Review on thyroid carcinoma of molecular pathology

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Abstract

Recently studies indicated that the genesis of thyroid cancer is closely correlated with suppressor gene, metastasis-associated gene and so on. Their expression is different in varied types of thyroid carcinoma. By the detection of the above tumor molecular markers, combining with fine needle aspiration (FNA) of thyroid gland and immunohistochemistry technique, the property of thyroid tumor could be evaluated, and provide new molecular foundation for tumor grading and prognosis. [Life Science Journal. 2007; 4(2): 33 – 36] (ISSN: 1097 – 8135).

Keywords: thyroid carcinoma; p53; RET; telomerase; nm23; metastasis-associated gene

1 Introduction

Thyroid carcinoma is a common malignant tumor of endocrine glands, and the most common cancer in head and neck. With the development of molecular research recent years, clinical and basical research on thyroid carcinoma have got full-grown improvement. Similar to other malignant tumor, the genesis and development of thyroid carcinoma is correlated to diverse oncogene, tumor suppressor gene and metastasis-associated gene. The recent progression of thyroid carcinoma molecular pathology will be introduced in this article.

2 Molecular Biology Base Research

Cancer is the gene related disease. The gene include oncogene, tumor suppressor gene and metastasis-associated gene, etc. In gene research of malignant tumor, many scholars proposed the multi-genes synergistic action hypothesis[1], which said that different stages of tumor are related with at least two kinds, dys-activated, different oncogene act differently butsynergistically, result in carcinogenesis finally. As the most commonmalignant tumor of endocrine system, the pathogenesis of thyroid carcinoma hasn't been clear completely now, but its genesis is related to dys-expressed and synergistic action of varied oncogenes.

3 p53

p53 is one of the highest correlative genes with human tumor so far, its structure abnormality usually betide at exon 5 – 8 of remarkably stenoplastic sequence, and more than 95% abnormality is gene mutation. In the process of gene mutation, function of p53 is also changed, losting the function of inhibiting tumor genesis. Recently, it has been discovered that p53 is related to different types of thyroid carcinoma. For instance, between undifferentiated type and differentiated type of thyroid carcinoma, between lymphatic metastasis and without lymohatic metastasis, the expressions of p53 were significantly different[2–3]. Some scholars considered that p53 mutation possibly induced thyroid gland from poor differentiation to cancerization. The malignance of papillary thyroid carcinoma with p53 mutation is higher[4]. Other research indicated that p53 mutation is possibly the fundamental causes of thyroid gland canceration caused by ionising radiation[5]. So it could be concluded that p53 mutation has an effect on infiltration, lymphatic metastasis and prognosis of thyroid carcinoma.

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4 RET Oncogene

RET oncogene is firstly discovered in NIH/3T3 cell of transformed mouse, locating at 10q11.2 and encodes a kind of transmembranous tyrosine protein kinase receptor. By interaction with the acceptor on differentiation region of tyrosine phosphorylation, RET oncogene activates intracellular signal and controls cell differentiation and cell proliferation. RET oncogene is the gene most related with thyroid carcinoma differentiation by far[6–7]. RET oncogene mutation can cause papillary thyroid carcinoma (PTC), multiple endocrine neoplasia type2 (MEN2) and sporadic medullary thyroid carcinoma (MTC)[5]. The activated mechanism of RET in PTC is gene rearrangement, and the major types of rearrangement are PTC1, PTC2 and PTC3, and RET/PTC1 is the main type among them. But in MEN2 and MTC, gene mutation is also found. Gene mutation in MEN2 is at the level of germ line, and can transmit to offsprings. The screening for RET oncogene mutation in MTC high-risk group has been evolved internationaly now, and whether offsprings may be inherite it or not is to analyze the mutated gene location, at the germ line or somatic cell [8–9].

5 Oncoproteins (Oncogene Proteins)

With "Post Human Genome Project" penetrated deeply, research on oncoproteins is more thoroughly and widespread. Through detection of oncogene proteins, researchers on relationship between oncogene, tumor suppressor gene and thyroid carcinoma gradually increases. Many researches have discovered[7] that the detection of oncoprotein is helpful to evaluate the differentiation and the lymph node metastasis[10–13]. Some scholar discovered that there were one or more kinds of oncogene products expression in thyroid carcinoma tissues by detection of various oncoproteins (such as c-erbB-2, P21, P53, bcl-2, c-myc, P16), and the expression of oncogene proteins is markedly different between tissue thyroid adenoma and-tissue adjacent to thyroid adennoma, which indicated that the thyroid carcinoma may be the result of different genes' interaction[14]. The expression of c-erbB-2 increases with the differentiation level increasing, while P53 decreases with it and is nagative correlated with c-erbB-2. In the cases with lymph node metastasis, the c-erbB-2 positive rate increases obviously. It is believed that c-erbB-2, P21 plays vital role in thyroid cancerization possibly, especially in papillary thyroid carcinoma. The excessive expression of P16 oncoprotein possibly participated in the development and prognosis of thyroid carcinoma, but P53 may be closely relative with thyroid carcinoma differentiation.

