REVIEW

Variable clinical expression in patients with a germline *MEN1* disease gene mutation: clues to a genotype–phenotype correlation

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Multiple endocrine neoplasia type 1 is an inherited endocrine tumor syndrome, predominantly characterized by tumors of the parathyroid glands, gastroenteropancreatic tumors, pituitary adenomas, adrenal adenomas, and neuroendocrine tumors of the thymus, lungs or stomach. Multiple endocrine neoplasia type 1 is caused by germline mutations of the multiple endocrine neoplasia type 1 tumor suppressor gene. The initial germline mutation, loss of the wild-type allele, and modifying genetic and possibly epigenetic and environmental events eventually result in multiple endocrine neoplasia type 1 tumors. Our understanding of the function of the multiple endocrine neoplasia type 1 gene product, menin, has increased significantly over the years. However, to date, no clear genotype–phenotype correlation has been established. In this review we discuss reports on exceptional clinical presentations of multiple endocrine neoplasia type 1, which may provide more insight into the pathogenesis of this disorder and offer clues for a possible genotype–phenotype correlation.

KEYWORDS: Multiple Endocrine Neoplasia type 1; MEN1; Menin; Genotype–Phenotype Correlation; Clinical Expression.

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INTRODUCTION

''It is an old experience that through her errors, Nature often grants us unexpected insights into her secrets which are otherwise a closed domain'', William Harvey, 1657.

Multiple endocrine neoplasia type 1 (MEN1) is an inherited endocrine tumor syndrome, characterized predominantly by tumors of the parathyroid glands, gastroenteropancreatic tumors, pituitary adenomas, adrenal adenomas, and neuroendocrine tumors of the thymus, lungs or stomach. MEN1 is caused by germline mutations of the *MEN1* tumor suppressor gene. It appears that in the MEN1 syndrome, clinical expression differs between families. This may be the result of the specific *MEN1* gene mutation in a family (genotype–phenotype correlation). As a rule, the development of a tumor depends on a series of genetic events (multistep tumorigenesis). Thus, additional co-segregating modifying factors such as germline mutations in other genes are likely to play a role in the interfamilial variability of MEN 1. Moreover, clinical expression can also vary between individual members of the same family, possibly because of additional genetic or epigenetic factors. To date, a clear correlation between genetic events and the variable clinical expression of MEN1 has not been established (1–5). Further understanding of the genetic aspects of MEN1 and the pathogenesis of MEN1-related tumors could enable more tailored clinical screening and treatment strategies.

In this review, we discuss recent reports on aberrant clinical expression of MEN1, which may allow us a glimpse into the pathogenesis of this intriguing disorder.

In 1903, Erdheim described the case of an acromegalic patient with a pituitary adenoma and three enlarged parathyroid glands. Fifty years later, Underdahl et al. reported eight patients with a syndrome of pituitary-, parathyroid-, and pancreatic islet adenomas. In 1954, Wermer found that the syndrome was transmitted as a dominant trait (6). In 1968, Steiner et al. introduced the term ''multiple endocrine neoplasia'' (MEN) to describe disorders featuring combinations of endocrine tumors; they designated the Wermer syndrome as MEN1 and the Sipple syndrome as MEN2. Gorlin subdivided type 2 into A and B. Then, in 1975, Khairi (7) suggested that type 2B be called type 3; however, this was not generally accepted. More recently, in 2006, families with multiple endocrine tumors but without *MEN1* or *RET* (MEN2) gene mutations were identified (8). This related syndrome is referred to as MEN4.

No potential conflict of interest was reported.

DISCOVERY OF THE *MEN1* GENE

In positional cloning, gene mapping precedes, and eventually leads to, gene identification. The first step is mapping the gene to a specific chromosomal region by linkage analysis. The second step is identifying the correct gene among all possible candidate genes within that particular chromosomal region. After the gene has been identified, it is possible to study its (patho)physiologic function.

In 1996, two groups independently identified the *MEN1* gene on chromosome 11q13 (9,10). To date, more than 1336 different *MEN1* gene mutations (both germline and sporadic) have been reported in the literature (4). Most of these mutations are clearly inactivating, in accordance with the notion that the *MEN1* gene is a tumor suppressor gene. There are no mutational hot spots in the *MEN1* gene.

