Neuroendocrine Neoplasms of the Small Intestine

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General

There are more than 15 types of neuroendocrine cells located within the gastrointestinal mucosa and pancreas producing peptides and hormones including chromogranin A and B, synaptophysin, gastrin, serotonin, insulin, glucagon, PP, ACTH, VIP, somatostatin, etc. These secretions regulate several gastrointestinal activities including motility, digestion, and metabolism.

Neuroendocrine cells originate from the endocrine system and contain metabolic enzymes such as neuron-specific enolase (NSE) and secretory vesicles filled with amines and hormonal peptides. Most of these cells have the capability to express glycoproteins such as chromogranin and high levels of somatostatin cell surface receptors.

Neuroendocrine tumors (NETs) originating from these cells have secretory function including chromogranins and proteins involved in amine uptake, e.g., VMAT (vesicular monoamine transporter) [1], as well as vesicular trafficking and fusion, e.g., SNAP25 [2] (synaptosomal-associated protein, 25 kDa). Tumors developing from these neuroendocrine cells throughout the body keep the capacity to express the aforementioned products. The term "carcinoid tumor" had been previously used to name these neoplasms which are believed to have low malignant potential. However, recently, the term "carcinoid" was replaced by the WHO with "neuroendocrine tumors/carcinomas."

The WHO classification of neuroendocrine neoplasms of the digestive system released in 2010 reflects the views of the Working Group participating to the Consensus Conference at the International Agency for Research on Cancer (IARC), Lyon, 10

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December 2009. This classification categorizes all neuroendocrine neoplasms of the digestive system, including the small intestine, in the following distinct categories:

1. Neuroendocrine tumor (NET), grade 1 (carcinoid)
2. Neuroendocrine tumor (NET), grade 2
3. Neuroendocrine carcinoma (NEC), high grade (large or small cell type)
4. Mixed adenoneuroendocrine carcinoma (MANEC)
5. Hyperplastic and preneoplastic lesions
6. EC-cell serotonin-producing NET
7. Gangliocytic paraganglioma
8. Gastrinoma
9. L-cell glucagon-like peptide-producing NET
10. PP/PYY-producing NETs
11. Somatostatin-producing NET

Small intestine neuroendocrine neoplasms (SI-NENs) derive from enterochromaffin (EC) cells of the embryonic neural crest. Although rare in general, SI-NENs are the most common malignancy of the small bowel and represent about half of all small intestine neoplasms. Midgut NETs are the most common type of NEN in the gastrointestinal tract and arise in the lower jejunum, ileum, appendix, and cecum. The most common site of the GI-NET is ileum.

The annual incidence of SI-NET is about two cases per 1 000 000 persons, but the rate is increasing due to improved sensitivity of advanced endoscopic and radiologic imaging.

Males are affected more than female (M:F ratio, 1.5:1) and patients usually present during their fifth or sixth decade.

NETs show a broadly variable size, natural history, and survival. The size of NETs ranges from as small as 0.5 cm to more than 10 cm. They grow slowly (Ki67 proliferating index is often <2 %), unless of high grade. The median survival ranges from approximately 6 months, in aggressive high-grade tumors, to up to 20 years in grade 1 tumors. The overall 5-year survival is approximately 60 % [3].

Many cases remain asymptomatic and are diagnosed only later in the course of the disease, after the development of signs of bleeding, obstruction, mesenteric ischemia, or carcinoid syndrome. In most well-differentiated GI-NETs, there is usually metastatic spread to regional lymph nodes (LNs) and to the liver at the time of diagnosis.

The pathognomonic carcinoid syndrome is a rare finding present in only 10 % of cases. This syndrome is usually manifested after the development of liver metastasis. The most common presenting symptoms of intestinal NETs include intestinal obstruction, which is a result of tumor-induced fibrosis. Approximately 58 % of SI-NETs patients will present with metastatic disease. Many SI-NETs are far smaller than the size detectable from conventional imaging modalities. Therefore, less than 50 % of GI-NETs (small bowel, colorectal, and stomach) are seen on CT scan and an even lower percent of these tumors can be detected by Octreoscan.

Available biomarkers have low specificity in detecting these tumors making the diagnosis a challenge [4–16].

