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Menin dynamics and functional insight: Take your partners

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ABSTRACT

Despite the large number of recent findings and novelties, menin, the protein encoded by the gene responsible for multiple endocrine neoplasia type 1 syndrome, still remains a mystery. Although we have extensive knowledge about its interactions and functions, but it seems that we still cannot see the story in its full complexity. Here, the authors summarize recent findings and former basics on menin dynamics and function by following the way from regulation of *MEN1* gene transcription and translation towards the role of menin within and outside of the nucleus, highlighting new data on the possible role of its interactions with nuclear receptors.

1. Introduction

Multiple endocrine neoplasia syndrome type 1 (MEN1, OMIM 131100), first described by Wermer in 1954, is an autosomal dominantly inherited tumor syndrome (Wermer, 1954). Parathyroid, endocrine pancreas and pituitary are frequently, while the adrenal gland, foregut and connective tissue are rarely affected (Brandi, 2000).

The product of MEN1 gene, menin, cloned by Chandrasekharappa et al. (1997), is a tumor suppressor protein localized predominantly within the nucleus (Guru et al., 1998), but its clear function in tumorigenesis, despite several attempts, still remains unclarified.

Based on data of the last decade it became obvious that menin functions depend on cell type, cell cycle, and dynamic interaction between cells of endocrine organs and their microenvironmental components (Balogh et al., 2006). Menin in the nucleus may represent an integrator of different signals affecting the fate of cells and may function as a switcher of cell cycle checkpoints. This function is even more evident in cells exposed to different stressors causing DNA damage. Our attempt in this review is to summarize already identified menin functions and raise new questions that still need to be investigated.

2. Regulation of transcription and expression of *MEN1*

2.1. Organization of MEN1

Menin is translated from a 2.8 kb transcript expressed ubiquitously and throughout the animal world, from mollusks to *Homo sapiens*. The *MEN1* gene is composed of 10 exons, but menin itself is encoded by exons 2–10. It shows no homology to other gene products (Guru et al., 2001; Karges et al., 1999), but two nuclear localization signals on its C-terminal region have been described, which proved to be important for menin localization to the nuclear compartment (La et al., 2006). Nonsense mutations upstream of these residues and missense mutations of amino acids in nuclear localization signal regions clearly affect nuclear localization of menin. However, disease-causing mutations have been described on the whole MEN1 gene, and no mutation hotspots and no genotype–phenotype correlations have been observed (Brandi, 2000; Balogh et al., 2004, 2007) suggesting that other functions of menin are important in tumor suppression. The double knockout of *Men1* in the mouse is lethal early during embryogenesis (Bertolino et al., 2003; Crabtree et al., 2001), and no homozygous mutation has ever been found in human. The potential importance of promoter region of *MEN1* is reflected by the fact that in 5–10% of MEN1 families no mutations within the coding region have been identified and these families may have disease-causing mutation in the promoter region. The region upstream of the most abundant exon1b is conserved (60%) between human and mouse, and it contains both inhibitory and stimulatory regions that regulate transcription of *MEN1*. However, the precise mechanisms have not been fully elucidated. An additional source of cryptic mutations can

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Table 1
Summary of the putative regulators of MEN1 expression.

Regulator	Via	Refs.
Up-regulation of MEN1		
Somatostatin	SSTR2A	Mensah-Osman et al. (2008)
DNA damage	?	Wrocklage et al. (2002)
Increased cell proliferation	?	Wrocklage et al. (2002)
Fibrinogenesis	TGF-B-dependent collagen a2(I)	Zindy et al. (2006)
Down-regulation of MEN1		
Forskolin	PKA/CREB phosphorylation?	Mensah-Osman et al. (2008)
PRL	STAT-Bcl6	Karnik et al. (2007)
Menin	Negative feedback on the *MEN1* gene promoter	Zablewska et al. (2003)

?: not yet identified.

be large deletions, which easily escape the traditional sequencing-based mutational analysis. Gross deletion of the MEN1 gene has been rarely reported (Fukuuchi et al., 2006), however, one study including a large cohort of patients with MEN1 syndrome, estimated its prevalence as 1%. (Owens et al., 2008).