FUNCTION OF THE *MEN1*-GENE PRODUCT

The *MEN1* gene product, menin, functions as an adaptor protein that is involved in interactions with multiple protein partners. *Men1* null mutant mice have indicated that menin is essential for viability (11). Menin is involved in neuroendocrine cell development and function. Later on, it is active in many cellular processes, including gene transcription regulation, DNA replication, DNA repair, and signal transduction.

Menin target genes that are important for development and proliferation, including homeobox domain (HOX) genes, the *CDKN2C* and *CDKN1B* cyclin-dependent kinase inhibiting genes, the human telomerase (*hTERT*) gene, and nuclear receptor target genes (12–15).

As a transcriptional co-regulator, menin may function as a co-activator or co-repressor by recruiting histone-modifying enzymatic activity (12,15,16). As a co-activator, menin is involved in the regulation of histone methylation by recruiting the mixed-lineage leukaemia (MLL) proteins MLL1 and MLL2 (12,17). In this way, menin can bind to nuclear receptors and activate nuclear receptor-mediated gene transcription (12,15). By tethering histone deacetylase activity to genes, menin can serve as a repressor of transcription (18).

In order to understand the role of menin as a tumor suppressor protein and as a co-factor of MLL fusion proteins, the structural basis had to be revealed. Recently, the crystal structure of menin in *Nematostella vectensis* was reported (19). Knowledge about the three-dimensional structure may elucidate the interactions essential to the function of menin. It appears that the Leucine, Leucine, Tryptophan, Leucine, Leucine (LLWLL) amino acids nuclear receptor interaction motif of menin is well-conserved and is located in an alpha-helix. In general, modeling gene mutations into this structure will be helpful in determining the effects on protein function. Inactivation of the *MEN1* gene results in predisposition to tumor formation (see Figure 1, Table 1).

ABERRANT CLINICAL EXPRESSION OF MEN1

A *MEN1* gene mutation may be completely detrimental to gene function. It may also result in a protein product with

