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The Role of Menin in the Thyroid Lesions

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Abstract

Multiple Endocrine Neoplasia type 1 is a hereditary syndrome, with an autosomal dominant transmission, characterized by hyperplasia/ tumours in endocrine organs (parathyroids, pituitary, gastro-intestinal system). The gene involved is MEN1 gene on chromosome 11q13 which encodes menin, an oncosuppressive nuclear protein according to Knudson "two hit" hypothesis. Expression of menin and its inactivation in the thyroid gland have long been debated.

Keywords: Menin • Morphology • Neoplasma • Tumors

About the Study

Thyroid pathology is not systematically searched in MEN1 patients and most of the lesions are an incidental discovery during ultrasound [1-3]. Studies showed that the incidence of thyroid lesions varies from 2.6-25% and consists in adenomas, goiters, rarely carcinomas and that 45% of the thyroid lesions are incidentalomas in MEN1 patients and 51% in non-MEN1 patients [4,5]. In order to search for the effects of menin in thyroid tissue, several murine models expressing certain oncogenes were needed. In our article, we studied whether the selective inactivation of MEN1 gene in transgenic mice might induce an increased index of proliferation and a more rapid development of thyroid hyperplasia and/ or tumours by determining several aspects including thyroid aspect, Ki 67 index of proliferation, cellular density and histological aspects [6]. As murine models we used mice with targeted inactivation of menin in the thyroid gland, MEN+/- menin heterozygote and MEN-/- menin homozygote, RET/PTC3 model with/ without inactivation of menin and E7 model with/ without inactivation of menin and wild type mice. We observed that E7 and RET/PTC3 thyroid glands had a higher weight than WT ones, and E7 thyroid glands were heavier than RET/PTC3 ones. The groups E7 MEN-/- and RET/PTC3 MEN-/- had a smaller weight and surface as compared to the other E7 and RET/PTC3 groups. Differences were also observed regarding the surfaces of the thyroid glands – E7 and RET/PTC3 thyroid glands were larger than WT, and RET/PTC3 thyroid glands were smaller than E7 ones. As regarding the Ki 67 index of proliferation, it was increased in E7 group versus WT one, but smaller than in the RET/PTC3 one and increased in RET/PTC3 group versus WT one. We observed a higher Ki67 index of proliferation in the groups MEN+/- and MEN-/- as compared to the WT one. Differences were also observed for the cellular density – in the E7 group it was not different from WT, but it was reduced as compared to the RET/PTC3 one and increased in RET/PTC3 group as compared to the one in the WT group. Another difference was observed in the group of thyroid glands with menin inactivation, in which the cellular density was increased than in the WT group.

The histopathological patterns were different in each group – in groups MEN+/- and MEN-/- the architecture of the thyroid gland was normal, with small and medium sized follicles lined with cubic cells. In the group expressing the E7 oncogene we observed a homogenous pattern of diffuse hyperplasia and also small papillary projections on the distended follicular wall lined with cubo-cylindrical epithelium, dense nuclei which gave a "palisade like" aspect. The most heterogeneous group was the one with the presence of RET/PTC3 oncogene. Here we observed several patterns like "Proliferative Papillary Cystic Changes" with spindle cells and remodelling – PPCC, cribriform (Cr) pattern, solid pattern and lesions termed "tumours" [7,8]. The most frequent pattern observed was PPCC with replacement of the normal architecture by large cysts lined by flattened follicular cells with exuberant pseudo papillary structures, more or less complex, with or without secondary small follicles. Despite the presence of tall, columnar cells, "palisade like" with hyperchromatic nuclei, we did not notice any morphologic changes specific of papillary carcinoma (ground glass appearance, clearing, grooves). In rare cases, we also observed oncocytic metaplasia made of large eosinophilic cells with irregular nuclei with rare pseudo inclusion figures. Other lesions in this group were benign dystrophic epidermoid metaplasia, spindle cell areas and a fibrous dense stroma, containing some chronic inflammatory cells, macrophages and cholesterol. The lesions termed "tumours", consisted of macroscopically visible nodules, 1-5 mm in diameter, not or partially circumscribed with an architectural pattern of growth trabecular or solid and necrosis foci in the centre of the lesions. The cells were fusiform, round or polygonal, with abundant basophilic cytoplasm and showed obvious atypical nuclear features with mitoses. These changes were independent from the menin status in either group.

