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Review

In search of tumor suppressing functions of menin

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Abstract

Human hereditary tumor syndromes serve as an ideal model for studying molecular pathways regulating tumorigenesis. Multiple endocrine neoplasia type 1 (MEN1), a human familial tumor syndrome, results from mutations in the *Men1* gene. *Men1* encodes a novel tumor suppressor, menin, of unknown biochemical function. Recently, significant progress has been made in identifying menin as a regulator of gene transcription, cell proliferation, apoptosis, and genome stability, leading to a new model of understanding menin's tumor-suppressing function. These findings suggest that menin's diverse functions depend on its association with chromatin and its control over gene transcription. This knowledge will likely be translated into new strategies to improve therapeutic interventions against MEN1 and other related cancers.

Keywords: Menin; MEN1; Cell proliferation; Apoptosis; Genome stability; Transcription; Epigenetics

Contents

1. Introduction

Multiple endocrine neoplasia type 1 (MEN1) is an inherited tumor syndrome characterized by development of tumors in multiple endocrine organs including the parathyroid glands, pancreatic islets, and the pituitary gland, and also in some non-endocrine organs (Marx et al., 1999b; Pannett and Thakker, 1999). MEN1 was first described as an autosomal dominant familial syndrome, and the gene mutated in MEN1 patients, *MEN1*, was identified in 1997 (Chandrasekharappa et al., 1997; Lemmens et al., 1997). *Men1* encodes a novel protein, menin, of unknown biochemical function. Because menin does not display an obvious homology to any known protein motifs, it is challenging to elucidate how menin functions as a tumor suppressor.

To date, over 300 germline mutations in MEN1 patients have been identified (Leotlela et al., 2003; Marx et al., 1999b; Pannett and Thakker, 1999). Tumors from MEN1 patients with one mutated germline *MEN1* allele often lose the normal *MEN1* allele (loss of heterozygosity, LOH). Mice heterozygous for the disrupted *Men1* allele also develop tumors in various endocrine glands with LOH of the *Men1* allele in the tumors, closely

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resembling the human MEN1 syndrome (Crabtree et al., 2001; Bertolino et al., 2003). These observations indicate that menin is a *bona fide* tumor suppressor.

Emerging evidence suggests that menin plays a vital role in regulation of gene transcription, cell proliferation, apoptosis, and genome stability, which are among the hallmarks dysregulated in cancer cells. These observations provide novel insights into how menin suppresses tumorigenesis. In the present review, we will focus on the recent progress in understanding how menin regulates cellular homeostasis and functions as a tumor suppressor. In particular, how menin modulates gene transcription, cell proliferation, apoptosis and genome stability will be critically evaluated.

2. Regulation of gene transcription

Numerous studies demonstrate a crucial role for menin in regulating gene transcription. For instance, menin interacts with a number of transcriptional factors such as JunD, NF-κB, Smad3, and homeobox-containing DNA binding protein Pem (Poisson et al., 2003), and inhibits the activities of JunD and NF-κb (Agarwal et al., 1999; Heppner et al., 2001). Ectopic expression of menin inhibits the promoter activity of the prolactin and insulin genes in pituitary tumor cells or insulinoma cells, respectively (Namihira et al., 2002; Sayo et al., 2002). Ectopic menin expression also inhibits insulin-induced endogenous *c-Fos* expression (Yumita et al., 2003). Several reports have recently shown that menin binds to the loci of several menin-dependent genes, including $p18^{ink4c}$, $p27^{kip1}$, *Hoxa9*, and *Hoxc8*, and regulates the transcription of those genes (Chen et al., 2006; Hughes et al., 2004; Karnik et al., 2005; Milne et al., 2005; Yokoyama et al., 2005). Genetic evidence also reinforces an essential role for menin in regulation of various endogenous genes. For example, ablation of *Men1* reduces the expression of $p27^{kip1}$, $p18^{ink4c}$, *caspase 8* and *Hoxc8* in mouse embryonic fibroblasts (MEF)(Hughes et al., 2004; Milne et al., 2005; Schnepp et al., 2004b), but enhances the expression of *insulin-like growth factor binding protein 2* (*IGFBP-2*) (La et al., 2004a), a gene involved in regulation of cell proliferation (Hoeflich et al., 2001). Complementing the menin-null cells with menin restores optimal expression of *caspase 8* and represses the *IGFBP-2* expression. Together, these studies strongly suggest an essential role for menin in regulating the transcription of endogenous genes.

