REARRANGED DURING TRANSFECTION (RET) RECEPTOR AT A GLANCE

Receptor tyrosine kinases (RTK) are transmembrane (TM) proteins featuring an intracellular domain containing the tyrosine kinase (TK) enzyme. RTKs are often involved in cancer formation [1-3]. Notable examples are epidermal growth factor receptor (EGFR/HER1) and anaplastic lymphoma kinase (ALK) in non-small cell lung carcinoma (NSCLC) [4], KIT in gastrointestinal stromal tumors (GIST) [5], FLT3 in acute myeloid leukemia (AML) [6], and HER2/ERBB2/neu in breast cancer [7].

In some cases, cancer cells up-regulate expression of the RTK (as an example HER2 in breast cancer), its cognate growth factor or both, in other cases, structural alterations such as chromosomal rearrangements leading to the RTK recombination to heterologous genes (as an example EML4-ALK in lung adenocarcinoma) or point mutations (as EGFR, KIT or FLT3 mutations in NSCLC, GIST, or AML, respectively), lead to unchecked kinase and oncogenic activity [1-3].

This notion has stimulated the search for agents, such as monoclonal antibodies against the RTK extracellular domain (like trastuzumab for HER2 or cetuximab for EGFR) or ATP-competitive small molecule protein kinase inhibitors (PKIs) (like gefitinib and erlotinib for EGFR or crizotinib for ALK), to combat cancers driven by oncogenic RTKs [1-3].

The RET RTK was originally identified as an oncogene activated by a rearrangement occurred in vitro during transfection of NIH3T3 cells with human lymphoma DNA [8]. RET protein belongs to a cell-surface complex able to bind glial-derived neurotrophic factor (GDNF) ligands (GDNF, neurturin, artemin, and persephin) in conjunction with co-receptors of the GDNF receptor α family, designated GFRα 1-4 [9]. Binding to the ligand-co-receptor complex leads to RET dimerization and kinase activation. RET expression is tightly regulated during development and in the adulthood is limited to specific tissues, including neural crest-derived cells. RET is essential for the development of the enteric nervous system and kidney, and germline loss-of-function mutations in RET cause Hirschsprung disease (aganglionic megacolon) and congenital anomalies of the kidney or lower urinary tract [10,11].

RET gene maps to chromosome 10q11.2. Fig. 1 shows that it is splitted in 21 coding exons. Exons 1-10 code for the extracellular region; exon 11 codes for the COOH-terminal part of the extracellular region, the TM domain, and the intracellular juxtamembrane domain. Finally, exons 12-21 code for the intracellular domain. An alternative splicing at exon 19 determine the synthesis of three RET protein isoforms with different C-terminal tails. In RET9 (1072 aa), exon 19 is unspliced; in RET51 (1114 aa), exon 19 is spliced to exon 20; in RET43 (1106 aa), exon 19 is spliced to to exon 21 [12-15]. RET9 and RET51 are the most abundant and well characterized isoforms (Fig. 1). RET protein features an extracellular portion (RET-EC) that...
includes the cleavable signal peptide (SP), four cadherin-like repeats (CLD1-4) and a cysteine-rich domain (CRD), a TM portion and an intracellular portion with the TK (RET-TK) domain split in two subdomains by a short insert (Fig. 1) [16,17].

The intracellular region of RET contains several tyrosine residues that undergo phosphorylation upon RET activation (Fig. 1) [18,19]. Tyrosine 905 map in the kinase A-loop (activation loop) and contributes to RET kinase activation; Y1015 is a docking site for phospholipase C\(\gamma\); Y1062 acts as a binding site for different proteins, including Shc, ShcC, IRS1/2, FRS2, and DOK1/4/5, that, in turn, lead to stimulation of the RAS/MAPK and phosphatidylinositol-3-kinase/AKT pathways [18-22].