Gross Features

A GI-NET grossly appears as a tan mass with homogeneous surface. Hemorrhage and/or necrosis may be seen occasionally. Well-differentiated tumors usually show a well-circumscribed invasive edge while the malignant ones have an invasive infiltrative growth pattern. GI-NETs are slow-growing malignant tumors with metastatic potential and ileal NETs have the highest metastasis potential.

Microscopic Features

"Gastrointestinal NETS have different histologic patterns: (1) solid, nodular, and narrow cords; (2) trabeculae or ribbons with frequent anastomosing patterns; (3) tubules and glands forming rosette-like patterns; (4) poorly differentiated or atypical patterns; and (5) mixed tumors." The glandular subtype seems to have better prognosis when compared to the nested pattern. They often show peripheral palisading.

Most grade 1 GI-NETs have minimal cytoplasm, nuclear hyperchromasia, little or no cellular pleomorphism, little mitotic activity, and unclear cell borders. Their small, round to oval central nuclei have well-defined, regular nuclear membranes and a "salt-and-pepper" chromatin distribution. Eosinophilic cytoplasmic granules may be identified. Invasion of tumor cells in between the muscle fibers separates the muscle fibers apart but does not destroy them. There is prominent desmoplastic response to the invading tumor, which causes fibrosis and thickening of the bowel wall. Vascular sclerosis frequently is seen in large mesenteric vessels and can lead to ischemia. Elastosis and fibrosis can also involve tumor cell nest borders and lymph nodes resulting in fibrous adhesions [10, 17, 42]. Retroperitoneal fibrosis can occur during the development of neuroendocrine tumor [43].

Diagnosis

Duodenal

Duodenal NETs are more common within the first or second part of the duodenum and include gastrinoma, somatostatinoma, gangliocytic paraganglioma, and nonfunctioning NET. The most common duodenal NET is gastrinoma.

Gastrinoma can be sporadic or occur in association with multiple endocrine neoplasia 1/Zollinger-Ellison syndrome (MEN-1/ZES), whereas somatostatinomas are mostly associated with von Recklinghausen's disease (neurofibromatosis type 1) and usually occur in the ampullary/periampullary region. Mixed exocrine-endocrine tumors with both neuroendocrine and glandular differentiations (goblet cell carcinoids) are extremely rare in this region but they do exist [44].

Tumors that invade beyond the submucosa or present with lymph node or distant metastases usually have an aggressive behavior. Although distant metastasis is not very common (approximately 25 % in duodenal NETs), when present, it negatively affects the 5-year survival. Moreover, metastasis to lymph nodes may be seen in tumors less than 1 cm in diameter. For tumor less than 2 cm, confined to mucosa and/or submucosa of the bowel and without metastatic disease, endoscopic resection can be advised. If there is any evidence of lymph node involvement and/or if the tumor is larger than 2 cm, surgical resection should be performed [45].

Jejunoileal

Terminal ileum NETs are the most common type of GEP-NETs. Unlike the duodenal NETs, ileal NETs (INETs) are a primarily sporadic neoplasm (D'adda et al. 2002) [17]. INETs are more common in male population with the median age of diagnosis around 66 years. The growth of INETs is mainly dependent on angiogenesis and usually shows a very slow pattern of growth. However, there is a rare subtype of well-differentiated INETs with a more aggressive behavior and worse survival due to a downregulation in the expression of succinate dehydrogenase (SDHB) causing increased cellular proliferative activity (MIB1). The diagnosis of INET is late and usually, the patient has already advanced-stage disease. Regardless of the size of the primary tumor, liver and regional lymph node involvements are already present at diagnosis. INETs have nonspecific symptoms which range from abdominal pain, GI bleeding, to intermittent ischemia. In some cases, mesenteric fibrosis, nodal metastases, and desmoplastic reactions can cause bowel obstruction. The classic carcinoid syndrome is only seen in 20 % of cases, usually after liver metastasis. The liver metastasis is a strong predictor of survival and when present, the 5-year survival will significantly deteriorate. Ninety percent of INETs have an aggressive behavior since they deeply invade the bowel wall, the muscularis propria and beyond, or metastasize. Tumor grade and stage, according to WHO/AJCC/ENET criteria, are still the most important predictors of prognosis and to determine the appropriate therapeutic approach. Surgical resection is curative only in early stages of disease. However, the presence of liver metastasis does not preclude the need for surgery and it is still recommended for delaying the progression and to block local invasion.

