CANCER MECHANISMS

Multiple Endocrine Neoplasia Type 1 (MEN1) as a Cancer Predisposition Syndrome: Clues into the Mechanisms of MEN1-related Carcinogenesis

Valeria Busygina\textsuperscript{a,b,*} and Allen E. Bale\textsuperscript{b}

\textsuperscript{a}Department of Biophysics and Biochemistry, Yale University School of Medicine, New Haven Connecticut; and \textsuperscript{b}Department of Genetics, Yale University School of Medicine, New Haven, Connecticut

Cancer is a major public health problem in the United States and around the world with millions of new cases diagnosed each year. While most of the cancers occur sporadically, a number of familial cancer predisposition syndromes have been identified in recent years. Cancer susceptibility syndromes are responsible for an estimated 5 to 10 percent of all cancer cases. Genes responsible for hereditary cancers are often also mutated in sporadic cancers. Studies of cellular functions of cancer susceptibility genes have made an invaluable contribution to our understanding of tumorigenesis.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant cancer predisposition syndrome, the gene for which encodes a nuclear protein: menin. The biochemical function of this protein is largely unknown, but several studies have shown a role in transcriptional modulation through interaction with histone deacetylases and histone methyltransferases. Tumors in MEN1 arise through a two-hit mechanism, suggesting that menin either negatively regulates cell growth or participates in maintenance of genomic integrity.

In this work, we provide a general overview of the hereditary cancer syndromes with both dominant and recessive mode of inheritance. We then discuss recent advances in understanding the biological role of MEN1 gene and the mechanisms by which inactivation of MEN1 may lead to neoplastic transformation.

HEREDITARY CANCER PREDISPOSITION SYNDROMES

Despite the complexity of cancer as a disease, there are some common features shared by all cancer cells that distinguish them from their normal counterparts. They are immortal and have a high proliferative potential. They no longer require external growth signals to activate the proliferation.
program and are insensitive to growth inhibitory signals. They have developed mechanisms for evading senescence and programmed cell death, or apoptosis. In order to ensure tumor growth, the cells of solid tumors must promote the formation of new blood vessels for oxygen and nutrient supply. And, finally, malignant cells fail to exhibit normal cell-cell interactions, which results in their ability to invade and to metastasize and grow in an abnormal cellular environment [1]. The acquisition of these qualities is not a single event but rather the result of an accumulation of multiple genetic alterations leading to escape from normal control of growth regulation and differentiation [2].

Genes with very diverse cellular functions have been implicated in carcinogenesis. This includes genes involved in intracellular signaling cascades, cell cycle control, cell differentiation, apoptosis, protein synthesis and degradation, organization of cytoskeleton, cell migration, cell-cell interaction, regulation of transcription, chromatin remodeling, and DNA damage sensing and repair [3-5]. Understanding how the disruption of these cellular processes leads to tumor formation is the key to rational development of effective cancer therapies.

Because the development of cancer is a multi-step process, it may take years between the occurrence of the first genetic lesion and the actual formation of malignant neoplasm. Thus, the incidence of cancer increases with age. In rare cases, however, individuals inherit a mutant allele of a cancer predisposition gene, which increases the mutation rate and promotes the development of cancer. Thus, individuals with cancer predisposition syndromes have both a greater risk of developing cancer and an average earlier age of onset compared to the general population.

In 1971, Knudson proposed his famous “two-hit” hypothesis [6]. By observing patients with familial and sporadic retinoblastoma, he suggested that individuals with familial cases inherited the first genetic lesion, or “hit,” and that they only needed to acquire one more hit to develop cancer. These patients developed retinoblastoma at an earlier age than individuals with sporadic tumors who needed to acquire two somatic hits in the same cell. This hypothesis was confirmed with the discovery of the retinoblastoma (RB1) gene in 1986 [7]. Indeed, individuals with familial retinoblastoma inherited a germline mutation in one allele of the RB1 gene with the remaining wild type allele being lost in tumors, often through a process involving large deletions with loss of heterozygosity (LOH) for surrounding polymorphic loci [7].

Since the discovery of RB1, multiple tumor-predisposition genes have been identified by the study of familial cancer syndromes. It is estimated that 5 to 10 percent of all cancers develop in individuals who have inherited a mutation conferring cancer susceptibility [8]. Analysis of the genes responsible for hereditary cancer predisposition and the pathways in which they act has been critically important in providing insight into cancer formation, because the same genes that are affected in cancer-predisposition syndromes are often responsible for the majority of somatic cancer cases as well. For example, germline mutations in the APC gene account for less than one percent of all colorectal cancers, but APC is also inactivated in nearly all sporadic colon cancers [2].