**RET POINT MUTATIONS IN CANCER**

Activating point mutations of RET have been identified as a major driver for medullary thyroid carcinoma (MTC) [19,23-25]. MTC (about 5% of thyroid cancers) is a malignant tumor arising from neural crest derived thyroid parafollicular C cells. MTC occurs sporadically in 75% of the cases; in about 25% of cases, MTC is inherited as a component of the autosomal dominant multiple endocrine neoplasia type 2 (MEN2A, MEN2B, FMTC) syndromes [19,23-25]. MTC has full penetrance in all MEN subtypes and it is usually the first manifestation of the syndrome. MEN2A is the most common (80-90% of cases) subtype and is characterized by MTC, pheochromocytoma, and hyperparathyroidism. More rarely, MEN2A patients develop aganglionic megacolon (Hirschsprung disease) or cutaneous lichen [19]. MEN2B is the least common (5-10% of the cases) MEN2 subtype and it is characterized by aggressive MTC, pheochromocytoma, ganglioneuromatosis of the intestine, thickening of corneal nerves and marfanoid habitus. FMTC features MTC as the only phenotype and it is currently regarded as a low penetrance MEN2A subtype [24,25].

Germline RET mutations are responsible for virtually all MEN2 cases. Most common mutations target exons 10 and 11 encoding CRD of the RET extracellular domain or exons 13-16 encoding part
of the TK domain of RET (Fig. 1). Most frequent (85% of the cases) MEN2A mutations affect cysteine 634 (in exon 11) in the CRD; less commonly, MEN2A is caused by mutations of cysteines C609, C611, C618, C620 (in exon 10), or C630 (in exon 11) [19]. Other rare single or double mutations, small insertions or deletions, have been described in MEN2A cases [19]. FMTC mutations are evenly distributed among the various cysteines of CRD [19]. FMTC can be also associated to mutations of the RET-TK (E768D, L790F, Y791F, V804L, V804M, and S891A) (Fig. 1). MEN2B mutation is caused in most (> 97%) of the cases by M918T mutation in RET-TK (exon 16); more rarely (2%), MEN2B patients harbor the A883F substitution (exon 15), or double mutations (Fig. 1) [19]. Importantly, RET mutations (mainly M918T) occur at the somatic level in about half sporadic MTC.

MTC-associated RET mutations have a gain-of-function effect and convert RET into an oncogene. Extracellular cysteine RET mutants form covalent dimers stabilized by disulfide-bonds and display growth factor independent kinase activity [26]. In unstimulated conditions, the RET-TK adopts a trans-inhibited head-to-tail inactive dimer conformation in which the substrate-binding site of each monomer is occluded by the contralateral one [17]. Some mutations targeting the TK domain (most notably M918T) hit trans-inhibited dimer contact points and may therefore destabilize this inactive dimer conformation and activate RET [17]. Moreover, methionine 918 localizes in the P + 1 kinase loop, a site that is involved in substrate binding. Accordingly, its replacement by a threonine residue modifies RET signaling specificity [26,27].

RET REARRANGEMENTS IN CANCER

At least three types of human cancer (papillary thyroid carcinoma [PTC], lung adenocarcinoma, and chronic myelomonocytic leukemia [CMML]) feature genomic rearrangements leading to the recombination of the RET-TK domain to heterologous proteins. Breakpoint in RET is virtually always in intron 11, so that RET exon 12 (encoding the N-ter of the RET-TK) is fused to the 5'-end of heterologous genes (Fig. 1). Fusion to heterologous proteins containing protein homodimerization motives results in constitutive RET kinase dimerization, growth factor independent activation, and signalling. Furthermore, replacement of the RET transcriptional promoter with that of the fusion partners likely de-regulates RET expression. The expression of a constitutively dimerized and active RET kinase leads to chronic exposure of cancer cells to the activation of intracellular signalling pathways, such as the RAS-RAF-MAPK, that are activated by RET [18]. Intriguingly, this pathway includes RAS and BRAF that are very commonly mutated in the same cancer types in which RET is involved [4,28].

RET gene rearrangements were initially discovered in PTC [29]. PTC arises from follicular thyroid cells and is the most prevalent thyroid cancer type [28]. In PTC, chromosomal aberrations, most commonly a paracentric inversion of the long arm of chromosome 10, cause the illegitimate recombination of the RET-TK (from exon 12 to the 5'-end) to the promoter sequence and 5'-terminal exons of heterologous genes [28]. Most common RET/PTC rearrangements (90% of the cases) are RET/PTC1 (CCDC6-RET) and RET/PTC3 (NCOA4-RET) [30,31]. RET/PTC3 is particularly frequent in PTC consequent to the Chernobyl disaster and in young patients [28]. Close proximity of the fusion partners in thyrocyte chromatin may favour their recombination [32,33]. RET/PTC prevalence (average 25% of the cases) varies considerably in different patient series [28]. An important factor for this variability is methodology used for the detection [34].

