Molecular Pathogenesis of Neuroendocrine Tumors: Implications for Current and Future Therapeutic Approaches

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Abstract

The treatment landscape and biologic understanding of neuroendocrine tumors (NET) has shifted dramatically in recent years. Recent studies have shown that somatostatin analogues have the potential not only to control symptoms of hormone hypersecretion but also have the ability to slow tumor growth in patients with advanced carcinoid. The results of clinical trials have further shown that the VEGF pathway inhibitor sunitinib and the mTOR inhibitor everolimus have efficacy in patients with advanced pancreatic NETs. The efficacy of these targeted therapies in NET suggests that the molecular characterization of NETs may provide an avenue to predict both which patients may benefit most from the treatment and to overcome potential drug resistance. Recent genomic studies of NETs have further suggested that pathways regulating chromatin remodeling and epigenetic modification may play a key role in regulating NET growth. These observations offer the potential for new therapeutic and diagnostic advances for patients with NET.

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Introduction

The Surveillance Epidemiology and End Results (SEER) database has suggested an increasing incidence of neuroendocrine tumors (NET) from 1.09 cases per 100,000 in 1973 to 5.25 per 100,000 in 2004 (1). Although several advances in the treatment of NETs have been made in recent years, additional therapeutic options are needed.

Molecular Pathways

Angiogenesis

NETs are vascular tumors exhibiting a high expression of several proangiogenic molecules, such as the angiogenic cytokine VEGF (2). Several VEGF pathway inhibitors, including the VEGF inhibitor bevacizumab and the VEGF receptor (VEGFR)–targeted tyrosine kinase inhibitors sunitinib, pazopanib, and sorafenib have shown clinical activity in NET. In 2011, sunitinib was evaluated in a randomized, placebo-controlled clinical trial of pancreatic NET (PanNET) and showed more than double progression-free survival (PFS), leading to its approval for this indication by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These data form the rationale for the use of antiangiogenic therapies in NET (3). Despite these advances, some tumors show intrinsic resistance to antiangiogenic therapies, whereas acquired resistance develops in others.

Both intrinsic resistance and acquired resistance share similar molecular and cellular mechanisms (Fig. 1). With both mechanisms, resistance is caused by the expression of multiple proangiogenic factors, including VEGFs, fibroblast growth factors (FGF), angiopoietins, and ephrins, which can overcome single-agent VEGF–VEGFR–targeted therapy (4, 5). Several mechanisms have been postulated to be inducers of upregulation of these proangiogenic factors, including intratumor hypoxia with hypoxia-inducible factor-1α (HIF-1α) accumulation, inducing a hypoxia-stress expression program that includes many proangiogenic factors (6, 7). Among the genes directly regulated by HIF-1, c-Met is involved in the invasive and metastatic behavior of tumor cells after the exposure to hypoxia. Recent studies have shown that inhibition of c-Met can reduce the invasive and metastatic capabilities promoted following VEGF-pathway inhibition, suggesting that inhibition of c-Met, together with VEGF-targeted therapy, may diminish resistance (8).
Additional strategies to overcome these resistance mechanisms have been explored in animal models and in the clinical setting (9). For example, studies in xenograft models have shown that the combination of bevacizumab and HIF-1 or Sp1 inhibitors may increase the therapeutic efficacy of antiangiogenic treatment (10, 11). Cotargeting of VEGF and FGF signaling pathways has also been shown to improve efficacy and overcome adaptive resistance to VEGF inhibition in the RIP-Tag2 model of PanNETs (12).

**mTOR pathway**

mTOR is the convergence hub of a variety of extracellular and intracellular signals. As a master regulator of different cell functions, mTOR activation is subjected to tight and coordinated regulations through diverse positive and feedback regulatory loops (Fig. 2; ref. 13). Moreover, mTOR forms 2 distinct protein complexes, commonly referred as mTORC1 and mTORC2, which are activated in different ways and exert different but related functions (14). Mutations in the mTOR pathway have been reported in 15% of PanNETs (15). Loss-of-function mutations in TSC1 and TSC2, tumor suppressor genes that inhibit mTOR, occur in tuberous sclerosis, a hereditary cancer syndrome that is associated with the development of PanNET (16). Phosphatase and tensin homolog (PTEN), which regulates the activity of mTOR through the Akt pathway, together with TSC2, are downregulated in approximately 75% of PanNETs, and their low expression is associated with shorter disease-free and overall survival (17).

