Neuroendocrine Tumorigenesis

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Before the year 2000, gastroenteropancreatic neuroendocrine tumors (GEP NETs) were not well characterized [3]. The GEP NET incidence has increased worldwide over the last decades [2, 4]. Considering the constantly evolving imaging technology, small asymptomatic lesions in the gut can be identified [5]. NETs are a heterogeneous group found in different locations of the body, e.g., pancreas, foregut, midgut, hindgut, and lung [5, 6]. The regional distribution of NETs over the entire body is schematically displayed in Fig. 7.1. Gastroenteropancreatic (GEP) NETs are with two thirds the most common primary NETs [4, 7]. With one quarter of NETs, they occur in the lung as the second most location [2].

NETs arise from neuroendocrine-programmed cells, which are found throughout the body and are known to excessively produce and secrete molecules like neuropeptides and biologically active neuramines, such as insulin, serotonin, and somatostatin [7–9]. An overview of neuroendocrine-programmed cells is displayed in Fig. 7.2.

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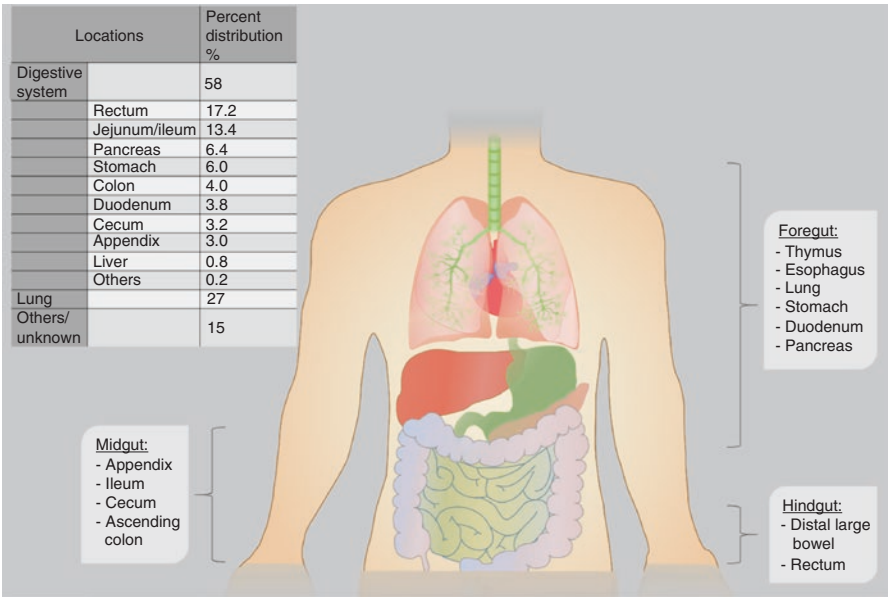

Fig. 7.1 Overview of NET occurrence in the human body (Adapted of Yao) [4]. NETs are found all over the body; the gastropancreatic system is with 58% the most frequent region, followed by 27% NETs in the lung