More recently, RET has been demonstrated to play an important role also in a subset of NSCLC cases, in particular lung adenocarcinoma. In about 1% NSCLC, inversions of chromosome 10 cause the fusion of the RET-TK domain to different 5'-terminal exons (15, 16, 22, 23, or 24) of KIF5B (kinesin family member 5B) gene [35-37]. The RET/PTC1 (CCDC6-RET chimera) oncogene has been found in one lung adenocarcinoma sample [38]. As in the case of RET/PTC, also KIF5B-RET fusion proteins likely form active homodimers through the coiled-coil domain present in the NH2-ter portion of KIF5B. It is important to note that lung adenocarcinoma is commonly associated to mutations targeting also RTKs other than RET, such as EGFR, ROS1, and ALK [4]. Mutations in EGFR, ROS1, ALK, and RET are mutually exclusive.

CMML is a neoplastic myeloid disorder [39]. Very recently, gene rearrangements causing the fusion of the RET encoding TK domain (from exon 12) in one case to the 5'-terminal four exons of breakpoint cluster region (BCR) and in another case to the 5'-terminal 12 exons of fibroblast growth factor receptor 1 oncogenic partner (FGFR1OP) genes have been described in CMML [40]. Prevalence of RET rearrangements in CMML is still unknown.

RET OVER-EXPRESSION IN CANCER

In some cancers, RET upregulation rather than structural altera-
tion has been reported. This is worth mentioning in the case of breast and pancreatic adenocarcinoma. A positive correlation was demonstrated between RET over-expression and estrogen receptor-positive breast carcinoma [41,42]. Importantly, RET inhibition restored a hormone-sensitive phenotype in anti-estrogen resistant breast cancer cells [43]. Furthermore, RET protein was overexpressed in pancreatic carcinoma and involved in neural invasion of pancreatic cancer cells [44,45].

RET AS A TUMOR SUPPRESSOR

In contrast to its well-established role as an oncogene for several cancer types, RET has been recently proposed to play tumor suppressor roles in colorectal cancer (CRC) and pituitary adenoma [46, 47]. Such tumor suppressor role might be functionally linked to a pro-apoptotic role exerted by RET by behaving as a “dependence” receptor [48]. Dependence receptors display pro-apoptotic activity when not bound to cognate growth factor; in the case of RET, this leads to caspase-3-mediated cleavage of its cytosolic portion (after aspartic acid residues 707 and 1017) which, in turn, releases a cytosolic peptide (aa 708-1016) that is able to induce cell death [48]. Thus, loss-of-function of RET may abrogate this effect and foster tumor development.

In CRC, RET promoter methylation commonly silenced RET expression [47]. Moreover, in rare CRC samples, somatic mutations (V145G, R360W, and G593E) in RET extracellular domain impaired RET-mediated apoptosis of colon epithelial cells; thus, either RET downregulation or mutations causing loss of RET-mediated apoptosis may be selected during CRC formation [47].

Similarly, RET was expressed in somatotroph-derived pituitary adenomas, where it acted as a two-sided tumor regulator. When stimulated by GDNF, it behaved as as an oncogene able to activate intracellular signaling and cell survival. Instead, in the absence of GDNF, RET behaved as a tumor suppressor; caspase-mediated RET processing induced Pit-1 expression, that, in turn, caused p19Arf and p53 upregulation and apoptosis [46,49].

RET KINASE INHIBITORS FOR CANCER TREATMENT

The advent of small-molecule drugs and monoclonal antibodies made RTK targeting a feasible cancer therapeutic strategy [2]. Most RTK-directed small-molecule drugs are PKIs that obstruct kinase activity by binding to the ATP pocket of the kinase in competition with cellular ATP [2,3]. Prototypic examples of anti-neoplastic PKIs are imatinib, an inhibitor of ABL, KIT and platelet-derived growth factor receptor (PDGFR), in BCR-ABL-positive chronic myelogenous leukemia and KIT or PDGFR-α mutant GISTs and EGFR-directed inhibitors (gefitinib and erlotinib) for EGFR mutant lung adenocarcinoma [4,50].

