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Differentiated thyroid cancer: growth factors, oncogenes and environmental influences

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ABSTRACT

The present data of growth factors, oncogenes, tumor-suppressor-genes and environmental factors can be summarized in thus: thyrotropin, growth factors and other hormones do increase thyrocyte growth and specific mutations of growth factor receptors (thyrotropin receptor [TSH-R], alpha subunit of hetero-trimeric transducer protein [GSP]) cause autonomously functioning thyroid tissue and differentiated thyroid carcinoma. In the thyroid, as in other organs, genes that are found to be differentially expressed between normal thyroid tissue and thyroid carcinomas can be used as targets for molecular-based diagnosis and therapy. Deregulation of tumor suppressor gene p53, however, parallels dedifferentiation of papillary and follicular thyroid cancer but has been found in few cases only. Iodide inhibiting thyrocyte growth will have to be investigated more intensively after sodium-iodide-symporter (NIS) has been cloned, and studies may now be available that could lead to form of conservative treatment in especially dedifferentiated thyroid cancer.

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Epidemiology of goiter distribution and different thyroid cancers

The incidence of thyroid diseases and histological variations of thyroid cancer changes in different areas with different iodine intake (1). Whether external iodine intake is the only major factor influencing goiter development and thyroid cancer growth has been questioned, however, and familial predominance of goiters and specific expression of oncogenes as well as tumor suppressor genes have been investigated by numerous authors (2-5).

In the countries with low iodine intake, until the end of 60s, such as Germany and Austria, the incidence of thyroid diseases is still high in the elderly, who lived for a longer period of iodine deficiency (Austria: 34.3% in women and 21.3% in men; Germany: 34.4% in women and 31.1% in men) which is in contrast with our nowadays expectations that women are much more in danger for thyroid disease, including goiter (6,7). On the other hand the prevalence of differentiated thyroid cancer in areas with different iodine intake is not different, however, with an autopsy prevalence of thyroid cancer in the USA, Germany and Italy of 5% to 8% (7). This is also true for mortality due to thyroid cancer, which ranges between 4 to 8 cases/100.000 inhabitants (8).

The distribution of thyroid histology in thyroid cancer is iodine dependent: 70%-85% papillary thyroid cancer, 12%-18% follicular and 1%-3% anaplastic cancer in areas of high iodine intake; 50%-60% papillary thyroid cancer, 25%-30% follicular thyroid cancer and 5%-7% or 1%-3% anaplastic cancer in areas of medium iodine deficiency; in areas of severe iodine deficiency 40%-50% will demonstrate follicular thyroid cancer, about 25% papillary thyroid cancer and more than 10% dedifferentiated and anaplastic malignant tumors of thyroid gland (7).

The question arises, therefore, how do the variations in iodine intake cause the described changes of the thyroid gland, and what may be the background of iodine independent diseases?

Importance of iodine in the development of goiter and its influence on distribution of thyroid cancer - physiological and pathophysiological explanations

The growth inhibiting effect of iodine in thyroid tissues and thyroid cells in culture was well known for a long time but its molecular mechanism has not been demonstrated until very recently (9). Iodide is inserted into thyroid cells by an active process mediated by the sodium-iodide-symporter (NIS), an integral plasma membrane protein of the basolateral membrane of thyroid follicular cells (643 amino acids, molecular weight of 70-90 kDa) (10). The cloning of the gene encoding NIS led to better characterization of the molecular mechanisms involved in iodide transport under physiological and pathological conditions (11,12). Several studies have shown that thyrotropin (TSH) increases NIS gene and protein expression. This process is mediated by stimulation of intracytoplasmic adenylate cyclase activity leading to an increase of the second messenger cyclic AMP (cAMP) (13,14). Several other factors may influence NIS expression, however, most data were obtained from rat cell lines derived from thyroid tumors (10). Overexpression of NIS has been demonstrated in Graves' disease and hyperfunctioning thyroid nodules. In cold thyroid nodules as well as in differentiated thyroid cancer NIS expression has been reported normal, lower and higher than in normal thyroid tissue (10,13,14). In most follicular thyroid cancer and dedifferentiated cancer NIS is underexpressed (7,9), and therefore stimulation of NIS may be used for increasing the efficacy of radioiodide in thyroid cancer with low iodide uptake. However, it is important to note that in thyroid cancer tissues human NIS gene expression does not always correlate with protein expression and correct targeting to the plasma membrane. Therefore this analysis should be combined with immunohistochemical analysis when the data will be used for therapeutic decisions and the planning of radioiodine therapy.