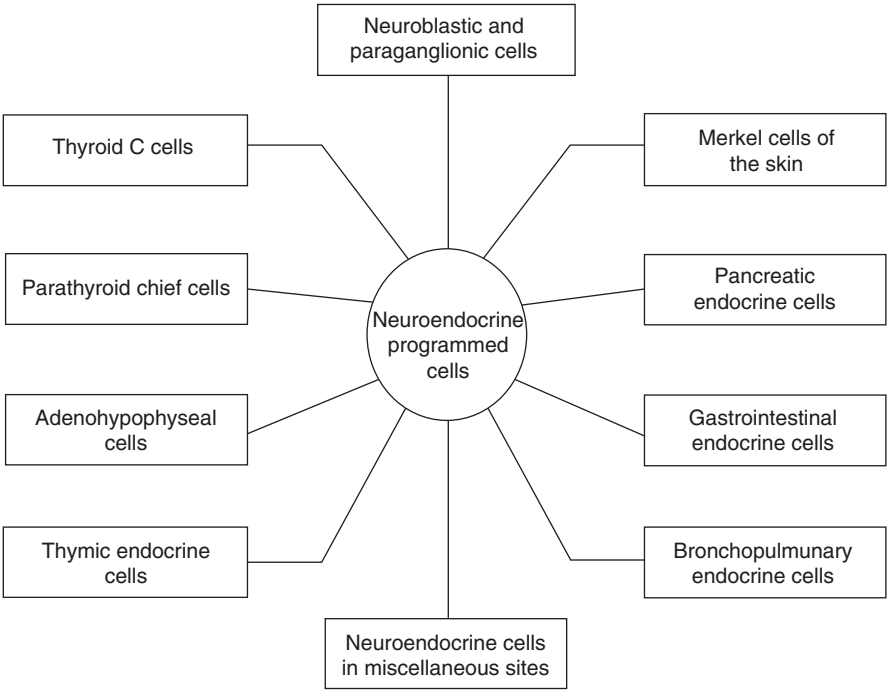

Fig. 7.2 Schematic overview of neuroendocrine-programmed cells (Adapted from Tischler and DeLellis) [10]

The classification of neuroendocrine tumors is based on size, tissue invasion, Ki67 index, and mitotic activity, according to the current WHO classification [5]. KI-67 is a proliferation marker and helps to determine tumor grade and prognosis [11].

There is still no balanced therapy for NETs [5]. Total resection in early stages is unchallenged in curative treatment compared to therapies, such as those with somatostatin analogues, radiotherapy, and chemotherapy, because they are still insufficient [4, 7, 12]. Knowledge on how to suppress hypersecretion or neoplastic growth could lead to a new therapeutic and palliative approach [13]. Due to the lack of mechanistic insights regarding this disease, many whole-genome sequencing approaches on NET patient tissues were initiated in order to identify mutations, which correlate with the development, prediction, or diagnosis of NETs [14]. The most frequent gene alterations in NET patients were found in the following genes: *MEN-1* (encodes menin), *DAXX* (death domain-associated protein), *ATRX* (alpha thalassemia/mental retardation syndrome X linked), and mTOR (mammalian target of rapamycin) with the related pathway members [14–17].

7.1 MEN-1

NETs occur either sporadically or as manifestation of a syndrome, like the multiple endocrine neoplasia type 1 (*MEN-1*) syndrome [16]. A germline mutation in the *MEN-1* tumor suppressor gene, located on the chromosome 11q13, causes this autosomal dominantly inherited condition [15, 16]. This gene encodes the 610 amino acid nuclear protein menin, which is associated with regulation of transcription, genomic stability, cell division, and cell cycle control [10, 18–20]. Over 450 different germline mutations have been identified to date. About two thirds of these mutations are predicted to lead to truncations on the protein [18]. Either truncations or missense in *Men-1* leads to lower protein levels because of proteolytic degradation via the ubiquitin pathway [16, 21]. Mutations in *MEN-1* are associated with a prolonged survival compared to patients without *MEN-1* mutation [14].

7.2 DAXX/ATRX

Likewise, NET patients with mutations in *DAXX/ATRX* have a better survival rate [17, 22]. These mutations affect incorporation of the histone H3.3 complex into telomeres by inducing alternative lengthening of telomeres and chromosomal instability [17, 22].

7.3 mTOR Signaling

Some NET patients were reported to have mutations in the *PTEN*, *PI3K*, and *TSC2*, genes of the mTOR pathway [14]. It seems that these mutations are relevant only for few NET patients because alterations in expression of mTOR pathway members are found in most patients [14, 23, 24]. Therefore, whole-genome sequencing of NETs can help to identify patients which would benefit from therapy with mTOR inhibitors [14].

Chromosomal instability in NET patients is associated with tumor progression. As the extent of genomic changes seems to correlate with disease stage, indicating alterations accumulate during tumor progression [10, 19].

7.4 Biomarkers of Neuroendocrine Neoplasms

At the beginning of their formation, NETs usually do not show specific symptoms over a long time period. The low proliferation rate of most NETs might be an explanation for this phenomenon [25]. Due to their origin, NETs secrete different molecules. This might be a way to look for a tumor marker. Four biomarkers for NETs have been established: chromogranin A (CgA), synaptophysin (SYP), neuron-specific enolase (NSE), and urinary 5-hydroxyindole-3-acetic acid (5-HIAA) [26].

Neuroendocrine cells secrete their products via large dense-core or small synaptic-like vesicles. Those vesicles store proteins like CgA and synaptophysin and therefore serve as markers for neuroendocrine cells [11]. CgA is a member of the chromogranin family and is often observed to be elevated in serum of patients [27]. Immunohistochemistry for CgA can confirm the origin in the tissue [11]. It also seems that CgA is a prognostic marker because it positively correlates with disease progression, liver metastases, and treatment efficiency [8, 11].