European Neuroendocrine Tumour Society (ENETS) in 2012 has provided new guidelines to improve the quality of diagnosis and therapy for jejunoileal NETs with liver and distant metastasis [27, 45, 46].

Molecular Features

Gastrointestinal NETs overexpress p53 and have high cell proliferation rate, telomerase activation, Rb loss, p16 loss, and K-ras amplification [18].

Similar to other malignancies, angiogenesis and inflammation may have role in SI-NETs [11]. In addition, SI-NETs are regulated at a developmental level and the activation of hypoxic pathways, a regulator of malignant stem cell expression, and activation of genes involved in apoptosis and cell proliferation are responsible for tumorigenesis.

Expressions of core secretory regulatory elements, e.g., CPE, PCSK1, and secretogranins, including genes involved in depolarization, e.g., SCN3A, as well as transcription factors associated with neurodevelopment (NKX2-2, NeuroD1, INSM1) and glucose homeostasis (APLP1) have been involved in NET tumorigenesis recently. Genomic examination has shown that, in general, SI-NET tumors may consist of two different subtypes, serotonin-producing neoplasms, and serotonin/substance P/tachykinin lesions [16].

Genetic Profiling

Genes known to have an important role in the pathogenesis of neuroendocrine tumors include those involved in genetic syndromes such as MEN-1, RET, VHL, TSC1, and TSC2. MEN-1 mutation is the most common form of genetic predisposition to neuroendocrine tumors [19].

Recent studies have contributed an expanded gene expression profile linked to the development of SI-NET [5]. Novel genes proposed to play an important role in the pathogenesis of SI-NET include:

PNMA2, SPOCK1, SERPINA10, GRIA2, GRP112, OR51E1, CXCL14, NKX23, NAP1L1, MAGE-D2, MTA-1, and APLP [5, 16]. NAP1L1, NKX2-3, TGFβR2, CD302 [16], and overexpression of GPCR signaling regulators [19], cAMP synthetase, ADCY2, and protein kinase A (PRKAR1A).

In addition, SI-NETs express neural GPCRs that activate different CREB targets associated with cell proliferation and secretion and thus with transcripts associated with cell proliferation and secretion. BEX1, BICD1, CHGB, CPE, GABRB3, SCG2, ADCY2, and PRKAR1A have been shown to be upregulated in SI-NET [20]. The candidate metastasis-associated transcription factor, ST18, is also highly expressed. In contrast, studies have shown that the expression of some genes, previously known to be associated with neoplasia, e.g., CEBPA and SDHD, is decreased in SI-NETs [16]. Beside the usefulness of genetic profiling in detecting primary tumors, proteomic signature can be helpful in classifying SI-NETs, as well. In particular, four proteins have shown usefulness in the diagnosis of primary tumors: IGF1, IL1a, SHKBP1, and EGR3. IL1a, XIAP, STX2, and SKBP1 are significant in lymph node metastasis. IGF1, IL1a, IGFBP2, MAML3, and SHKBP1 have been suggested as liver metastasis proof [11].

CDX-2

CDX-2 is a homeobox gene product essential for intestinal development and differentiation. High CDX-2 expression is seen in all ileal and appendiceal WDNET while low levels were seen in WDNETs from stomach, duodenum, and rectum. Low levels of CDX-2 expression are seen in one third of nonfunctional pancreatic WDNET, as well. CDX-2 expression has been detected more commonly in metastatic disease, especially in metastatic ileal WDNETs. CDX-2 has also been shown to be expressed at high levels in intestinal NEC, suggesting a dysregulation in the expression of homeobox genes in NEC [21].

Chromosomal Abnormalities

Chromosomal-based alterations that may be associated with NEN include loss of 18q22-mer or SMAD4 loss of heterozygosity (LOH) [16].

Hemizygous loss of all or most of chromosome 18 is the most frequently observed genetic shift in SI-NETs followed by arm-level gains of chromosomes 4, 5, 14, and 20. Loss of heterozygosity on chromosome arms 9p and 16q has also been observed. The majority of tumors show loss of chromosome 18 while a subgroup of tumors have intact chromosome 18, but gain of chromosome 14. Gain of chromosome 14 is a predictor of poor survival.