Several small-molecules have been identified at the preclinical level to target cancer cells showing increased RET activity [51-53]. These agents are multitargeted and able to inhibit several kinases besides RET. Vandetanib (ZD6474) is an anilinoquinazoline that docks in the ATP-binding pocket of the RET kinase and inhibits RET kinase with an inhibitory concentration 50 of 100-130 nM [17, 54]. Some RET mutations, like V804M/L, and Y806C cause resistance to [55,56]. Other compounds with anti-RET activity include sorafenib, sunitinib, lenvatinib (E7080), and cobezanibib (XL-184) [57-60]. Some of them already entered clinical experimentation [61-63]. These compounds share with vandetanib the capability of targeting vascular endothelial growth factor receptors (VEGFR2/KDR; VEGFR3/Flt-4; VEGFR1/Flt-1) [64,65]. In addition, vandetanib targets the EGFR [66]. Based on the results of the ZETA trial, vandetanib has been recently registered for locally advanced or metastatic MTC [62] and may represent a promising agent for other RET-driven cancers.

As most cancers are the result of a number of mutations and feature multiple altered signaling pathways, it may be anticipated that PKIs able to target multiple kinases or a rational combination of them will be more clinically effective than agents blocking a single kinase. Multi-targeting or combination therapies may also attenuate resistance formation [67]. By using a chemical genetic approach and a Drosophila model of MEN2 new PKIs able to inhibit simultaneously RET, RAF, SRC, and S6K have shown increased potency and reduced toxicity [68].

CONCLUSIONS

After about three decades since its discovery [8], RET has raised a great interest as a gene involved in human developmental diseases as well as epithelial, neuroendocrine and hematological cancers. This knowledge has been already transferred to the bed of patients, as illustrated by RET genotyping to identify MEN2 carriers [69]. Moreover, this knowledge has also led to the use of RET-directed therapeutics for the treatment of thyroid cancer.
 ACKNOWLEDGEMENTS

We gratefully acknowledge members of our laboratory for continuous support.