2.2. Regulators of MEN1 expression

Overviewing the literature, it is hard to find evidence for extracellular regulators of menin expression. Somatostatin has been shown to increase menin expression by inhibiting protein kinase A, and menin is highly expressed in cells expressing somatostatin receptors (e.g. SSTR2A). Via the SSTR2A receptor, which couples to Gi proteins, the suppression of the cAMP–PKA signaling pathway enhances menin expression. Underlying these findings, menin expression was found to be suppressed by PKA inducer forskolin, and vice versa: suppression of PKA (with siRNA) increased the basal levels of menin. Furthermore, it has been presumed that activated PKA phosphorylates the transcription factor CREB, which binds to the promoter of the MEN1 gene and suppresses its transcription. Although the CREB binding site within the menin promoter has not been identified yet (Mensah-Osman et al., 2008), this menin-mediated action of somatostatin could give an explanation for its main effects: inhibition of hormone release and cell growth.

Another study showed that lactogenic hormones, such as prolactin, can decrease menin expression via augmenting the STAT5–Bcl6 pathway, thus, causing transcription inhibition of p18 and p27, which results in pancreas β-cell proliferation. Furthermore, steroids such as progesterone and dexamethasone can inhibit the mitogenic effects of prolactin on β-cells, and it has been shown that simultaneous administration of prolactin and progesterone attenuated the inhibitory effect of prolactin on menin transcription (Karnik et al., 2007).

It has been shown by Zablewska et al. (2003) that down-regulation of menin levels activates the *MEN1* gene promoter as a compensatory mechanism, and overexpression of menin down-regulated its own expression. Furthermore, menin was found to be up-regulated in sporadic pituitary adenomas compared to non-neoplastic adenohypophysis (Wrocklage et al., 2002), suggesting also a compensatory mechanism as a reaction for increased proliferation. This raises the possibility that menin may act as a genome guardian, and its level is up-regulated in case of DNA damage and increased cell proliferation.

Another study has confirmed in hepatocellular carcinomas and cirrhotic liver tissue that menin is up-regulated in correlation with activated fibrinogenesis and has emphasized the causative (and a putative tumor-promoting) role of menin via the modulation of TGF-B-dependent collagen a2(I) expression (Zindy et al., 2006), however, the compensatory role of menin still cannot be excluded. All these mechanisms are summarized in Table 1.

2.3. Postranscriptional regulation of menin activity

Few data are available about regulation of menin by postranscriptional mechanisms. Phosphorylation of residues Ser543 and Ser583 of menin failed to affect its subcellular localization, the histone methyl-transferase activity, or the degradation and the binding of menin to the *Hoxc8* locus. Furthermore, no impact on the cell cycle was shown, and vice versa, changes in the levels of phosphorylation of these two residues were not detected during the different cell cycle phases (MacConaill et al., 2006). The role of these phosphorylations still remains unclear and no further post-translational modification of menin itself has been revealed.

Table 2
Effects of menin inside and outside the nucleus.

Effects	Mechanism/involved proteins	Refs.
Within the nucleus		
G1/S checkpoint	Repressing ASK	Schnepp et al. (2004a,b)
	Regulating the expression of CDK inhibitors (e.g. p18, p27)	Kottemann and Bale (2009)
Response to DNA damage	Interacting with FANCD2/CHES	Jin et al. (2003) and Busygina et al. (2006)
Transcription regulation	Participating in the histone methyl-transferase complex	Karnik et al. (2005), La et al. (2007) and Hughes et al. (2004)
	Participating in the histone deacetylase complex	Kim et al. (2003)
	Interacting with transcription factors (e.g. JunD, Smad3, NF-κB)	Agarwal et al. (1999), Heppner et al. (2001), Kim et al. (2003) and Canaff (2004)
	Interacting with nuclear receptors (e.g. ER, VDR, PPAR-gamma)	Dreijerink et al. (2006) and Dreijerink et al. (2009a,b)
From the nucleus to the cytoplasm		
Transcription regulation	Contributing to β-catenin transport	Cao et al. (2009)
Outside of the nucleus		
Apoptosis regulation	Enhancing caspase 8 transcription	La et al. (2007)
?	Interacting with vimentin and glial fibrillary acidic protein	Lopez-Egido et al. (2002)

?: not yet identified.