More than 50 cancer predisposition syndromes have been identified to date [8, 9] with both dominant and recessive modes of inheritance (Table 1). Activating mutations in oncogenes occur only in a few cases, such as RET in multiple endocrine neoplasia type 2 (MEN2) [10] and MET in familial papillary renal carcinoma [11]. Activated oncogenes function dominantly in the cell, and mutation of the second allele is not required. Most of the dominantly inherited cancer syndromes, however, have an inactivating mutation in a tumor suppressor, and disease formation follows the two-hit rule. The first hit is a germline mutation that exists in every cell of the body. Somatic inactivation of the second allele of the same locus in certain tissues may initiate neoplastic transformation. Thus, cancer predisposition syndromes often have dominant mode
of inheritance at the level of the organism, but at the cellular level they are recessive because inactivation of both copies of the gene is required for cancer formation.

Genes whose inactivation leads to tumorigenesis are divided into two distinct groups: gatekeepers and caretakers. Gatekeepers are usually "classical" tumor suppressors that directly regulate cell growth, differentiation, and death in certain tissues. Dysregulation of a gatekeeper is necessary to initiate neoplastic transformation. Examples of gatekeepers include APC for colon epithelia, RB1 for retinal epithelia, NF1 for Schwann cells, and VHL for kidney cells [2, 12]. Inactivation of both homologs of these genes is found both in hereditary forms of cancer and in the majority of sporadic cancers of the same type. In contrast to gatekeepers, caretaker genes do not directly regulate cell growth. Caretaker genes are involved in DNA repair and maintenance of genomic integrity. Inactivation of a caretaker does not directly promote tumor formation but facilitates the development of mutations in gatekeeper genes and other cancer-related genes. Caretakers, like gatekeepers, may be tissue-specific, but mutation in a caretaker is neither necessary nor sufficient for the development of cancer. Mutations in some caretaker genes cause human cancer by the two-hit mechanism. For example, patients with familial breast cancer syndromes inherit one mutant copy of BRCA1 or 2, and LOH for the second allele is found in tumors of breast and ovary [13-16]. Similarly, in hereditary non-polyposis colorectal cancer (HNPCC), one mutant copy of mismatch repair genes such as MLH1, MSH2, or MSH6 is inherited, and the wild type allele is lost in tumors of the colon [17]. However, unlike gatekeepers, mutations in caretakers are uncommon in sporadic tumors of the types seen in the hereditary disease [18].

A number of human cancer predisposition syndromes have a recessive mode of inheritance (Table 1). These syndromes are also called genetic instability syndromes, because one of the hallmarks of these diseases is chromosomal instability and hyper-sensitivity to various DNA damaging insults. The genes mutated in these diseases, such as ATM, Fanconi anemia complementation group, NBS1, Xeroderma pigmentosum-associated genes (XPA, XPC, etc.), BLM, and RECQL4, function in DNA damage sensing or repair [4,8,9] and can be classified as caretakers by analogy with the BRCA and HNPCC genes.

Since the identification of the first cancer predisposition gene (RB1) in 1986, tremendous advances have been made in understanding the function of multiple genes implicated in both sporadic and hereditary cancers. However, the mechanism of action of many more recently identified genes is not well understood. Further studies are necessary to provide new insights into human neoplasia and improve the diagnosis and treatment of both sporadic and hereditary cancers.

**MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)**

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant cancer predisposition syndrome characterized by parathyroid, pancreatic islet, and pituitary tumors as well as other neoplasms such as gastrinomas, carcinoids, lipomas, angiofibromas, angiomylipomas and thyroid tumors [19]. Clinical manifestations depend on the affected organ. Most MEN1-associated tumors are not metastatic but create clinical effects by overproduction of hormones such as insulin, glucagon, prolactin, parathyroid hormone, gastrin, growth hormone, or adrenocorticotropic hormone [19, 20]. The most common manifestation of the disease is parathyroid adenoma, with prevalence reaching almost 100 percent by the age of 50 [19]. Major causes of morbidity and mortality in MEN1 are gastrinomas and foregut carcinoids, which are often highly metastatic [19]. The estimated prevalence of MEN1 is one in 30,000 [21].

