Tissue Selectivity in Multiple Endocrine Neoplasia Type 1-Associated Tumorigenesis

Ana Gracanin,1 Koen M. A. Dreijerink,2,3 Rob B. van der Luijt,4 Cornelis J. M. Lips,3 and Jo W. M. Hoppener5,6

1Department of Clinical Sciences of Companion Animals, Faculty of Veterinary Medicine, Utrecht University; Departments of 2Physiological Chemistry, 3Internal Medicine and Endocrinology, Medical Genetics, and 4Metabolic and Endocrine Diseases, University Medical Center Utrecht; and 5Netherlands Metabolomics Center, Utrecht, The Netherlands

Abstract
The phenotype of the multiple endocrine neoplasia type 1 (MEN1) syndrome cannot be explained solely by the expression pattern of the predisposing gene MEN1 and its encoded protein, menin. This review addresses putative factors determining MEN1-associated tissue-selective tumorigenesis. Menin’s interaction with mixed-lineage leukemia protein-containing histone methyl transferase (MLL-HMT) complex mediates tissue-selective tumor-suppressing and tumor-promoting effects of menin, and as such could be decisive for the predisposition of individual tissues to MEN1-associated tumorigenesis. In tissues in which menin acts as a tumor suppressor, tumorigenesis could depend on the inability of such tissues to adequately compensate for MEN1 gene loss, whereas the variable clinical presentation of MEN1 in individual patients could be a reflection of additional epigenetic factors and/or modifier genes. Further research on this topic may facilitate development of novel therapeutic strategies that could prevent or delay the onset of MEN1-associated tumorigenesis. [Cancer Res 2009;69(16):6371–4]

Background
Multiple endocrine neoplasia (MEN) syndromes are characterized by the presence of neoplasms in two or more different endocrine tissues in individual patients. MEN type 1 (MEN1) patients develop neoplasms mainly in parathyroid glands, endocrine pancreas, and anterior pituitary gland. The clinical presentation of MEN1 varies, however, between individual patients, both to age of onset and to presence of additional endocrine manifestations (notably, adrenal cortical tumors and carcinoid tumors) and nonendocrine manifestations (notably, facial angiofibroma, truncal collagenoma, epedymoma, and meningioma; ref. 1).

The mechanism of tissue-selective tumorigenesis in hereditary tumor syndromes, in general, is poorly understood. The vast majority of familial MEN1 patients carries a germline mutation of the predisposing gene, MEN1, on chromosome 11, (2), and somatic MEN1 gene mutations have been detected in sporadic MEN1-associated tumors. Altogether, more than 500 different somatic and germline MEN1 gene mutations have been identified, but without obvious genotype-phenotype correlations (3). The MEN1-encoded protein, menin, has functions in DNA stability and gene regulation and can function as a tumor suppressor (4). However, the ubiquitous nature of menin expression fails to explain the predominant endocrine phenotype of MEN1 and its variable clinical manifestation. The diversity of organs and/or tissues affected in MEN1 might suggest a very early defect during embryonal development. In agreement with this notion, menin-deficient mouse embryos develop abnormalities in multiple endocrine and nonendocrine tissues (3).

Mechanism of MEN1 Loss-Related Tumorigenesis
In cultured cells, menin expression generally is negatively correlated with cell proliferation, and several menin-interacting proteins involved have been identified (Fig. 1). The antiproliferative effect could be mediated by a menin-dependent switching of JunD from growth promoter to growth suppressor (5) and/or menin’s inhibitory interactions with nuclear factor κB (NF-κB). Similarly, transforming growth factor-β (TGFβ)-induced growth inhibition of pituitary and parathyroid cell proliferation depends on menin’s interaction with Smad3 (6). Furthermore, menin was found to be part of a distinct mixed-lineage leukemia protein (MLL)-containing complex with histone methyl transferase (HMT) activity. This MLL-HMT complex specifically promotes trimethylation of lysine 4 on histone H3 (H3K4), thereby activating gene transcription. Menin-dependent recruitment of MLL-HMT was shown to activate transcription of homeobox domain (HOX) genes and cyclin-dependent kinase inhibitors (CDKNs) CDKN2C/p18ink4c and CDKN1B/p27kip1 (4). Antiproliferative effects are also mediated through inhibition of human telomerase reverse transcriptase (hTERT) gene expression, but the menin-interacting proteins involved are as yet unknown. In addition to affecting gene expression, menin can interfere with DNA replication by inhibiting the activator of S-phase kinase (ASK; ref. 4). Furthermore, three menin-interacting proteins, checkpoint suppressor 1 (CHEST), replication protein A2 (RPA2), and Fanconi anemia complementation group D2 (FANCD2), are involved in DNA damage-dependent cell cycle arrest or the subsequent DNA damage repair (4). Menin-depleted cells and MEN1-associated tumors have been suggested to have impaired DNA repair mechanisms, resulting in accumulation of point mutations and chromosomal instability (4, 7). Mouse studies have suggested that the observed chromosomal instability in MEN1 patients may not be a prerequisite for tumor development, but involvement of increased point mutation frequencies could not be excluded (8). Altogether, these data imply that menin can suppress tumor formation by inhibiting cell proliferation and maintaining DNA stability.

