Focus on hereditary endocrine neoplasia

Allen M. Spiegel*

Molecular Pathophysiology Section, National Institute on Deafness and Communication Disorders, National Institutes of Health, Bethesda, Maryland 20892
*Correspondence: spiegela@extra.niddk.nih.gov

Introduction

While many organs not classified as endocrine glands, e.g., fat, are now known to produce hormones, cytokines, and other chemical messengers and secrete them directly into the bloodstream, the pituitary, thyroid, parathyroids, pancreatic islets, adrenals, testes, and ovaries, i.e., the "classical" endocrine glands (Figure 1), are the focus of this review. As with other tissues and organs, endocrine neoplasia may be benign or malignant, and may occur on a sporadic or hereditary basis. Sporadic forms of benign endocrine neoplasia involving the classic endocrine glands, and sporadic endocrine malignancies, of which thyroid cancers are the most common (see Segev et al., 2003, for recent review), and others such as adrenocortical cancer, much rarer (see Sidhu et al., 2004, for review), are beyond the scope of this review. The focus of this article is on seven endocrine neoplasia syndromes which often involve multiple endocrine glands, with or without prominent involvement of nonendocrine organs (Table 1). There are additional hereditary tumor predisposition syndromes whose phenotype may include endocrine neoplasia: gonadal tumors in Peutz-Jeghers syndrome caused by *LKB1* mutations, adrenocortical cancer in Li-Fraumeni syndrome caused by *TP53* mutations, islet cell tumors in tuberous sclerosis caused by *TSC1* and *2* mutations, follicular thyroid cancer in Cowden syndrome caused by *PTEN* mutations, papillary thyroid tumors in familial adenomatous polyposis caused by *APC* mutations, and pheochromocytomas in neurofibromatosis caused by *NF1* mutations. These have been reviewed recently (Nagy et al., 2004) and will not be discussed further here.

Recent advances in understanding the molecular pathogenesis of endocrine neoplasia syndromes have ushered in a new era of diagnosis, and in some cases new forms of treatment and prevention. Despite the rareness of these endocrine neoplasia syndromes, insights gained from understanding their molecular pathogenesis should lead to improvements in management of both hereditary and sporadic endocrine and nonendocrine neoplasms. Following a general discussion of the genetics, clinical manifestations, and management of these syndromes, I will highlight specific features, including molecular pathogenesis, of each.

Genetics

Hereditary endocrine neoplasia syndromes were first recognized based on a common pattern of endocrine (and nonendocrine) manifestations inherited in a Mendelian manner, typically autosomal dominant. Recognition that these disorders were caused by single gene mutations led to efforts to identify such genes by linkage and positional cloning. Most hereditary tumor predisposition syndromes are caused by germline loss-of-function mutations of a single allele; frequent somatic loss of the wild-type allele leads to clonal neoplasms, and accounts for the high penetrance of the tumor phenotype, as well as apparent autosomal dominant inheritance (Vogelstein and Kinzler, 2004; Nagy et al., 2004). Germline mutations in such tumor suppressor genes (TSG) are the cause of five of the seven endocrine neoplasia syndromes, including multiple endocrine neoplasia type 1 (MEN1), Carney complex (CC), von Hippel-Lindau disease (VHL), hyperparathyroidism-jaw tumor syndrome (HPT-JT), and hereditary paranganglioma syndrome (PGL). For CC and HPT-JT, the evidence for loss of the wild-type allele in tumors is not definitive (Bossis et al., 2004; Carpten et al., 2002), and it remains possible for these and other TSG that loss of a single allele, because of haploinsufficiency, confers a selective growth advantage. Multiple endocrine neoplasia type 2 (MEN2) is exceptional in being caused by a germline-activating mutation of the *RET* oncogene, a receptor-tyrosine kinase (Gertner and Kebebew, 2004). In