*MEN1* was localized to chromosome 11q13 by linkage analysis, and the gene was later identified by positional cloning [23, 24]. Tumors in MEN1 arise through the two-
hit mechanism with germline mutation in one copy of the gene and somatic loss of the normal allele [22]. Germline mutations in MEN1 are mainly nonsense or frameshift and are presumed to cause inactivation of the gene. The transcript of the MEN1 gene contains an open reading frame predicted to encode 610 amino acid proteins. Analysis of the sequence of the protein menin showed two nuclear localization signals near the carboxyl terminus but has not provided any other clues to its function. Immunocytochemical studies of interphase somatic cells show that the protein is located in the nu-

| Cancer syndrome | Type of tumors | Gene(s) | Function |
|-----------------|----------------|---------|----------|
| Familial retinoblastoma | Retinoblastoma, Osteosarcoma | RB | Regulator of cell proliferation |
| Li-Fraumeni syndrome | Soft tissue, Osteosarcoma, Breast cancer, Leukemia | p53, CHK2 [68] | Transcription factor, DNA damage response, Kinase, regulator of p53 activity |
| Gorlin syndrome | Basal cell carcinoma | PTCH | Transmembrane receptor for hedgehog |
| Familial adenomatous polyposis (FAP) | Colorectal cancer | APC | Regulation of ß-catenin |
| Hereditary non-polyposis colorectal cancer (HNPCC) | Colorectal cancer | MSH2, 6, MLH1, PMS1, 2 | Mismatch repair |
| Neurofibromatosis type 1 | Neurofibromas | NF1 | GAP for p21 |
| Neurofibromatosis type 2 | Schwannomas, Meningiomas | NF2 | Links membrane proteins to cytoskeleton |
| Familial breast/ovarian cancer syndrome | Breast cancer, Ovarian cancer | BRCA1/2 | DNA repair |
| von Hippel-Lindau syndrome | Renal cancer (clear cell) | VHL | Transcription elongation factor |
| Hereditary papillary renal cancer (HPRC) | Renal cancer (papillary) | MET | Transmembrane receptor for HGF |
| Familial melanoma | Melanoma | p16 | Cyclin-dependent kinases CDK4 and CDK 6 inhibitor |
| Multiple endocrine neoplasia type 1 (MEN1) | Pituitary Parathyroid adenoma, Pancreatic islet | MEN1 | Transcriptional regulator, modulator of AP-1 activity |
| Multiple endocrine neoplasia type 2 (MEN2) | Medullary thyroid cancer | RET | Transmembrane receptor |
| Cowden disease | Breast cancer, Thyroid cancer | PTEN | PI3kinase/AKT inhibitor, phosphatase |
| Tuberous sclerosis | Rabdomyoma, Renal cancer | TSCI/2 | Regulation of cell size and proliferation through insulin signaling |
nucleus [25]. Studies in human and mouse show that MEN1 is expressed widely in adult and fetal tissues with high levels in the CNS, lung, liver, kidney, testis, and fetal thymus [23,26-28].

Among the earliest studies of menin function was a yeast two-hybrid analysis showing interaction between menin and JunD, a component of the AP-1 transcription factor [29]. Studies in mammalian tissue culture systems showed that the N-terminal half of menin could inhibit JunD-mediated transcription. Menin did not bind to other AP-1 components such as c-Jun, JunB, or four members of the Fos family. Further investigation of menin’s involvement in JNK and other MAP kinase signaling cascades revealed that overexpression of MEN1 in some cell lines inhibited ERK-mediated phosphorylation of JunD and Elk1 and JNK-dependent phosphorylation of JunD and c-Jun [30]. In addition, overexpression of menin in CHO-IR cells suppressed insulin-induced activation of AP-1 and transcriptional induction of c-Fos [31]. Similarly, menin was shown to bind to and inhibit transcriptional activation by several members of the NF-kB family of transcription factors [32]. Binding of menin to SMAD3 appears to enhance transcriptional activation function, and loss of menin blocks TGF beta signaling [33]. The homeobox-containing protein Pem [34] has also been shown to bind menin in biochemical assays. These data suggest that menin may act as a transcriptional regulator. Our investigations of the Drosophila MEN1 homolog showed in vivo interaction of MEN1 with JNK signaling pathway components. We also found that when tethered to DNA, Drosophila menin acts as a transcriptional repressor. Menin does not have any recognizable DNA binding motifs, and data are conflicting as to whether menin can directly bind DNA and whether it binds in a sequence-specific manner [35,36].