The importance of iodide and tumor-suppressor-genes in growing thyroid tissue and differentiated thyroid carcinomas

Investigating the effect of iodide in suppressing thyroid growth, it could be demonstrated that iodide itself and iodide enriched lipid (iodolactone) inhibit



thyroid cell growth by stimulating transformin growth factor B (TGF- β) expression, the longest known physiologic inhibitor of thyrocyte growth (15). Beside TGF- β thyroid specific differentiation factors i.e. thyroid transcription factors 1-2 (TTF-1, TTF-2) and PAX-8, interleukin-1 and tumor necrosis factor- α are proven to inhibit thyrocyte growth by influencing NIS expression as well as retinoids (10,16). Tumor suppressor genes that have been studied in tumor tissues include p53, p16 and p15. While p53 mutations were mainly demonstrated in dedifferentiated and anaplastic carcinomas, p15 and p16 alteration were only important for the growth of thyrocyte cell lines in culture, that have been established from human thyroid cancer tissue (16). Mutations in all three tumor suppressor genes are known to transfer tumor cells into more aggressive once by reducing phosphorylation of specific proteins that are important in cell cycle. The clinical implication of these findings, however, is still questionable.

Thyrotropin and constitutively overactive mutations of the thyrotropin-receptor and its second messenger system

Growth factors, a large number of different families were investigated, using thyrotropin (TSH), estrogen and other hormones as well as epithelial-growth factor (EGF), insulin like growth factor (IGF-1), and hepatocyte growth factor (HGF) and their receptors. Many authors demonstrated that TSH increases thyrocyte activity and cell growth in normal thyroid tissue, benign tumors and in some differentiated thyroid cancer (2, 7, 9). The pathway from receptor activation to cell cycle stimulation was described and included oncogenic heterotrimeric GTP-binding proteins (GSP, RAS) and second messenger cyclic AMP (cAMP)(16). Constitutively overactive proteins caused by mutations were confirmed, when tumor tissue from autonomously functioning thyroid adenomas and some other tumors were investigated. TSH receptor proteins with constitutively overactive mutations have thus been found as germ-line mutations in children with early onset of hyperthyroidism and goiter and as somatic mutations in autonomously functioning thyroid adenomas (9). These findings also explain, why long-term conservative treatment of hyperthyroidism caused by thyroid autonomy has no rational, rather than only preparing patients for definitive ablative (radioiodine or surgery) therapy. Other growth factor binding receptors (EGF-R, IGF-R, HGF-R, Estrogen-R, etc.) have also been investigated but results lack any clinical relevance, although these factors do play certain roles in cellular regulation of epithelial cells, including thyrocytes.

Ret-PTC activation by thyroid specific translocation

Ret, a membrane receptor protein (tyrosine-kinase receptor) is stimulated by glial derived growth factor (GLDF) and was found by translocation in papillary thyroid cancer, exclusively (17). Thus genetic alterations have never been demonstrated in normal thyroid tissue and follicular thyroid adenomas but neither in "normal" tissue surrounding papillary thyroid cancer. This is surprising, since papillary thyroid cancer is often multicentric and should therefore be detectable also in some "normal thyroid tissue" of contralateral thyroid lobe after total thyroidectomy. Altogether PTC oncogene and especially radiation induced PTC-3, as a distinct tissue specific oncogene, may cause new cellular and tissue structure as well as increased cell growth. Thus PTC-3 demonstrated with more aggressive forms of papillary thyroid cancer, whereas tissues harboring PTC 1-2 mutations did not cause different clinical setting, when compared to PTC negative papillary thyroid cancer (18).

Cytogenetic and immunohistochemical findings in dedifferentiated papillary and follicular thyroid cancer

Dedifferentiated follicular and papillary thyroid cancer demonstrate increased genetic instability and thus increased prevalence of gene mutations. CD97, beta-1-integrin, proteases, platelet derived growth factor and e-cadherin were found even in rather stable cell surface molecules and cellular bindings proteins as well as in adhesion molecules changes in structure and altered

expression profiles (19,20,21). Since e-cadherin expression was decreased and protease activity increased in some of these tissues we could assume that these tumor cells are more likely to metastasize and invade surrounding structures. This was proven in vitro studies but specific help for clinical decision regarding aggressiveness and applied treatment could not yet be depicted from these studies. Finally all these studies were summarized and flowcharts drawn to describe an adenoma to carcinoma sequence in thyroid tumors, comparable to that of colonic epithelial tumors. Such sequence has not been proven of any clinical importance in thyroid tumors, however, when patients had been followed for years. Whether a longitudinal dedifferentiation can be proven in thyroid tumors, could only be important in the development of anaplastic thyroid cancer from low differentiated follicular and papillary thyroid cancer. Question is unanswered for development of highly differentiated thyroid cancer, whether some of these tumors may derive from follicular adenomas. This hypothesis is rather unlikely in view of the present clinical data.

