6. GROWTH FACTORS AND THEIR RECEPTORS IN THE GENESIS AND TREATMENT OF THYROID CANCER[1]

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INTRODUCTION

The oncogenes and/or tumor suppressor genes that are implicated in the transformation and progression of the majority of thyroid neoplasms remain unknown. Mutations that have been identified in other human malignancies are restricted to a relatively small subset of thyroid neoplasms, if they are identified at all. It would appear that novel genetic alterations are implicated including the well-characterized ret/PTC rearrangements. Numerous factors have been shown to govern thyroid cell differentiation and proliferation. Indeed, increasing evidence suggests that many of these growth factors and their receptors can also be implicated in tumor cell progression in genetically transformed thyrocytes. The molecular mechanisms underlying dysregulated thyroid cell growth and their potential role in the tumorigenic pathway will be discussed.

GROWTH FACTORS AND RECEPTORS

Overview

Growth factors are polypeptides of several major families that regulate cell replication and functional differentiation by directly altering the expression of specific genes (1). They are considered to play an important role in the multistep pathway of tumorigenesis. A number of oncogene products are homologous to growth factors, their receptors,

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or enzymes that participate in the mitogenic process. In several systems, growth factors have been shown to interact with specific membrane receptors in regulating cell growth and gene expression in an autocrine or paracrine manner. Some are known to affect hormone production and some are, in turn, modulated by hormones (2). A few have been identified in the thyroid where they are considered to play a physiological role in endocrine cell regulation (3;4).

Endocrine cells including thyrocytes are the site of both synthesis and action of growth factors. A number of growth factors have been identified in endocrine cells, including insulin-like growth factors-I and -II (IGF-I, IGF-II) (5;6), epidermal growth factor (EGF) (7;8), transforming growth factor-α (TGFα) (9–11), transforming growth factor-TGF-ß, platelet-derived growth factor (12;13) and basic fibroblast growth factor (bFGF; FGF-2) (14). Growing evidence suggests that human thyroid tumor cells produce multiple peptides that regulate their own function in vitro. The relative significance of these different growth factors in human thyroid neoplasia, however, remains to be established.

THE EPIDERMAL GROWTH FACTOR FAMILY

The EGF family of ligands includes EGF, TGF-α, amphiregulin, heparin-binding EGF-like growth factor (HB-EGF), and betacellulin (BTC) (15). An additional family of EGF-related agonists include neuregulins which include glial growth factors (GGFs), neu differentiation factors (NDFs)/heregulins, ligands for erbβ-3 and erbβ-4. It is still not very clear which specific subsets of erbB receptors become activated in response to each of these ligands.

Transforming growth factor-α

Transforming growth factor-α is expressed as a membrane-anchored protein (16) that may alter pituitary production of TSH as well as cell proliferation (17). TGFα is thought to mediate estrogen-induced cell proliferation in several tissues (18–20). Estrogen stimulation has been implicated in thyroid tumorigenesis most aptly in rodents using a number of synthetic estrogenic compounds. Using a two-stage thyroid tumorigenesis model, one week administration of N-bis(2-hydroxypropyl)nitrosamine, gonadectomized F344 rats of both sexes were implanted with fused pellets containing EB for 32 weeks (21). Thyroid gland weights were increased by EB pellet in a dose-dependent and increased the occurrence of thyroid proliferative lesions in male and female animals. These data provide suggestive evidence for the potential significance of this growth factor in thyroid tumorigenesis.

Epidermal growth factor and receptor (EGF; EGF-R)

The common receptor of EGF and TGF-α, EGF-R, is a 170-kD plasma membrane tyrosine kinase product of the protooncogene v-*erbβ*. EGF-R is over-expressed in several types of human cancers that correlate with tumor aggressiveness. In the thyroid, EGF promotes growth but may inhibit some functional parameters. The normal thyroid displays EGF and EGF-R staining that is variable, but largely cytoplasmic, for both EGF

and EGF-R(4;8;22). Nuclear positivity for EGF and EGF-R has been described in both follicular adenomas and follicular carcinomas. In marked contrast, nuclear staining has been reported as almost absent in papillary carcinomas. The absence of nuclear EGF and EGF-R in papillary carcinomas would suggest that the role played by EGF in growth control differs between papillary carcinoma and follicular adenomas/carcinomas of the thyroid (23).