Multiple lines of evidence exist to support menin’s involvement in transcriptional control and chromatin modification. Human menin was found to bind and control the ac-

Table 1. Familial cancer syndromes and cancer predisposition genes [8-9] (cont.).

| Cancer syndrome                   | Type of tumors                  | Gene(s)             | Function                               |
|-----------------------------------|---------------------------------|---------------------|----------------------------------------|
| Bloom syndrome                    | Solid tumors                    | BLM                 | Helicase, DNA repair                   |
| Ataxia telangiectasia (AT)        | Lymphoma                       | ATM                 | DNA repair, DNA damage response        |
| Nijmegen breakage syndrome (NBS)  | Lymphoma, Glioma, Medulloblastoma | NBS1               | Double strand break repair             |
| Xeroderma pigmentosum             | Skin cancer                     | XPB, XPD, XPA       | Nucleotide excision repair             |
| Rothmund Thompson syndrome        | Basal cell carcinoma, Squamous cell sarcoma | RECQL4             | Helicase                               |
| Werner syndrome                   | Osteosarcoma, Meningioma        | WRN                 | Helicase                               |
| Fanconi anemia                    | Leukemia, Squamous cancers      | FANCD2, FANCA, FANCB, C, FANCE F, FANCG, L | DNA repair, DNA damage response |

Abbreviations: GAP – GTPase-activating protein; MSN – mut S homolog; MLH – mut L homolog; PMS – postmeiotic segregation; HGF – hepatocyte growth factor; BRCA – breast cancer associated; PTEN – phosphatase and tensin homolog.
tivity of multiple transcription factors. Menin interacts with mSin3a, a component of the Sin3/Rpd3 HDAC complex [37], and with a histone methyltransferase complex containing the trithorax family proteins MLL2 and Ash2L [38-41]. In addition, menin was found to bind to the promoter regions of several homeobox genes and to regulate their expression [38,39]. Genome-wide analysis of genomic binding sites showed menin's localization to the promoters of multiple genes [42,43]. Recently, two other transcription targets of menin were identified. Cyclin-dependent kinase inhibitors p27kip1 and p18ink4c are downregulated in menin-deficient cells, which also exhibited increased proliferation [40]. Thus, menin may control cell proliferation through regulating transcription of genes involved in cell cycle control.

That tumors in MEN1 arise through two-hit mechanism suggests that menin may act in the regulation of cell growth or in the maintenance of genomic integrity, as discussed above. Several lines of evidence suggest that menin might participate in DNA damage sensing or repair. Peripheral blood lymphocytes from MEN1 patients have an elevated frequency of chromosomal abnormalities after exposure to the cross-linking agent diepoxybutane (DEB) [44]. Menin-deficient mouse embryonic fibroblasts (MEFs) are hypersensitive to DEB [45]. Menin interacts with FANCD2, a gene that underlies the genetic instability syndrome Fanconi anemia. Moreover, this interaction is strengthened after the exposure of cells to γ-irradiation [45]. In addition, menin was shown to interact with replication protein A (RPA) [46], a protein that binds single strand DNA and is important for several DNA repair pathways [47]. Studies from our laboratory show a role for the Drosophila homolog of MEN1 in maintenance of genomic integrity. We found that inactivation of Men1 in Drosophila results in flies that are sensitive to certain types of DNA damage, in particular to ionizing radiation and DNA cross-linking agents. In addition, Men1-deficient flies have an elevated mutation rate both at baseline and after treatment with ionizing radiation and nitrogen mustard (a cross-linking agent) [48]. Menin-deficient tissues from both Drosophila and mammals fail to undergo S-phase arrest in response to DNA damage by ionizing radiation [49]. These data suggest that tumor pathogenesis in the human disease may relate to genomic instability.

Studies also support a direct role for MEN1 in the control of cell growth and differentiation. Overexpression of menin represses the proliferation and tumorigenesis of Ras-transformed NIH3T3 cells and insulinoma cells [50]. Data are conflicting as to whether menin-deficient mouse cells have increased proliferative capacity. One study found no cell-autonomous proliferative defects in Men1−/− embryonic stem (ES) cells or embryonic fibroblasts (MEF) [51]. However, another study showed that Men1−/− MEFs have increased proliferative capacity, and reintroduction of wild type menin suppresses their growth, possibly through an interaction with activator of S-phase kinase (ASK), a component of the Cdc7/ASK kinase complex [52]. Some phenotypes seen in mouse models of MEN1 suggest a direct role in growth control. For example, tissue-specific gene inactivation in pancreatic islet cells of the mouse leads to widespread hyperplasia, consistent with a similar role for the gene postnattally [53].