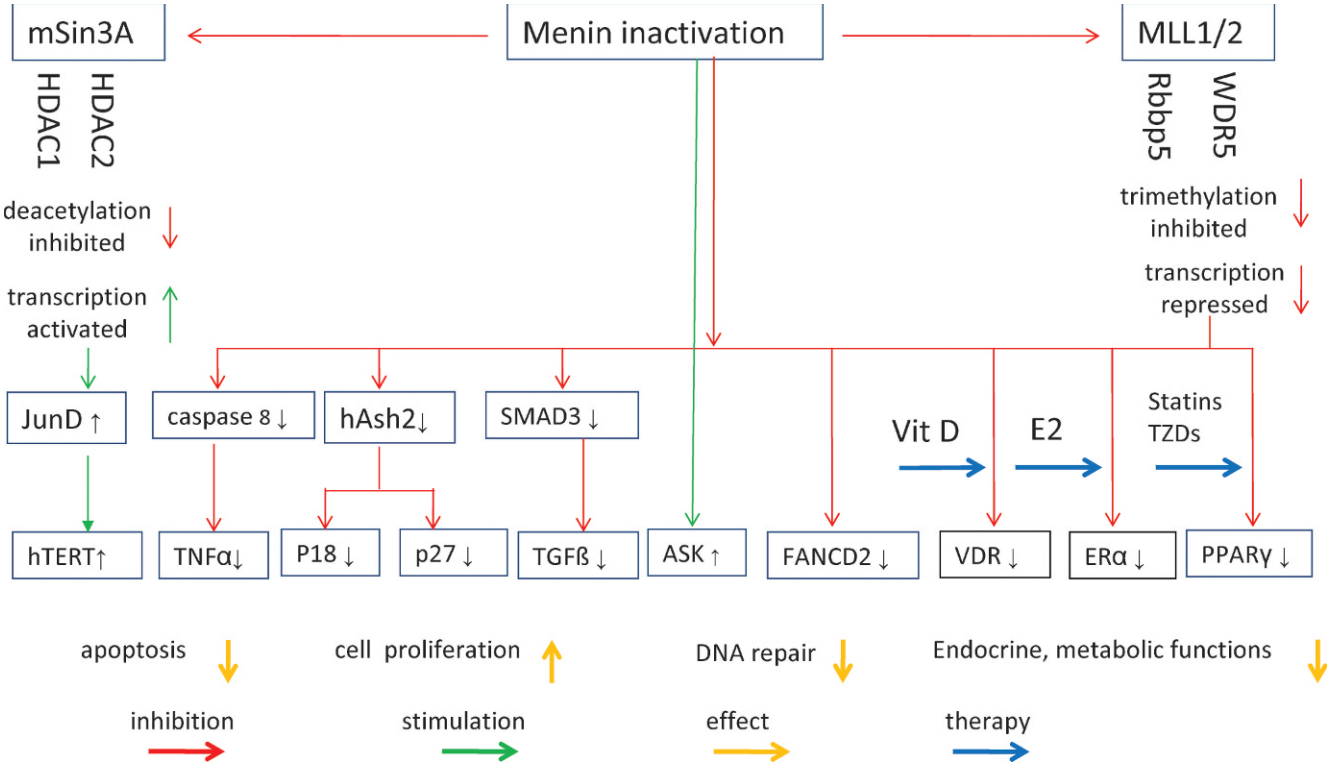

Figure 1 - In MEN1 tumors, inactivating mutations in the *MEN1* gene result in alterations of histone protein modifications: both deacetylation (left) and trimethylation (right) are repressed. In this way, the normal function of menin acting as co-repressor and co-activator of gene transcription is disabled. Consequently, the normal function of menin (preservation of differentiation of the cell by modification of histone proteins and transcription of genes responsible for inhibition of cell division) is defective. Red arrows indicate inhibition of apoptosis, cell differentiation, DNA repair, and endocrine metabolic functions, whereas stimulators of cell division are indicated in green. Opportunities for tumor treatment are indicated in blue. E2 = estradiol; TZDs = thiazolidinediones; VDR = Vitamin D receptor.

Table 1 - Menin-interacting proteins.

Protein	Function	Reference
A Chromatin modification proteins		
HDAC1*	Chromatin modification	Kim et al. (18)
MLL	Chromatin modification	Yokoyama et al. (17)
MLL2	Chromatin modification	Hughes et al. (12)
mSin3A*	Chromatin modification	Kim et al. (18)
LEDGF	Chromatin-associated	Yokoyama et al. (20)
B Transcription factors		
JunD	Gene transcription	Agarwal et al. (21)
NF-κB	Gene transcription	Heppner et al. (22)
Pem	Gene transcription	Lemmens et al. (23)
Smad	Gene transcription	Kaji et al. (24)
TGF-β	Gene transcription	Shattuck et al. (25)
WNT/β-catenin*	Gene transcription	Chen et al. (26)
ERα	Gene transcription	Dreijerink et al. (27)
VDR	Gene transcription	Dreijerink et al. (27)
PPARγ	Gene transcription	Dreijerink et al. (27)
FOXO1*	Gene transcription	Wuescher et al. (28)
C DNA repair proteins		
RPA2	DNA replication	Sukhodolets et al.(29)
ASK	Cell cycle regulation	Schnepp et al. (30)
CHES1(FOXN3)	DNA repair/ Transcription	Busygina et al. (31)
FANCD2	DNA repair	Jin et al. (32)
D Cytoplasmic proteins		
Vimentin	Cytoplasmic	Lopez-Egido et al. (33)
AKT1	Signal transduction	Wang et al. (34)
GFAP	Cytoplasmic	Lopez-Egido et al. (33)
NM23	GTP-ase	Ohkura et al. (35)
IQGAP1	Cell adhesion	Yan et al. (36)
NMHC	Myosin	Obungu et al. (37)

*Proteins in a complex with menin, possibly not through a direct interaction.

some residual function. An aberrant menin protein may be impaired in its function by several mechanisms: menin can interact with many different proteins. Possibly, germline mutations in the *MEN1* gene selectively affect menin binding to its partners, leading to distinct phenotypes.