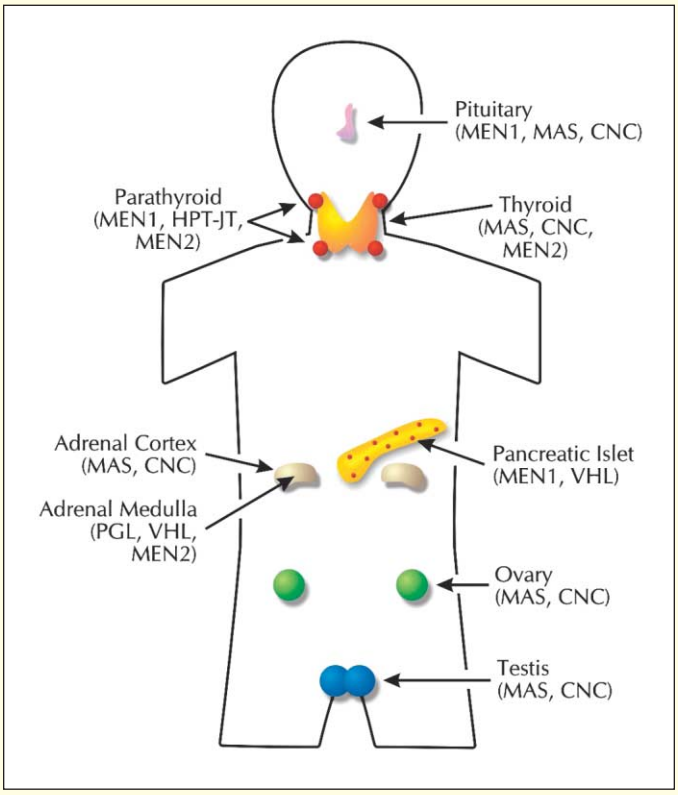

Figure 1. Major sites developing benign and/or malignant tumors in endocrine neoplasia syndromes

Multiple endocrine neoplasia types 1 and 2 (MEN1 and MEN2, respectively), McCune-Albright syndrome (MAS), Carney complex (CNC), hyperparathyroidism-jaw tumor syndrome (HPT-JT), hereditary paranganglioma syndrome (PGL), and von Hippel-Lindau disease (VHL).

Table 1. Endocrine neoplasia syndromes

Syndrome	Gene/ protein	Subcellular localization	Biochemical function	Pathway	Tissue expression	Endocrine manifestations	Nonendocrine manifestations
MEN1	*MEN1*/ MENIN	Nuclear	?	?	Ubiquitous	Anterior pituitary, parathyroid, enteropancreatic	Facial angiofibromas, collagenoma, lipomas, leiomyomata
HPT-JT	*HRPT2*/ PARAFIBRO-MIN	Nuclear	?	?	Ubiquitous	Parathyroid cystic tumor/carcinoma	Ossifying jaw fibroma, renal cyst, Wilm's tumor
McCune-Albright	*GNAS*/Gsα	Plasma membrane	7TM receptor coupling	cAMP signaling	Ubiquitous	Anterior pituitary, adrenal cortex, gonads, thyroid	Fibrous dysplasia of bone, café-au-lait skin pigmentation
Carney complex	*PRKAR1A*/ PKA RIα	Cytoplasmic	PKA cAMP-binding subunit	cAMP signaling	Ubiquitous	Anterior pituitary, adrenal cortex, gonads, thyroid	Skin lentigines, myxomas
PGL	*SDHB/C/D*	Mitochondrial	Succinate to fumarate	Krebs cycle/ electron transport chain	Ubiquitous	Head/neck paraganglioma, pheochromocytoma, thyroid CA? (SDHB)	Renal cell CA? (SDHB only)
von Hippel-Lindau	*VHL*	Cytoplasmic	Ubiqutin ligase complex	O_2-sensing	Ubiquitous	Pancreatic islet, pheochromocytoma	Renal cell CA, hemangioblastomas
MEN2	*RET*	Plasma membrane	Tyrosine kinase	Growth factor signaling	Neural crest-derived	Medullary CA of thyroid, pheochromocytoma, parathyroid (2A only)	Hirschsprung disease (2A only), ganglioneuromas (2B only)