Focal region of recurrent gain on 14q has been plotted to the locus of the gene encoding the antiapoptotic protein DAD1 and immunohistochemical staining has confirmed DAD1 protein expression in those tumor samples. However, no alterations in the tumor suppressor genes DPC4/SMAD4 and DCC, located on chromosome 18, are found in these tumors, indicating that other, currently unknown, genes are important for pathogenesis of SI-NET [22–26].

To date, only one gene with statistically significant recurrent somatic mutations and deletions in SI-NET cases has been identified: the cell cycle regulator CDKN1B, the cyclin-dependent kinase inhibitor gene, which encodes p27 protein. Small insertions and deletions within CDKN1B gene in some cases lead to frameshift mutations and hemizygous deletions involving CDKN1B. These observations suggest that the p21/p27/p57 family has an insufficient tumor suppressor activity in SI-NETs and implicates cell cycle dysregulation as the etiology of SI-NETs. Loss of P27 is associated with poor prognosis [25, 27].

There is a correlation between the loss of SDHB expression, increased Ki67 labeling index, and biological aggressiveness of advanced midgut neuroendocrine tumors [28].

TCEB3C (Elongin A3) is currently the only imprinted gene on chromosome 18 and it has been confirmed that TCEB3C (Elongin A3) has a role as a tumor suppressor gene in SI-NETs. TCEB3C gene expression is epigenetically regulated and it is

specific in each tumor cell type. Its regulation involves both DNA and histone methylation [29].

Hypomethylation and Promoter Methylation

Hypomethylation and promoter methylation of tumor suppressor genes are associated with downregulation of tumor suppressor gene expression and DNA copy number alterations in SI-NETs. This is particularly true for SI-NET lymph node metastases.

Promoter methylation in SI-NETs has been observed in WIF1, RASSF1A, CXCL14, NKX2–NKX3, P16, LAMA1, and CDH1 genes. Other genes including APC, CDH3, HIC1, P14, SMAD2, and SMAD4 only had low levels of methylation.

WIF1 WIF1 is a Wnt antagonist that inhibits the interaction of Wnt with its receptor, and it is a heavily methylated gene, which is downregulated in ileal NET metastases as compared to the primary tumor.

RASSF1A RASSF1A regulates tubulin dynamics and localizes to centromeres and mitotic spindles during cell motility inhibition and cell-to-cell binding. RASSF1A contributes to cancer development by modulating cyclin D1 accumulation, inhibition of the JNK pathway 25, and pro-apoptotic activities achieved by binding to MST1 (Mammalian Sterile Twenty 1) and other apoptotic agents. RASSF1A hypermethylation has been shown in SI-NETs and has been associated with distant metastasis. Low RASSF1A expression is associated with shorter survival.

CXCL14 and NKX2–NKX3 Downregulated mRNA expression for CXCL14 and NKX2–NKX3 has been described in progressive SI-NETs.

P16 P16 promoter methylation has a limited role on cancer progression. However, downregulated P16 has been reported to be associated with less favorable patient outcome [30].

Cancer-Related Pathways

There are several cancer-related pathways involved in SI-NET pathogenesis, mainly including PI3K/Akt/mTOR signaling, the TGF-β pathway (through alterations in SMAD genes), the SRC oncogene, VEGF pathway, EGFR pathway, IGF-1R pathway, and histone deacetylase pathway (Figs. 1 and 2). Protein degradation