A mouse model with targeted disruption of the Men1 gene showed that menin has an essential role in development [54]. The phenotype of heterozygotes was very similar to the human MEN1 phenotype with tumors of the parathyroid, pituitary, pancreatic islets, thyroid, and adrenal cortex. Homozygous mice died in utero. They appeared normal at E9.5 but by E11.5-12.5 were developmentally delayed and smaller than normal littermates. Virtually all fetuses were resorbed by E14.5. Morphological defects included an open neural tube, hypoplastic myocardium, and an extremely malformed liver with abnormal organization of the epithelial and hematopoietic compartments and increased apoptosis [51]. Conditional knockout of Men1 in mouse pituitary and pancreatic islets showed that both these organs were
able to develop normally even if Men1 was deleted in early embryogenesis. Pancreatic islets developed β-cell hyperplasia and later, in six- to 12-month-old mice, pancreatic islet adenomas. Insulinomas and prolactinomas developed in some animals starting at nine months. The late tumorigenesis in these mice suggests that additional somatic events are necessary to promote cancer formation [53,55].

Two studies suggested a function of menin related to telomeres. Investigations in our laboratory [56] showed that menin localizes to telomeres during meiotic prophase in mouse spermatocytes. Menin foci were seen only at this location and not in other regions of meiotic cells. The foci were apparent as soon as axial elements began to form, and signals increased in intensity throughout prophase. However, menin did not co-localize with telomeric proteins, such as TRF2, in somatic cells at any stage of the cell cycle. Furthermore, telomeres of MEN1-related tumors were no different in length than telomeres of histologically similar sporadic tumors arising without MEN1 mutations. Overexpression of menin did not influence telomerase activity as assessed by TRAP assays. Another study, which systematically examined the effects of tumor suppressor genes on telomere maintenance, suggested that loss of menin function might stimulate telomerase (hTERT) expression [57] and that menin might be involved in tumorigenesis through this mechanism.

Menin has also been found to associate with several cytoskeleton components. Menin’s interaction with the intermediate filament proteins GFAP and vimentin was suggested to control its nuclear import [58]. Another cytoskeletal interactor of menin is nonmuscle myosin II-A heavy chain protein, which was found to co-localize with menin at the cleavage furrow during cytokinesis [59].

CONCLUSIONS AND OUTLOOK

In the 10 years since the MEN1 gene was first cloned, a wealth of information concerning its possible function in tumorigenesis has been obtained. The accumulated genetic and biochemical data show that menin has multiple binding partners in a cell. By virtue of interacting with several transcription factors, menin is proposed to be involved in signaling pathways such as JNK, MAPK, TGF beta, and NF-κB; all of which have a well-documented role in cancer formation [60-63]. At the same time, through its role in chromatin modification, menin has been shown to affect the expression of c-Fos, hTERT, p27kip1, and p18ink4c, which are also linked to neoplastic transformation [57,60,64,65]. On the cellular level, menin has been shown to regulate cell cycle progression and genomic integrity, both of which are often associated with a cancer phenotype.

The multiple functions of MEN1 are not altogether unconnected. As a regulator of transcription, menin could control the expression of multiple factors involved in cell cycle regulation and the DNA damage response (see the examples above). The transcription regulation is likely achieved through menin’s function in chromatin modification. At the same time, there is a wealth of evidence connecting the modification of chromatin with the maintenance of genome integrity [66]. Finally, the possibilities of MEN1’s involvement in cell cycle regulation and genome maintenance are not mutually exclusive. MEN1 was shown to regulate proper S-phase arrest in response to exogenous DNA damage [49]. Similar regulation is necessary in the cell as endogenous DNA damage occurs every cell cycle during DNA replication [67].

Taken together, the accumulated knowledge of MEN1’s potential functions and cellular partners suggests several possible mechanisms of its involvement in cancer formation. The key question is which of these functions or interactions play critical role in cancer development. One possible way to address this challenging problem is systematic investigation of tumors obtained from Men1 heterozygous mice as well as from MEN1 patients. One such study generated p18(-/-)Men1(+/+) and p27(-/-)Men1(+/+) mice and found that p18 functionally collaborates with
MEN1 in suppressing lung and neuroendocrine tumors [64,65]. Another important question is whether menin aids in the maintenance of genome integrity by regulating the cell cycle or by serving as a structural component of DNA repair machinery. To this end, analysis of mutational spectra could point to a DNA repair step(s) most deficient in cells lacking MEN1. Careful examination of interactions between menin and known DNA repair proteins is also necessary. Addressing these issues is of key importance for the understanding of MEN1-related carcinogenesis and for the development of effective therapeutic approaches.

