al. 2017, Hyndman et al. 2017). Together, RET's oncogenic roles make it an important therapeutic target across many cancer types, and it is likely that this will only increase as we delve more broadly into diverse cancer genomes.

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