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GENOMIC INSTABILITY IN ONCOCYTIC FOLLICULAR ADENOMA OF THE THYROID

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Resume

Oncocytic follicular adenomas of the thyroid are neoplasmas of follicular cell origin that are predominantly composed of large polygonal cells with eosinophilic and granular cytoplasm. However, the pathological characteristics of these tumors are the largely unexplored. The diagnosis of malignancy is reliably based on histological evidence of capsular invasion or vascular invasion, extrathyroidal local tissue invasion, and nodal or distant metastasis. Both the initiation and progression of cancer can be caused by an accumulation of genetic mutations that can induce genomic instability.

***Keywords**: adenoma, oncocytic cells, tumor, nuclear foci.*

Резюме

ГЕНОМНАЯ НЕСТАБИЛЬНОСТЬ ПРИ ОНКОЦИТАРНОЙ ФОЛЛИКУЛЯРНОЙ АДЕНОМЕ ЩИТОВИДНОЙ ЖЕЛЕЗЫ

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Онкоцитарная фолликулярная аденома (ОФА) диагностируется при отсутствии доказательств о капсулярной и сосудистой инвазии, а также при отсутствии ядерных особенностей папиллярной карциномы при щитовидных поражениях заключенных в капсулу, также и онкоцитарная фолликулярная карцинома диагностируется при проявлении как сосудистых, так и\или капсулярных инвазии при отсутствии ядерных особенностей папиллярной карциномы. Тем не менее, клиническое значение онкоцитарного изменения в опухоли щитовидной железы остается неясным и спорным. Диагноз злокачественного новообразования надежно основывается на гистологических данных о капсулярной или сосудистой инвазии, инвазии в экстратиреоидную локальную ткань и узловых или отдаленных метастазах. Как возникновение, так и прогрессирование рака может быть вызвано накоплением генетических мутаций, которые могут вызвать нестабильность генома.

***Ключевые слова:** аденома, онкоциты, опухоль, ядерные очаги.*

Түйіндеме

ҚАЛҚАНША БЕЗІ ФОЛЛИКУЛЯРЛЫҚ ІСІКТЕРІ ОНКОЦИТАРЛЫҚ ТҮРІНІҢ ГЕНОМДЫҚ ТҰРАҚСЫЗДЫҒЫ

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Онкоцитарлық фолликулярлық аденома капсулалық және тамырлы инвазия белгілері болмаған кезде, сондай-ақ қалқанша безінің капсулдалған зақымдануында папиллярлық карциноманың ядролық белгілері болмаған кезде

диагноз қойылады, ал онкоцитарлық фолликулярлық карцинома капсулалық және тамырлы инвазия белгілері болғанда диагноз қойылады. Дегенмен, қалқанша безінің ісігіндегі онкоцитарлы өзгерістің клиникалық мәні түсініксіз және даулы болып қала береді. Қатерлі ісік диагнозы капсулалық және тамырлық инвазияның, экстратиреоидты жергілікті инвазияның, орталықты және шектелген метастаздардың гистологиялық көріністерімен нақты негізделеді. Қалқанша безі ісіктерінің онкоцитарлық өзгерістерінің клиникалық маңыздылығы түсініксіз және даулы болып қалуда. Қатерлі ісіктің пайда болуы және дамуы генетикалық мутациялардың жинақталуымен себеп болады, өз кезегінде геномдық тұрақсыздыққа әкелуі мүмкін. Осы зерттеменің мақсаты- қалқанша безі фоликуллярлық ісіктері онкоцитарлық түрінің геномдық тұрақсыздығының дәрежесін бағалау болды.

Түйінді сөздер: *аденома, онкоцитарлық жасушалар, ісік, ядролық фокус.*

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Background

Oncocytic follicular adenomas (FA) of the thyroid, also known as oxyphilic adenomas or Hurthle cell adenomas, are neoplasms of cells of follicular origin, predominantly consisting of large polygonal cells with eosinophilic granular cytoplasm rich in mitochondria [1].

Oncocytic follicular adenoma (OFA) shall be diagnosed in the absence of evidence of capsular and vascular invasion, as well as in the absence of nuclear features of papillary carcinoma in encapsulated thyroid lesions, and oncocytic follicular carcinoma shall be diagnosed in the presence of both vascular and/or capsular invasion in the absence of nuclear features of papillary carcinoma [4,7].

The clinical significance of oncocytic changes in thyroid tumors remains unclear and controversial. It is believed that the transformation of Hurthle cells is caused by an imbalance between mitochondrial proliferations on the one hand, and mitochondrial destruction on the other hand, which leads to the accumulation of mitochondria (Figure 1).