Following evidence in phase II studies that mTOR inhibitors had activity in NETs, the mTOR inhibitor everolimus was evaluated in randomized, placebo-controlled trials enrolling patients with advanced PanNET or other advanced extrapancreatic NET (carcinoid). The phase III study of everolimus enrolled 410 patients with PanNET and showed a significant increase in PFS in patients receiving everolimus as compared with those receiving placebo (11 vs. 4.6 months), leading to its approval by the FDA and EMA.
for this indication (18). A parallel study in patients with advanced extrapancreatic NET/carcinoid also suggested that everolimus might have some activity, although the study did not meet its predefined efficacy endpoint (19).

Everolimus is known to specifically inhibit mTORC1, although prolonged drug exposure might impair mTORC2 activity in a cell type-specific manner. The efficacy of everolimus and other rapamycin analogues may be compromised by feedback loop mechanisms that include the concomitant activation of the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathway (Fig. 2; refs. 20–22). Strategies to counteract this feedback loop have included the development of ATP-competitive mTOR inhibitors, targeting both mTOR complexes.

In vitro and in vivo data suggest that these new compounds have therapeutic benefit over rapamycin, but concerns exist about their potential toxicity (13). An alternative approach is the use of dual PI3K/mTOR inhibitors, for which several clinical trials are under way (23). Potential clinical benefit has also been shown in patients with PanNET who have been treated with a combination of everolimus and somatostatin analogues (24). One rationale for this combination relies on the known effect of somatostatin analogues in dampening the insulin-like growth factor receptor (IGFR)/PI3K/Akt axis (25). Strategies using dual mTOR inhibitors targeting mTORC1 and mTORC2, combining mTOR inhibition and inhibition of PI3K, and combining mTOR inhibitors with somatostatin analogues are thus of significant interest.

**Somatostatin receptor signaling**

Somatostatin and its synthetic analogs (e.g., lanreotide, octreotide) act through a family of 5 G-protein coupled receptors termed sst1–sst5 to exert a variety of functions, including inhibition of endocrine and exocrine secretions and of tumoral cell growth (26, 27).

Although somatostatin analogues are associated with high symptomatic response rates initially, patients may develop resistance to treatment over time (28–30). The molecular mechanisms underlying the development of resistance remain poorly understood. However, recent studies have identified novel truncated sst5 receptor variants in rodents (31, 32) and humans (33), which at variance with full-length canonical sst5, display selective responses to somatostatin and cortistatin and exhibit distinct tissue distribution and a unique subcellular localization. One
variant, sst5TMD4, which is barely expressed in normal human tissues, shows a marked upregulation in tumors, where it seems to entail pathologically relevant functions. Thus, for example, expression of sst5TMD4 in pituitary adenomas causing acromegaly is related to the reduced ability of octreotide at normalizing hormone secretion in poorly responsive tumors in vivo (34). In breast cancer, the presence of sst5TMD4 (which is negligible in the normal mammary gland) is associated with markers of poor prognosis [lower levels of estrogen receptor (ER), HER2/Neu, and p53], and its expression in breast cancer model cell lines was shown to increase malignancy features (cell proliferation, signaling, invasiveness, and migration) by disrupting normal sst2 function (35). Such observations suggest a potential role for these novel truncated receptor variants in tumor diagnosis as a prognostic marker and as therapeutic targets.

Target Discovery in Neuroendocrine Tumors

Sequencing efforts in NET

The recognition of driver oncogene mutations in a number of human cancers has provided a compelling rationale for targeted therapies (Table 1). Recently, full-exome sequencing of approximately 18,000 genes in sporadic well-differentiated PanNETs revealed 157 mutations in 149 genes. The most common of these were multiple endocrine neoplasia type 1 (MEN1), death domain associated protein (DAXX), ATRX, PTEN, and TSC2 (15). A MEN1 mutation was carried by 44% of tumors, and 43% had either a DAXX or ATRX mutation.

Mutations have been identified at multiple sites in the MEN1 gene (36). The majority of PanNETs show qualitative and/or quantitative alterations in menin localization (36). In 30% of cases, this was associated with MEN1 mutations affecting sequences involved in nuclear localization or protein–protein interaction. Details of the crystal structure of menin have recently been published and provide structure–function explanations for the distinct interactions with the MLL and JUND proteins (37). These insights offer the potential for molecular targeting and specific drug development.

