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MEN1 and microRNAs: The link between sporadic pituitary, parathyroid and adrenocortical tumors?

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ABSTRACT

Sporadic tumors of the pituitary, parathyroids and adrenal cortex are unique, as their benign forms are very common, but malignant forms are exceptionally rare. Hereditary forms of these tumors occur in multiple endocrine neoplasia syndrome type 1 (MEN1). We hypothesize that the pathogenic link among the sporadic tumors of these organs of different germ layers might be represented by common molecular pathways involving the MEN1 gene and microRNAs (miR). *miR-24* might be a microRNA linking the three tumor entities, but other candidates such as *miR-142-3p* and microRNAs forming the DLK1-MEG3 miRNA cluster might also be of importance.

Introduction

From an oncological point of view, tumors of the pituitary, parathyroids and the adrenal cortex can be regarded as unique, as their benign forms are very common, but malignant forms are exceptionally rare. Pituitary adenomas are the most common intracranial neoplasms with an incidence of 77.6-94/100000/year [1–3]. In contrast, pituitary cancer is extremely rare, representing only 0,2–1% of all pituitary tumors [4–6]. Similarly, despite the high incidence of parathyroid adenomas, parathyroid cancer is exceptional, only less than 1% of all primary hyperparathyroidism cases [7,8]. Moreover, the prevalence of adrenocortical adenomas reaches 4.4–6% [9] in elderly people contrasting the very low incidence of 0.5–2/million/year related to adrenocortical cancer [10].

It is unclear what differentiates these three organs from other organs where there is no such great discrepancy in the frequency of benign and malignant tumors (e.g. both benign and malignant tumors are common in the breast, liver and colon). These three organs derive from different germ layers (pituitary – ectoderm, adrenal cortex – mesoderm, parathyroid – endoderm) that make a potential molecular link between these three organs even more intriguing.

Multiple endocrine neoplasia type 1 syndrome (MEN1) is a rare hereditary tumor syndrome (prevalence: 1:30.000) caused by mutations of the MEN1 gene. Its major clinical manifestations include primary hyperparathyroidism, duodenopancreatic neuroendocrine tumors (gastrinoma, insulinoma, hormonally inactive tumors etc.) and pituitary adenomas. Moreover, adrenocortical tumors are also observed in 9–40% of MEN1 cases [11–13]. Whereas MEN1-related neuroendocrine tumors can be malignant, parathyroid lesions are always benign (hyperplasia) and pituitary lesions are also predominantly benign, however, their aggressive growth is common. MEN1-linked adrenocortical tumors are almost always benign, as well [14].

MicroRNAs are major regulators of gene expression at the post-transcriptional level that target the 3′ untranslated region of messenger RNAs and induce their degradation or translational inhibition. Altered expression of microRNAs is considered to be a major event in tumor formation and there are already plenty of data in many different organs and tumors showing their pathogenic relevance [15]. Differential expressions of microRNAs have been described between normal tissues, benign and malignant tumors of the pituitary [16–18], parathyroid [19,20] and adrenal cortex [21–24], as well.

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We hypothesize that interactions between MEN1 and microRNAs might represent the link between sporadic pituitary, parathyroid and adrenocortical tumors.

Multiple endocrine neoplasia type 1 (MEN1) syndrome

The MEN1 syndrome arises due to germ-line mutations of the MEN1 gene that encodes a putative tumor suppressor, menin. Menin is involved in many molecular pathways including NF-κB, TGF-β, BMP, PI3K/Akt and Wnt signaling pathways [25], affects the levels of transcription factors e.g. JunD, influences genome stability, inhibits cell proliferation and regulates gene expression by epigenetic mechanism e.g. histone methylation and acetylation [26].

Somatic mutations of the MEN1 gene are found in sporadic pituitary, parathyroid and adrenocortical tumors [27]. Intragenic deletions of the MEN1 gene were identified as the most prevalent somatic events in sporadic primary hyperparathyroidism [28]. Recent studies applying next generation sequencing revealed that somatic mutations in MEN1 represent the main driver mutation in 35% of cases [29,30]. Sporadic MEN1 mutations are also found in 0,6–3,5% of pituitary tumors [26,31]. In sporadic adrenocortical tumors MEN1 gene alterations were described in 2–7% of cases [31,32,34].

Although the prevalence of these somatic gene alterations is variable, MEN1-related pathways are considered as potentially relevant in linking the pathogenesis of these three tumor entities [32–35].

Beside somatic genetic alterations, epigenetic gene expression regulation by microRNAs appears also to be involved in the regulation of MEN1 gene expression. The MEN1 mRNA has been shown to be targeted by different microRNAs [36,37], thus epigenetic regulation of MEN1 pathways by microRNAs can contribute to tumorigenesis.