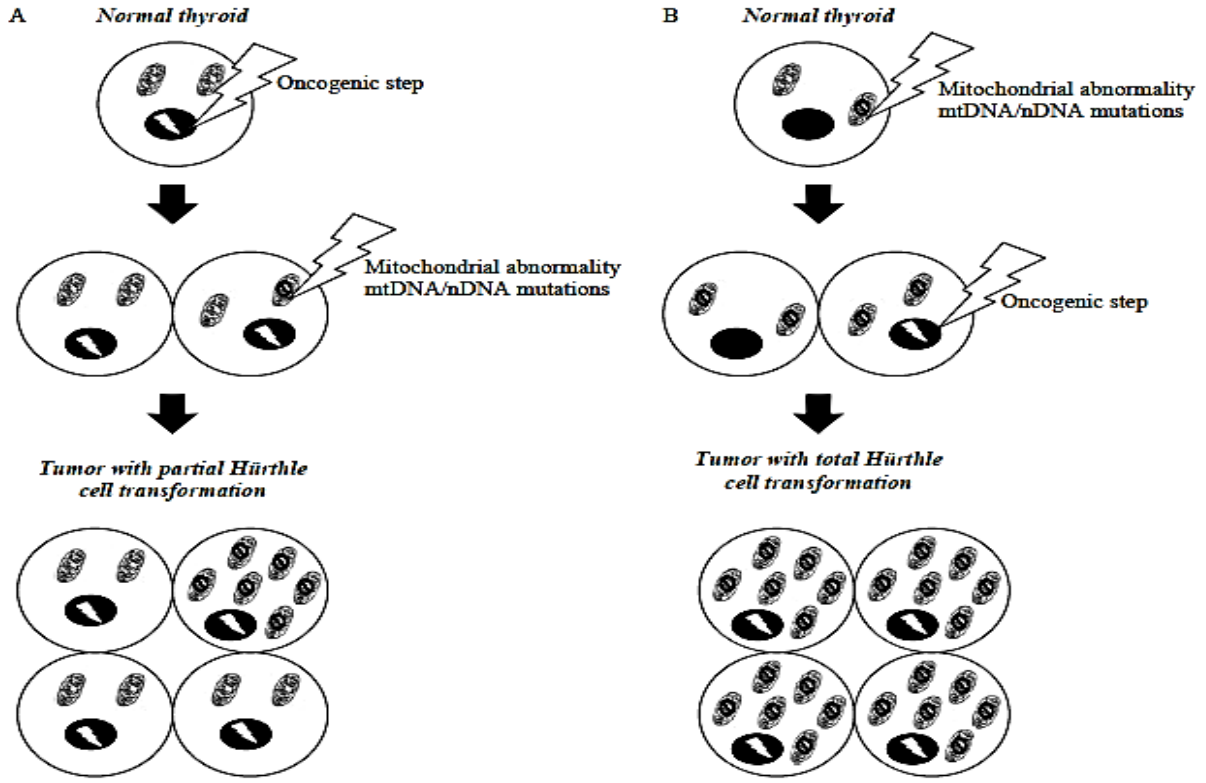

Figure 1. Depiction of case (A) with partial transformation of Hurthle cells and case (B) with complete transformation of Hurthle cells. If oncogenic mitochondrial pathology, the tumor may have partial Hurthle cell transformation (A); if mitochondrial pathology is preceded by an oncogenic stage, it is likely that the tumor demonstrates a general transformation of Hurthle cells (B).

Some studies have shown that oncocytic carcinomas are more "aggressive" than the usual types of highly differentiated thyroid cancers, and as a result lead to a higher metastasis rate and low survivability; therefore, an aggressive surgical regimen is recommended for all oncocytic follicular tumors. On the other hand, other studies show that oncocytic follicular tumors are not more "aggressive" than their conventional counterparts [5,3,9].

53BP1 is a nuclear protein that rapidly localizes to DNA double-strand breaks and activates p53 along with other kinases that play a key role in DNA repair, cell cycle arrest, and apoptosis [8,10,11]. Expression of 53BP1 in immunofluorescenceanalysis shows different patterns of gene expression, which are distinguished by different malignant activity of the tissue. nuclear foci expression of 53BP1 episodically show the occurrence of a response to DNA damage in cancer cells [2,4]. The presence of episodic DDR (protein DNA damage response) for episodic DSB (DNA double-strand breaks) is one of the biological future indicators for comparative genomic hybridization.

Aim. To assess the degree of genomic instability in oncocytic follicular adenoma of the thyroid gland.

Materials and methods

A total of 24 surgically resected formalin-fixed, paraffin-embedded (FFPE) thyroid tumors, including 12 oncocytic and 12 normal follicular adenomas, were available for this study.

CGH analysis was performed based on comparative genomic hybridization array (aCGH) for genomic DNA analysis.

A standard immunofluorescence method was used to detect 53BP1 with anti-53BP1 polyclonal antibodies.