Menin has been shown to associate with chromatin (Farley et al., 2006; Jin et al., 2003) and bind multiple endogenous genes including *hTERT* and *Hoxc8* (Hughes et al., 2004; Lin and Elledge, 2003). Menin also interacts with nuclear proteins such as transcription factors, histone methyltransferases (HMT) (Hughes et al., 2004; Kim et al., 2003) and histone deacetylases (HDAC). Thus, menin may function as a scaffold protein to regulate transcription of its target genes by associating with one of several of these various interacting proteins. These multiple interactions of menin and the various nuclear proteins may facilitate regulation of gene transcription and cellular homeostasis (Fig. 1).

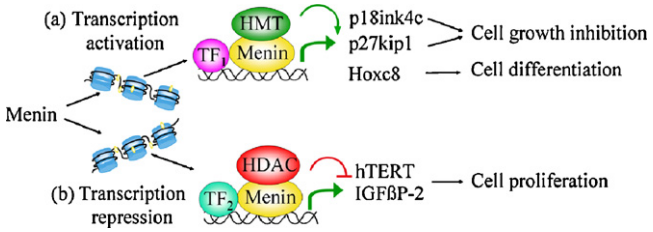

Fig. 1. A schematic model explaining how menin regulates gene transcription. (a) Menin and a hypothetically specific DNA binding protein (TF_1), together with transcription-activating histone methyltransferases (HMTs), such as MLL or MLL2, target to the loci of $p18^{ink4c}$, $p27^{kip1}$ and *Hoxc8* genes in chromatin. This HMT-containing complex methylates lysine 4 on histone H3, and changes chromatin structure and subsequently activates gene transcription. Activation of $p18^{ink4c}$, $p27^{kip1}$ and *Hoxc8* genes leads to cell growth inhibition or cell differentiation. (b) Menin and a hypothetically specific DNA binding protein (TF_2), together with a histone deacetylase (HDAC), may target the loci of menin target genes such as *hTERT* and *IGFBP-2*, to remove acetyl groups on histones and thus repress the target gene transcription. Inhibition of *hTERT* and *IGFBP-2* may result in reduced cell proliferation and maintenance of genomic stability. Interaction of menin and HDACs in regulating endogenous genes remains to be determined.

2.1. Regulation of gene transcription by menin via associating with histone methyltransferases

Menin regulates gene transcription at least in part by modulating chromatin structure. Menin has been shown to associate with a protein complex containing Drosophila *trithorax*-like histone lysine methyltransferases, the mixed lineage leukemia (*MLL*) gene products, MLL and MLL2, both of which are SET domain-containing methyltransferases (Hughes et al., 2004; Yokoyama et al., 2004). This complex contains multiple proteins that are homologous to the members of the yeast SET1 complex (COMPASS) and three mammalian SET1-like complexes, including activating signal cointegrator 2 complex (ASCOM), the HCF-1 complex and the MLL complex (Hughes et al., 2004), which had previously been found to methylate histone H3 lysine 4 (H3K4) and activate gene transcription. The menin-interacting complex isolated from mouse embryonic fibroblasts (MEF) also methylates H3K4 *in vitro* (Hughes et al., 2004). These results support a model that menin recruits histone methyltransferases (HMT) and thus upregulates gene transcription (Fig. 1a).

The menin complex has recently been shown to upregulate *p18ink4c* and *p27kip1* transcription by upregulating H3K4 methylation at the *p18ink4c* and *p27kip1* loci in both cultured cells and the murine pancreatic islets (Karnik et al., 2005; Milne et al., 2005). We and others have also showed that menin-HMT complex bind to the *Hoxa9* locus *in vivo* and promotes H3K4 methylation at the *Hoxa9* locus (Chen et al., 2006; Yokoyama et al., 2005). The trimethylated H3K4 recruits chd1, a methylated H3K4-specific binding protein of a chromatin remodeling complex, and activates gene transcription via chromatin remodeling (Chen et al., 2006; Pray-Grant et al., 2005).

The interaction between menin and HMT suggests that menin facilitates epigenetic regulation of gene transcription by histone modifications. It is likely that the cooperation between menin and MLL enhances the activity of menin in epigenetic control of gene expression (Fig. 1a). However, it is still unclear whether