Thoracic and duodenopancreatic neuroendocrine tumors in multiple endocrine neoplasia type 1: natural history and function of menin in tumorigenesis

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Abstract

Mutations of the multiple endocrine neoplasia type 1 (*MEN1*) gene lead to loss of function of its protein product menin. In keeping with its tumor suppressor function in endocrine tissues, the majority of the MEN1-related neuroendocrine tumors (NETs) show loss of heterozygosity (LOH) on chromosome 11q13. In sporadic NETs, *MEN1* mutations and LOH are also reported, indicating common pathways in tumor development. Prevalence of thymic NETs (thNETs) and pulmonary carcinoids in MEN1 patients is 2–8%. Pulmonary carcinoids may be underreported and research on natural history is limited, but disease-related mortality is low. thNETs have a high mortality rate. Duodenopancreatic NETs (dpNETs) are multiple, almost universally found at pathology, and associated with precursor lesions. Gastrinomas are usually located in the duodenal submucosa while other dpNETs are predominantly pancreatic. dpNETs are an important determinant of MEN1-related survival, with an estimated 10-year survival of 75%. Survival differs between subtypes and apart from tumor size there are no known prognostic factors. Natural history of nonfunctioning pancreatic NETs needs to be redefined because of increased detection of small tumors. MEN1-related gastrinomas seem to behave similar to their sporadic counterparts, while insulinomas seem to be more aggressive. Investigations into the molecular functions of menin have led to new insights into MEN1-related tumorigenesis. Menin is involved in gene transcription, both as an activator and repressor. It is part of chromatin-modifying protein complexes, indicating involvement of epigenetic pathways in MEN1-related NET development. Future basic and translational research aimed at NETs in large unbiased cohorts will clarify the role of menin in NET tumorigenesis and might lead to new therapeutic options.

Key Words
- multiple endocrine neoplasia type 1
- neuroendocrine tumors
- menin
- epigenetics
- natural history
- lung NET
- thymic NET
- duodenopancreatic NET
- pancreatic NET
- MEN1

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Introduction

Thoracic and duodenopancreatic neuroendocrine tumors (dpNETs) can occur either sporadically or as a manifestation of an inherited syndrome, most importantly the multiple endocrine neoplasia type 1 (MEN1) syndrome. This is an autosomal dominantly inherited disease that is caused by germline mutations in the *MEN1* gene. NETs associated with MEN1 are lung NETs, thymic NETs (thNETs), gastrin NETs, and dpNETs. MEN1-related NETs are an important cause of morbidity and presently malignant dpNETs and thNETs are the main cause of MEN1-related death (Schaaf *et al.* 2007, Goudet *et al.* 2010).

In the past decade, understanding of the genetic and molecular aspects of NETs has increased and important steps have been made in the therapy of advanced disease. New tumor classification and staging systems have improved patient care and uniformity in patient selection for clinical trials. It is important to recognize similarities in the tumorigenesis of MEN1-related and sporadic NETs, because MEN1-related NETs may be regarded as a model for sporadic disease. On the other hand, it is also essential to be aware of potential differences in tumor behavior between these two entities, as this influences diagnostic and therapeutic strategies.

In this review, we provide a comprehensive overview of the literature concerning tumor development of MEN1-related dpNETs and thoracic NETs (Box 1). The complete spectrum, from epidemiologic characteristics and natural history to important molecular findings associated with loss of the *MEN1* gene, is discussed. Differences between and similarities with their sporadic counterparts are highlighted. Table 1 provides a list of some of the abbreviations used in the text.

MEN1 gene

The *MEN1* gene was initially localized to chromosome 11q13 by linkage analysis and tumor deletion mapping studies (Larsson *et al.* 1988, Friedman *et al.* 1989, Byström *et al.* 1990, Lubensky *et al.* 1996), which led to the identification of the gene in 1997 (Chandrasekharappa *et al.* 1997, Lemmens *et al.* 1997). More than 450 different germline *MEN1* mutations have been identified in MEN1 patients (Lemos & Thakker 2008). *MEN1* consists of ten exons and mutations are found scattered throughout the gene. The protein product is the 610-amino acid protein, called menin. Most *MEN1* gene mutations are predicted to lead to truncation of the protein (Lemos & Thakker 2008). Missense mutations have been reported in about 20% of the cases. Both truncated and missense mutations result in reduced levels of protein due to proteolytic degradation via the ubiquitin–proteasome pathway (Yaguchi *et al.* 2004). A small percentage of patients who are considered to have the MEN1 syndrome (based on the clinical definition) may not harbor a germline mutation within the coding region of the *MEN1* gene (Agarwal *et al.* 1997). Possibly, these patients have mutations in the promoter region or large deletions on chromosome 11q13 (Cavaco *et al.* 2002). Currently, in clinical practice, inconclusive DNA sequencing is followed by multiplex ligation-dependent probe amplification analysis for detection of large deletions. An alternative explanation for the MEN1 syndrome of these patients may include epigenetic silencing of *MEN1* (e.g. by DNA methylation) or mutations in other genes, which cause MEN1-like manifestations.

The *MEN1* gene is a tumor suppressor gene for endocrine tissues. According to Knudson's 'two-hit hypothesis', biallelic inactivation of *MEN1* is required for tumor development (Knudson 1971). This second hit typically involves large chromosomal deletions in chromosome 11q13. Loss of heterozygosity (LOH) of *MEN1* is demonstrated in most reported MEN1-related pancreatic NETs (pNETs) (Lubensky *et al.* 1996, Debelenko *et al.* 1997*b*, Hessman *et al.* 2001, Perren *et al.* 2007). However, the frequency of LOH of chromosome 11q13 in MEN1-related primary duodenal gastrinomas is only 21–45% (Lubensky *et al.* 1996, Debelenko *et al.* 1997*b*). LOH of chromosome 11q13 has also been shown in MEN1-related pulmonary carcinoids (Debelenko *et al.* 1997*b*, Dong *et al.* 1997). Intriguingly, no LOH was found in thNETs (Teh *et al.* 1994, 1998, Hessman *et al.* 2001, Gibril *et al.* 2003). In these cases, other events might be involved in silencing the second *MEN1* allele.

Box 1: Search strategy
The contents of this review are based on the experience of the authors and on an extensive search in PubMed. The following terms were used in the search string: 'MEN1' and all relevant synonyms OR 'menin' and all relevant synonyms. For lung NET, this search string was combined with 'bronchial' OR 'pulmonary' OR 'lung' (and relevant synonyms) AND 'carcinoid' OR 'neuroendocrine'. For thNET this search string was combined with 'thymic' OR 'thymus' OR 'mediastinal' AND 'carcinoid' OR 'neuroendocrine'. For dpNET, this search string was combined with all relevant synonyms for 'pancreas' and 'duodenum' AND all relevant synonyms for 'neuroendocrine tumor' OR 'gastrinoma' OR 'insulinoma' OR 'glucagonoma' OR 'VIPoma'.

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Table 1 Abbreviations used in the text

AC	Atypical carcinoid
DIPNECH	Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
dpNET	Duodenopancreatic neuroendocrine tumor
H3K4me3	Trimethylation of lysine 4 on histone 3
HDAC	Histone deacetylase
LOH	Loss of heterozygosity
MEN1	Multiple endocrine neoplasia type 1
NET	Neuroendocrine tumor
NF	Nonfunctioning
NF-pNET	Nonfunctioning pancreatic neuroendocrine tumor
NR	Nuclear receptor
pNET	Pancreatic neuroendocrine tumor
thNET	Thymic neuroendocrine tumor
TC	Typical carcinoid
TF	Transcription factor
VIPoma	Vaso-active intestinal peptide producing neuroendocrine tumors

Somatic mutations in MEN1-related tumors have been reported as an alternative mechanism leading to the inactivation of this second *MEN1* allele (Pannett & Thakker 2001). Post-transcriptional reduction in menin levels by specific microRNAs may mimic the second hit (Luzi *et al*. 2012). In sporadic NETs, somatic mutations of the *MEN1* gene have been found. The reported frequency for *MEN1* mutations in sporadic pNETs is up to 44% in well-differentiated tumors (Jiao *et al*. 2011). In accordance with Knudson's hypothesis, LOH of chromosome 11q13 is also observed in sporadic pNETs (Debelenko *et al*. 1997*b*, Hessman *et al*. 1998, Gortz *et al*. 1999). Also, in sporadic pulmonary carcinoids, mutations in the *MEN1* gene and LOH of chromosome 11q13 are reported with a frequency of 18–45% (Debelenko *et al*. 1997*b*, Walch *et al*. 1998, Gortz *et al*. 1999, Petzmann *et al*. 2001, Vageli *et al*. 2006, Veschi *et al*. 2012) and up to 73% in a single report (Finkelstein *et al*. 1999). Apparently, MEN1-related tumors and their sporadic counterparts share common pathways in tumor development.