Interestingly, the compound ZD6474, a low molecular weight EGF tyrosine kinase inhibitor was recently shown to have enzymatic functions on RET-derived oncoproteins. This agent blocks the *in vivo* phosphorylation and signaling of the RET/PTC3 and RET/MEN2B oncoproteins and of an EGF-R/RET chimeric receptor. This inhibition was associated with morphological reversion and prevented the growth of human PTC cell lines that carry spontaneous RET/PTC 1 rearrangements (24).

As mentioned previously, the EGF-R is one of four highly homologous tyrosine kinase receptors that include erbβ2/HER2/neu/p185, erbβ-3 (HER3), and erbβ-4 (HER4). Growing evidence in support of functional cross-talk between the different members of this receptor family is now well recognized (25). Ligand-induced stimulation can result in transphosphorylation of *neu* via EGF-R (25;26). Over-expression of a wild type EGF-R and heterocomplex formation with *neu* dramatically increases receptor autophosphorylation and binding of EGF (25;27).

Erb β-2/neu in thyroid neoplasia

The specific role of the erbβ-2 proto-oncogene in human carcinomas was investigated in human thyroid tumours including nodular hyperplasias, follicular carcinomas and papillary carcinomas (without and with tall-cell features, insular, or anaplastic de-differentiation). There was no evidence of DNA amplification of erbβ-2 gene itself. Furthermore, sequencing of the transmembrane domain revealed no activating point mutations of the of erbβ-2 gene. The level of mRNA expression, however, was variable with nearly a third of papillary carcinomas showing statistically significant elevated mRNA levels compared with corresponding normal thyroid tissue. These findings, however, did not correlate with other indicators of poor prognosis. Moreover, in contrast to the elevated mRNA levels in thyroid tumours, the level of protein staining correlated with the degree of differentiation. Normal and hyperplastic tissue being strongly positive and poorly differentiated tumours showing negative of erbβ-2 immunostaining. Thus, these studies indicate the absence of mutations or amplifications of the erbβ-2 gene in human thyroid tumours. Elevated erbβ-2 mRNA expression in some thyroid tumours was not associated with clinical features of poor prognosis. Nevertheless, the significance of the elevated mRNA levels remains unclear, as it did not result in protein overexpression. Instead, cytoplasmic erbβ-2 protein detection by immunohistochemistry appears to correlate with differentiation of human thyroid tumours and may be a feature of good prognosis. There does not appear to be a positive relationship between erbβ-2 expression and the well-characterized ret/PTC rearrangements indicating that the two events are likely to be mutually exclusive in genesis and action of these two putative thyroid oncogenes (28).

THE TRANSFORMING GROWTH FACTOR-β

Transforming growth factor (TGF)-β has been implicated in the regulation of normal and neoplastic cell function. TGF-β regulates the expression of various proteins, including p27Kip1 (p27), a cell cycle inhibitory protein. Enhancement of tumor cell growth and invasiveness by transforming growth factor-β (TGF-β) requires constitutive activation of the ras/MAPK pathway. How MEK activation by epidermal growth factor (EGF) influences the response of fully differentiated and growth-arrested thyroid epithelial cells in primary culture to TGF-β1 is not clear. The epithelial tightness was maintained after single stimulation with EGF or TGF-β1 for 48 hours. In contrast, co-stimulation abolished the trans-epithelial resistance and increased the paracellular flux of labeled inulin. Reduced levels of the tight junction proteins claudin-1 and occludin accompanied the loss of barrier function. N-cadherin, expressed only in few cells of untreated or single-stimulated cultures is increased and co-localizes with E-cadherin at adherens junctions. TGF-beta1 only partially inhibited EGF-induced Erk phosphorylation. The MEK inhibitor U0126 prevents Erk1/2 phosphorylation and abrogated the synergistic responses to TGF-β1 and EGF. These observations indicate that concomitant growth factor-induced MEK activation is necessary for TGF-β1 to convert normal thyroid epithelial cells to a mesenchymal phenotype providing evidence for the role of these growth factors in thyroid cell transdifferentiation.(29).