The type of missense mutation (e.g. replacement of arginine with glycine) may have a differential effect on the function of menin (38): in-frame or missense mutations differ from frameshift/nonsense mutations (39), whereas missense and in-frame mutations may affect the interactions of a menin domain with transcription factors such as JunD, Smad3 and NFkappaB and nuclear receptors (1), or impair sensitization to apoptosis from caspase-3, p53 or p21 (40). A *MEN1* gene missense mutation may result in protein instability, and enhanced and early proteolytic degradation via the ubiquitin–proteasome pathway (41).

It was generally assumed that, in contrast to MEN2, in MEN1 there is no clear genotype–phenotype correlation (1,3–5). However, several reports challenge this assumption.

Familial aberrant expression

1. MEN1 Burin. Four large kindreds from the Burin peninsula/Fortune Bay area of Newfoundland with prominent features of prolactinomas, in addition to carcinoids, and parathyroid tumors (referred to as MEN1Burin) have been described, and they show linkage to 11q13, the same locus as that of MEN1. Haplotype analysis with 16 polymorphic markers now reveals that representative affected individuals from all four families share a common haplotype over a 2.5 Mb region. A nonsense mutation in the *MEN1* gene has been found to be responsible for the disease in the affected members in all four of the MEN1-Burin families. This suggests that either a common ancestral mutation in the *MEN1*-Burin gene or a modifying gene on 11q13 is responsible for this prolactinoma variant of MEN1 (42–45).

2. Familiar isolated hyperparathyroidism and *MEN1* gene missense mutations. Familial isolated primary hyperparathyroidism (FIHP) is an autosomal dominant disorder that can represent an early stage of either MEN1 caused by an allelic variant of the *MEN1* gene, or of hyperparathyroidism–jaw tumor (HPT-JT) syndromes; alternatively, the condition can be caused by an allelic variant of the hyperparathyroidism 2 (*HRPT2*) gene, or caused by a mutation at another locus. Interestingly, the major proportion of *MEN1* gene germline mutations that have been found in FIHP are seemingly mild missense mutations or in-frame deletions (46–55). In MEN1, roughly 80% of patients harbor nonsense mutations.

3. Predominant mutations in MEN1 pancreatic neuroendocrine tumors. Schaaf performed mutation analysis of the *MEN1* gene in tumors from 306 patients with MEN1, and found that patients with gastroenteropancreatic tumors more often had truncating mutations, very probably leading to completely inactivated menin (56).

4. Mild/late onset versus malignant phenotypes. To date, several disease-related *MEN1* gene intron mutations have been reported. These intron mutations may affect mRNA splicing and cause mild phenotypes, with late, and relatively low, penetrance of the disease (57–59). However, clinical expression at a young age may occur. This may be explained by interpatient variations in gene transcription and translation of the *MEN1* gene.

Two recent case reports described families with a high penetrance of malignant neuroendocrine tumors of the pancreas (60,61). Both these families carried germline mutations that completely abolish menin function.

The earliest manifestation of MEN1 was a pituitary adenoma in a 5-year-old boy who had a missense mutation leading to a H139D substitution in the *MEN1* protein (62). Functional analysis of the mutant protein revealed severely reduced protein stability (41), reduced binding to JunD (16), reduced binding to the estrogen receptor alpha and absent histone-methylation recruiting capacity. Thus, functional analysis of this potentially mild missense *MEN1* gene mutation shows that the protein product is, in fact, completely inactivated.

5. Metabolic effects of aberrant expression of the *MEN1* gene. In *MEN1* disease-gene carriers, all vitamin D receptors (VDRs) and peroxisome proliferator-activated receptors (PPARs)-γ are expressed but are probably less activated because of impaired menin function.