Thoracic NETs in MEN1

Pathology and pathogenesis

According to the World Health Organization, lung and thymus NETs are classified into typical carcinoids (TCs), atypical carcinoids (ACs), and high-grade neuroendocrine carcinomas based on mitotic count and the presence of necrosis (Travis *et al*. 2004). High-grade tumors are divided into large-cell neuroendocrine carcinomas and small-cell carcinomas. Small (<0.5 cm) pulmonary tumors with carcinoid morphology are called tumorlets (Travis *et al*. 2004). For thNETs, alternative grading systems exist, which is important to realize when comparing and interpreting results from different studies (Fukai *et al*. 1999, Moran & Suster 2000*a*, Gal *et al*. 2001, Gaur *et al*. 2010).

Pulmonary carcinoids have a different clinical presentation and genetic profile compared with high-grade tumors and must be regarded as a separate entity (Swarts *et al*. 2012). High-grade lung NETs are not seen in association with MEN1. Moreover, in contrast to sporadic pulmonary carcinoids, mutations in the *MEN1* gene and LOH at chromosome 11q13 are rare in high-grade lung NETs (Swarts *et al*. 2012). This sharp distinction is absent in thNETs (Moran & Suster 2000*b*) and MEN1-related thNETs include both well- and poorly-differentiated neuroendocrine carcinomas.

The cell of origin for pulmonary carcinoids is thought to be the pulmonary neuroendocrine cell (Swarts *et al*. 2012), although, some suggest an uncommitted progenitor cell (Warren & Hammar 2006). Pulmonary neuroendocrine cells are evenly distributed throughout the airways, but absent from the alveoli, and comprise 0.4% of all lung epithelial cells (Boers *et al*. 1996). In response to various triggers, reactive neuroendocrine cell hyperplasia can occur, which is not associated with the development of pulmonary carcinoids. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), on the other hand, is a rare disorder that is considered preneoplastic to pulmonary carcinoids (Aguayo *et al*. 1992, Travis *et al*. 2004). Only one case of a MEN1-patient with DIPNECH has been published to date (Davies *et al*. 2007). However, in published cases of MEN1-related pulmonary carcinoids, pathology of surrounding lung tissue was not reported, so the true prevalence of DIPNECH among MEN1-patients is unknown.

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The cell of origin for thNETs is not known and there are no known precursor lesions. thNETs were first described in 1972 and in the same year the association with MEN1 was reported (Rosai & Higa 1972, Rosai *et al.* 1972). It was then hypothesized that these tumors arise from neuroendocrine cells residing within the normal thymus. In different series, family clustering of MEN1-related thNETs was demonstrated (Teh *et al.* 1997, 1998, Ferolla *et al.* 2005, Goudet *et al.* 2009). In those series, no apparent *MEN1* genotype–phenotype correlation was seen, suggesting the involvement of other genetic factors.

Epidemiology

The prevalence of thNETs among MEN1 patients is 2–8% (Teh *et al.* 1997, Burgess *et al.* 1998*b*, Gibril *et al.* 2003, Goudet *et al.* 2011, Sakurai *et al.* 2013). Approximately one-fifth of all thNETs are MEN1-related (Teh *et al.* 1997), therefore the diagnosis of a thNET should always prompt further evaluation of a possible underlying MEN1 syndrome (de Laat *et al.* 2012). Mean age at diagnosis of thNETs in MEN1 is 39–47 years (Teh *et al.* 1997, 1998, Gibril *et al.* 2003, Ferolla *et al.* 2005, Goudet *et al.* 2009, Sakurai *et al.* 2013). In series from USA, Europe, and Australia 95–100% of the patients are male (Teh *et al.* 1997, 1998, Gibril *et al.* 2003, Ferolla *et al.* 2005, Goudet *et al.* 2009), whereas in a recent Japanese series 64% of thNETs occurred in males (Sakurai *et al.* 2013). Age at diagnosis is 43–58 years in sporadic thNET and male predominance, although less pronounced (67–86%), is also seen (de Montpreville *et al.* 1996, Soga *et al.* 1999, Moran & Suster 2000*a*, Gaur *et al.* 2010, Hamaji *et al.* 2012). It is important to note that most MEN1-patients with thNETs are heavy smokers (Teh *et al.* 1997, 1998, Gibril *et al.* 2003, Ferolla *et al.* 2005).

The exact prevalence of pulmonary carcinoids in MEN1 is unknown. Commonly reported figures are 3–8% (Marx *et al.* 1998, Karges *et al.* 2000, Goudet *et al.* 2011). However, in a large Tasmanian family ($n=129$), prevalence among patients screened with thoracic computed tomography ranged from 11% if only pathology proven cases were included to 31% based on radiological findings (Sachithanandan *et al.* 2005). Reported age at diagnosis of MEN1-related pulmonary carcinoids is mid-forties (Sachithanandan *et al.* 2005). Although initially a female predominance was reported (Duh *et al.* 1987, Farhangi *et al.* 1987, Shepherd 1991, Sachithanandan *et al.* 2005), the prevalence appears to be equal between genders in a large recent study (Goudet *et al.* 2011).

Natural history and prognostic factors: pulmonary carcinoids

Very little is known about the natural course and prognosis of pulmonary carcinoids in MEN1. Evidence is limited to one small series and several case reports or descriptions, either separately published or mentioned within larger MEN1 patient series. Among sporadic pulmonary carcinoids, TCs are much more frequent than ACs (10–27% in series also including nonsurgical patients; Fink *et al.* 2001, Pusceddu *et al.* 2010, Naalsund *et al.* 2011, Okoye *et al.* 2013). This seems to be similar in MEN1, but classifications are rarely reported (Murat *et al.* 1997, Snabboon *et al.* 2005, Lourenco-Jr *et al.* 2007, Abe *et al.* 2008, Divisi *et al.* 2008, Matsuda *et al.* 2010, Montero *et al.* 2010). As in other MEN1 manifestations, multiplicity seems to be common in pulmonary carcinoids (Marx *et al.* 1998, Sachithanandan *et al.* 2005). In its sporadic counterpart, multiplicity is seen in <1–9% (Daddi *et al.* 2004, Garcia-Yuste *et al.* 2007, Ferolla *et al.* 2009, Okoye *et al.* 2013). Ectopic hormone production is not reported in MEN1-related pulmonary carcinoids, in contrast to sporadic disease (Boddaert *et al.* 2012, Garby *et al.* 2012, Simonds *et al.* 2012).

The overall survival of MEN1-related pulmonary carcinoids is unknown. In series focusing on MEN1-related mortality, 5–9% of the MEN1-related deaths occurring before 1990 were attributed to pulmonary carcinoids (Wilkinson *et al.* 1993, Goudet *et al.* 2010), with no deaths due to pulmonary carcinoids reported after 1990 (Geerdink *et al.* 2003, Wilson *et al.* 2008, Goudet *et al.* 2010). In line with these findings, pulmonary carcinoids do not give an increased risk of death in MEN1 patients (Goudet *et al.* 2010).

The prevalence of lymph node or distant metastases is difficult to establish in MEN1-related pulmonary carcinoids. In a total of only 33 cases reported in literature, information on metastases is available, with 24% lymph node metastases and 12% distant metastases (Underdahl *et al.* 1953, Williams & Celestin 1962, Dry *et al.* 1975, Farhangi *et al.* 1987, Shepherd 1991, Murat *et al.* 1997, Sachithanandan *et al.* 2005, Snabboon *et al.* 2005, Lourenco-Jr *et al.* 2007, Abe *et al.* 2008, Divisi *et al.* 2008, Waldmann *et al.* 2009, Fabbri *et al.* 2010, Matsuda *et al.* 2010, Montero *et al.* 2010).