REFERENCES

1. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100(1):57-70.
2. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. Cell. 1996;87(2):159-70.
3. Cooper GM. Oncogenes. 2nd ed. Sudbury, Massachusetts: Jones and Bartlett Publishers; 1995.
4. Sherr CJ. Principles of tumor suppression. Cell. 2004;116(2):235-46.
5. Creas WD, Seto E. Histone deacetylases, transcriptional control, and cancer. J Cell Physiol. 2000;184(1):1-16.
6. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA. 1971;68(4):820-3.
7. Friend SH, Bernards R, Rogelj S, Weinberg RA, Rapaport JM, Albert DM, Dryja TP. A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature. 1986;323(6089):643-6.
8. Garber JE, Offit K. Hereditary cancer predisposition syndromes. J Clin Oncol. 2005;23(2):276-92.
9. Fearon ER. Human cancer syndromes: clues to the origin and nature of cancer. Science. 1997;278(5340):1043-50.
10. Mulligan LM, Eng C, Healey CS, Clayton D, Kwok JB, Gardner E, et al. Specific mutations of the RET proto-oncogene are related to disease phenotype in MEN 2A and FMTC. Nat Genet. 1994;6(1):70-4.
11. Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, Choyke P, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas. Nat Genet. 1997;16(1):68-73.
12. Knudson AG. Antioncogenes and human cancer. Proc Natl Acad Sci USA. 1993;90(23):10914-21.
13. Cannon-Albright LA, Skolnick MH. The genetics of familial breast cancer. Semin Oncol. 1996;23(1 Suppl 2):1-5.
14. Lancaster JM, Wooster R, Mangion J, Phelan CM, Cochran C, Gumbs C, et al. BRCA2 mutations in primary breast and ovarian cancers. Nat Genet. 1996;13(2):238-40.
15. Miki Y, Katagiri T, Kasumi F, Yoshimoto T, Nakamura Y. Mutation analysis in the BRCA2 gene in primary breast cancers. Nat Genet. 1996;13(2):245-7.
16. Teng DH, Bogden R, Mitchell J, Baumgard M, Bell R, Berry S, et al. Low incidence of BRCA2 mutations in breast carcinoma and other cancers. Nat Genet. 1996;13(2):241-4.
17. Yuen ST, Chan TL, Ho JW, Chan AS, Chung LP, Lam PW, et al. Germline, somatic and epigenetic events underlying mismatch repair deficiency in colorectal and HNPPC-related cancers. Oncogene. 2002;21(49):7585-92.
18. Kinzler KW, Vogelstein B. Cancer-susceptibility genes. Gatekeepers and caretakers. Nature. 1997;386(6627):761, 763.
19. Schussheim DH, Skarulis MC, Agarwal SK, Simonds WF, Burns AL, Spiegel AM, Marx SJ. Multiple endocrine neoplasia type 1: new clinical and basic findings. Trends Endocrinol Metab. 2001;12(4):173-8.
20. Trump D, Farren B, Wooding C, Pang JT, Besser GM, Buchanan KD, et al. Molecular pathology of the MEN1gene. Ann NY Acad Sci. 2004;1014:189-98.
21. Larsson C, Skogseid B, Oberg K, Nakamura Y, Nordenskjold M. Multiple endocrine neoplasia type 1 gene maps to chromosome 11 and is lost in insulinoma. Nature. 1988;332(6159):85-7.
22. Chandrasekharappa SC, Guru SC, Manickam P, Olufemi SE, Collins FS, Emmert-Buck MR, et al. Positional cloning of the gene for multiple endocrine neoplasia type 1. Science. 1997;276(5311):404-7.
23. Lemmens I, Van de Ven WJ, Kas K, Zhang CX, Giraud S, Wautot V, et al. Identification of the multiple endocrine neoplasia type 1 (MEN1) gene. The European Consortium on MEN1. Hum Mol Genet. 1997;6(7):1177-83.
24. Guru SC, Goldsmith PK, Burns AL, Marx SJ, Spiegel AM, Collins FS, Chandrasekharappa SC. Menin, the product of the MEN1 gene, is a nuclear protein. Proc Natl Acad Sci USA. 1998;95(4):1630-4.
25. Bassett JH, Rashbass P, Harding B, Forbes SA, Pannett AA, Thakker RV. Studies of the murine homolog of the multiple endocrine neoplasia type 1 (MEN1) gene. The European Consortium on MEN1. Hum Mol Genet. 1997;6(7):1177-83.
during development. Oncogene. 1998;17 (19):2485-93.
29. Agarwal SK, Guru SC, Heppner C, Erdos MR, Collins RM, Park SY, et al. Menin interacts with the AP1 transcription factor JunD and represses JunD-activated transcription. Cell. 1999;96(1):143-52.
30. Gallo A, Cuozzo C, Esposito I, Maggiolini M, Bonofiglio D, Vivaquaa A, et al. Menin uncouples Elk-1, JunD and c-Jun phosphorylation from MAP kinase activation. Oncogene. 2002;21(42):6434-45.
31. Yumita W, Ikeo Y, Yamashita K, Sakurai A, Hashizume K. Suppression of insulin-induced AP-1 transactivation by menin accompanies inhibition of c-Fos induction. Int J Cancer. 2003;103(6):738-44.
32. Heppner C, Bilimoria KY, Agarwal SK, Kester M, Whitty LJ, Guru SC, et al. The tumor suppressor protein menin interacts with NF-kappaB proteins and inhibits NF-kappaB-mediated transactivation. Oncogene. 2001;20(36):4917-25.