A. PPARγ2 is a transcription factor that plays a key role in adipocyte differentiation. Polymorphisms in this gene may contribute to the variability in body mass index and insulin sensitivity in the general population. PPARγ is the receptor for the thiazolidinediones, which act as PPARγ agonists and lower the blood glucose levels in patients with type 2 diabetes mellitus by increasing insulin sensitivity. Individuals with dominant-negative PPARγ gene mutations manifest a syndrome that combines lipodystrophy with features of the metabolic syndrome, including insulin resistance, type 2 diabetes, hepatic steatosis, dyslipidemia, hypertension and (in women) polycystic ovary syndrome. In patients with MEN1, decreased activation of PPAR may result in insulin resistance and weight gain (63).

B. Vitamin D receptors (VDRs) are found in a large number of tissues beyond the classic target tissues gut, bone and kidney. These tissues include endocrine glands such as pituitary, parathyroid glands, pancreatic islets, etc.

Lourenço et al. discussed the increased bone loss pattern found in patients with MEN1 compared with that of patients with sporadic primary HPT (64). Besides increased bone loss, resistance to vitamin D may be associated with insulin resistance and beta cell dysfunction, leading to increased risk for type 2 diabetes in patients with MEN1 (65,66).

Effect of gender

The prevalence and probability of pancreatic tumors among patients with MEN1 were higher in males than in females. This difference was due to the differential occurrence of gastrinomas. The prevalence and probability of developing pituitary adenomas were significantly greater in females. Thymic tumors are found nearly exclusively in male MEN1 patients (67).

The difference in clinical expression between the genders may be explained by the difference in transcription regulation of estrogen and androgen receptors. Menin can act as a co-activator of nuclear hormone receptors including estrogen (ERα) and possibly androgen (AR) receptors. A defect in the *MEN1* gene, together with gender-specific differences in concentrations of the hormones involved and tissue-specific distribution of their receptors, may contribute to the observed gender-specific differences in prevalence of prolactinoma and gastrinoma.

Additional genetic effects

1. Loss of heterozygosity; the AIP gene. In accordance with the tumor suppressor function of menin, MEN1-associated tumors exhibit loss of the wild-type allele. This second hit occurs as a somatic mutation and often involves deletion of a larger chromosomal region containing multiple genes [loss of heterozygosity (LOH)].

The gene encoding the aryl hydrocarbon receptor interacting protein (AIP) is located on 11q13, in the vicinity of the *MEN1* gene. Recently, it was found that inactivating mutations in the *AIP* gene are the underlying cause of low-penetrance pituitary adenoma predisposition. The finding of a truncated gene and LOH indicates that *AIP* acts as a tumor suppressor gene (68,69). In northern Finland, *AIP*-germline mutations accounted for 16% of cases of acromegaly in young patients. The tumor suppressor genes *AIP* and *MEN1* are located 3 Mb apart. Concomitant deletions of these genes may underlie predisposition to MEN1 and pituitary adenoma. To what extent deletion of the *AIP* gene is present in MEN1 tumors has yet to be established. Inactivation of this gene in animal models may reveal a potential causative role in MEN1-associated tumors.

2. Genetic predisposition for other diseases. Genetic predisposition for other diseases may contribute to enhancement of tumor formation in patients with MEN1 (70). For instance, normally the vitamin D receptor on parathyroid cells inhibits production and release of parathyroid hormone (PTH). In families with inactivating mutations in the gene encoding VDR, this is associated with end-organ resistance to calcitriol.

In the parathyroid glands of patients with MEN1, there exists a decreased activation of the VDR. An additional defect in the VDR or calcium receptor may contribute to hyperactivity, hyperplasia, and adenoma (71).

3. Additional, somatic mutations involved in acceleration of tumor growth.

3a). Data from other familial neuroendocrine tumor syndromes. How can we identify acquired mutations that are responsible for acceleration of tumor growth in MEN1? Clues for modifier genes may be found in other familial neuroendocrine tumor syndromes such as MEN2 and MEN4 (the latter is also referred to as MENX). Which are their traditional pathogenetic pathways and are these involved in aberrant clinical MEN1 expression? Overlap between MEN1 and MEN2 and additional genetic events have to be explored (e.g. p18/p27 knock-out mice develop both MEN1- and MEN2-associated tumors) (72,73).