Given the paucity of data on pulmonary carcinoids in MEN1 and the absence of head-to-head comparisons, it is unclear whether the natural history differs between MEN1-related and sporadic pulmonary carcinoids. There are a few studies in sporadic tumors that show somatic

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MEN1 mutations, LOH at 11q13, or reduced *MEN1* gene expression to be an adverse prognostic factor (Debelenko *et al*. 1997*a*, Petzmann *et al*. 2001, Swarts *et al*. 2011).

Factors predicting development of metastases or survival are not known in MEN1-related pulmonary carcinoids. In their sporadic counterparts ACs, lymph node metastases, distant metastases, and higher proliferation rate (Ki67 labeling index or mitotic index) have been repeatedly identified as adverse prognostic factors (Cao *et al*. 2011, Daddi *et al*. 2013). Results on the prognostic values of gender, age, and tumor size are contradictory.

Natural history and prognostic factors: thNET

Six case series including more than five patients have been published on thNETs in MEN1 (Teh *et al*. 1997, 1998, Gibril *et al*. 2003, Ferolla *et al*. 2005, Goudet *et al*. 2009, Sakurai *et al*. 2013). In these series, classifications are often not reported (Teh *et al*. 1997, 1998, Gibril *et al*. 2003, Sakurai *et al*. 2013). When mentioned, 100% are AC in one series and 38% poorly differentiated neuroendocrine carcinomas in another (with the distinction between TC and AC for the other 62% not reported; Ferolla *et al*. 2005, Goudet *et al*. 2009). In sporadic thNETs the reported frequencies vary greatly, TCs are reported in 0–67% in different series and 81% in a literature review from 1999 (de Montpreville *et al*. 1996, Fukai *et al*. 1999, Soga *et al*. 1999, Moran & Suster 2000*a*, Gaur *et al*. 2010, Cardillo *et al*. 2012). Patient selection and differences in the use of grading systems may explain this variation. Cushing's syndrome due to ectopic adrenocorticotropic hormone production is rare in MEN1-related thNETs (0–5%; Teh *et al*. 1997, 1998, Gibril *et al*. 2003, Ferolla *et al*. 2005, Goudet *et al*. 2009, Sakurai *et al*. 2013), but it has been observed in 5–31% of the sporadic cases (Moran & Suster 2000*a*, Kondo & Monden 2003, Cardillo *et al*. 2012).

Among the manifestations of the MEN1 syndrome, thNETs carry the highest risk of death (Goudet *et al*. 2010) with an estimated 10-year survival of 30–36% (Goudet *et al*. 2009, Sakurai *et al*. 2013). Although mortality is high, the course of MEN1-related thNETs may be protruded, with one series reporting a median survival of 9.6 years (Goudet *et al*. 2009). When comparing six MEN1 patients with thNETs with 22 patients with sporadic thNETs, Crona *et al*. (2013) found no survival difference between these groups.

In MEN1-related thNETs, 90% disease-related mortality was reported among patients with advanced stage disease in a series with a mean 3.6 years follow-up (Teh *et al*. 1997). In the other series, patients were followed for a mean 5–7 years and metastases occurred in 32–71% of the patients. Disease-related mortality in these series ranged from 0 to 43% (Teh *et al*. 1998, Gibril *et al*. 2003, Ferolla *et al*. 2005, Goudet *et al*. 2009, Sakurai *et al*. 2013). In one of the two series reporting no mortality, the majority was discovered incidentally at prophylactic thymectomy or by screening (Gibril *et al*. 2003).

No data are available on prognostic factors with regard to overall survival, recurrence, or metastases in MEN1 patients. In series reporting on sporadic thNETs, prognostic factors related to decreased survival are higher tumor grade, more advanced disease, higher Ki67 labeling index (cut-off 10%), and larger tumor size (Moran & Suster 2000*a*, Gal *et al*. 2001, Gaur *et al*. 2010, Cardillo *et al*. 2012, Crona *et al*. 2013).

dpNETs in MEN1

Pathology and pathogenesis

dpNETs are classified according to the European Neuroendocrine Tumor Society/World Health Organization grading system into three grades based on proliferation rate (Rindi *et al*. 2006, Bosman *et al*. 2010).

The hallmark of dpNETs in MEN1 is multiplicity, which is in contrast to the mostly solitary sporadic dpNETs (Thompson *et al*. 1984, Pipeleers-Marichal *et al*. 1993, Crippa *et al*. 2012). All histologic subtypes can occur in MEN1. At pathology, all MEN1 patients have multiple micro-adenomas (pNETs <5 mm without clinical syndrome) dispersed throughout the pancreas associated with one or more NETs ≥ 5 mm (Thompson *et al*. 1984, Kloppel *et al*. 1986, Le Bodic *et al*. 1996, Anlauf *et al*. 2006*b*). These multiple dpNETs in MEN1 arise from independent clonal events, as demonstrated by different allelic deletion and retention patterns in synchronous tumors (Debelenko *et al*. 1997*b*, Hessman *et al*. 1999, Perren *et al*. 2007). Apart from these tumors other lesions such as islet cell hyperplasia/enlargement, nesidioblastosis, and atypical or monohormonal endocrine cell clusters are frequently observed in the MEN1 pancreas, leading to different theories as to the cell of origin for pNETs (Thompson *et al*. 1984, Le Bodic *et al*. 1996, Vortmeyer *et al*. 2004, Perren *et al*. 2007). Normal pancreatic islets and alternatively ductal/acinar cells are proposed to be the precursor cells for pNETs (Vortmeyer *et al*. 2004, Perren *et al*. 2007).

Gastrinomas take a special place among the MEN1-related dpNETs, as the vast majority are not pancreatic but located submucosal in the duodenum (Pipeleers-Marichal

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et al. 1990). Sporadic gastrinomas are located in the duodenum less frequently than in MEN1 (Pipeleers-Marichal *et al*. 1990, Donow *et al*. 1991, Pipeleers-Marichal *et al*. 1993, Anlauf *et al*. 2006*a*). Duodenal NETs in MEN1 are almost always multiple, while sporadic duodenal NETs are usually solitary (Pipeleers-Marichal *et al*. 1990, Donow *et al*. 1991, Anlauf *et al*. 2006*a*). In MEN1, they are associated with multifocal hyperplasia of gastrin and somatostatin producing cells, which are proposed to be precursor lesions (Anlauf *et al*. 2005).

Epidemiology

The clinical prevalence of dpNETs in MEN1 is over 50% in recent large series (Goudet *et al*. 2011, Sakurai *et al*. 2012*a*) and the penetrance of clinically manifest dpNETs at the age of 80 is 84% (Triponez *et al*. 2006*a*).

dpNETs are classified as hormonally active or non-functioning (NF) based on the combination of clinical features, laboratory results, and findings at immunohistochemistry. In the MEN1 syndrome, synchronous dpNETs may secrete different hormones based on immunohistochemistry (Le Bodic *et al*. 1996, Anlauf *et al*. 2006*b*). As these findings do not always correlate with clinical symptoms, classifications should not be based on immunohistochemistry alone.

When sought for, additional NF-pNETs are found in all patients undergoing surgery for functional tumors, so the prevalence of NF-pNETs is probably equal to dpNETs in general (Tonelli *et al*. 2006, Lopez *et al*. 2011, Giudici *et al*. 2012). Gastrinoma is the most prevalent hormonally active dpNET (29–55% of all dpNETs in studies published in the last decade), followed by insulinoma (2–24%) and rare functioning tumors seen in <10% such as glucagonoma, vaso-active intestinal peptide-producing NET (VIPoma), and somatostatinoma. (Lourenco-Jr *et al*. 2007, Vierimaa *et al*. 2007, Pieterman *et al*. 2009, Waldmann *et al*. 2009, Goudet *et al*. 2011, Sakurai *et al*. 2012*a*). It is important to realize that 76% of all cases of growth hormone (GH)-releasing hormone-producing pNETs reported in literature are MEN1-related (Garby *et al*. 2012). This diagnosis should therefore always raise suspicion of an underlying MEN1 syndrome. Separating different types of dpNETs in MEN1 is somewhat artificial, because most patients with hormonally active tumors will harbor additional NF-pNETs (Tonelli *et al*. 2006, Lopez *et al*. 2011, Giudici *et al*. 2012), patients with NF-pNETs can develop hormonally active tumors (Thomas-Marques *et al*. 2006, Davi *et al*. 2011), and co-occurrence of different hormonally active tumors has also been described (Tonelli *et al*. 2006, Giudici *et al*. 2012).