A high degree of evolutionary conservation between the human MEN1 gene and the mouse Men1 gene has enabled the creation of...
mouse MEN1 models. Homozygous Men1 knockout mice die in utero, but heterozygous knockout (Men1+/-) mice are viable and develop a hyperplasia and tumor repertoire similar to that observed in MEN1 patients (9). Although Men1+/- mice develop tumors also in thyroid, testes, and ovaries, they are very useful for studying the development of MEN1-associated pathogenesis (3, 9).

Interestingly, morphological and genetic features of human and mouse pituitary, parathyroid, pancreatic, and duodenal MEN1-associated lesions, suggest that even within the group of affected tissues there are differences in sensitivity to a loss of MEN1/Men1 alleles in terms of tumor initiation and progression. Although loss of a single MEN1 gene allele seems sufficient to induce hyperplasia of pancreatic islets and gastrin-producing cells, lesions in pituitary and parathyroid glands develop only after a biallelic loss of the MEN1 gene (9–13). Altogether, these findings imply that reduction of menin levels could lead to an altered sensitivity of cells to the local, intra- and extracellular environment (e.g., local growth factors, growth inhibitors, and DNA damaging agents). The neoplastic transformation of such affected cells could require a complete loss of the MEN1 gene and involve additional somatic mutations in general growth regulatory pathways.

Factors Determining Tissue Selectivity in MEN1

Menin’s tissue-selective functions. Although historically defined as a tumor suppressor, menin was recently shown to promote tumorigenesis in leukemia (MLL) and prostate cancer (14, 15). Apparently, menin can function as a tumor suppressor or a tumor promoter, depending on the tissue context. Tissue selectivity in MEN1 tumorigenesis could, therefore, be determined by the same mechanism(s) that enable(s) menin’s tissue-selective functions. In this regard, MLL-HMT—dependent menin target genes were shown to mediate both tumor-promoting and tumor-suppressive effects of menin. For example, whereas regulation of HOX genes is linked to leukemia (MLL), regulation of p18Ink4c and p27Kip1 links to tumor suppression. A role for p18Ink4c and p27Kip1 in MEN1 etiology is strongly supported by the MEN1-like phenotype of Cdkn2c and Cdkn1b double knockout mice and the identification of CDKN1B germline mutations in MEN1 suspected patients without MEN1 gene mutations (1, 16). But which mechanism(s) could mediate tissue-selective regulation of target genes by menin-MLL-HMT? One mechanism could involve the ability of menin-dependent H3K4 HMT activity to affect the function of nuclear receptors known to play important roles in endocrine processes. More specifically,
menin was shown to coactivate estrogen receptor alpha (ERα)- and vitamin D receptor (VDR)-mediated gene transcription (17). Secondly, menin was shown to interact with β-catenin, thereby increasing H3K4 methylation at a known Wnt target gene promoter (18). This crosstalk between menin-MLL-HMT and the Wnt pathway is of interest because of the known cell type-specific transcriptional response to canonical Wnt signaling. A third putative mechanism involves menin-dependent, transient recruitment of additional (tissue-selective) factors to MLL-HMT. For example, the MLL-HMT complex was recently shown to physically interact with the lens epithelium-derived growth factor (LEDGF) in a menin-dependent manner (19). Although this interaction seems relevant for both tumor-suppressive and tumor-promoting effects of menin-MLL-HMT (19), its potential relevance for tissue selectivity in MEN1 has not been addressed so far.

The level of menin expression. Differences between MEN1 patients and Men1+/− mice with regard to the tumor pattern, as well as the variable clinical manifestation of MEN1 in individual patients, suggest that even among tissues in which menin has a tumor-suppressive function, partial MEN1 gene loss will not, by definition, always cause tumor development. Tissue-selective loss of the MEN1 wild-type allele has initially been rejected as the mechanism of tissue selectivity in MEN1, by showing that conditional deletion of the Men1 gene in liver does not lead to tumor development (20). However, it remains unresolved whether in tissues in which menin does have a tumor suppressive function, loss of the second MEN1 allele determines the tissue selectivity of arising tumors. Furthermore, although MEN1 expression was reported in all tested human and mouse tissues, the level of expression differs between and within tissues and may vary across the cell cycle (1, 21). Physiological regulation of menin expression was shown to affect growth of pancreatic islets in pregnant mice (22), implicating the importance of mechanisms regulating menin expression for proliferation of specific endocrine cells. Interestingly, downregulation of menin levels has been shown to activate the MEN1 gene promoter in a compensatory manner, a phenomenon also suggested by studies in parathyroid tumors and lymphoblastoid cells in which loss of one MEN1 allele did not result in reduced menin transcript or protein levels, respectively (ref. 23 and references therein). In contrast, hyperplastic pancreatic β cells in conditional Men1−/− mice did show reduction (~50%) of menin protein compared with islets from wild-type animals (12). Therefore, with respect to tissue selectivity in MEN1, it would be relevant to determine whether tissues affected in MEN1 differ in their ability, and/or requirement, for compensatory induction of the remaining MEN1 allele. In this regard, microRNAs are interesting candidates for mediating tissue-selective regulation of menin levels, because of their differential spatial and temporal expression. The MEN1 gene has been predicted to be a putative target of microRNA miR-24 (24). Interestingly, miR-24 was reported to be deregulated in sporadic pituitary adenomas and endocrine pancreatic tumors (25). The link between miR-24 and MEN1-associated tumorigenesis remains to be investigated.