REFERENCES

1. Krause DS, Van Etten RA: Tyrosine kinases as targets for cancer therapy. N Engl J Med 353:172-187, 2005
2. Baselga J: Targeting tyrosine kinases in cancer: the second wave. Science 312:1175-1178, 2006
3. Zhang J, Yang PL, Gray NS: Targeting cancer with small molecule kinase inhibitors. Nat Rev Cancer 9:28-39, 2009
4. Herbst RS, Heymach JV, Lippman SM: Lung cancer. N Engl J Med 359:1367-1380, 2008
5. Corless CL, Barnett CM, Heinrich MC: Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer 11:865-878, 2011
6. Daver N, Cortes J: Molecular targeted therapy in acute myeloid leukemia. Hematology 17 Suppl 1:S59-S62, 2012
7. Takahashi M, Ritz J, Cooper GM: Activation of a novel human transforming gene, ret, by DNA rearrangement. Cell 42:581-588, 1985
8. Arakinski MN, Saarma M: The GDNF family: signalling, biological functions and therapeutic value. Nat Rev Neurosci 3:383-394, 2002
9. Runeberg-Roos P, Saarma M: Neurotrophic factor receptor RET: structure, cell biology, and inherited diseases. Ann Med 39:572-580, 2007
10. Jain S: The many faces of RET dysfunction in kidney. Organogenesis 5: 177-190, 2009
11. Tahira T, Shiraiishi M, Ishizaka Y, Ikeda I, Sakai R, Sugimura T, Nagao M: A TaqI RFLP in the human ret proto-oncogene. Nucleic Acids Res 18: 7472, 1990
12. Myers SM, Eng C, Ponder BA, Mulligan LM: Characterization of RET proto-oncogene 3’ splicing variants and polyadenylation sites: a novel C-terminus for RET. Oncogene 11:2039-2045, 1995
13. Ivanuchk SM, Eng C, Cavenee WK, Mulligan LM: The expression of RET and its multiple splice forms in developing human kidney. Oncogene 14:1811-1818, 1997
14. Ivanuchk SM, Myers SM, Mulligan LM: Expression of RET 3’ splicing variants during human kidney development. Oncogene 16:991-996, 1998
15. Scott RP, Iblance CE: Determinants of ligand binding specificity in the glial cell line-derived neurotrophic factor family receptor alpha S. J Biol Chem 276:1450-1458, 2001
16. Knowles PP, Murray-Rust J, Kjaer S, Scott RP, Hannah S, Santoro M, Ibáñez CF, McDonald NQ: Structure and chemical inhibition of the RET tyrosine kinase domain. J Biol Chem 281:33577-33587, 2006
17. Takahashi M: The GDNF/RET signaling pathway and human diseases. Cytokine Growth Factor Rev 12:361-373, 2001
18. de Groot JW, Links TP, Plukker JT, Lips CJ, Hofstra RM: RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. Endocr Rev 27:535-560, 2006
19. Melillo RM, Santoro M, Ong SH, Billaud M, Fusco A, Hadari YR, Schlessinger J, Lax I: Docking protein FRS2 links the protein tyrosine kinase RET and its oncogenic forms with the mitogen-activated protein kinase signaling cascade. Mol Cell Biol 21:4177-4187, 2001
20. Melillo RM, Carlomagno F, De Vito G, Formisano P, Vecchio G, Fusco A, Billaud M, Santoro M: The insulin receptor substrate (IRS-1) recruits phosphatidylinositol 3-kinase to Ret: evidence for a competition between Sch and IRS-1 for the binding to Ret. Oncogene 20:209-218, 2001
21. Melillo RM, Castellone MD, Guarino V, De Falco V, Cirafici AM, Salvatore G, Ciaizzo F, Basolo F, Giannini R, Kruhoffer M, Orntoft T, Fusco A, Santoro M: The RET/PTC-RAS-BRAF linear signaling cascade mediates the motile and mitogenic phenotype of thyroid cancer cells. J Clin Invest 115:1068-1081, 2005
22. Wells SA Jr, Santoro M: Targeting the RET pathway in thyroid cancer. Clin Cancer Res 13:7119-7123, 2007
23. Eng C: Common alleles of predisposition in endocrine neoplasia. Curr Opin Genet Dev 20:251-256, 2010
24. Eng C: Mendelian genetics of rare: and not so rare: cancers. Ann N Y Acad Sci 1214:70-82, 2010
25. Santoro M, Carlomagno F, Romano A, Bottaro DP, Darhan NA, Grieco M, Fusco A, Vecchio G, Marotka B, Kraus MH, Di Fiore PP: Activation of RET as a dominant transforming gene by germinal mutations of MEN2A and MEN2B. Science 267:381-383, 1995
26. Songyang Z, Carraway KL 3rd, Eck MJ, Harrison SC, Feldman RA, Mohammadi M, Schlessinger J, Hubbard SR, Smith DP, Eng C, Lorenzo MA, Ponder BA, Mayer BJ, Cantley LC: Catalytic specificity of protein-tyrosine kinases is critical for selective signalling. Nature 373:536-539, 1995
27. Nikiforov YE, Nikiforova MN: Molecular genetics and diagnosis of thyroid cancer. Nat Rev Endocrinol 7:569-580, 2011
28. Fusco A, Grieco M, Santoro M, Berlingeriti MR, Pilotti S, Piotter M, Della Porta G, Vecchio G: A new oncogene in human thyroid papillary carcinomas and their lymph-nodal metastases. Nature 328:170-172, 1987
29. Grieco M, Santoro M, Berlingeriti MR, Melillo RM, Doughri R, Bongarzone I, Piotter MA, Della Porta G, Fusco A, 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
30. Santoro M, Darhan NA, Berlingeriti MR, Bongarzone I, Paulin C, Grieco M, Piotter MA, Vecchio G, Fusco A: Molecular characterization of RET/PTC3; a novel rearranged version of the RETproto-oncogene in a human thyroid papillary carcinoma. Oncogene 9:509-516, 1994
31. Nikiforova MN, Stringer JR, Blough R, Medvedovic M, Fagin JA, Nikiforov YE: Proximity of chromosomal loci that participate in radiation-induced rearrangements in human cells. Science 290:138-141, 2000
32. Gandhi M, Evdokimova VN, K TC, Nikiforova MN, Kelly LM, Stringer JR, Bakkenist CJ, Nikiforov YE: Homologous chromosomes make contact at the sites of double-strand breaks in genes in somatic G0/G1-phase human cells. Proc Natl Acad Sci U S A 109:9454-9459, 2012
33. Zhou Z, Campi R, Nikiforova MN, Gandhi M, Nikiforov YE: Prevalence of RET/PTC rearrangements in thyroid papillary carcinomas: effects of the detection methods and genetic heterogeneity. J Clin Endocrinol Metab 91:3605-3610, 2006
34. Lipson D, Capelletti M, Yelensky R, Otto G, Parker A, Jarett M, Curran JA, Balasubramanian S, Bloom T, Brennan KW, Donahue A, Downing SR, Frampton GM, Garcia L, Juhn F, Mitchell KC, White E, White J, Zwikko Z, Perez T, Nechushtan H, Soussan-Gutman L, Kim J, Sasaki H,
Identification of RET gene fusion by exon array analyses in “pan-negative” lung cancer from never smokers. Cell Res 22:928-931, 2012