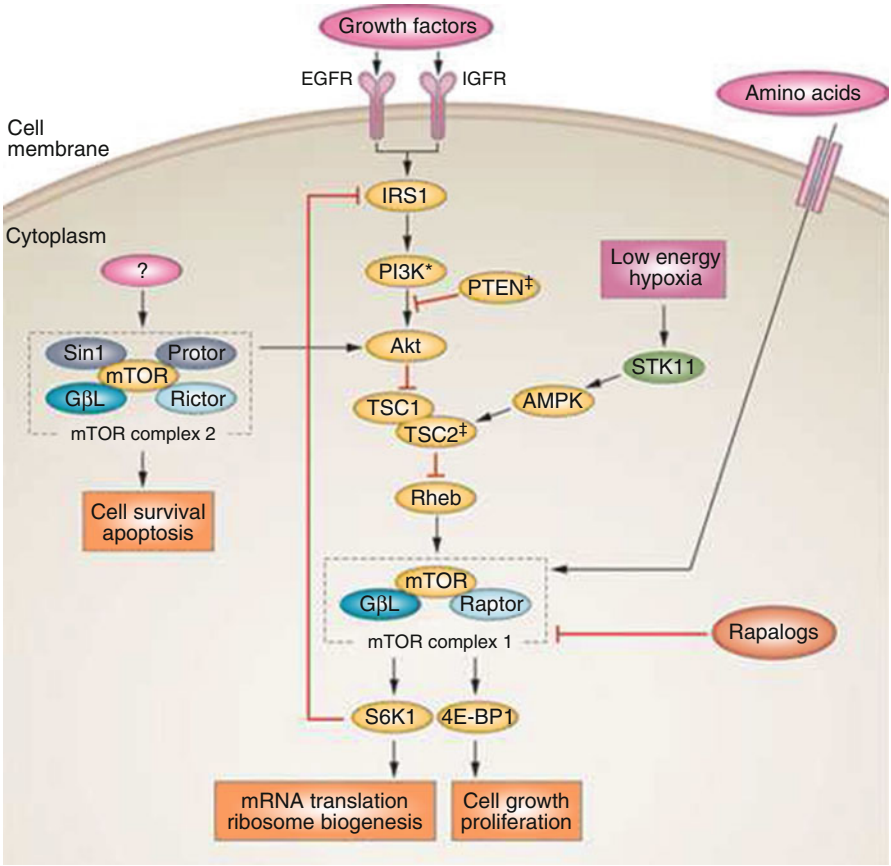

Fig. 1 mTOR signaling pathway [47]

pathways, c-kit, and PDGFR pathways have also been under investigation in an effort to recognize their role in NET development [3, 13, 31] (Fig. 3).

PI3K/Akt/mTOR Pathway

mTOR (the mammalian target of rapamycin, an intracellular serine-threonine kinase) expression and its phosphorylated downstream targets 4EBP1, S6K, and eIF4E are involved in pathogenesis of GEP-NET. mTOR expression and activity are higher in foregut than in midgut tumors and are even higher when distant metastases are present in foregut tumors. Strong mTOR activity is correlated with higher cell proliferative capacity and in patients with stage IV midgut tumors. Strong p-S6K expression can be associated with poor disease-specific survival [13, 32].

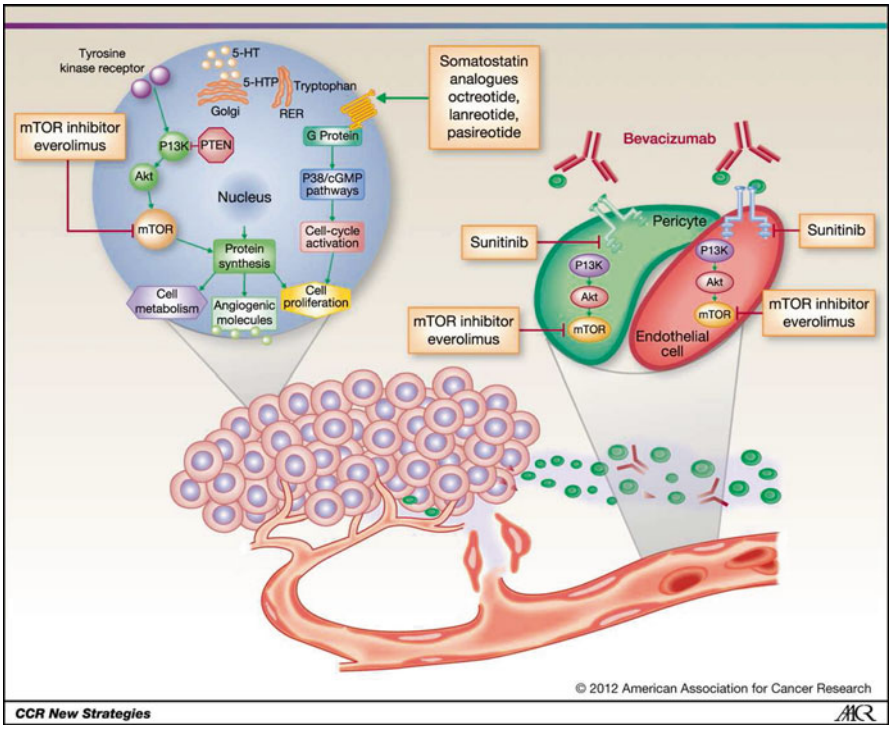

Fig. 2 mTOR (@ 2012 American Association for Cancer Research) [48]