general, germline-activating mutations of oncogenes are embryonic lethal, as are homozygous, inactivating mutations of TSG. The restricted range of expression of the *RET* oncogene may explain why germline-activating mutations of this gene are not embryonic lethal. The McCune-Albright syndrome (MAS) is included in this review because of its pleiotropic endocrine and nonendocrine phenotype, but it is not a hereditary syndrome. It is caused by somatic activating mutations of *GNAS*, encoding Gsα, the ubiquitously expressed G protein, coupling many receptors to stimulation of cAMP formation. In some respects, constitutively activated Gsα behaves like an oncogene, and germline activating mutations would likely be embryonic lethal. MAS, however, results from early postzygotic *GNAS* mutations that occur in a mosaic distribution (Spiegel and Weinstein, 2004).

General clinical features and management of hereditary endocrine neoplasia syndromes

Features unique to hereditary endocrine neoplasia syndromes include multiplicity of tumors for a given endocrine organ, e.g., multiple parathyroid tumors in MEN1, MEN2, and HPT-JT, bilateral adrenal cortical tumors in CC, bilateral adrenal medullary tumors in MEN2, and multiple enteropancreatic tumors in MEN1, as well as multiplicity of endocrine organs developing tumors, e.g., MEN1 and MEN2 by definition, but also CC, VHL, PGL, and MAS. This reflects the consequences of mutation of TSG/oncogenes expressed in every cell of the susceptible tissue, and contrasts with the single endocrine tumor pattern seen in typical sporadic cases caused by somatic mutation in a single cell. A related difference is that the age of onset of tumors is typically significantly younger in hereditary compared with sporadic cases. Since surgical removal is the primary mode of treatment for most endocrine tumors, this difference in tumor multiplicity is critical in management. Removal of a single tumor is generally not curative because of the high likelihood of residual or recurrent tumor.

An important, largely unresolved question is the basis for the specific phenotypes associated with mutations of the genes responsible for these endocrine neoplasia syndromes. In MEN2, the involvement of neural crest-derived tissues such as the C cells of the thyroid and the adrenal medulla reflects the somewhat restricted range of expression of the RET oncogene. But in MEN1, for example, it is not at all clear why loss of function of this ubiquitously expressed gene should lead to a relatively unique pattern of endocrine and nonendocrine neoplasia (Table 1). Possible explanations include tissue-specific differences in somatic loss of the wild-type allele, in availability of alternative growth regulatory pathways, and in expression of key proteins interacting with TSG products. A related question concerns the extent of correlation between genotype and phenotype. In MEN2, VHL, and PGL, unique phenotypic patterns are associated with specific gene mutations (see later sections), but for MEN1, CC, and HPT-JT, such correlations either do not exist or are not yet apparent. There is substantial variation in penetrance and in pattern of tumor formation in these syndromes both between different families and even within families, suggesting that other modifying genes and/or environmental factors may play a role.

The clinical manifestations of the endocrine tumors associated with these syndromes often reflect the biochemical consequences of excess hormone secretion, e.g., hypercalcemia due to hyperparathyroidism and hypoglycemia due to hyperinsulinemia. Increased hormone secretion also serves as a tumor marker, e.g., calcitonin secretion in medullary thyroid carcinoma (MTC). Tumor mass effects, however, from both benign (e.g., pituitary adenoma encroachment on the optic chiasm) and malignant (e.g., metastatic disease associated with MTC and parathyroid and pancreatic islet carcinomas) endocrine tumors may also dominate the clinical picture.