For the histopathological diagnosis of NETs, CgA and synaptophysin have to be present [28]. SYP is a calcium-binding integral membrane glycoprotein [11]. It is present in epithelial and neuronal types [10]. SYP is expressed independently from other NET biomarkers [28].

Neuron-specific enolase (NSE) plays a role in glucose metabolism. This enzyme was shown to be present in thyroid and prostatic carcinoma, neuroblastoma, small cell lung carcinoma, carcinoid, gastropancreatic tumor, and neoplasms with a neuroendocrine differentiation [26, 29]. Based on its lacking sensitivity and specificity as biomarker, it is mostly used to confirm the diagnosis or to control the treatment efficacy during follow-up [29].

Serotonin is one of the most hypersecreted hormones in NETs. 5-Hydroxyindoleacetic acid (5-HIAA) has serotonin as substrate and is excreted via the urine, where high levels of 5-HIAA are detected in patients with NETs [30, 31]. Although tryptophan- or serotonin-rich food can elevate 5-HIAA levels, the specificity of this marker is about 88% in NETs [31].

References

1. Modlin IM, Shapiro MD, Kidd M. Siegfried oberndorfer: origins and perspectives of carcinoid tumors. Hum Pathol. 2004;35(12):1440–51.
2. Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. Cancer. 2003;97(4):934–59.

3. Solcia E, Klöppel G, Sobin LH. Histological typing of endocrine tumours. 2nd ed. WHO, World Health Organization, International Histological Classification of Tumours; 2000.
4. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063–72.
5. Niederle MB, Hackl M, Kaserer K, Niederle B. GEPNET: the current incidence and staging based on the WHO and ENETS classification: an analysis based on prospectively collected parameters. Endocr Relat Cancer. 2010;17(4):909–18.
6. Klöppel G. Tumour biology and histopathology of neuroendocrine tumours. Best Pract Res Clin Endocrinol Metab. 2007;21(1):15–31.
7. Adler DG. Neuroendocrine tumors: review and clinical update. Hosp Physician. 2007:12–21.
8. Nikou GC, Marinou K, Thomakos P, Papageorgiou D, Sanzanidis V, Nikolaou P, Kosmidis C, Moulakakis A, Mallas E. Chromogranin a levels in diagnosis, treatment and follow-up of 42 patients with non-functioning pancreatic endocrine tumours. Pancreatology. 2008;8(4–5): 510–9.
9. Marx SJ. Molecular genetics of multiple endocrine neoplasia types 1 and 2. Nat Rev Cancer. 2005;5(5):367–75.
10. DeLellis RA. The neuroendocrine system and its tumors: an overview. Am J Clin Pathol. 2001;115(Suppl. 1):5–16.
11. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, Caplin M, Delle Fave G, Kaltsas GA, Krenning EP, Moss SF, Nilsson O, Rindi G, Salazar R, Ruszniewski P, Sundin A. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9(1):61–72.
12. Pfragner R, Behmel A, Hoger H, Beham A, Ingolic E, Stelzer I, Svejda B, Moser VA, Obenauf AC, Siegl V, Haas O, Niederle B. Establishment and characterization of three novel cell lines - P-STS, L-STS, H-STS - derived from a human metastatic midgut carcinoid. Anticancer Res. 2009;29(6):1951–61.
13. Bajetta E, Ferrari L, Martinetti A, Celio L, Procopio G, Artale S, Zilembo N, Di Bartolomeo M, Seregni E, Bombardieri E. Chromogranin A, neuron specific enolase, carcinoembryonic antigen, and hydroxyindole acetic acid evaluation in patients with neuroendocrine tumors. Cancer. 1999;86:858–65.
14. Jiao Y, Shi C, Edil BH, De Wilde RF, Klimstra DS, Maitra A, Schulick RD, Tang LH, Wolfgang CL, Choti A, Velculescu VE, Jr LAD, Vogelstein B, Kinzler KW, Hruban RH, Papadopoulos N. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. Science. 2011;331(6021):1199–203.
15. Agarwal SK, Kester MB, Debelenko LV, Heppner C, Emmert-Buck MR, Skarulis MC, Doppman JL, Kim YS, Lubensky IA, Zhuang Z, Green JS, Guru SC, Manickam P, Olufemi SE, Liotta LA, Chandrasekharappa SC, Collins FS, Spiegel AM, Burns AL, Marx SJ. Germline mutations of the MEN1 gene in familial multiple endocrine neoplasia type 1 and related states. Hum Mol Genet. 1997;6(7):1169–75.
16. Pieterman CRC, Conemans EB, Dreijerink KMA, De Laat JM, Timmers HTM. Thoracic and duodenopancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1: natural history and function of menin in tumorigenesis. Endocr Relat Cancer. 2014;21(3):R121–42.
17. Marinoni I, Kurrer AS, Vassella E, Dettmer M, Rudolph T, Banz V, Hunger F, Pasquinelli S, Speel EJ, Perren A. Loss of DAXX and ATRX are associated with chromosome instability and reduced survival of patients with pancreatic neuroendocrine tumors. Gastroenterology. 2014;146(2):453–460.e5.
18. Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. Hum Mutat. 2008;29(1):22–32.
19. Asa SL. Pancreatic endocrine tumors. Mod Pathol. 2011;24(Suppl. 2):S66–77.
20. Larsson C, Skogseid B, Oberg K, Nakamura Y, Nordenskjöld M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. Nature. 1988;332(6159):85–7.