VASCULAR ENDOTHELIAL GROWTH FACTOR

Vascular endothelial growth factor (VEGF) also known as vascular permeability factor (VPG) exists in a number of isoforms in human and rodent tissues including VEGF206h/205r, VEGF189h/188r, VEGF165h/164r, VEGF145h/144r and VEGF121 that differ in their molecular masses and biological activities. The VEGF isoforms bind with two tyrosine-kinase receptors, KDR/flk-1 and flt-1. In addition, VEGF165 binds with co-receptor, neuropilin-1, which is expressed in human endothelial cells and several types of non-endothelial cells including solid tumors. Recent studies on the role of estrogen in the regulation of tumor angiogenesis demonstrated that this steroid induces neovascularization in parallel with early induction of VEGF and the VEGFR2- (flk-1/KDR) protein expression in both blood vessels and non-endothelial cells (30). Moreover, estrogen-induced rat pituitary tumors in Fisher 344 rats express higher VEGF164 and neuropilin-1 levels compared to control untreated rats (31). These findings suggest that over-expression of VEGF and its receptor (VEGFR-2) may play an important role in the early phases of estrogen induced tumor angiogenesis in some endocrine tissues.

FIBROBLAST GROWTH FACTORS & RECEPTORS

Fibroblast growth factors (FGFs)

Basic Fibroblast Growth Factor (now known as FGF-2) is one of an ever-expanding family of FGFs several of which possess mitogenic, angiogenic, and hormone regulatory functions (32). FGF-2 immunoreactivity was described originally in the non-hormone

producing folliculo-stellate cells of the pituitary (33). In one mouse model, estrogen-induced tumorigenesis was associated with parallel increases in the expression of a pituitary tumor transforming gene (PTTG) as well as FGF-2 (33). In turn, both PTTG and FGF-2 have been shown to be increased in mRNA expression in papillary thyroid cancer that was also associated with lymph nodal invasion and distant metastasis. These findings were upheld even after consideration of other known prognostic factors such as age and gender of the patient and size and type of the tumor (34). Similarly, increased concentrations of FGF-2 in the serum of patients with differentiated papillary thyroid carcinoma has also been reported (35).

Fibroblast growth factor receptors (FGFRs)

There are 4 mammalian FGFR genes encoding a complex family of transmembrane receptor tyrosine kinases (RTKs) (36). Each prototypic receptor is composed of 3 immunoglobulin (Ig)-like extracellular domains, 2 of which are involved in ligand binding, a single transmembrane domain, a split tyrosine kinase, and a COOH-terminal tail with multiple autophosphorylation sites. Multiple forms of cell-bound or secreted receptors are produced by the same gene. Tissue-specific alternative splicing, variable polyadenylation sites and alternative initiation of translation result in truncated receptor forms (37;38). The first two extracellular loops of FGFR1 can be secreted as soluble circulating FGF binding proteins (39) but their physiological importance remains to be established. Different FGFRs can dimerize, so that truncated forms of FGFR1 block signalling through FGFR1, 2, and 3 (40).

Structural alterations of FGFRs may play a role in human tumorigenesis. FGFR1 is highly expressed in the brain (41) but the shorter (2 Ig-domain) form of FGFR1 is more abundant in some CNS glioblastomas (42). Anti-sense targeted interruption of FGFR1 reduces malignant melanoma cell proliferation and differentiation (43). FGFR2 exon switching has been observed to accompany prostate cell transformation (44).