Although the MEN1 gene has been well studied, the functions of DAXX and ATRX are less well understood.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Mutated gene</th>
<th>Targeted therapy</th>
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<tbody>
<tr>
<td>Medullary thyroid</td>
<td>RET</td>
<td>Sorafenib, vandetanib</td>
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<tr>
<td>GIST</td>
<td>KIT</td>
<td>Imatinib</td>
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<td>CML</td>
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<td>Lung cancer</td>
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<td>Colon cancer</td>
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<td>Breast cancer</td>
<td>BRCA1/2</td>
<td>PARP inhibitors</td>
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Table 1. Driver gene mutations and cancer

Abbreviations: CML, chronic myelogenous leukemia; EGFR, EGFR receptor; GIST, gastrointestinal stromal tumor.

DAXX and ATRX proteins form a complex that localizes to chromatin and PML bodies (38). DAXX is a histone H3.3 chaperone, and the ATRX–DAXX complex assembles H3.3 into nucleosomes. ATRX can recruit DAXX to deposit H3.3 at telomeres or pericentromeric heterochromatin. How chromatin remodeling mediated by ATRX and DAXX contributes to NET pathogenesis remains to be defined, but one potential mechanism is the regulation of telomeres. Alternative lengthening of telomeres occurs through DNA recombination and has been shown to be positive in 61% (25 of 41) of PanNETs; 19 of these tumors had mutations in ATRX or DAXX (39). Further investigations on how chromosome structure alters and the consequence of the switched "on" and "off" genes when cells lack ATRX–DAXX may facilitate the identification of novel molecular targets for future diagnostic modality and therapeutic intervention in PanNETs.

Protein kinases

Protein kinases represent another potential therapeutic target in NET. Of 356 kinase genes studied in the sequencing project, 3 mutations in primary PanNET were identified in the ATM and KIT genes (40). In cell lines, mutations in the following genes were also identified: FGFR3, FLT1, and P38KCA. KIT membrane expression is associated with shorter patient survival in patients with PanNETs (40).

Additional potential targets for the treatment of NETs are the Src family kinases (SFK). Members of the SFK are over-expressed in PanNETs (41), and inhibition of their activity impairs adhesion, spreading, and migration of PanNET cells (42). A novel role for SFKs in controlling mTOR activity in PanNET cells has also been reported (43). The increased mTOR activity controlled by SFK leads to translation of a subset of mRNAs for cell-cycle progression. Moreover, the concomitant inhibition of SFK and mTOR activities strongly impaired cell growth, compared with the effect exerted by the single agents. Notably, whereas treatment with mTOR inhibitors triggered the activation of a prosurvival feedback dependent on P38K/Akt signaling, the simultaneous inhibition of SFKs blocked this escape signal. These results, and the recent findings of an important role for the Src pathway in modulating the growth of neuroendocrine cancer stem cells (CSC) in vitro and in vivo (44), support the need for further preclinical studies with SFK inhibitors.

Epigenetic characterization of NETs

Epigenetic mechanisms are an essential component of normal development and gene expression patterns in mammals. Disruption of such processes can result in altered gene function and malignancy through changes in DNA methylation, histone modifications, inappropriate nucleosome positioning, and noncoding RNAs, specifically microRNA (miRNA) expression (45). Mutations in epigenetic regulators have the potential to lead to misregulation of gene expression that contributes to tumorigenesis, and it has been suggested that epigenetic rather than genetic changes may play a key role in NETs (46).

The longstanding observation that menin mutations are associated with NETs supports a role for epigenetic
regulation in the pathogenesis of this disease. Menin is part of a histone methyltransferase complex; it associates with p27Kip1 and p18Ink4c promoters to methylate histone H3 and enhance their transcription. Menin deficiency results in downregulation of p27Kip1 and p18Ink4c (47, 48). Histone H3 methylation is reduced in islet tumors from MEN1-mutant mice. In addition, mice deficient for both p27Kip1 and p18Ink4c develop pituitary tumors much more rapidly than either deficiency alone, suggesting the 2 inhibitors collaborate to suppress tumorigenesis (49). Collectively, these observations point to a key role for menin in epigenetic regulation.

**P53 and MDM2**

The tumor suppressor p53 plays a critical role in maintaining genomic stability and tumor prevention (50). The p53 pathway is tightly regulated by a number of proteins, including the critical negative regulators MDM2, MDM4, and WIP1 (50). Extra gene copies of MDM2 (22%), MDM4 (30%), and WIP1 (51%) have been reported in PanNET, which may lead to an attenuated p53 function (51). Thus, development of MDM2 inhibitors and related molecules can restore p53 tumor suppressor function and may provide tangible therapeutic options for PanNETs.