REFERENCES

1. Nagataki S, Nystrom E. Epidemiology and primary prevention of thyroid cancer. *Thyroid* 2002;12(10):889-96.
2. Goretzki PE, Dotzenrath C, Simon D, Roher HD. Studies of oncogenes and tumor-suppressor genes in human thyroid carcinomas, and their clinical implications. *Langenbeck's Arch Surg* 1999;384:1-8
3. Musholt TJ, Musholt PB, Petrich T, Oetting G, Knapp WH, Klempnauer J. Familial papillary thyroid carcinoma: genetics, criteria for diagnosis, clinical features, and surgical treatment. *World J Surg* 2000;24:1409-17.
4. Takano T, Hasegawa Y, Matsuzuka F, Miyauchi A, Yoshida H, Higashiyama T et al. Gene expression in thyroid carcinomas. *Br J Cancer* 2000;83(11):1495-502.
5. Kjellman P, Learoyd LD, Messina M, Weber G, Hoog A, Wallin G et al. Expression of the RET proto-oncogene in papillary thyroid carcinoma and its correlation with clinical outcome. *British J Surg* 2001;88:557-63.
6. Lind P, Kummig G, Heinisch M, Igerc I, Mikosch P, Gallowitsch HJ et al. Iodine supplementation in Austria: methods and results. *Thyroid* 2002;12(10):903-7.
7. Goretzki PE. Thyroid nodules and differentiated cancers: growth factors, oncogenes and environmental influences. In: Volume I: Thyroid neoplasms, 7th International Postgraduate Course in Endocrine Surgery, Saint Jean de Luz, France, 2002.
8. Sherman S. Thyroid carcinoma. *Lancet* 2003;361:501-11.
9. Goretzki PE, Simon D, Dotzenrath C, Schulte KM, Roher HD. Growth regulation of thyroid and thyroid tumors in humans. *World J Surg* 2000;24(8):913-22.
10. Wagner S, Aust G, Schott M, Scherbaum WA, Feldkamp J, Seissler J. Regulation of sodium-iodide-symporter gene expression in human thyrocytes measured by real-time polymerase chain reaction. *Exp Clin Endocrinol Diabetes* 2002;110(8):398-402.
11. Dai G, Levy O, Carrasco N. Cloning and characterization of the thyroid iodide transporter. *Nature* 1996;379:458-60.
12. Smanik PA, Liu Q, Furminger TL, Ryu KY, Xing S, Mazzaferri EL et al. Cloning of the human sodium iodide symporter. *Biochem Biophys Res Comm* 1996;226:339-45.
13. Ajan RA, Kamaruddin NA, Crisp M, Watson PF, Ludgate M, Weetman AP. Regulation and tissue distribution of the human sodium/iodide symporter gene. *Clin Endocrinol* 1998;49:517-23.
14. Saito T, Endo T, Kawaguchi A, Ikeda M, Katoh R, Kawaoi A et al. Increased expression of the sodium/iodide symporter in papillary thyroid carcinomas. *J Clin Invest* 1998;101:1296-300.
15. Imamura Y, Jin L, Grande JP, Li CY, Zheng TR, Erickson LA et al. Analysis of TGF- β and TGF- β -RII in Thyroid Neoplasms from the United States, Japan, and China. *Endocr Pathol* 1998;9(3):209-16.
16. Tallini G. Molecular pathobiology of thyroid neoplasms. *Endocr Pathol* 2002;13(4):271-88.
17. Eng C. RET Proto-Oncogene in the Development of Human Cancer. *J Clin Oncol* 1999;17(1):380-93.
18. Kjellman P, Learoyd LD, Messina M, Weber G, Hoog A, Wallin G et al. Expression of the RET proto-oncogene in papillary thyroid carcinoma and its correlation with clinical outcome. *Br J Surg* 2001;88:557-63.
19. Steinert M, Wobus M, Boltze C, Schutz A, Wahlbuhl M, Hamann J et al. Expression and regulation of CD97 in colorectal carcinoma cell lines and tumor tissues. *Am J Pathol* 2002;161(5):1657-67.
20. Ensinger C, Obrist P, Bacher-Stier C, Mikuz G, Moncayo R, Riccabona G. beta-1-integrin expression in papillary thyroid cancer. *Anticancer Res* 1998;18:33-40.
21. Sobrinho-Simoes M, Oliveira C. Different types of epithelial cadherin alterations play different roles in human carcinogenesis. *Adv Anat Pathol* 2002;9(6):329-37.