MEN1-related dpNETs are seen one to two decades earlier than their sporadic counterparts (Jensen 1998, Nikfarjam *et al*. 2008, Anlauf *et al*. 2009, Crippa *et al*. 2012, Singh *et al*. 2012). Insulinomas have the lowest age of onset (patients are usually in their twenties to thirties at diagnosis), patients with gastrinomas and NF-pNETs are usually diagnosed in their thirties (Jensen 1998, Cougard *et al*. 2000, Triponez *et al*. 2006*a*, Sakurai *et al*. 2012*b*). At the age of 60, the penetrance of gastrinoma is significantly higher in men (55%) compared with women (33%), while the other dpNET types do not show gender differences (Goudet *et al*. 2011).

Natural history

dpNETs are the most important determinant of MEN1-related survival. In historical series, ulcer disease due to gastrinoma was the most important cause of MEN1-related death (Ballard *et al*. 1964), while this presently is malignant dpNETs (Schaaf *et al*. 2007, Goudet *et al*. 2010). In patients with MEN1-related dpNETs, estimated 10-year survival is 75% (Carty *et al*. 1998, Kouvaraki *et al*. 2006). Risk of death seems to differ between the various subtypes, with the rare functioning tumors presenting the highest risk followed by NF-pNETs and gastrinoma, while insulinomas do not seem to increase the risk of death (Goudet *et al*. 2010).

However, the natural history of NF-pNETs is not well-established yet. Estimated 10-year survival rates of 23–62% have been reported (Levy-Bohbot *et al*. 2004, Kouvaraki *et al*. 2006), whereas this was 100% in a recent series (Lopez *et al*. 2011). One has to keep in mind that with endoscopic ultrasound, more small NF-pNETs are currently diagnosed. They are usually indolent and demonstrate slow growth, with a doubling time of 5–10 years (Kann *et al*. 2006, Sakurai *et al*. 2007). When 46 patients with NF-pNETs <2 cm without surgical treatment were followed over 10 years, 17% showed increase in size, 11% developed a functional syndrome, 65% displayed stable disease, 2% died due to metastatic NF-pNETs, 2% due to other causes, and 2% was lost to follow-up (Triponez F, Goudet P, AFCE, & GTE unpublished observations presented at ENETS 2013, Barcelona, Spain). In the largest reported series on NF-pNETs ($n=108$), metastases, mostly distant, are seen in 19% and disease-specific survival is 91% after a mean follow-up of 4 years (Triponez *et al*. 2006*a*). In smaller series from the last decade, distant metastases are reported in 6–22% (Bartsch *et al*. 2005, Davi *et al*. 2011, Lopez *et al*.

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2011), whereas in a report from 1992 distant metastases were observed in 57% (Grama *et al*. 1992). Mean tumor size in this latter series was 6.7 cm (Grama *et al*. 1992).

In MEN1-related insulinomas, reported survival rates in series with more than ten patients are 93–100% after 9–10 years of follow-up (Van Box Som *et al*. 1995, Cougard *et al*. 2000, Proye *et al*. 2004). Multiple insulinomas are seen in 25–83% (Van Box Som *et al*. 1995, Thompson 1998, Giudici *et al*. 2012), whereas in sporadic insulinomas multiplicity is seen in ∼4% (Nikfarjam *et al*. 2008, Anlauf *et al*. 2009, Crippa *et al*. 2012).

Malignancy in MEN1-related insulinomas has been reported in 5–27% in series including more than ten patients (Cougard *et al*. 2000, Proye *et al*. 2004, Crippa *et al*. 2012). In these malignant insulinomas, liver metastases were only seen once (Proye *et al*. 2004).

The natural history of gastrinomas in MEN1 is difficult to establish for several reasons. First, gastrinomas in MEN1 are predominantly located in the duodenum (Pipeleers-Marichal *et al*. 1990). In series on MEN1-related gastrinomas, high rates of pancreatic tumors might be reported, but most of these will not be the gastrinomas. Rates of pancreatic gastrinomas are only 0–18% in series that include immunohistochemistry in the classification of pNETs as gastrinomas (Tonelli *et al*. 2006, Dickson *et al*. 2011, Imamura *et al*. 2011, Lopez *et al*. 2013). Second, MEN1-related gastrinomas are almost invariably accompanied by NF-pNETs (Thompson 1998, Dickson *et al*. 2011). If distant metastases arise, these can not only be caused by the gastrinoma, but also by the accompanying NF-pNETs and even by NETs of other locations, which cannot be separated if no pathology or immunohistochemistry results are available. Third, when interpreting the results of clinical series, it is important to realize that in surgical series synchronous metastases will most likely be underrepresented, since diffuse liver metastases are seen as a contra-indication for surgery, whereas in series with low surgical rates nodal status will most likely be underrepresented, because this is difficult to establish on imaging (Skogseid *et al*. 1998). Finally, since the publication of guidelines for periodic evaluation, MEN1 patients must be viewed as a screened population, making comparison with sporadic cases more difficult (Thakker *et al*. 2012).

The reported 10-year survival of gastrinomas in MEN1 is 86–94% (Thompson 1998, Norton *et al*. 2001, Ito *et al*. 2013), with two series reporting 63 and 75% (Melvin *et al*. 1993, Ruszniewski *et al*. 1993). In MEN1-related gastrinoma, synchronous lymph node metastases are reported in 45–69% (Ruszniewski *et al*. 1993, Thompson 1995, Weber *et al*. 1995, Jensen 1998, Norton *et al*. 1999, 2001, Imamura *et al*. 2011, Singh *et al*. 2012, Ito *et al*. 2013), with two series reporting 23–35% (Thompson 1998, Cadiot *et al*. 1999) and two series reporting 80%. (Dickson *et al*. 2011, Lopez *et al*. 2013). Synchronous distant metastases are reported in 4–29% in series also including nonsurgical patients (Jensen 1998, Ito *et al*. 2013).

Owing to its rarity, very few data are available on functioning pNETs other than gastrinomas and insulinomas. The largest combined experience comes from the French Endocrine Tumor Study Group, reporting on five glucagonomas, three VIPomas, and two somatostatinomas in MEN1, comprising 3.3% of the MEN1-related dpNETs (Levy-Bohbot *et al*. 2004). Four of these ten patients had liver metastases (40%). Ten-year survival was 54% (Levy-Bohbot *et al*. 2004).

Natural history: comparison with sporadic dpNET

Some series including MEN1 and sporadic dpNETs of all subtypes report MEN1 to be associated with better survival. However, no separate baseline characteristics are provided for MEN1 patients, so selection bias cannot be excluded (Tomassetti *et al*. 2005, Fendrich *et al*. 2007, Rindi *et al*. 2012). In one study including only patients operated upon for advanced dpNETs (all subtypes), patients with MEN1 had a trend toward better survival and developed no new distant metastases, while 46% of the patients with sporadic dpNETs did develop new distant metastases (Fendrich *et al*. 2006). The meaning of these findings is difficult to discern, given the highly selected source population.

With regard to different subtypes of dpNETs, no studies are available comparing MEN1-related and sporadic NF-pNETs. In series comparing MEN1-related with sporadic insulinomas, a higher rate of malignancy was seen in MEN1 (Service *et al*. 1991, Anlauf *et al*. 2009, Goretzki *et al*. 2010, Crippa *et al*. 2012). On gastrinomas more data are available, mostly from different reports of the prospective study on Zollinger–Ellison syndrome by the National Institutes of Health (Weber *et al*. 1995, Jensen 1998, Norton *et al*. 1999, Yu *et al*. 1999). In two of these reports, MEN1 patients had a better overall survival than patients with sporadic gastrinomas but also less advanced disease at baseline, indicating potential lead-time bias (Weber *et al*. 1995, Jensen 1998). When comparing patients in the same stage of disease, no survival difference was observed between MEN1-related and sporadic gastrinomas (Weber *et al*. 1995, Norton *et al*. 1999). Several other studies also point

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to a similar natural course for MEN1-related and sporadic gastrinomas (Stabile & Passaro 1985, Ruszniewski *et al.* 1993, Yu *et al.* 1999, Ellison *et al.* 2006). In contrast, in one series a survival benefit was found for MEN1 patients, but separate baseline characteristics were not provided (Melvin *et al.* 1993). Another series also found survival benefit in MEN1, with no significant baseline differences in liver metastases (MEN1 6% vs sporadic 24%, $P=0.24$), but this might be due to the small number of patients and selection or referral bias cannot be excluded (Singh *et al.* 2012). Overall, the available data seem to point to a similar natural course for MEN1-related and sporadic gastrinoma.