The expression of FGF-2 and one of its receptors FGFR1 was recently compared in differentiated thyroid cancers, normal thyroids, multinodular goiters, and Graves' disease specimens. The investigators noted that FGF-2 was significantly over-expressed in thyroid carcinomas compared with normal thyroid tissue. More interestingly, increased FGF-2 mRNA expression was independently associated with lymph nodal invasion and distant metastasis at tumor presentation (34).

The biological relevance of the FGF signaling system in thyroid cell growth has been further hinted at from genetically altered mice. Mice deficient for FGFRR2-IIIb were generated by placing translational stop codons and an IRES-LacZ cassette into exon IIIb of FgfR2. Expression of the alternatively spliced receptor isoform, FgfR2-IIIc, is not affected in these mice. The FGFR2-IIIb deficient mice, however, show dysgenesis of several non-endocrine as well as endocrine tissues including the thyroid, adrenals, pancreas, and pituitary. These findings are particularly interesting in view of the fact that FGF ligand expression is not altered with normal FGF8, FGF10, Bmp4, and Msx1 in this animal model (45).

In contrast, gain-of-function mutations in the FGFR-3 gene have been described to result in inhibition of cartilaginous cell growth in the growth plate suggesting an important growth inhibitory signal for this receptor. RT-PCR examination confirmed the expression of this growth factor in papillary thyroid carcinomas. Over-expression of FGFR-3 was successful in specific binding of 125I-FGF-2. Growth rates of cells over-expressing FGFR-3, however, were similar to those of control cells (46). Cells over-expressing FGFR3 continued to grow beyond the density of control cells. These interesting findings suggest a role for FGFR3 in thyroid cancer cell adhesion and/or invasiveness.

The nerve growth factor family

NGF is a growth factor that generally results in anti-proliferative and anti-invasive effects in neuroendocrine tumors. NGF inhibits thyrocyte invasion and reverts the effect of retinoic acid in these cells. This effect is likely mediated by an increase in adhesion to the extracellular matrix proteins laminin and collagen IV and the inhibition of cell migration. NGF also induces expression of its receptor p75 NGF receptor. This receptor can be the subject of rearrangements. Indeed, the thyroid TRK oncogenes are generated by chromosomal rearrangements juxtaposing the neurotrophic tyrosine receptor kinase type 1 (NTRK1) tyrosine kinase domain to foreign activating sequences. TRK oncoproteins display a constitutive tyrosine kinase activity in NIH3T3 cells (47). The TRK oncoproteins' signal transduction involves several signal transducers activated by the NGF-stimulated NTRK1 receptor including fibroblast growth factor receptor substrate (FRS) FRS2 and FRS3, two related adapter proteins activated by fibroblast growth factor and NTRK1 receptors, in the signaling of the thyroid TRK-T1 and TRK-T3 oncogenes. FRS2 and FRS3 are recruited and activated by TRK-T1 and TRK-T3. Expression studies show different expression patterns of the FRS adapters in normal and tumor thyroid samples. FRS3 is expressed in both normal and thyroid tumor samples, whereas FRS2 is not expressed in normal thyroid but is differentially expressed in some tumors. These data are consistent with the notion that the FRS2 and FRS3 adapter proteins may have a role in thyroid carcinogenesis triggered by TRK oncogenes and provide the basis for a new dimension of pharmaco-therapeutic possibilities.

CONCLUSIONS

Thyroid tumors are common neoplasms that exhibit a wide range of biologic behavior. Numerous factors have been shown to govern thyrocyte proliferation. In particular, hormones and growth factors likely play a role as promoters of tumor cell growth in genetically transformed cells. In some instances enhanced growth factors and their receptors may serve as survival signals for neoplastic cells. In other instances, however, abnormal forms of growth factor receptors (such as members of the EGF-R/HER2/neu) may also be important in the early stages of cell transformation and chromosomal instability consistent with the clonal composition of thyroid neoplasms. More detailed structure/function studies of growth factor/receptor

functional interactions in morphologically characterized thyroid nodules are required. It is anticipated that these studies will identify signaling patterns that will provide the basis for the development of more specific and effective pharmacotherapeutic agents.

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