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