Phenotypic overlap between MEN1- and MEN2-like syndromes was identified in the rat and named MENX. The syndrome is caused by a germline inactivating mutation in the *CDKN1B* gene encoding $p27^{Kip1}$ (8). $p27^{Kip1}$ has a key role in cell cycle regulation and is involved in differentiation, apoptosis, and angiogenesis.

Subsequently, germline mutations in the *CDKN1B* gene were identified in the germline of a MEN1-like family. In these patients, germline mutations of the *MEN1* gene could not be detected (8). However, only the menin-coding region and splice junctions were analyzed. The patients were also negative for *RET* gene mutations (MEN2). Mutations in *CDKN1B* and related genes, but without *MEN1* gene mutations, are a rare cause of MEN1-like phenotype (74–76). As a consequence of mutations in the p27 gene, a novel human MEN syndrome was recognized and named MEN4.

In mice, the *Cdkn2c* gene encoding $p18^{Ink4c}$ was shown to collaborate with menin in suppression of neuroendocrine tumor development (77). Whether occurrence of somatic mutations in $p18^{Ink4c}$ and/or $p27^{Kip1}$ accelerates tumor growth in human MEN1 tumors has yet to be established. In

transgenic MEN2 mice and human patients with MEN2, inactivating mutations in p18 will promote tumor growth (72,73,78,79). Reduced expression of *CDKN1B*, but not *CDKN2C*, has been observed in parathyroid adenomas from patients with MEN1.

3b). Clues from sporadic parathyroid adenomas, pituitary tumors, and pancreatic NETs

i) Sporadic Parathyroid adenoma. A high rate of somatic *MEN1* gene mutations is seen in sporadic parathyroid adenomas. There exists an interaction between menin and the transforming growth factor (TGF)-beta/Smad signaling pathway. *In vitro* experimentation has demonstrated that the presence of menin is required for TGF-beta to effectively inhibit parathyroid cell proliferation and PTH production (80).

ii) Pituitary tumors. The pituitary tumor transforming gene (PTTG; securin) was the first transforming gene found to be highly expressed in pituitary tumor cells, and seems to play an important role in the process of oncogenesis. Cell signaling abnormalities have been identified in pituitary tumors, but their genetic basis is unknown. Both Raf/mitogen activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase(PI3K)/Akt/mammalian target of rapamycin (mTOR) pathways are over-expressed and/or over-activated in pituitary tumors (81). These pathways share a common root, including initial activation by a tyrosine kinase receptor.

Pit-1 is a direct transcriptional target of VDR. Recruitment of histone deacetylase 1 is involved in the repressive effect of VDR on Pit-1 expression (82).

There is a critical role for the growth factor activin in regulating inhibition of pituitary cell growth and Pit-1/PRL expression through the Smads and menin (83). Alterations in the activin/TGF-beta downstream signaling pathways may be critical steps towards tumor formation and progression (84). To date, the occurrence of additional TGF-beta, Pit-1, PTTG, or VDR mutations in MEN1-associated tumors has not been published.

iii) Pancreatic neuroendocrine tumors. In nonfamilial pancreatic neuroendocrine tumors (PanNETs) the most commonly mutated genes specify proteins implicated in chromatin remodeling: 44% of the tumors had somatic inactivating mutations in *MEN1.* Clinically, mutations in the *MEN1* gene were associated with better prognosis. Also, mutations in genes in the mTOR pathway were found in 14% of the tumors, a finding that could potentially be used to stratify patients for treatment with mTOR inhibitors (85).

Loss of menin expression is associated with over-expression of the Raf/MEK/ERK and P13K/AKT/mTOR pathways in pancreatic tumors (34). Intact menin has an essential role in WNT/β-catenin signaling, and inhibits mouse pancreatic islet tumor proliferation (26). Menin regulates subcellular localization of β-catenin via nuclear-cytoplasmic shuttling. Loss of menin leads to Wnt/β-catenin signaling activation. Expression of p27 was found to be repressed in pancreatic islet cell tumors (86).