**Cyclin-dependent kinases and Rb**

Cyclin-dependent protein kinase 4 (CDK4) and 6 are involved in phosphorylation of the retinoblastoma (Rb) tumor suppressor gene leading to inactivation (52). Loss of Rb function results in unchecked transcriptional activation that can occur either by loss of Rb protein itself via RB1 gene mutations or by aberrations in other regulatory elements of the Rb pathway that increase phosphorylation of the Rb protein. In fact, 80% of cancers maintain an intact Rb protein but display genetic alterations of other components of the Rb pathway (53). CDK4/6 amplification and expression have been shown in PanNETs as well as its activator, cyclin D (54). Loss of Rb protein via RB1 gene mutation is also frequently observed in poorly differentiated and high-grade NETs (55). Furthermore, growth of the human PanNET cell line QGP1 can be inhibited in a xenograft mouse model by the CDK4/6-specific inhibitor PD 0332991, which reactivates the Rb pathway (54). Thus, gene amplification and overexpression of CDK4 and CDK6 suggest that a subset of patients with PanNETs may respond favorably to CDK4/6 inhibitors that are currently entering clinical trials.

**Biomarker Discovery in Neuroendocrine Tumors**

**Circulating tumor cells**

The CellSearch platform for cancer detection, among other technologies, has permitted research into circulating tumor cells (CTC) as prognostic biomarkers in a number of malignancies (56). This platform requires the expression of epithelial cell adhesion molecule (EpCAM), a transmembrane glycoprotein, to isolate CTCs. EpCAM expression has been shown in all midgut and PanNETs with variable expression in bronchial NETs (57). CTCs have been reported in blood samples from a number of patients with metastatic NETs, including pancreas, midgut, and bronchial NETs, the latter having the highest levels (57). The same study neither reported any correlation between Ki-67 and CTC count nor any relationship between chromogranin A (CgA) and CTC count.

Because CTCs are shed into the circulation, studies are required to investigate the relationship between CTCs and angiogenesis. Discordance of Her-2 expression between CTCs and primary tumor in breast cancer (58) and differential expression of synaptophysin and CD56 in CTC in NETs (57) suggest CTCs may be heterogeneous. In the study discussed earlier, 82% of CTCs in NETs expressed synaptophysin and 21% expressed CD56, suggesting CTCs in NETs may be heterogeneous (57). This heterogeneity may have implications as mutations may arise when shed from the primary tumor or could occur de novo in the circulation, the latter possibly as an escape mechanism from therapy. For example, in patients with lung cancer treated with anti-EGF receptor (EGFR) therapy, a resistance-associated EGFR mutation emerged in CTCs (59). Thus, molecular characterization of CTCs could potentially assist in understanding NET metastasis and resistance to therapy in addition to their use as biomarkers. Drugs chosen on the basis of primary tumor markers may be ineffective against CTCs and the tumors they seed. Future implications include harvesting CTCs and testing chemotherapeutic agents in situ to assay drug susceptibility (60). Using CTCs to investigate the pathogenesis of NETs is advantageous with the capability of being frequently sampled throughout the disease course; they represent tumor tissue and CTCs with a blood test is less invasive than tumor biopsy.

It is only recently that CSCs have been identified in NETs. In this study, aldehyde dehydrogenase-positive (ALDH+) cells, when cultured from tumor tissue, were highly tumorigenic compared with ALDH- cells from the same tissue (44). It is unclear whether some CTCs identified by the CellSearch system are indeed CSCs. In animal models, aggressive CTCs have been shown to colonize their tumor of origin in a process termed "tumor self-seeding." This may explain relationships between tumor size, vascularity, and prognosis and local recurrence seeded by disseminated cells following complete excision (61).

CTCs are associated with progressive NETs and could be used as a prognostic marker (57). In a prospective study of 120 patients with metastatic NETs, presence of CTCs conferred poorer overall survival, with an HR of 14 (62). Furthermore, a reduction of CTCs 3 to 5 weeks after treatment predicted response to therapy in addition to better survival compared with those patients in whom CTCs were increased (63). Thus, patients on ineffective or potentially toxic therapies can have their treatment changed appropriately and their management tailored according to CTC changes.