21. Yaguchi H, Ohkura N, Takahashi M, Nagamura Y, Kitabayashi I, Tsukada T. Menin missense mutants associated with multiple endocrine neoplasia type 1 are rapidly degraded via the ubiquitin-proteasome pathway. Mol Cell Biol. 2004;24(15):6569–80.
22. Cives M, Kunz PL, Morse B, Coppola D, Schell MJ, Campos T, Nguyen PT, Nandoskar P, Khandelwal V, Strosberg JR. Phase II clinical trial of pasireotide long-acting repeatable in patients with metastatic neuroendocrine tumors. Endocr Relat Cancer. 2015;22(1):1–9.
23. Missiaglia E, Dalai I, Barbi S, Beghelli S, Falconi M, Della Peruta M, Piemonti L, Capurso G, Di Florio A, Delle Fave G, Pederzoli P, Croce CM, Scarpa A. Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. J Clin Oncol. 2010;28(2):245–55.
24. Perren A, Anlauf M, Henopp T, Rudolph T, Schmitt A, Raffel A, Gimm O, Weihe E, Knoefel WT, Dralle H, Heitz PU, Komminoth P, Klöppel G. Multiple endocrine neoplasia type 1 (MEN1): loss of one MEN1 allele in tumors and monohormonal endocrine cell clusters but not in islet hyperplasia of the pancreas. J Clin Endocrinol Metab. 2007;92(3):1118–28.
25. Neary PC, Redmond PH, Houghton T, Watson GR, Bouchier-Hayes D. Carcinoid disease: review of the literature. Dis Colon Rectum. 1997;40(3):349–62.
26. Modlin IM, Moss SF, Gustafsson BI, Lawrence B, Schimmack S, Kidd M. The archaic distinction between functioning and nonfunctioning neuroendocrine neoplasms is no longer clinically relevant. Langenbeck's Arch Surg. 2011;396:1145–56.
27. Panzuto F, Severi C, Cannizzaro R, Falconi M, Angeletti S, Pasquali A, Corleto VD, Annibale B, Buonadonna A, Pederzoli P, Delle Fave G. Utility of combined use of plasma levels of chromogranin A and pancreatic polypeptide in the diagnosis of gastrointestinal and pancreatic endocrine tumors. J Endocrinol Investig. 2004;27(1):6–11.
28. Bumming P, Nilsson O, Ahlman H, Welbencer A, Andersson MK, Sjolund K, Nilsson B, Bümming P, Sjölund K. Gastrointestinal stromal tumors regularly express synaptic vesicle proteins: evidence of a neuroendocrine phenotype. Endocr Relat Cancer. 2007;14(3):853–63.
29. Andrén-Sandberg A. Pancreatic endocrine tumors. N Am J Med Sci. 2011;3(4):164–6.
30. Oberg K, Knigge U, Kwekkeboom D, Perren A. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012;23(Suppl. 7):vii124–30.
31. Modlin IM, Moss SF, Oberg K, Padbury R, Hicks RJ, Gustafsson BI, Wright NA, Kidd M. Gastrointestinal neuroendocrine (carcinoid) tumours: Current diagnosis and management. Med J Aust. 2010;193(1):46–52.