Prognostic factors

The most important adverse prognostic factor related to overall survival in MEN1-related dpNETs is the presence of liver or other distant metastases (Stabile & Passaro 1985, Cadiot *et al.* 1999, Kouvaraki *et al.* 2006, Triponez *et al.* 2006*a*, Ito *et al.* 2013). In a series including all subtypes of dpNETs, the estimated 10-year survival for patients with distant metastases was 34% (Kouvaraki *et al.* 2006). In patients with diffuse liver metastases from gastrinoma, 10- and 15-year survival of 88 and 52% are reported, while in patients with metastases from NF-pNET 8-year survival was 34% (Norton *et al.* 2001, Triponez *et al.* 2006*a*). Lymph node metastases are not related to survival (Gibril *et al.* 2001, Kouvaraki *et al.* 2006, Ito *et al.* 2013). Contradictory evidence exists with regard to the prognostic value of age. An older age (Burgess *et al.* 1998*a*, Cadiot *et al.* 1999, Kouvaraki *et al.* 2006, Vierimaa *et al.* 2007) as well as a younger age are reported as adverse prognostic factors (Gibril *et al.* 2001, Ito *et al.* 2013). Reports regarding the prognostic significance of pancreatic tumor size vary. No relation between tumor size and metastases, malignancy or overall survival is found in several series reporting on MEN1-related dpNETs (hormonally active and NF; Grama *et al.* 1992, Lowney *et al.* 1998, Lairmore *et al.* 2000, Bartsch *et al.* 2005, Kouvaraki *et al.* 2006, Lopez *et al.* 2011). In the subset of NF-pNETs, larger tumor size was related to a higher rate of metastases and a decreased overall survival (Triponez *et al.* 2006*a*,*b*). In gastrinoma series, pancreatic tumor size >3 cm was found to be associated with an adverse outcome (Cadiot *et al.* 1999, Gibril *et al.* 2001, Ito *et al.* 2013). However, it is unclear if these pNETs used as prognostic indicator were all gastrinomas and not (in part) coexisting NF-pNETs. Moreover, results from liver biopsy immunohistochemistry are often not reported, so the origin of the metastases cannot be verified. In the natural course of gastrinoma, an aggressive and nonaggressive variant based on tumor growth can be distinguished, with high prognostic relevance (Weber *et al.* 1995, Sutliff *et al.* 1997, Yu *et al.* 1999, Gibril *et al.* 2001). In MEN1-related gastrinomas, aggressive disease is reported in 15% and in sporadic gastrinomas in ~25% (Yu *et al.* 1999, Gibril *et al.* 2001, Ito *et al.* 2013). In MEN1 patients, 5-year survival was 100% for patients with nonaggressive disease and 88% for patients with aggressive disease (Gibril *et al.* 2001). Factors found to be associated with aggressive disease were pancreatic tumor size, liver and bone metastases, markedly increased fasting gastrin level, and the presence of a gastric NET (Gibril *et al.* 2001).

Mitotic count or Ki67 labeling index has proved to be a very important prognostic factor in sporadic dpNETs (Ekeblad *et al.* 2008, Scarpa *et al.* 2010, Rindi *et al.* 2012), but no information is available for MEN1-related dpNETs.

With regard to the possible prognostic value of genotype, results are contradictory. Nonsense and frameshift mutations in exon 2, 9, and 10 were found to be associated with a more malignant dpNET phenotype (Bartsch *et al.* 2000, 2005) and inactivating and frameshift mutations showed a trend toward more frequent occurrence in deceased patients (Ito *et al.* 2013). Others did not find any relation between genotype and the course of dpNETs (Lairmore *et al.* 2000, Kouvaraki *et al.* 2002).

Molecular background of MEN1

Menin

The *MEN1* gene product, menin, is highly conserved from nematodes and fruit flies to humans. Interestingly, the gene is absent in organisms like yeast and *Caenorhabditis elegans*. It is predominantly a nuclear protein, which is ubiquitously expressed in both endocrine and non-endocrine organs (Guru *et al.* 1998, Stewart *et al.* 1998, Ikeo *et al.* 2000). It has been challenging to elucidate its biological function, as menin lacks enzymatic activity and initially no homologous domains to other proteins were found. Abolition of menin during mouse embryogenesis is lethal at mid gestation and results in defects in neural tube, liver, and heart (Bertolino *et al.* 2003*a*). Its function is tissue-specific, sometimes showing opposite effects between different organs. Many interacting proteins involved in gene transcription and various signaling pathways have been identified (Matkar *et al.* 2013). Recently, the crystal structure of menin has been

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elucidated (Murai *et al*. 2011, Huang *et al*. 2012). Menin contains a deep pocket that can bind mixed-lineage leukemia 1 (MLL1 or KMT2A) protein or the transcription factor (TF) JUND, with opposite effects on gene transcription (Huang *et al*. 2012). Further evidence supports a role for menin in DNA repair, through association with replication protein A2 (RPA2; Sukhodolets *et al*. 2003) and Fanconi anemia complementation group D2 protein (FANCD2; Jin *et al*. 2003). Subsequent functional experiments characterized menin both as an activator and a repressor of gene transcription. Growing evidence indicates that menin is involved in epigenetic regulation of gene transcription as menin has been shown to be part of chromatin-modifying protein complexes (Box 2). However, it is important to note that most studies focusing on menin interaction partners and its function were conducted in nonendocrine cell lines (Table 2).

Menin as an epigenetic repressor of gene transcription

Menin associates with proteins in removing acetylation marks from histones (Gobl *et al*. 1999, Kim *et al*. 2003). These histone deacetylases (HDACs) form complexes with menin through the general co-repressor mSin3A (Kim *et al*. 2003; Fig. 2A). Deacetylation of histones at promoters of target genes is associated with downregulation of gene transcription. *GAST* (gastrin) was identified as a potential target of menin/mSin3A/HDAC complexes (Mensah-Osman *et al*. 2011).

Recently, menin was shown to interact directly with protein arginine methyltransferase 5 (PRMT5), resulting in repression of the Hedgehog signaling pathway through increasing PRMT5-mediated dimethylation of arginine 3 on histone 4 (H4R3me2) at the *GAS1* and *GLI1* promoter (Gurung *et al*. 2013*a*,*b*; Fig. 2B). The Hedgehog signaling pathway is involved in various biological processes including (neuroendocrine) tumorigenesis (McMillan & Matsui 2012). Menin can be recruited to the promotor of the homeobox gene *GBX2* through interaction with the histone lysine methyltransferase SUV39H1. This interaction induced H3K9 trimethylation at the gene promoter, providing the repressive chromatin environment for downregulation of *GBX2* transcription (Yang *et al*. 2013; Fig. 2C).

Menin as an epigenetic activator of gene transcription

Menin stably associates with MLL1 and MLL2 (KMT2B)-containing protein complexes (Hughes *et al*. 2004, Yokoyama *et al*. 2004). The functional domain in MLL protein family members is the so-called SET domain that harbors histone methyltransferase activity for trimethylation toward lysine 4 of histone 3 (H3K4me3; Ruthenburg *et al*. 2007). H3K4me3 is associated with activation of gene transcription (Santos-Rosa *et al*. 2002, Guenther *et al*. 2007). MLL translocations leading to MLL1-fusion proteins are frequently seen in mixed lineage leukemia (Krivtsov & Armstrong 2007). In contrast to other menin interactors, the menin–MLL1/2 interactions are rather stable and have been detected in several cellular systems (Hughes *et al*. 2004, Yokoyama *et al*. 2004). The menin–MLL1/2 complexes induce trimethylation on H3K4, and menin disease-derived mutants fail to recruit histone methyltransferase activity (Hughes *et al*. 2004). Genome-wide analysis showed menin occupancy on promoters of many active genes, which is often accompanied with MLL1 or MLL2 and H3K4me3 (Scacheri *et al*. 2006, Agarwal & Jothi 2012). Menin–MLL1/2 complexes are positive regulators of several target genes, including genes of the *HOX* cluster (Hughes *et al*. 2004, Yokoyama *et al*.