All of the clinical features discussed above have important implications for patient management. Biochemical measures of endocrine function and noninvasive imaging methods were previously the mainstays of family screening, but identification of the genes responsible for these syndromes provides the opportunity for genetic, including prenatal, diagnosis (see Shapiro et

al., 2003, for listing of CLIA-certified labs) and genetic counseling for at-risk family members. When the family history is positive or suggestive, the need to screen for mutation is evident, but individuals with phenotypic features of a hereditary endocrine neoplasia syndrome lacking a positive family history may also deserve mutation screening, since identification of de novo germline mutations has important implications for counseling and screening of offspring. Prospective management of family members in whom disease-causing mutations have been identified poses numerous challenges. Measurement of hormone secretion and imaging studies remain important, and in selected cases (see discussion of MEN2), prophylactic surgical removal of endocrine glands is appropriate. There are excellent surgical or pharmacologic treatments for excessive hormone secretion in these syndromes, but with the exception of C cell neoplasia in the thyroid, the endocrine cancers are difficult to prevent or cure.

Multiple endocrine neoplasia type 1 (MEN1)

Hyperparathyroidism is the most frequent (nearly 100% penetrance) and generally earliest manifestation of MEN1. Anterior pituitary tumors, most commonly prolactinomas, occur in ~30% of cases, and enteropancreatic tumors in 30%–80% (Nagy et al., 2004). MEN1 is defined as occurrence of 2 of these 3 features, and familial MEN1 as an MEN1 case having at least one first-degree relative with one tumor. The overall incidence is estimated at 1–2/100,000. Other less striking features include adrenal cortical and medullary tumors, thymic and foregut carcinoids, lipomas, facial angiofibromas, collagenomas, and leiomyomas. Zollinger-Ellison syndrome, caused by duodenal gastrinomas, was formerly the major cause of mortality, but with more effective treatment with proton pump inhibitors, malignant enteropancreatic tumors and thymic carcinoids are now the major cause of mortality. Since enteropancreatic tumors are multifocal and difficult to remove completely, and not all are functional, there is no consensus on surgical management. Thymic carcinoids, especially in males, may be malignant; hence, prophylactic transcervical thymectomy is advised at the time of initial parathyroidectomy. Indications for genetic testing include confirmation of diagnosis in atypical cases, e.g., MEN1 tumors without family history, but the role of testing in at-risk relatives is unclear, because of the lack of consensus regarding the role of prophylactic surgery.

The *MEN1* gene encodes MENIN, a highly conserved nuclear protein that is not a member of any known gene family and which lacks identified functional domains (Agarwal et al., 2004). Multiple menin-interacting proteins, such as junD and the MLL histone methyltransferase complex, have been reported, but as yet, the role of any in tumorigenesis is unproven. Several hundred germline loss-of-function mutations have been identified, and loss of the wild-type allele in MEN1 tumors supports a tumor suppressor gene function. There is no evidence for genetic heterogeneity, but because mutations are widely dispersed throughout the gene, only ~75% of MEN1 cases have had mutations identified. Although unique phenotypic variants exist, e.g., high prolactinoma occurrence, no clear genotype/phenotype correlations have emerged. Somatic mutations have been identified in 20%–30% of sporadic parathyroid and islet tumors.

Familial isolated hyperparathyroidism (FIHP) has been considered a possible *forme fruste* of MEN1 (cf. familial MTC in MEN2), but MEN1 mutations have been identified in only a minority of cases. Mutations of the hyperparathyroidism-jaw tumor syndrome gene (see below) are also a rare cause of FIHP (Simonds et al., 2004), as are calcium-sensing receptor gene mutations. Mutation of a distinct gene as the cause of most cases of FIHP, as is evidently the case for familial somatotroph tumors linked to 11q13 (Luccio-Camelo et al., 2004), remains a possibility.