Moreover, there are also data indicating that menin as a transcription factor participates in the biogenesis of miRNAs e.g. *let-7* and *miR-155* [38]. The loss of menin due to mutations of the MEN1 gene might thus alter the microRNA expression pattern in various tissues and thus a bidirectional communication between microRNAs and menin can be envisaged that could be relevant in tumor formation.

miR-24 as a validated microRNA targeting the MEN1 mRNA

Up-regulation of *miR-24* was described in MEN1 associated tumors, such as gastropancreatic neuroendocrine, parathyroid and pituitary tumors.

In parathyroid tumors, *miR-24-1* was shown to target the MEN1 mRNA, and thereby could contribute to the loss of MEN1 gene expression. In this way, this could represent an "incoherent regulatory feed-back loop" as termed by Luzi et al. contributing to the Knudson's two hit model of tumorigenesis [39]. Moreover, in BON-1 cells derived from a lymph node metastasis of a pancreatic neuroendocrine tumor, menin was shown to target the pri-microRNA form of *miR-24-1* thus facilitating its degradation [40]. Furthermore, irrespective of the fact that the tumor is bearing MEN1 mutations or not, increased expression of *miR-24* was observed in sporadic parathyroid tumors relative to normal tissues [Grolmusz et al. submitted].

In pancreatic endocrine tumors, Volinia et al. detected overexpressed level of *miR-24* relative to normal tissues [41], and in a recent *in vitro* study *miR-24* has been validated to bind 3′UTR region of MEN1 gene resulting in the down-regulation of menin expression leading to decreased level of cell cycle inhibitors and enhanced proliferation. Moreover, a similar hypothetic regulatory feed-back loop as in parathyroid tumors was suggested: menin and its partner protein MLL bind to the chromosomal locations of *miR-24* and positively affect its transcription [42].

Although craniopharyngeomas are derived from Rathke's pouch and not from pituitary tissue, it is worth noting that *miR-24* is underexpressed in craniopharyngiomas relative to normal pituitary tissues, as well. Additionally, *miR-24* targets directly the tumor's most important driver gene, CTNNB1 [43].

miR-24 is expressed in the adrenal cortex too, and beside potentially targeting the MEN1 mRNA, it has been shown to be involved in the posttranscriptional regulation of aldosterone and cortisol synthesis by regulating 11ß-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) expression [44].

miR-24 and MEN1 thus seem to be implicated in a complex interplay that could be relevant in different tumors including the three tumor entities discussed.

Another potential mechanism of MEN1-microRNA interplay: menin targets miR-142-3p

Another potential link between MEN1 and microRNAs is represented by *miR-142-3p* that has been shown as a microRNA gene regulated by menin in human osteosarcoma tissues [45]. Adrenocorticotropin (ACTH) stimulating the adrenal cortex was shown to induce *miR-142-3p* expression that was validated to target the glucocorticoid receptor gene [46]. We could hypothesize a regulatory loop involving MEN1, *miR-142-3p* and the glucocorticoid receptor that might be implicated in adrenocortical tumorigenesis (Fig. 1) Underexpressed MEN1 in adrenocortical tumors would result in decreased *miR-142-3p* expression and thus increased

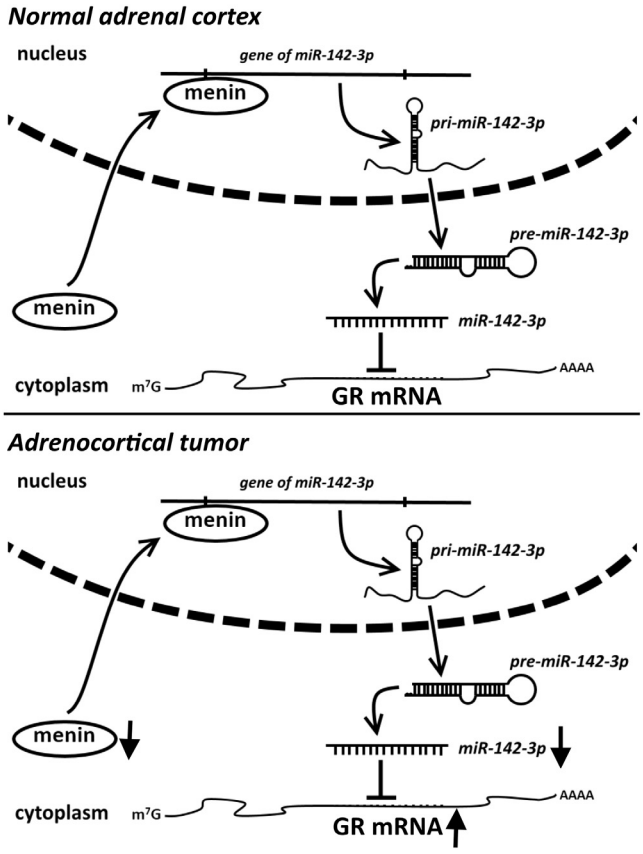

Fig. 1. Hypothetic interactions between MEN1, *miR-142-3p* and the glucocorticoid receptor (GR) in the adrenal cortex. Downward arrows represent down-regulation, upward arrows up-regulation.