Box 2: Gene transcription regulation

In the nucleus of eukaryotic cells, DNA is wrapped around octamers of histone proteins to form nucleosomes. Chromatin is formed by repeating nucleosomes to form beads on a string structures that are converted to the higher order chromatin structures. Chromatin architecture is dynamic and changes in chromatin status influence gene transcription activity (Fig. 1).

Gene transcription in eukaryotic cells depends on the formation of the so-called pre-initiation complex, which consists of RNA polymerase II and general TFs in relation to the chromatin context. The formation and recruitment of the pre-initiation complex to DNA of gene promoters is modulated by cofactors. These processes are initiated when DNA sequence-specific TFs (e.g. JUND) bind to their corresponding response element on the DNA upstream of the promoter region. Several mechanisms are required for tight control of transcription regulation in a gene-specific and tissue-specific manner. Chromatin status is one important mechanism, as DNA accessibility is a prerequisite for gene transcription.

Post-translational covalent modifications of histone tails are involved in regulation of gene transcription, either directly by changing chromatin packing or through recruitment of other effector proteins to chromatin (chromatin 'readers'; Fig. 1). Histone modifications are 'written' or 'erased' by histone-modifying enzymes (Kouzarides 2007). Menin is involved in trimethylation of lysine 4 on histone 3 (H3K4me3). This methylation mark is associated with activation of gene transcription (Kouzarides 2007). Histone acetylation is correlated with activation of gene transcription and deacetylation of histone tails with transcription repression. Epigenetic alterations, including deregulation of histone modifications contribute to cancer development (Chi *et al*. 2010). Deregulation of chromatin-modifying complexes by loss of menin is involved in MEN1 tumorigenesis.

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Table 2 Cell systems used to study menin interaction partners

Reference	Protein complex	Cell type (origin)	Menin level
Hughes *et al*. (2004)	Menin–MLL2	293T (human embryonic kidney)	Endogenous
Yokoyama *et al*. (2004)	Menin–MLL1/2	K562 (myelogenous leukemia)	Endogenous
Milne *et al*. (2005)	Menin–MLL1/2	HeLa (human cervical cancer)	Endogenous
Yokoyama & Cleary (2008)	Menin–MLL1/2–PSIP1	REH cells (human leukemia)	Endogenous
Huang *et al*. (2012)	Menin–MLL1–PSIP1	Recombinant protein	*In vitro*
		293T (human embryonic kidney)	Overexpressed
van Nuland *et al*. (2013))	Menin–MLL1/2	HeLa (human cervical cancer)	Overexpressed
Agarwal *et al*. (1999)	Menin–JUND	293T (human embryonic kidney)	Endogenous, overexpressed
Gobl *et al*. (1999)	Menin–JUND	Recombinant protein	*In vitro*
Mensah-Osman *et al*. (2011)	Menin–JUND	AGS (human gastric adenocarcinoma)	Overexpressed
Huang *et al*. (2012)	Menin–JUND	Recombinant protein	Bacterial expressed
		293T (human embryonic kidney)	Overexpressed
Kim *et al*. (2003)	Menin–HDAC–mSin3A	293T (human embryonic kidney)	Overexpressed
Kaji *et al*. (2001)	Menin–SMAD3	Cos7 (monkey kidney)	Overexpressed
Heppner *et al*. (2001)	Menin–NFκB	293 (human embryonic kidney)	Endogenous, overexpressed
Sierra *et al*. (2006)	Menin–β-catenin	CRC (human colorectal cancer)	Endogenous
Dreijerink *et al*. (2006)	Menin–ERα	Recombinant protein	*In vitro*
Dreijerink *et al*. (2009)	Menin–PPARγ	Recombinant protein	*In vitro*
Gurung *et al*. (2013*b*)	Menin–PRMT5	293 (human embryonic kidney)	Endogenous, overexpressed
Yang *et al*. (2013)	Menin–SUV39H1	293T (human embryonic kidney)	Endogenous, overexpressed
Shi *et al*. (2013)	Menin–Hlbx9	MIN6 (mouse insulinoma)	Endogenous, overexpressed

This table summarizes studies referred to in this review.

2004) and cyclin-dependent kinase (*CDK*) inhibitor genes (Milne *et al*. 2005) (Fig. 3A). *HOX* genes are characterized by a conserved DNA sequence, the homeobox. They encode homeodomain-containing TFs, which are essential in cell differentiation and the body plan during embryogenesis. Several *HOX* genes are identified as direct menin–MLL1/2 targets, such as *HOXA9*, Hoxc6, and Hoxc8 (Hughes *et al*. 2004, Yokoyama *et al*. 2004, Huang

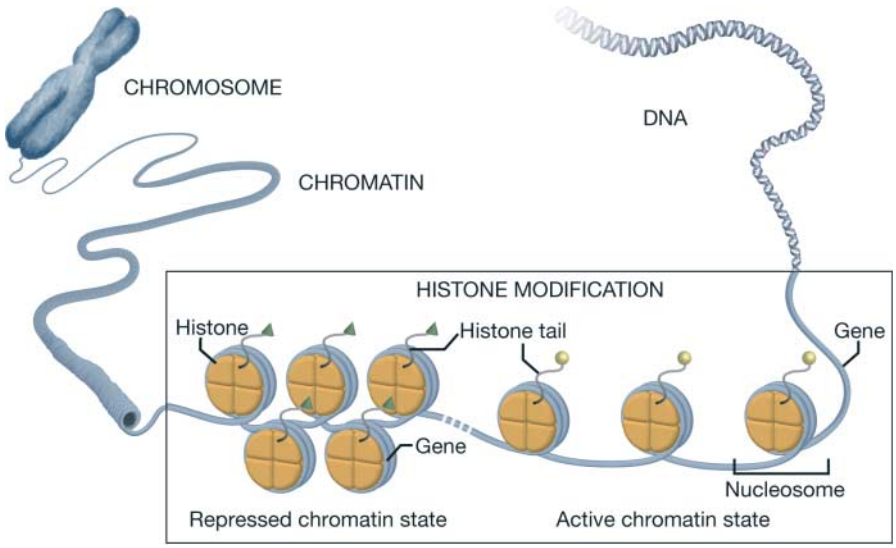

Figure 1
Chromatin structure and histone modifications. DNA is wrapped around octamers of histones into nucleosomes. Chromatin state is influenced by post-translational modifications of histone tails. These modifications are associated with chromatin accessibility for the effector proteins such as transcription factors and lead to an active or a repressed chromatin state. For simplicity, not all histone tails are represented in this figure. Adapted from the National Institutes of Health Common Fund Website, source: http://commonfund.nih.gov/epigenomics/figure.aspx, with permission.

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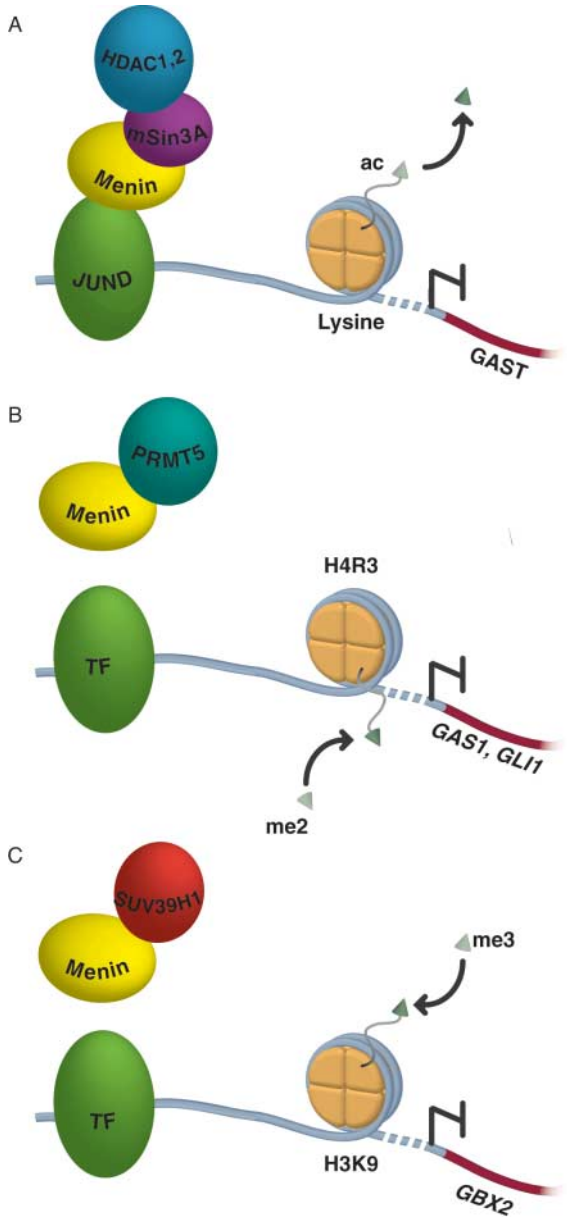