Activation of phosphatidylinositol 3-kinase and extracellular signal-regulated kinase is required for glial cell line-derived neurotrophic factor-inhibition of tumor growth. Oncogene 26:2015-2028, 2007

Targeted therapies for thyroid tumors. Mod Pathol 24 Suppl 2:S44-S52, 2011

The effects of four different tyrosine kinase inhibitors on medullary and papillary thyroid cancer cells. J Clin Endocrinol Metab 96:E991-E995, 2011

Identification of RET kinase sensitivity to ZD6474. Endocr Relat Cancer 16:233-241, 2009

The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 114:937-951, 2009

A role for glial cell derived neurotrophic factor induced expression of inflammatory cytokines and RET/GFR alpha 1 receptor up-regulation in breast cancer. Cancer Res 67:11732-11741, 2007

Identification of novel genes that co-cluster with estrogen receptor alpha in breast tumor biopsy specimens, using a large-scale real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A novel mechanism for Hirschsprung disease. EMBO J 19:4056-4063, 2000

Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nat Med 18:382-384, 2012

The effects of four different tyrosine kinase inhibitors on medullary and papillary thyroid cancer cells. J Clin Endocrinol Metab 96:7617-7624, 2011

Identification of novel ALK and RET gene fusions from colorectal cancer.

Targeted RET receptor tyrosine kinase activation in cancer. Clin Cancer Res 16:5936-5941, 2010

Identification of thyroid oncogenic RET kinase inhibitors by a real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

Identification of RET gene fusion by exon array analyses in “pan-negative” lung cancer from never smokers. Cell Res 22:928-931, 2012

Activation of phosphatidylinositol 3-kinase and extracellular signal-regulated kinase is required for glial cell line-derived neurotrophic factor-inhibition of tumor growth. Oncogene 26:2015-2028, 2007

Targeted therapies for thyroid tumors. Mod Pathol 24 Suppl 2:S44-S52, 2011

The effects of four different tyrosine kinase inhibitors on medullary and papillary thyroid cancer cells. J Clin Endocrinol Metab 96:E991-E995, 2011

Identification of RET kinase sensitivity to ZD6474. Endocr Relat Cancer 16:233-241, 2009

The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 114:937-951, 2009

A role for glial cell derived neurotrophic factor induced expression of inflammatory cytokines and RET/GFR alpha 1 receptor up-regulation in breast cancer. Cancer Res 67:11732-11741, 2007

Identification of novel genes that co-cluster with estrogen receptor alpha in breast tumor biopsy specimens, using a large-scale real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A novel mechanism for Hirschsprung disease. EMBO J 19:4056-4063, 2000

Identification of novel ALK and RET gene fusions from colorectal cancer.

Targeted RET receptor tyrosine kinase activation in cancer. Clin Cancer Res 16:5936-5941, 2010

Identification of thyroid oncogenic RET kinase inhibitors by a real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A role for glial cell derived neurotrophic factor induced expression of inflammatory cytokines and RET/GFR alpha 1 receptor up-regulation in breast cancer. Cancer Res 67:11732-11741, 2007

Identification of novel genes that co-cluster with estrogen receptor alpha in breast tumor biopsy specimens, using a large-scale real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A novel mechanism for Hirschsprung disease. EMBO J 19:4056-4063, 2000

Identification of novel ALK and RET gene fusions from colorectal cancer.