Hyperparathyroidism-jaw tumor syndrome (HPT-JT)

Hyperparathyroidism caused by multiple, often cystic, and occasionally malignant parathyroid tumors is the defining and most common feature of HPT-JT. Ossifying fibromas of the mandible or maxilla occur in up to 30% of cases, as do renal cysts; more rarely, Wilm's tumor, Hurthle cell thyroid adenomas, pancreatic adenocarcinoma, and testicular germ cell tumors are seen (Thakker, 2004). HPT-JT is caused by germline loss-of-function mutations in a gene, *HPRT2*, encoding a protein termed PARAFIBROMIN (Carpten et al., 2002). PARAFIBROMIN is highly conserved in most species and shows homology to the yeast cdc73p gene that encodes an accessory protein of the RNA polymerase II complex. Recent evidence suggests that human PARAFIBROMIN occurs in the nuclear paf complex in association with RNA polymerase II, but its specific biochemical function, and how its loss leads to tumorigenesis, remain to be defined (Agarwal et al., 2004). *HPRT2* somatic mutations have been identified in sporadic cystic parathyroid tumors (Carpten et al., 2002). *HPRT2* mutations were also identified in 10/15 cases of sporadic parathyroid carcinoma, with three of the mutations found in the germline in one study (Shattuck et al., 2003), and somatic mutations in four of four sporadic parathyroid carcinomas in another (Howell et al., 2003). These results emphasize the importance of genetic diagnosis even in apparently sporadic parathyroid carcinoma, and the need for imaging for possible jaw and renal lesions. Genetic screening of family members offers the possibility of defining those at-risk who require careful monitoring with serum calcium. Although prophylactic parathyroidectomy is a theoretical option, potential complications and insufficient data regarding likelihood of metastatic parathyroid cancer in specific cases restrain this approach. Early en bloc resection of parathyroid cancer is the only current curative procedure, but novel approaches such as immunotherapy using parathyroid hormone as antigen may lead to both reversal of hypercalcemia and regression of lung metastases (Betea et al., 2004).

McCune-Albright syndrome (MAS)

MAS is classically defined by the triad of polyostotic fibrous dysplasia, café-au-lait skin lesions, and gonadotropin-independent sexual precocity, although these patients may also develop tumors (or nodular hyperplasia) of pituitary somatotrophs, thyroid, or adrenal cortex with associated hormonal oversecretion, and other nonendocrine abnormalities (e.g., cardiomyopathy, sudden death, liver abnormalities, and intramuscular myxomas). Activating *GNAS* mutations encode substitutions of either Arg^{201} or Gln^{227}, and lead to constitutive, agonist-independent cAMP stimulation by disrupting the intrinsic GTPase activity that normally terminates G protein activation (Spiegel and Weinstein, 2004). It is believed that the somatic mutation in MAS patients occurs early in development, and therefore the clinical spectrum in each individual is determined by the tissue distribution of mutant-bearing cells. Somatic, activating *GNAS* mutations may also occur later in development, causing more focal forms of fibrous dysplasia, pituitary somatotroph, and thy-

roid tumors. Sporadic and inherited forms of thyroid and testicular Leydig cell neoplasia may also be caused by somatic and germline mutations, respectively, of the Gs-coupled thyrotropin and luteinizing hormone receptors (Spiegel and Weinstein, 2004). The common pathogenetic mechanism in each of these disorders is the ability of constitutive cAMP activation to stimulate cell proliferation in endocrine and some nonendocrine tissues. Because regulation of hormone secretion and cell proliferation are linked in endocrine tissue (cf. hyperplasia secondary to demand for increased hormone secretion), a primary defect in regulation of hormone secretion such as Gsα mutation can cause benign, if not malignant, neoplasia (Marx, 1999). A similar mechanism, but involving a different G protein pathway, is involved in parathyroid neoplasia in neonatal severe primary hyperparathyroidism caused by loss of function of both alleles of the calcium-sensing receptor.