Figure 2
Menin in epigenetic repression of gene transcription. (A) Menin transiently interacts with mSin3A and represses *GAST* transcription via recruitment of HDAC1, 2 and acetylation (ac) of histone tails. The protein complexes bind to the transcription factor (TF) JUND. (B) Menin transiently interacts with PRMT5 and represses gene transcription of *GAS1* and *GLI1* through dimethylation (me2) of histone H4R3. In this case, it is not known to which TF the protein complexes bind. (C) Menin transiently interacts with SUV39H1 and represses gene transcription of *GBX2* through trimethylation of histone H3K9. In this case, it is not known to which TF the protein complexes bind.

et al. 2012). It was shown in pancreatic islet-like endocrine cells that *HOX* gene expression is regulated by menin through H3K4 methylation (Agarwal & Jothi 2012). Menin–MLL1 complexes stimulate the expression of *CDKN1B* and *CDKN2C* genes encoding $p27^{Kip1}$ and $p18^{Ink4c}$ proteins respectively. Loss of function of menin or MLL1 resulted in downregulation of $p27^{Kip1}$ and $p18^{Ink4c}$ and displayed effects on cell growth (Milne *et al*. 2005). $p27^{Kip1}$ and $p18^{Ink4c}$ belong to two distinct families of CDK inhibitors which regulate cell-cycle progression (Besson *et al*. 2008). Reduced expression of these proteins

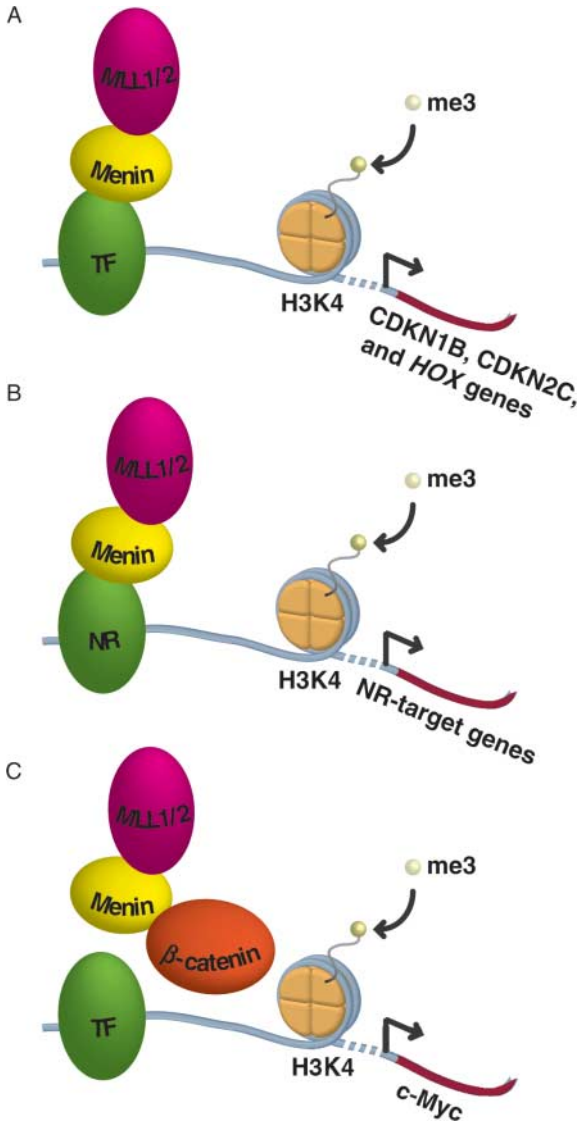

Figure 3
Menin in epigenetic activation of gene transcription. (A) Menin interacts with MLL1/2, which results in trimethylation (me3) of histone H3K4 (H3K4me3) and activation of transcription of *CDKN1B*, *CDKN2C*, and *HOX* genes. The interacting transcription factor (TF) is not known in this case. (B) Menin–MLL1/2 complexes bind to nuclear receptors (NRs), induce H3K4me3, and activate transcription of NR-target genes. (C) Interaction of menin–MLL1/2 protein complexes with β-catenin activates *c-Myc* transcription through H3K4me3. The interacting TF is not known in this case.

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contributes to tumor development in various tissues (Malumbres & Barbacid 2001).

Recruitment of menin–chromatin modifying protein complexes to target genes

Proteins can be recruited to gene promoters through specific interactions with DNA sequence-specific TFs. Menin stably interacts with the DNA sequence-specific TF JUND (Agarwal *et al*. 1999, Huang *et al*. 2012; Fig. 2A). Several MEN1-derived missense mutants failed to bind JUND efficiently *in vitro* and their repressive effect on transcription was lost (Agarwal *et al*. 1999). Interactions between menin and other TFs are less stable than menin–JUND interactions. Menin can be tethered to DNA through the nuclear receptor (NR) for estrogen ERα, the NR peroxisome-proliferator-activated receptor γ (PPARγ), and the vitamin D3 receptor (Dreijerink *et al*. 2006, 2009; Fig. 3B). NRs have the ability to bind DNA directly and translate changes in hormone levels into alterations in gene transcription. Transcriptional activation through menin–NR interactions is associated with H3K4me3 upregulation (Dreijerink *et al*. 2006, 2009). Furthermore, menin–MLL1/2 complexes are transcriptional co-activators of the Wnt-signaling pathway. Together with the TF CTNNB1 (β-catenin), the menin–MLL2 complex was shown to be recruited to the enhancer of the oncogene *c-Myc* (Sierra *et al*. 2006; Fig. 3C). Menin interacts and regulates NFKB1 (NF-κB) TFs (Heppner *et al*. 2001). Transforming growth factor β (TGFβ) signaling causes inhibition of proliferation in various cell types. Menin interacts with the TGFβ-regulated TF SMAD3. Inactivation of menin in pituitary cells disrupted SMAD3 binding to DNA, thereby blocking TGFβ signaling (Kaji *et al*. 2001). Recently, TF Hlxb9 was shown to be a menin interaction partner specifically in mouse β-cells and to be involved in the regulation of β-cell proliferation rate and expression of insulin-modulating genes (Shi *et al*. 2013).

Besides DNA sequence-specific TF-mediated recruitment of menin–MLL1/2 complexes to target genes, interactions with chromatin-binding protein PC4 and SFRS1 interacting protein 1 (PSIP1) (also known as LEDGF/p75) are important for tethering these complexes to target genes. The transcription co-activator PSIP1 co-localizes with menin–MLL1 complexes at specific menin target genes, including *HOXA9*, *CDKN1B,* and *CDKN2C* (Yokoyama & Cleary 2008, Huang *et al*. 2012). The association of several menin mutants with PSIP1 was disrupted, resulting in reduced transcription of *HOXA9* (Yokoyama & Cleary 2008).