**New biomarkers—an unmet need**

Sensitive and specific biomarkers are still largely lacking, and current assays fail to identify biomarkers at an early stage in disease progression. Studies that use proteomics...
and tissue arrays are needed to develop new biochemical and tissue-specific markers. Global transcriptome analysis provides valuable information about the expression of genetic variants within cancer cells. An effective strategy may be to measure circulating mRNA to detect disease and conduct amplification with quantitative real-time PCR (qRT-PCR) to construct a gene terrain map that can be used to discriminate cell type and identify genes and mutations with prognostic potential (64). miRNA-133a was downregulated during progression from primary to metastatic carcinoid tumor, suggesting that it may have an important role in carcinoid tumor development and progression with use for diagnosis and/or prognosis (65).

**Novel methods of biomarker analysis**

Cancer companion diagnostics is a pathway-oriented approach to cancer analysis that integrates mutational analyses with protein activity biomarkers in clinical samples from patients treated with molecularly directed drugs. The goal is to develop diagnostics that better predict patient response to a drug and to create improved methods for monitoring therapy. Padlock probes, such as selector probes, are highly selective probes that generate circular molecules by target-dependent ligation upon perfect hybridization to pairs of sequences within a targeted molecule. The padlock probe technique enables detection of single-nucleotide variants and other tumor- or cell-specific transcriptomic markers in tissue specimens in situ at the single cell level (66).

The proximity ligation assay (PLA) is an immunoassay for protein analysis for measurement and characterization of proteins with high specificity and sensitivity via DNA ligation and amplification reactions. The method relies on converting detection reactions to DNA reporter sequences (Fig. 3). The sensitivity of the PLA technique for plasma protein measurement renders the technique suitable for detection and identification of rare protein molecules in blood, potentially allowing for new classes of promising biomarkers to be identified from biobanked samples. The PLA method can also be combined with standard fluorescent microscopy for detection of proteins or protein–protein interactions and posttranslational protein modifications as activation markers in tissue sections using in situ PLA (67).

**Future Directions**

The efficacy of VEGF pathway and mTOR inhibitors in NET suggests that the molecular characterization of VEGF and mTOR pathway components in NETs may shed light on predictive markers as well as mechanisms by which treatment resistance can be overcome. The discovery that some somatostatin receptors are truncated, resulting in aberrant signaling, suggests that more detailed examination of somatostatin receptor status in tumor tissue may also offer the opportunity to tailor more selective and effective treatments.

Remarkably, exome sequencing of PanNETs has suggested additional pathways of interest; in particular, these studies revealed a high prevalence of mutations in DAXX and ATRX genes implicated in chromatin remodeling. How these mutations correlate with the biologic or clinical characteristics of NET remains unknown and is the subject of ongoing studies, although these observations suggest that epigenetic changes may play a key role in NET growth. The development of high-throughput sequencing technology and other analytic techniques has facilitated the large-scale analysis of tumor tissue and other biospecimens and is likely to provide an effective way to correlate molecular features with clinical behavior.
Finally, the development of novel biomarkers in NET is likely to facilitate both patient care and the discovery of novel treatment targets. CTCs have been identified in patients with NET, in whom they seem to have prognostic significance. Analysis of such cells may provide a practical way to assess biologic changes that occur in tumors over time and during treatment. Circulating miRNAs in patients with NET may also prove to be effective predictive and prognostic biomarkers to the extent that the detection of specific miRNAs may reflect underlying tumor biology and may further point the way to novel pathways and targets.

Disclosure of Potential Conflicts of Interest
K. Oberg has received honoraria from the speakers’ bureau and is a consultant/advisory board member of USD. E.U. Casanovas has received honoraria from the speakers’ bureau of Ipsen and Pfizer and is a consultant/advisory board member of TIEVA and Ipsen. J.P. Castaño has a commercial research grant from Ipsen and has received honoraria from the speakers’ bureau of Ipsen and Novartis. D. Chung is a consultant/advisory board member of Ipsen. M.S. Khan has received honoraria from the speakers’ bureau of Ipsen and Novartis. M.H. Kulke has commercial research grants from Novartis and Ipsen and is a consultant/advisory board member of Ipsen, Novartis, Pfizer, and Lexaion. B. Wiedenmann has received honoraria from the speakers’ bureaus of Pfizer, Novartis, and IOSEN Biotech and is a consultant/advisory board member of Pfizer, Novartis, and Ipsen. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P. Harris

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