Translational Research in Endocrine Surgery

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KEYWORDS

• Endocrine cancer • Heritable cancer syndromes
• Pancreatic neuroendocrine tumors • Thyroid surgery • MEN2

KEY POINTS

- Basic science research has identified the genes responsible for several hereditary endocrine tumor syndromes, and has elucidated the cell-signaling pathways critical to development of endocrine cancer.
- Genetic testing for these mutations allows identification of at-risk individuals for screening before the onset of symptoms, and in some cases permits prophylactic surgery.
- Mutations in genes of the MAP-kinase signaling pathway (most commonly *RET* or *BRAF*) are found in most familial and sporadic thyroid cancers and cause constitutive proliferative signaling, leading to malignancy.
- Small-molecule kinase inhibitors block aberrant promalignant signaling in several endocrine cancers, and represent an active area of research with great potential. Improvements in progression-free survival have been reported with these drugs for thyroid, adrenal, and endocrine pancreatic cancer, but responses are usually not durable, and efforts to understand and overcome inhibitor resistance are ongoing.
- In pancreatic neuroendocrine tumors, drugs targeting somatostatin receptors alleviate symptoms, are useful for imaging, and can prolong life. Targeted radiotherapy directed toward these receptors and the development of additional receptor targets promise to improve the treatment of these tumors in the future.

INTRODUCTION

The past 30 years have seen astounding advances in the science of endocrine surgery. From early successes in mapping and cloning genes responsible for heritable endocrine cancer syndromes, to sequencing the human genome, to adoption of next-generation sequencing techniques, a broad understanding of genes responsible

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for familial and sporadic endocrine cancers now exists. This development has enabled genetic testing of at-risk family members and even prophylactic surgery for some carriers of mutant genes. Parallel efforts to determine the function of these altered genes have defined cell-signaling pathways susceptible to treatment. High-throughput gene expression methodologies now give insight into entire networks of cellular processes perturbed in endocrine malignancy. The knowledge gained has led to development of small-molecule kinase inhibitors and other therapies that are able to specifically target the genes, pathways, and cells responsible for disease. New treatments based on rational drug development and targeted therapies continue to be the focus of aggressive investigation and ongoing clinical trials. Diagnosis and prognostication in endocrine cancer has likewise been improved using the results of mutation and gene-expression data. The aim of this article is to review advances in the basic science of endocrine cancer, and highlight how these discoveries are being translated into real-world tests and therapies that will affect the practice of endocrine surgery today and in the near future. Heritable and sporadic tumors of the thyroid, parathyroids, adrenals, and pancreas are emphasized. It is expected that familiarity with these breakthroughs and with the ongoing challenges in endocrine cancer surgery will enhance clinicians' ability to apply the latest scientific developments to the optimal care of their patients.

THYROID

Overview of Mitogen-Activated Protein Kinase

The mitogen-activated protein kinase (MAPK) cascade is a cellular signaling pathway now established as central to thyroid cancer. In this cascade, extracellular signals such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and many others activate membrane-bound receptor tyrosine kinases, including RET, which cause RAS activation and induction of the RAS-RAF-MEK-ERK-MAP signaling cascade (**Fig. 1**).[1,2] Activation of the MAPK pathway influences diverse cellular processes including cell-cycle control, proliferation, differentiation, motility, and apoptosis.[3,4] The pathway is highly regulated through expression of multiple isoforms of component proteins and cross-talk with related pathways, such as phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR), Janus-kinase, PKC/NF-κB, and Wnt/β-catenin, each contributing to different functional roles in different tissues and contexts.[2,5,6] Apart from its physiologic role in thyroid differentiation, growth, and function, the MAPK pathway can also contribute to development of thyroid cancer by aberrant activation at several points. In sporadic and hereditary medullary thyroid cancer (MTC), mutant RET activates RAS, causing constitutive MAPK signaling,[7] while mutations in both *RET* and *RAS* are common in follicular thyroid cancer.[8] Downstream in the pathway, mutation in the BRAF serine/threonine kinase has emerged as the most common genetic abnormality in papillary thyroid cancer (PTC), and is also present in anaplastic thyroid cancer (ATC).[9,10] In total, mutation in some element of the MAPK pathway is present in more than 70% of thyroid cancers, marking this as the central cellular control element in thyroid oncogenesis.[11] Over the past 25 years, basic and translational research has defined the role of the MAPK pathway in thyroid cancer and has produced promising new diagnostic and therapeutic strategies for this heterogeneous disease.

RET Proto-Oncogene

Although the phenotype and autosomal dominant inheritance pattern of multiple endocrine neoplasia type 2 had been recognized for some time, it was not until