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The hypothesis of our study was that the selective inactivation of menin in transgenic mice could lead to a more aggressive pattern of thyroid dysplasia and a more increased index of proliferation. We did observe an increased Ki67 index of proliferation in the MEN+/- and MEN-/-thyroids which is explained by the oncosuppressive properties of menin and its role in the cell cycle division and apoptosis. Loss of the sequence of menin which interacts with the DNA by its C terminal region results in a failure to suppress the cell proliferation and no longer blocks the G2-M and G1-S phases during the cell division cycle [9]. We did not observe any tumor formation and this could be explained by the fact that the oldest mouse in our groups was 18 months old. In the presence of RET/PTC3 and E7 oncogenes, the selective inactivation of menin determined a more reduced thyroid surface and weight explained by a possible crosstalk between signalisation pathways, but did not change the Ki67 index of proliferation or the cellular density. We did not see either any tumour formation which could be explained by a possible loss of expression of the transgenes during repeated breading or by the fact that our wild type strain increases to a lesser extent the rate of tumour formation.

The histological lesions could resemble the human poorly differentiated thyroid carcinoma, the papillary thyroid carcinoma due to oncocytic metaplasia or the diffuse sclerosing variant of PTC due to extensive fibrosis, chronic inflammation, malpighian metaplasia but there is an uncertain degree of malignancy.

The limitations of our study are the reduced number of aged mice which are prone to develop more aggressive features of thyroid histology and the lack of hormonal status evaluation, since TSH stimulation is known to induce a "solid" pattern in the RET/PTC1 severely hypothyroid mice [10,11].

In conclusion, our preliminary results show that the selective menin inactivation in the thyroid gland of transgenic mice does not induce thyroid tumours but influences the proliferation of follicular cells. There is a disorganization of the thyroid architecture in the presence of the RET/PTC3 and E7 oncogenes and so, further immunohistochemical and molecular studies of genes involved in proliferation are needed.

References

1. Moldawer, MP, Nardi GL and Raker JW. "Concomitance of multiple adenomas of the parathyroids and pancreatic islets with tumor of the pituitary: a syndrome with a familial incidence." Am J Med Sci 228 (1954): 190-206.
2. V Thakker, Rajesh, Paul J Newey, Gerard V Walls and John Bilezikian, et al. "Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1)." J Clin Endocrinol Metab 97 (2012): 2990-3011.
3. G. Knudson, Alfred. "Hereditary cancer: two hits revisited." J Cancer Res Clin Oncol 122 (1996): 135-140.
4. Lodewijk, Lutske, Pim J Bongers, Jakob W Kist and Elfi B Conemans, et al. "Thyroid incidentalomas in patients with Multiple Endocrine Neoplasia type 1." Eur J Endocrinol 172 (2015): 337-342.
5. Dagdelen, Selcuk, Nese Cinar and Tomris Erbas. "Increased thyroid cancer risk in acromegaly." Pituitary 17 (2014): 299-306.
6. Căpraru, Oana-Maria, Nicole Berger, Nicolas Gadot and Myriam Decaussin-Petrucci, et al. "Histopathological changes induced by selective inactivation of menin on the thyroid gland in RET/PTC3 and E7 transgenic mice. A study of 77 cases." Rom J Morphol Embryol 57 (2016): 1-8.
7. Burniat, Agnès, Ling Jin, Vincent Detours and Natacha Driessens, et al. "Gene Expression in RET/PTC3 and E7 Transgenic Mouse Thyroids: RET/PTC3 But Not E7 Tumors Are Partial and Transient Models of Human Papillary Thyroid Cancers." Endocrinology 149 (2008): 5107-5117.
8. Jin, L, Burniat A, Dumont J-E and Miot F, et al. "Human thyroid tumours, the puzzling lessons from E7 and RET/PTC3 transgenic mice." Br J Cancer. 99 (2008): 1874-1883.
9. Balogh, Katalin, Károly Rácz, Attila Patócs and László Hunyady, et al. "Menin and its interacting proteins: elucidation of menin function." Trends Endocrinol Metab 17 (2006): 357-364.
10. Căpraru, Oana-Maria, Nicole Berger, Nicolas Gadot and Myriam Decaussin-Petrucci, et al. "Consequences of the loss of selective expression of the Men1 gene in the murine thyroid on the neoplastic transformation induced by the expression of the RET / PTC3 oncogene." Ann Endocrinol 76 (2015): 306.
11. J. Powell, Daniel, John Russell, Ken-ichi Nibu and Guoqi Li, et al. "The RET/PTC3 Oncogene: Metastatic Solid-Type Papillary Carcinomas in Murine Thyroids." Cancer Res 58 (1998): 5523-5528.

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