6 Telomerase

Telomerase is a kind of reverse transcriptase, and can replicate on the template of its own RNA. It can catalyse and lengthen ribonucleprotein (RNP) of telomerase end, and sustain the length of telomere and cell fissionability, so as to escape apolexis, death and obtain immortalization. Therefore telomerase aberrant activation focuses on the malignant tumor cell infinite multiplication[15–18]. Umbricht[19] believed that telomerase is helpful for discriminating thyroid adenoma from follicular thyroid carcinoma. In follicular thyroid carcinoma, telomerase positive rate is 100%, but it is only 19% in thyroid adenoma. The telomerase activity is expressed highly in thyroid carcinoma, and also closely correlated with infiltration, the Ki-67 mark index and differentiation. Telomerase activity detection has potential value on estimating tumor progress and prognosis clinically. The high specificity and sensitivity of detection has a more vital significance in preoperative diagnosis by fine needle aspiration[10].

Human telomerase contains three principal compositions, namely the telomerase catalytic subunit hTERT, the RNA component, and the telomerase related protein hTP1. In the immortal cells and cancer cells, hTERT gene expression is intensive. Saji[20] examined the hTERT expression in 37 samples of thyroid nodule and 12 samples of normal thyroid glands tissues. Results showed that the hTERT expression rate of folicular thyroid carcinoma is 100%, 69.2% of PTC, 28% of the benign thyroid gland tubercle, and no expression in the normal tissue. In 37 thyroid nodule samples with telomerase positive, 35 cases are hTERT positive. Therefore, telomerase and telomerase reverse transcriptase are both significant in understanding thyroid carcinoma pathogenesis, diagnosis, therapy and prognosis.

7 Metastasis-associated Gene

Papillary thyroid carcinoma often has lymphatic metastasis. The tumor metastasis-associated gene has been widely concerned, especially of nm23[21–22], CD44V6[23–24] and epidemal growth factor receptor (EGFR) gene, which participate in tumor metastasis[25–26]. Through the single-factor and the multi-factor analysis, researchers draw the

conclusion that CD44V6, EGFR expression had a positive correlation with cervical lymphatic metastasis of papillary thyroid carcinoma, but the nm23 gene expression had a negative correlation with lymphatic metastasis and envelope infiltration. nm23, CD44V6, EGFR possibly had synergistic effect on the lymphatic metastasis of papillary thyroid carcinoma. nm23, CD44V6, and EGFR together may be taken as the molecular biology appraisal index on evaluating papillary thyroid carcinoma metastasis tendency, and may provide some reference for scientifically selecting operation program[27].

7 Proteins

7.1 β-galactose-binding protein (Galectin-3)

Galectin-3 is one of the agglutinin family members, and is a kind of multi-peptide composed by the carbohydrate identification zone of carboxyl group final part and the amino acid final part area, unified to β-galactoside. The multi-peptides play a vital role in cell-cell interaction, cell-matrix interaction and mRNA precursor montage, and participate in cell growth regulation, tumor transformation and metastasis. Studies discovered that Galectin-3 had a higher expression in thyroid papillary carcinoma [28]. The results of thyroid follicular carcinoma research have certain difference at present, but the most researchers also thought Galectin-3 was highly expressed in thyroid follcular carcinoma. Orlandi detected Galectin-3 positively in 17 examples of follicular carcinoma, and 82.5% are in cytoplasm while 82.5% negativein the follicular adenoma[29]. Studies indicated Galectin-3 could be more reliable tumor molecular biology marker, diagnosing microinvasion follicular cancer, and it is of significance in the distinction of benign tumors and malignant tumors.

7.2 Matrix metal protease (MMP) -1, MMP-9, tissue inhibitor of metal protease (TIMP) -1

MMP is a group of zinc ions dependent proteinase family. According to its structure and substrate, MMP is divided into three kinds: the collagen enzyme class, the matrix lysatin and the gelatinase class. They can degrade the nearly all matrix membrane skeleton ingredient. It has been known that whether there is infiltration of blood vessel and amicula is to distinguish thyroid follicular cancer from thyroid adenoma. The infiltration is by degrading collagen of the basal membrane under blood vessel endothelium and amicula, which also is the formation mechanism of follicular cancer blood metastasis. MMP-1 is one of MMP family members, and may degrade type I, II, III collagen. TIMP is the MMP active inhibitor. Their combination inactivates the MMP. In the past, it wasthought that TIMP-1 and MMP-1 existed in the stroma around thyroid cancer. *In vitro* experiment discovered that the normal thyroid gland cell may secrete TIMP-1, while thyroid cancer cell secrets TIMP-1 or MMP-1[30–32]. They prompt thyroid carcinogensis and the tumor correlation inflammation cell possibly secrets some kind of factor, which stimulates TIMP-1 or MMP-1 expression. MMP-9 (gelatinase B) is the other member of MMP family, and it mainly acts to gelatin and IV/V type collagen. In the follicular cancer, the MMP-9 was expressed more than the follicular adenoma, with statistical significance[33]. The mechanism influencing infiltration and metastasis of thyroid cancer is still unclear, but MMP is confirmed to be an effective factor, andMMP will become the important auxiliary method for fine needle aspiration diagnosis.

8 Conclusion

In brief, thyroid carcinoma pathogenesis is closely correlated with the aberrant expression of p53, RET, telomerase, nm23, etc. By the examination of the tumor molecular markers clinically, combined with thyroid gland fine needle aspiration biopsy and immunohistochemistry technique, we can evaluate the malignance of thyroid tumor exactly, and provide new molecular foundation for classification and the malignance forecasting. Simultaneously, it provides important clue for the research.of thyroid carcinoma molecular pathology.

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