3c) Pathways in multistep carcinogenesis. It appears that interaction of components of the PI3K/AKT pathway is involved in neuroendocrine tumor formation (87,88). Deregulation of the PI3K/AKT pathway in neuroendocrine tumors can occur through a range of processes (see Figure 2), including gain of function by oncogenic mutations of PI3K signalling, loss of function of the tumor suppressor PTEN through gene deletion, mutation, micro-RNA expression or epigenetic silencing, upstream activation through receptor tyrosine kinase (RTK) signaling, and/or downstream loss of the tumor suppressors p18 and p27.

A combination of a mutation in the *MEN1* disease gene with other specific mutations of genes in the PI3K/AKT pathway may be associated with acceleration of tumor growth.

In addition, inactivated or absent menin promotes RAS expression; activating mutations of RAF, MEK, or ERK may accelerate cell proliferation (89).

Ecogenetic factors

Common environmental factors may interact with genetic predisposition to MEN1 and contribute to enhancement of tumor formation (70). In the parathyroid glands of patients with MEN1, a diet low in vitamin D or calcium may result in tumor growth. In the lactotropic cells of the pituitary gland, estrogenic or neuroleptic drugs may stimulate cell division. In the gastrin-producing cells of the stomach, presence of achlorhydria or use of histamine-H2 receptor or proton pump blockers may promote tumor growth (90). Lifestyle factors such as smoking and exposure to radiation may have deleterious effects on menin function and tumor growth, as with many types of cancer.

CONCLUDING REMARKS

Careful observation of patients and collaboration between disciplines, including molecular endocrinology, has opened new directions in the management of MEN1 syndrome, and has promoted development of novel target-directed therapy. Since 1980, life expectancy and quality of life have improved considerably.

By contrast, thymic tumors and duodenopancreatic tumors, including nonsecreting pancreatic tumors increase the risk of death (91). Rare, but aggressive, adrenal tumors may also cause early death. In *MEN1* disease gene carriers in MEN1 families, most deaths were related to the disease, and probably resulted from additional mutations.

It is possible that consecutive and specific pathogenetic pathways are involved in MEN1 tumor formation. We presume that, through the inherited germline mutation resulting in organ-specific cell division, the patient is rendered vulnerable to additional, somatic mutations in these organs. These mutations may occur spontaneously or may be triggered by life style and/or environment. Predisposition and expression of other genetic diseases may also be involved. A complex genotype–phenotype relationship may be present. Unfortunately, for the majority of the patients it is not currently possible to predict the course of the disease.

Germline mutations that result in complete inactivation of the gene product apparently cause more severe disease.

Consequently, extensive periodical clinical examination has to be performed in all carriers of the *MEN1* disease gene. In the near future, tumor gene-expression profiles and high throughput sequencing may permit more insight into additional genetic and epigenetic events that cause progression of tumor development. Functional analysis of *MEN1* gene mutations is sometimes required to study the true effect of the mutation. In addition, as already suggested by Sir William Harvey, it is very helpful to investigate rare presentations of diseases (92). Eventually, this insight may allow target-directed and mutation-specific therapy.