Results

In this study, we classified 53BP1 immunoreactivity into three types: I) stable: no or weak nuclear staining; II) intermediate: one or two discrete nuclear foci; III) unstable: three or more discrete nuclear foci and intense heterogeneous nuclear staining (Figure 2).

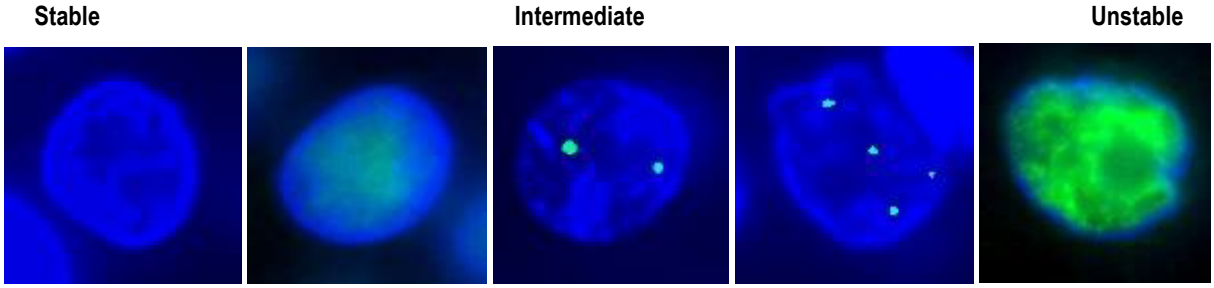

Figure 2. Representative images of 53BP1 staining patterns: stable type; intermediate type; and unstable type.

Expression of 53BP1 in oncocytic follicular adenomas shows the formation of focis with intense heterogeneous nuclear staining and in normal follicular adenomas shows one discrete nuclear foci. In relation to the stable type of 53BP1 expression, the unstable type showed an increase during carcinogenesis [6].

It should be noted that in this study, the frequency of unstable expression of 53BP1 was significantly higher in oncocytic follicular adenoma than in normal, according to Fisher's exact test (p = 0.0028), as shown in the table.

Table 1.

Comparison of the expression type of 53BP1 in oncocytic and normal follicular adenomas.

Types	53BP1 expression types		
	Stable	Intermediate	Unstable
Normal follicular Adenomas (n=12)	9 (75%)	3 (25%)	0
Oncocytic (n=12)	1 (8.3%)	5 (41.7%)	6 (50%)
p-value	0.0028**		

Then, we investigated the association between 53BP1 expression pattern and genomic instability using comparative genomic hybridization. Statistical analysis showed that total CNAS length (abberation copy number) was significantly longer in oncocytic follicular adenomas ((p = 0.0350, mean 884.3 MBP, range 466-1526) than in normal follicular adenomas (mean 84.5 MBP, range 21-239), as well as the total number of CNAS was also significantly higher in the oncocytic variant ((p = 0.0432, mean 109.5 genes, range 21-179) compared with normal follicular adenomas (mean 20.5 genes, range 3-54).

Based on the aCGH results, we further examined certain chromosomal loci where significantly higher amplification occurs. Chromosome 1 amplification was found in the oncocytic variant, but not in normal follicular adenomas. To test this finding, we evaluated by FISH analysis and our result focused tumors on the TP73 protein. Correlation analysis between 53BP1 and TP73 expression showed a significant positive correlation (R = 0.5983, p = 0.0020), showing that unstable 53BP1 expression correlates with elevated levels of TP73 expression in oncocytic follicular adenomas.

Interpretation

This study shows for the first time the existence of differences in the type of expression of 53BP1 between oncocytic and normal follicular adenomas. The prevalence of unstable expression of 53BP1 immunoreactivity suggests the induction of endogenous DDR (DNA damage response) mechanisms, which was significantly higher in oncocytic than in normal follicular adenomas, indicating a higher level of genomic instability in oncocytic follicular adenomas. This study also showed higher levels of CNA in tumor DNA of

oncocytic follicular adenomas, showing unstable expression of 53BP1, providing further evidence for a role for genomic instability in oncocytic follicular adenomas variant and its association with the 53BP1 expression pattern.

Unstable expression of 53BP1 in oncocytic follicular adenoma showed an association with higher levels of CNA by aCGH and had a significant positive correlation with the level of expression of tumor protein 73.

Our data indicate a higher level of genomic instability in the oncocytic variant compared to conventional follicular adenomas.

Conclusion

Thus, this may be an assumption that mitochondrial dysfunction can block the process of apoptosis, which results in an increase in the survivability of genetically damaged cells and, at the same time, in genome instability during oncogenesis in oncocytic neoplasms.

Further study is required to elucidate the mechanisms underlying the increase in DNA double-strand breaks in oncocytic follicular adenomas.

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