33. Kaji H, Canaff L, Lebrun JJ, Goltzman D, Hendy GN. Inactivation of menin, a Smad3-interacting protein, blocks transforming growth factor beta signaling. Proc Natl Acad Sci USA. 2001;98(7):3837-42.
34. Lemmens IH, Forsberg L, Pannett AA, Meyen E, Piehl F, Turner JJ, et al. Menin interacts directly with the homeobox-containing protein Pem. Biochem Biophys Res Commun. 2001;286(2):426-31.
35. Chandrasekharappa SC, Teh BT. Functional studies of the MEN1 gene. J Intern Med. 2003;253(6):606-15.
36. La P, Silva AC, Hou Z, Wang H, Schneppe RW, Yan N, et al. Direct binding of DNA by tumor suppressor menin. J Biol Chem. 2004;279(47):49045-54.
37. Kim H, Lee JE, Cho EJ, Liu JO, Youn HD. Menin, a tumor suppressor, represses JunD-mediated transcriptional activity by association with an mSin3A-histone deacetylase complex. Cancer Res. 2003;63(19):6135-9.
38. Yokoyama A, Wang Z, Wysocka J, Sanyal M, Aufiero DJ, Kitabayashi I, et al. Leukemia proto-oncoprotein MLL forms a SET1-like histone methyltransferase complex with menin to regulate Hox gene expression. Mol Cell Biol. 2004;24(17):5639-49.
39. Hughes CM, Rozenblatt-Rosen O, Milne TA, Copeland TD, Levine SS, Lee JC, et al. Menin associates with a trithorax family histone methyltransferase complex and with the hoxc8 locus. Mol Cell. 2004;13(4):587-97.
40. Milne TA, Hughes CM, Lloyd R, Yang Z, Rozenblatt-Rosen O, Dou Y, et al. Menin and MLL cooperatively regulate expression of cyclin-dependent kinase inhibitors. Proc Natl Acad Sci USA. 2005;102(3):749-54.
41. Yokoyama A, Somerville TC, Smith KS, Rozenblatt-Rosen O, Meyerson M, Cleary ML. The menin tumor suppressor protein is an essential oncogenic cofactor for MLL-associated leukemogenesis. Cell. 2005;123(2):207-18.
42. Scacheri PC, Davis S, Odom DT, Crawford GE, Perkins S, Halawi MJ, et al. Genome-wide analysis of menin binding provides insights into MEN1 tumorigenesis. PLoS Genet. 2006;2(4):e51.
43. Agarwal SK, Impey S, McWeeney S, Scacheri PC, Collins FS, Goodman RH, et al. Distribution of menin-occupied regions in chromatin specifies a broad role of menin in transcriptional regulation. Neoplasia. 2007;9(2):101-7.
44. Itakura Y, Sakurai A, Katai M, Ikeo Y, Hashizume K. Enhanced sensitivity to alkylating agent in lymphocytes from patients with multiple endocrine neoplasia type 1. Biomed Pharmacother. 2000;54 Suppl 1:187s-90s.
45. Jin S, Mao H, Schneppe RW, Sykes SM, Silva AC, D’Andrea AD, Hua X. Menin associates with FANC D2, a protein involved in repair of DNA damage. Cancer Res. 2003;63(14):4204-10.
46. Sukhodolets KE, Hickman AB, Agarwal SK, Sukhodolets MV, Obungu VH, Novotny EA, et al. The 32-kilodalton subunit of replication protein A interacts with menin, the product of the MEN1 tumor suppressor gene. Mol Cell Biol. 2003;23(2):493-509.
47. Binz SK, Sheehan AM, Wold MS. Replication protein A phosphorylation and the cellular response to DNA damage. DNA Repair (Amst). 2004;3(8-9):1015-24.
48. Busygina V, Suphapeetiporn K, Marek LR, Stowers RS, Xu T, Bale AE. Hypermutability in a Drosophila model for multiple endocrine neoplasia type 1. Hum Mol Genet. 2004;13(20):2399-408.
49. Busygina V, Kottemann MC, Scott KL, Plon SE, Bale AE. Multiple Endocrine Neoplasia Type 1 Interacts with Forkhead Transcription Factor CHES1 in DNA Damage Response. Cancer Res. 2006;66(17):8397-403.
50. Kim YS, Burns AL, Goldsmith PK, Heppner C, Park SY, Chandrasekharappa SC, et al. Stable overexpression of MEN1 suppresses tumorigenicity of RAS. Oncogene. 1999;18(43):5936-42.
51. Bertolino P, Radovanovic I, Casse H, Aguzzi A, Wang ZQ, Zhang CX. Genetic ablation of the tumor suppressor menin causes lethality at mid-gestation with defects in multiple organs. Mech Dev. 2003;120(5):549-60.
52. Schneppe RW, Hou Z, Wang H, Petersen C, Silva A, Masai H, Hua X. Functional interaction between tumor suppressor menin and activator of S-phase kinase. Cancer Res. 2004;64(18):6791-6.
53. Biondi CA, Giartside MG, Waring P, Loffler KA, Stark MS, Magnuson MA, et al. Conditional inactivation of the MEN1 gene leads to pancreatic and pituitary tumorigenesis but does not affect normal development of these tissues. Mol Cell Biol. 2004;24(8):3125-31.
54. Crabtree JS, Scacheri PC, Ward JM, Garrett-Beal L, Emmert-Buck MR, Edgemon KA, et al. A mouse model of multiple endocrine neoplasia, type 1, develops multiple endocrine tumors. Proc Natl Acad Sci USA. 2001;98 (3):1118-23.