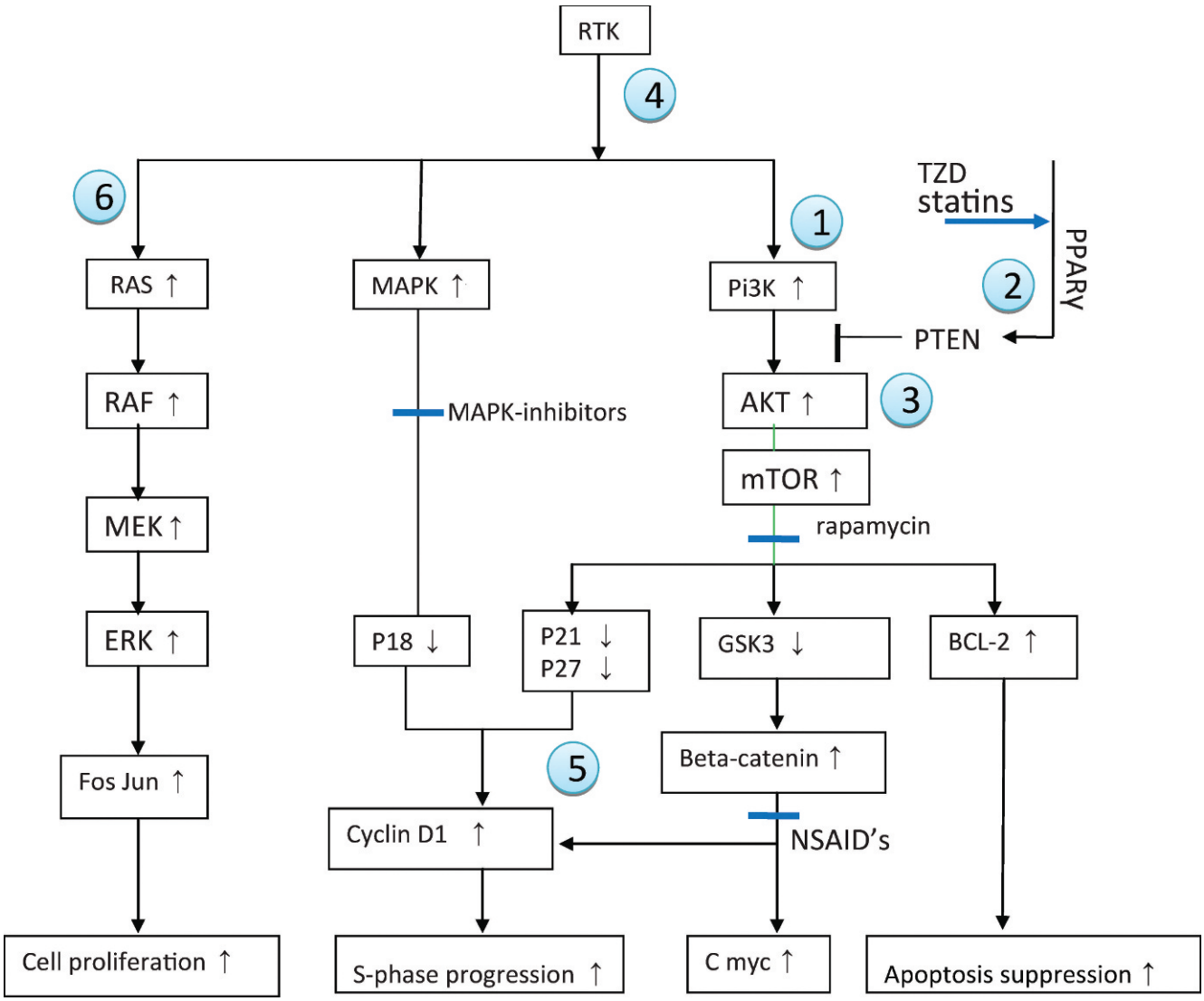

Figure 2 - Beyond inactivation of the *MEN1* gene, additional mutations in other genes may be responsible for acceleration of tumor growth, thus involving a process of multistep tumorigenesis. Deregulation of normal neuroendocrine development/differentiation can occur through a range of processes, e.g. activation of the PI3K pathway leads to AKT phosphorylation, triggering a downstream cascade of events. Deregulation of this pathway can occur through several mechanisms: 1) gain of function by oncogenic mutations of PIK3; 2) loss of function of the tumor suppressor PTEN through gene deletion, mutation, micro-RNA expression, or epigenetic silencing; 3) amplification or mutation of AKT isoforms; 4) upstream activation through RTK signalling; 5) downstream loss of the tumor suppressors p18 and p27; 6) increased RAS expression, or activating mutations of RAF, MEK, or ERK, which accelerate cell proliferation. Opportunities for treatment are in blue. NSAIDs = non-steroidal anti-inflammatory drugs; RTK = receptor tyrosine kinase; TZDs = thiazolidinediones.

AUTHOR CONTRIBUTIONS

Lips CJ conceived and designed the study and was also responsible for the manuscript writing and preparation of figures and table. Dreijerink KM searched the literature for important contents, provided assistance to the manuscript writing and to the molecular aspects of the menin protein. Höppener JW provided assistance to the study design, manuscript writing and final version of the manuscript.

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