In response to mTOR and Raf inhibitors, there is high compensatory activation of Akt and Erk signaling in NETs, and thus, downstream signaling of HSP90 can suppress both survival pathways [33].

TGF-β Pathway

Mutated or deleted SMAD genes have also been suggested as important regulators of growth in SI-NET through increased expression of TGF-β pathway. Gilbert et al. have shown high immunohistochemical levels of Hsp90, TGFBR1, IGF1R, and SSTR5 in SI-NETs [13, 34].

VEGF-R and IGF-R

There is an increased expression of VEGF-R and IGF-R in foregut and midgut carcinoids. Weak EGFR expression is observed in small-bowel NETs. IGF1/IGF1R system may play an important role, even in early stages of SI-NETs. IGF1

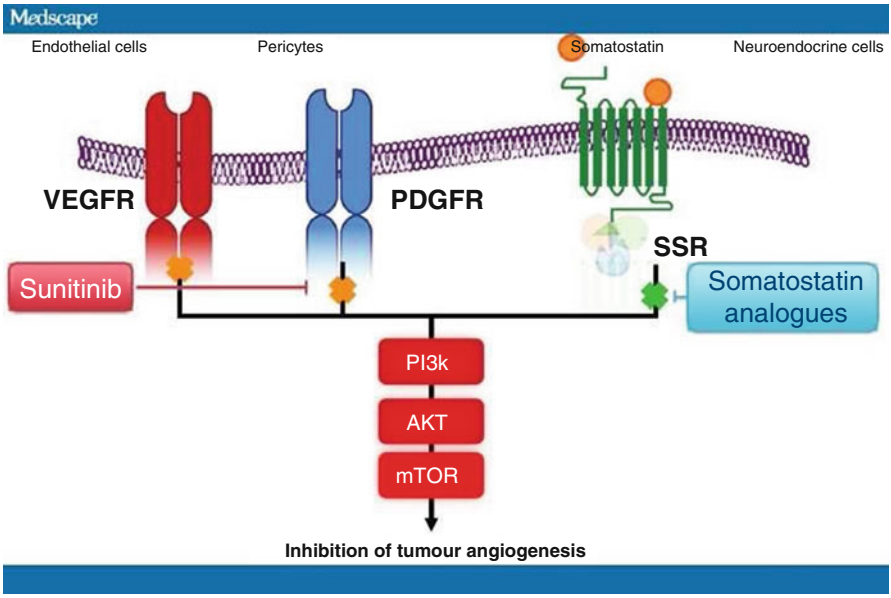

Fig. 3 Vascular endothelial growth factor receptor (*VEGF-R*) in endothelial cells and platelet-derived growth factor receptor (*PDGFR*) in pericytes resulting in the inhibition of angiogenesis in neuroendocrine tumors and somatostatin receptor involvement [50] (*Source*: Ther Adv Med Oncol ©2011 SAGA Publication Ltd)

expression levels can distinguish between normal and primary SI-NETs and it seems to represent a biomarker for SI-NET [11, 34, 35].

EpCAM Expression

Studies have shown EpCAM (epithelial cell adhesion molecule) expression in NETs. This finding is a demonstration of the epithelial features of these neural crest-derived tumors. NETs circulating tumor cells (CTC) have been detected especially in blood of patients with progressive and metastatic disease and may provide useful prognostic information given the variable survival rates of these patients [4].

Receptor and Membrane Proteins Changes in SI-NETs

Genes coding receptors and membrane proteins that may have a role and that are upregulated in SI-NETs include [36]:

BRS3 (bombesin-like receptor 3), GIPR, GPR98 (G-protein-coupled receptor 98), GPR113, GRM1 (metabotropic glutamate receptor 1), OPRK1 (k-opioid recep-

tor), GPR113 (G-protein-coupled receptor 113), and GPR116 (G-protein-coupled receptor 116) [6].