55. Crabtree JS, Scacheri PC, Ward JM, McNally SR, Swain GP, Montagna C, et al. Of mice and MEN1: Insulinomas in a conditional mouse knockout. Mol Cell Biol. 2003;23 (17):6075-85.

56. Suphapeetiporn K, Greally JM, Walpita D, Ashley T, Bale AE. MEN1 tumor-suppressor protein localizes to telomeres during meiosis. Genes Chromosomes Cancer. 2002;35 (1):81-5.

57. Lin SY, Elledge SJ. Multiple tumor suppressor pathways negatively regulate telomerase. Cell. 2003;113(7):881-9.

58. Lopez-Egido J, Cunningham J, Berg M, Oberg K, Bongcam-Rudloff E, Gobl A. Menin's interaction with glial fibrillary acidic protein and vimentin suggests a role for the intermediate filament network in regulating menin activity. Exp Cell Res. 2002;278 (2):175-83.

59. Obungu VH, Lee Burns A, Agarwal SK, Chandrasekharapu SC, Adelstein RS, Marx SJ. Menin, a tumor suppressor, associates with nonmuscle myosin II-A heavy chain. Oncogene. 2003;22(41):6347-58.

60. Heasley LE, Han SY. JNK regulation of oncogenesis. Mol Cells. 2006;21(2):167-73.

61. Zebisch A, CzemiloFSky AP, Keri G, Smigelskaite J, Sill H, Troppmair J. Signaling through RAS-RAF-MEK-ERK: from basics to bedside. Curr Med Chem. 2007;14 (5):601-23.

62. Matsuzaki K, Okazaki K. Transforming growth factor-beta during carcinogenesis: the shift from epithelial to mesenchymal signaling. J Gastroenterol. 2006;41(4):295-303.

63. Karin M, Greten FR. NF-kappaB: linking inflammation and immunity to cancer development and progression. Nat Rev Immunol. 2005;5(10):749-59.

64. Pei XH, Bai F, Smith MD, Xiong Y. p18Ink4c Collaborates with Men1 to Constrain Lung Stem Cell Expansion and Suppress Non-Small-Cell Lung Cancers. Cancer Res. 2007;67(7):3162-70.

65. Bai F, Pei XH, Nishikawa T, Smith MD, Xiong Y. p18Ink4c, but not p27Kip1, collaborates with Men1 to suppress neuroendocrine organ tumors. Mol Cell Biol. 2007;27 (4):1495-504.

66. Morrison AJ, Shen X. Chromatin modifications in DNA repair. Results Probl Cell Differ. 2006;41:109-25.

67. Sung P, Klein H. Mechanism of homologous recombination: mediators and helicases take on regulatory functions. Nat Rev Mol Cell Biol. 2006;7(10):739-50.

68. Staalesen V, Falck J, Geisler S, Bartkova J, Borresen-Dale AL, Lukas J, et al. Alternative splicing and mutation status of CHEK2 in stage III breast cancer. Oncogene. 2004;23 (52):8535-44.