Contribution of menin loss to NET development

Several studies have addressed the role of *MEN1* in endocrine pancreatic cell function and proliferation. Absence of *MEN1* does not seem to affect the initial pancreatic differentiation process from embryonic stem cells *in vitro* (Agarwal & Jothi 2012). β-cell specific disruption of *MEN1* leads to the formation of insulinomas (Bertolino *et al*. 2003*b*, Crabtree *et al*. 2003, Biondi *et al*. 2004). α-cell-specific knockout of *MEN1* was found to lead to transdifferentiation into insulin-producing cells and subsequent insulinoma development (Lu *et al*. 2010). Disturbance in epigenetic regulation of gene transcription is thought to contribute to MEN1-associated tumorigenesis. The most convincing evidence supporting this mechanism was reported recently (Lin *et al*. 2011). Mice with β-cell-specific knockout of *MEN1* showed reduced tumor formation and increased survival in combination with gene knockout of the retinoblastoma-binding protein 2 (RBP2 also known as JARID1A, KDM5A), which is a histone demethylase for H3K4me2/3. This indicates that compensation of the loss of H3K4 trimethylation mark on certain target genes may restore the function of menin in pancreatic tumors. Identification of relevant menin target genes could provide further insights into the development of MEN1-related tumors. Currently, it is not clear how the tumor-suppressing roles of menin in cultured cells are related to suppression of MEN1-associated tumor development. *HOX* genes are important for the development of endocrine organs (Manley & Capecchi 1998). Comparison of *HOX* gene expression profiles in MEN1-associated parathyroid tumors and nonfamilial parathyroid tumors revealed differently expressed genes between these groups. This indicates a role for *HOX* genes in MEN1-associated parathyroid tumor development (Shen *et al*. 2008). This has not been shown for other NETs. Several animal studies support that menin target genes *CDKN1B* and *CDKN2C* are involved in endocrine tumorigenesis. $p27^{kip1}$ or $p18^{ink4c}$-deficient mice develop pituitary tumors and hyperplasia in multiple organs, including the thymus, without elevation in GH levels (Fero *et al*. 1996, Kiyokawa *et al*. 1996, Nakayama *et al*. 1996, Franklin *et al*. 1998). Strikingly, mice lacking both $p27^{kip1}$ and $p18^{ink4c}$ developed hyperplasia and/or tumors predominantly in endocrine organs including the pancreas and duodenum. The tumor spectrum seen in these mice showed a remarkable overlap with the tumor spectrum seen in MEN1 patients (Franklin *et al*. 2000). Inactivating germline mutations in *CDKN1B* have been identified in patients with a MEN-like phenotype.

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Although, hyperparathyroidism and pituitary tumors are the most commonly described manifestations (Pellegata *et al*. 2006, Georgitsi *et al*. 2007), pNETs have also been described in association with *CDKN1B* mutations (Agarwal *et al*. 2009, Occhi *et al*. 2013). Based on these studies, a role for $p27^{kip1}$ and $p18^{ink4c}$ in MEN1-related tumor development seems reasonable. Menin–MLL1/2 complexes inhibit proliferation of pancreatic islet cells in mice by promoting H3K4me3 and transcription of $p27^{kip1}$ and $p18^{ink4c}$ (Karnik *et al*. 2005). Interestingly, $p18^{ink4c}$ and menin collaborate in repressing development and growth rate of mouse pNETs. This synergetic effect was not observed with $p27^{kip1}$ (Bai *et al*. 2007). Studies focusing on $p27^{kip1}$ protein and mRNA expression in pNETs from MEN1 patients show conflicting results (Milne *et al*. 2005, Lindberg *et al*. 2008, Occhi *et al*. 2013).

Tissue selectivity in MEN1-related tumorigenesis

Regarding the ubiquitous expression of menin, it is difficult to explain the tissue selectivity of tumorigenesis in MEN1 patients. Unfortunately, most studies focusing on menin interaction partners and its target genes are performed in nonendocrine cell lines (Table 2 and Supplementary Table 1, see section on supplementary data given at the end of this article). Menin acts as a tumor suppressor in endocrine organs, but it is an essential oncogenic cofactor in leukemogenesis (Yokoyama *et al*. 2005, Yokoyama & Cleary 2008). Understanding the predominance for endocrine tumor development resulting from *MEN1* loss might help to develop targeted therapies for MEN1 patients. Several factors have been suggested as potential important players in the tissue selectivity of this endocrine tumor syndrome (Gracanin *et al*. 2009). Tissues may differ in their ability and requirement to compensate for the loss of one *MEN1* allele (Gracanin *et al*. 2009). Physiological regulation of menin levels in response to increased insulin was shown to be important in adaptive β-cell proliferation during pregnancy in mice (Karnik *et al*. 2007). Intriguingly, mice with liver-specific loss of menin did not develop tumors (Scacheri *et al*. 2004). The expression levels of menin in lymphoblastic cell lines derived from MEN1 patients did not differ from healthy controls (Wautot *et al*. 2000) and downregulation of menin could activate the *MEN1* promoter in a compensatory manner in nonendocrine cell lines (Zablewska *et al*. 2003). However, it has been suggested that menin haploinsufficiency through loss of one *Men1* allele contributes to pNET development in mice (Crabtree *et al*. 2003, Lejonklou *et al*. 2012). In regard to tissue-specific regulation of menin expression, microRNAs are interesting candidates for further evaluation (Gracanin *et al*. 2009, Luzi & Brandi 2011). Menin interaction partners might be involved in the tissue-specific tumor formation in MEN1. For example, the TF HLXB9 was shown to be a β-cell-specific menin interaction partner (Shi *et al*. 2013). NRs are also potential candidates as they have tissue-specific functions.

Implications for further research

Although in the past decade significant progress has been made in understanding menin function, many questions remain. Its tumor-suppressive role in endocrine organs is not well understood and elucidation of underlying biology should be an important focus for future studies. Regarding the observed tissue selectivity in MEN1-related tumorigenesis, it is important to study menin–protein interactions and target genes in endocrine cell lines specifically. To date, most studies addressing menin interactions and target genes were performed in non-endocrine cell lines. Not only basic research projects but also translational studies in unbiased MEN1 patient cohorts are needed. These studies should clarify which molecular pathways involving menin actually contribute to MEN1 NET tumorigenesis and are clinically relevant. With regard to novel therapeutic strategies, the involvement of altered epigenetic regulation of gene expression resulting in MEN1 tumorigenesis is an interesting candidate for further evaluation. The development of compounds that interfere with epigenetic regulation of gene transcription has gained a lot of attention recently and such drugs have shown to have therapeutic potential in cancer treatment (Dawson & Kouzarides 2012). These findings highlight the importance of better insights into MEN1 tumorigenesis for the improvement of MEN1 patient care.

From a clinical point of view, identifying natural course and prognostic factors has been hampered by the rarity of the disease and generally low number of events regarding distant metastases and disease-related mortality. Therefore, it is important to follow large unselected cohorts over a long period of time, by national or even international collaboration.

When comparing natural history of MEN1-related NETs with their sporadic counterparts, insulinomas in MEN1 seem to be more aggressive, while natural history in MEN1-related gastrinomas seems to be similar to sporadic gastrinomas. Data on NF-pNETs and thoracic NETs are insufficient to permit comparisons. However, currently

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available evidence does not support MEN1-related NETs to be more indolent than sporadic NETs.

Among MEN1-related NETs, thNETs occur with low frequency and show a remarkable gender difference. Compared with other NETs, their prognosis is poor. These different epidemiologic and natural history characteristics cannot be explained with the currently available evidence and warrants further research.

Pulmonary carcinoids and NF-pNETs in MEN1 share the fact that they are more common than previously thought. Identification of these NETs will further increase in the coming decade due to increased sensitivity of imaging techniques and standardized screening. As little is known about the natural history of small NETs in MEN1, clinical significance of these findings remains to be determined. To assist clinical decision-making in this respect, studies with a long-term follow-up in unselected patient cohorts are needed.

All dpNETs are potentially malignant and dpNETs are the most important determinant of long-term survival in MEN1 patients. Although the estimated 10-year survival rate is 75%, it is important to remember that MEN1-patients are usually in their thirties when these tumors develop. Moreover, unless a total duodenopancreatectomy is performed, MEN1 patients are always at risk for developing new dpNETs and subsequent malignant transformation. This means that a satisfactory 10-year survival rate does not automatically equal normal life expectancy. Although, the percentage of MEN1 patients with dpNETs that develop distant metastases is small, prognosis is poor in this group. At present, apart from tumor size, there are no known clinical or tumor characteristics that reliably predict the development of distant metastases. This means that the impact of therapeutic interventions has to be weighed against the overall change of distant metastases and disease-related mortality. Identification of additional clinical and molecular prognostic factors in MEN1-related dpNETs should therefore be an important research focus. Factors known to be of prognostic value in sporadic dpNETs should be validated in MEN1 and new prognostic indicators sought for. These efforts should lead to early identification of tumors with an aggressive phenotype and subsequent individualized patient care based on risk stratification.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/ERC-13-0482.

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