Targeted RET receptor tyrosine kinase activation in cancer. Clin Cancer Res 16:5936-5941, 2010

Identification of thyroid oncogenic RET kinase inhibitors by a real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A role for glial cell derived neurotrophic factor induced expression of inflammatory cytokines and RET/GFR alpha 1 receptor up-regulation in breast cancer. Cancer Res 67:11732-11741, 2007

Identification of novel genes that co-cluster with estrogen receptor alpha in breast tumor biopsy specimens, using a large-scale real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A novel mechanism for Hirschsprung disease. EMBO J 19:4056-4063, 2000

Identification of novel ALK and RET gene fusions from colorectal cancer.

Targeted RET receptor tyrosine kinase activation in cancer. Clin Cancer Res 16:5936-5941, 2010

Identification of thyroid oncogenic RET kinase inhibitors by a real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A role for glial cell derived neurotrophic factor induced expression of inflammatory cytokines and RET/GFR alpha 1 receptor up-regulation in breast cancer. Cancer Res 67:11732-11741, 2007

Identification of novel genes that co-cluster with estrogen receptor alpha in breast tumor biopsy specimens, using a large-scale real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A novel mechanism for Hirschsprung disease. EMBO J 19:4056-4063, 2000

Identification of novel ALK and RET gene fusions from colorectal cancer.

Targeted RET receptor tyrosine kinase activation in cancer. Clin Cancer Res 16:5936-5941, 2010

Identification of thyroid oncogenic RET kinase inhibitors by a real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A role for glial cell derived neurotrophic factor induced expression of inflammatory cytokines and RET/GFR alpha 1 receptor up-regulation in breast cancer. Cancer Res 67:11732-11741, 2007

Identification of novel genes that co-cluster with estrogen receptor alpha in breast tumor biopsy specimens, using a large-scale real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A novel mechanism for Hirschsprung disease. EMBO J 19:4056-4063, 2000

Identification of novel ALK and RET gene fusions from colorectal cancer.

Targeted RET receptor tyrosine kinase activation in cancer. Clin Cancer Res 16:5936-5941, 2010

Identification of thyroid oncogenic RET kinase inhibitors by a real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A role for glial cell derived neurotrophic factor induced expression of inflammatory cytokines and RET/GFR alpha 1 receptor up-regulation in breast cancer. Cancer Res 67:11732-11741, 2007

Identification of novel genes that co-cluster with estrogen receptor alpha in breast tumor biopsy specimens, using a large-scale real-time reverse transcription-PCR approach. Endocr Relat Cancer 13:1109-1120, 2006

A novel mechanism for Hirschsprung disease. EMBO J 19:4056-4063, 2000

Identification of novel ALK and RET gene fusions from colorectal cancer.
63. Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, Gomez JM, Bonichon F, Leenhardt L, Soufflet C, Licour M, Schlumberger MJ: Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. Lancet Oncol 13:897-905, 2012

64. Lam ET, Ringel MD, Kloos RT, Prior TW, Knopp MV, Liang J, Sampler S, Hall NC, Wakely PE Jr, Vasko VV, Saji M, Snyder PJ, Wei L, Arbogast D, Collamore M, Wright JJ, Moley JE, Vilalona-Calero MA, Shah MH: Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer. J Clin Oncol 28:2323-2330, 2010

65. Kurzrock R, Sherman SI, Bull DW, Forastiere AA, Cohen RB, Mehra R, Pfister DG, Cohen EE, Janisch L, Nauling F, Hong DS, Ng CS, Ye L, Gagel RF, Frye J, Muller T, Ratain MJ, Salgia R: Activity of XL184 (Cabozantinib), an oral tyrosine kinase inhibitor, in patients with medullary thyroid cancer. J Clin Oncol 29:2660-2666, 2011

66. Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Masgrove HL, Graham GA, Hughes GD, Thomas AP, Stokes ES, Curry B, Richmond GH, Wadsworth PF, Bigley AL, Hennequin LF: ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. Cancer Res 62:4645-4655, 2002

67. Knight ZA, Lin H, Shokat KM: Targeting the cancer kinome through polypharmacology. Nat Rev Cancer 10:130-137, 2010

68. Dar AC, Das TK, Shokat KM, Cagan RL: Chemical genetic discovery of targets and anti-targets for cancer polypharmacology. Nature 486:80-84, 2012

69. American Thyroid Association Guidelines Task Force; Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H, Moley JE, Pacini F, Ringel MD, Schlumberger M, Wells SA Jr: Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 19:565-612, 2009