In pancreatic cancer, the upregulation of GPR113 and OXTR is not as high as in SI-NET, and this difference in membrane gene profile may be a discriminator between the two diseases.

OPRK1: OPRK1 is overexpressed in SI-NET relative to normal tissue.

OXTR: Oxytocin receptor is highly expressed in SI-NET tumors relative to the small-bowel normal mucosa [37]. OXTR overexpression is present in both primary and metastasis of SI-NETs. OXTR may represent a target for future imaging and therapeutic interventions [6, 37].

G-Protein-Coupled Receptors

Transcriptional signaling in NETs involves the activation of cAMP/PKA/pCREB pathways with involvement of G-protein-coupled receptors. For SI-NETs cell line, somatostatin and dopamine are the most involved G-protein-coupled receptors defined [16, 20].

SRC Oncogene Pathway

Src is a proto-oncogene which through kinase activity transduces signals from the plasma membrane to control cell cycle and adhesion and motility [38]. Activated SRC stimulates MTOR activity in neuroendocrine cell and amplification of the SRC gene suggested to have role in carcinogenesis of neuroendocrine tumors [13].

Somatostatin Receptor (SSTR)

There are five SSTR subtypes in the somatostatin receptor family [39]. Somatostatin type 2 receptor (SSTR2) is the most extensively expressed receptor in GEP-NETs and is found in 80–95 % of cases. However, not all tumors express high levels of somatostatin receptor type 2 (SSTR2) [36].

Gastric Inhibitory Polypeptide Receptor (GIPR)

The gastric inhibitory polypeptide receptor (GIPR), also known as the glucose-dependent insulinotropic polypeptide receptor, is a G-protein-coupled receptor related to the glucagon receptor. GIPR is expressed in neuroendocrine tissues

including pancreatic β cells [40]. Prabakaran *et al.* have shown that GIP increases proliferation and activation of the MAP kinase and mTOR pathways. GIPR is overexpressed in neuroendocrine tumors compared to normal tissue and hence suggesting the pro-malignant signaling mediated by this receptor involvement in NETs [6, 41].

Aldo-Keto Reductase Family One Member C3 (AKR1C3)

SI-NETs have the highest ratio of positive AKR1C3 among NE tumors and it could be a useful marker for the exclusion of the NE phenotype [42].

Biomarkers

Tumor cells with neuroendocrine differentiation show immunoreactivity for CgA and synaptophysin and are also often positive for carcinoembryonic antigen (CEA). Low-molecular-weight cytokeratin expression (CAM 5.2) is also common in these tumors [18].

When GEP-NET is suspected, the most commonly accepted approach would be the assessment of serum markers including chromogranin A, 24-h urinary 5-HIAA test, gastrin, histamine, serotonin, substance P, neuron-specific enolase, and neurokinin A levels. The serum biochemical markers are used not only as diagnostic test but also as prognostic indicators and for monitoring tumor response to treatment. Currently, CgA is the best tumor marker for well-differentiated NETs, whereas NSE is a better indicator for poorly differentiated NEC.

CgA and 5-HIAA levels are increased especially in metastatic tumors. PCR-based detection of CgA would be more sensitive than either H&E or CgA IHC for detecting lymph node metastases early on in SI-NETs.

Neurokinin A is a member of the tachykinin family found to be elevated in midgut neuroendocrine tumors. Neurokinin A is helpful in determining response to therapy in midgut neuroendocrine tumors. Elevated levels of neurokinin A failing to decrease after treatment are usually an indicator of worse survival. However, its reliability as a prognostic factor seeks further investigation.

Currently, it is difficult to detect WD-SI-NETs at early stages when metastases are not yet developed. New molecules have been proposed for the replacement of CgA for better detection, diagnosis, classification, and monitoring of these tumors. These molecules include IGFBP2, IGF1, SHKBP1, ETS1, IL1a, STX2, MAML3, EGR3, and XIAP.

Cytokeratin fragments (CKfr) have shown utility in patients with well-differentiated NET while both CKfr and progastrin-releasing peptide are good markers in patients with poorly differentiated NEC.