Factors unrelated to the biological function of menin. The region on chromosome 11 that often exhibits loss of heterozygosity (LOH) in tumors of MEN1 patients contains multiple genes, including MEN1 (2). Therefore, in addition to the MEN1 gene, MEN1-associated tumors often exhibit loss of at least one allele from other genes located within the LOH region. If functionally relevant in that tissue context, codeleted and/or additionally mutated genes (i.e., modifier genes) could influence the progression of MEN1-associated tumorigenesis. Moreover, MEN1-associated lesions arise mostly in tissues of endocrine origin, which are continuously exposed to high local concentrations of multiple hormones and growth factors. As reduction of menin levels could sensitize cells to their environment, local (epigenetic) factors could play a role in determining the MEN1 phenotype by regulating the impact of MEN1 gene loss in a tissue-selective manner.

Conclusions and Future Directions

Menin has been shown to function as a tumor suppressor or tumor promoter, depending on the tissue context. We postulate that MEN1-associated tissue-selective tumorigenesis is related to menin’s tissue-selective function. The menin-MLL-HMT complex could play an important role in this regard by determining the predisposition of individual tissues to MEN1-associated tumorigenesis. MLL proteins were shown to contain a high-affinity menin binding motif (hMBM) essential for menin binding and subsequent MLL-HMT function (14). Transgenic mice expressing MLL protein with an inactivated hMBM would have a fully functional menin protein but an impaired menin-MLL-HMT interaction. Therefore, targeted expression of mutant MLL-hMBM in mouse tissues might be expected to tissue selectively induce tumor formation. Moreover, putative appearance of thyroid and/or gonadal tumors in mutant MLL-hMBM transgenic mice would indicate that the observed differences in MEN1 tumor pattern between humans and mouse models are determined at the level of menin-MLL-HMT (e.g., species- and/or tissue-selective expression of menin-MLL-HMT—associated proteins) or by a downstream mechanism. In tissues in which menin acts as a tumor suppressor, progression of tumorigenesis could further be affected by loss of menin’s regulatory interactions with other growth- and DNA maintenance-regulating factors (Fig. 1). For example, in parathyroid glands and the pituitary gland, deregulation of TGFβ signaling might play an important role (6). Another tissue-selective factor may be the ability of tissues to compensate for a partial MEN1 gene loss (by upregulation of expression of the remaining wild-type allele) and/or tissue-selective loss of the wild-type allele. With respect to the latter, mice with targeted Men1 deletions in tissues in which menin is suspected to have a tumor-suppressive function, but which are rarely reported to develop tumors in MEN1 patients and Men1−/− mice, (e.g., intermediate pituitary, ref. 26) could shed light on this matter. Variable clinical presentation of MEN1 in individual patients could be a reflection of additional epigenetic factors and modifier genes (e.g., MEN1 codeleted genes) modulating the impact of MEN1 gene loss in tissues in which menin plays a tumor suppressive role. Future experiments, aimed at unraveling the mechanism(s) of tissue selectivity in MEN1-associated tumorigenesis will contribute to our understanding of the molecular pathogenesis of the MEN1 syndrome. Such experiments may include, for example, identification of proteins interacting with menin-MLL-HMT complex in different tissues and expression profiling of nuclear hormone receptor target genes in menin wild-type versus menin null cells. Ultimately, these findings may provide clues for development of novel therapeutic strategies that could prevent, or at least delay, the onset of MEN1-associated tumors.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

Received 2/20/09; revised 4/22/09; accepted 5/18/09; published OnlineFirst 8/4/09.


References

Tissue Selectivity in Multiple Endocrine Neoplasia Type 1-Associated Tumorigenesis

Ana Gracanin, Koen M. A. Dreijerink, Rob B. van der Luijt, et al.


Updated version
Access the most recent version of this article at:
doi:10.1158/0008-5472.CAN-09-0678

Cited articles
This article cites 26 articles, 15 of which you can access for free at:
http://cancerres.aacrjournals.org/content/69/16/6371.full.html#ref-list-1

Citing articles
This article has been cited by 2 HighWire-hosted articles. Access the articles at:
/content/69/16/6371.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.