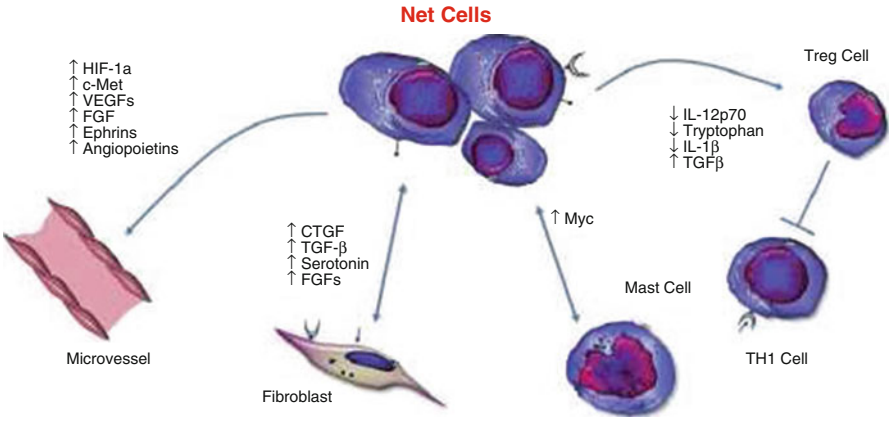

Fig. 4 Role of the microenvironment in the pathogenesis of neuroendocrine tumors (*NETs*). NET cells mutually interact with their microenvironment, prompting angiogenesis through cytokine secretion, inhibiting T-cell function by T-regulatory cell (*Treg*) dysregulation, prompting infiltration of mast cells via Myc upregulation, and driving fibroblast activation, which in turn enhances NET cell proliferation. *CTGF* connective tissue growth factor, *FGF* fibroblast growth factor, *HIF-1(α)* hypoxia-inducible factor alpha, IL interleukin, *TGF* transforming growth factor, *TH1* T-helper type 1 cell, *VEGF* vascular endothelial growth factor [49] (Information from Refs. [19, 22, 23])

Autoantibodies against the paraneoplastic MA antigen 2 and olfactory receptor 51E1 may be important in the detection of patient recurrences. Finally, *insulin-like growth factor 1 (IGF1)* has been previously described as a biomarker for SI-NETs (Fig. 4).

If the biochemical marker profile is suggestive of NET, the next clinical step would be to identify tumor location and assessment of mass lesion, fibrosis, and lymphadenopathy. 111Indium-labeled octreotide scan has 90 % sensitivity to detect tumor-related lesion and fibrosis [5, 7, 8, 11, 14, 43].

Prognosis

TNM staging and grading system is a reliable tool relevant to SI-NETs prognosis and can facilitate therapeutic approach [44, 45]. However, beside TNM system, other factors can be used to determine the overall disease prognosis. A better prognosis for midgut NETs usually can be expected with primary tumors <2.5 cm, in the absence of liver metastases and carcinoid symptoms, and a low Ki67 (Pape et al. 2008). In contrast, factors leading to bad prognosis include [5, 45] advanced age, LN involvement, presence of more than five liver metastases, lack of symptoms at the time of diagnosis, high levels of 5-HIAA, high levels of plasma chromogranin A or neuropeptide K, and the presence of carcinoid syndrome [5].

Treatment

Surgery is the only potential cure currently effective for SI-NETs. Treatment with cytotoxic, biological, and tumor-targeted radionucleotide agents can prolong survival and help to relieve symptoms [28]. NETs with high proliferative activity (Ki67 >20 %) are treated similar to lung small cell cancer with cisplatin-etoposide combination chemotherapy [28]. Surgery, radiofrequency ablation, and liver embolization all are included in current therapeutic approach for liver metastases [46].

Abbreviations

Cg	Chromogranin
GEP-NETs	Gastroenteropancreatic neuroendocrine tumors
INETs	Ileal neuroendocrine tumors
MANEC	Mixed adenoneuroendocrine carcinoma
NEC	Neuroendocrine carcinoma
NEN	Neuroendocrine neoplasm
NET	Neuroendocrine tumor
NSE	Neuron-specific enolase
SI-NENs	Small intestine neuroendocrine neoplasms
SI-NET	Small intestine neuroendocrine tumor
Syn	Synaptophysin

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