Carney complex (CNC)

CNC is a rare disorder ($\sim$400 cases in the NIH/Mayo registry) with pleiotropic endocrine and nonendocrine manifestations (Bossis et al., 2004). Primary pigmented nodular adrenocortical disease is the most common endocrine manifestation, occurring in $\sim$25% of affected cases. Cortisol hypersecretion may range from the classic picture of Cushing's disease to an insidious or cyclical form manifesting first with osteoporosis, myopathy, or cachexia. Pituitary, thyroid (rarely malignant), and testicular Sertoli cell tumors and ovarian cysts also occur. Nonendocrine features include early appearance of pigmented skin lesions, cardiac myxomas, and schwannomas. Surgical removal of hormone-hypersecreting tumors and of cardiac myxomas is the usual treatment, but appropriate management depends on recognition of the disorder.

Genetic diagnosis is now feasible with the discovery that germline loss-of-function mutations in the *PRKAR1A* gene within the 17q-linked locus are responsible for one form of the disease. A gene in another linked locus, 2p16, has yet to be identified. The *PRKAR1A* gene encodes one of the four regulatory subunits of cAMP-dependent protein kinase (PKA). Given the complexity in forms of PKA, a heterodimer composed of potentially multiple forms of regulatory and catalytic subunits, the biologic consequences of loss of this particular gene are not straightforward, but biochemical assays suggest a net increase in PKA activity following cAMP stimulation. In certain cell types (see MAS above), increased cAMP signaling is mitogenic and may account for the pleiotropic manifestations. Somatic mutations in the *PRKAR1A* gene in some sporadic adrenocortical and thyroid tumors further underscore the pathogenic importance of this pathway. As with MAS, inhibition of the cAMP pathway might provide a novel, targeted therapy.

Hereditary paraganglioma syndrome (PGL)

Tumors of the autonomic nervous system have been divided into head and neck paragangliomas (typically nonfunctioning) and adrenal medullary and extra-adrenal catecholamine-secreting pheochromocytomas (PC). Their estimated total yearly incidence is 1/300,000 (Neumann et al., 2004). Hereditary PC occur in PGL, VHL, MEN2, and NF1. In PGL, affected subjects typically have multiple head/neck paragangliomas and/or PC, with the latter manifesting clinically with paroxysmal hypertension and catecholamine hypersecretion. Tumor removal with adrenal cortical-sparing laparascopic surgery for PC is the main treatment. Despite the potential multiplicity of tumors, the morbidity of total adrenalectomy argues against prophylactic removal of both adrenals for PGL, as well as VHL and MEN2.

Four forms of PGL (1–4) are recognized; the gene responsible for PGL2 remains unidentified, but PGL1, 3, and 4 are caused by germline loss-of-function mutations in 3 of the 4 subunits of the succinate dehydrogenase (SDH) complex II of the mitochondrial electron transport chain, *SDHD*, *SDHC*, and *SDHB*, respectively (Eng et al., 2003). Only 4 families with *SDHC* mutations have been reported, but 10% of index patients in a large European registry of PC/paraganglioma had *SDHB*/*SDHD* germline mutations. Also, 25% of apparently sporadic, symptomatic PC subjects turn out to have germline mutations in *SDHB*, *SDHD*, *VHL*, or *RET* genes. Among the genotype/phenotype correlations described are a greater incidence of PC and paraganglioma in *SDHD* versus *SDHB* mutation-bearing subjects, when the maternal imprinting of the *SDHD* gene is taken into account, i.e., individuals inheriting *SDHD* mutations from their mother do not show tumors since the maternal allele is not expressed. *SDHB* mutations, however, are associated with a greater risk of malignant PC and with occurrence of renal and thyroid cancers. These correlations point to a strategy for prioritizing which gene to sequence first in subjects with different clinical presentations. Genetic diagnosis allows screening and prospective monitoring of at-risk family members with imaging and catecholamine measurements. How loss of SDH activity causes tumorigenesis, the basis for tissue-specific tumorigenesis, and the basis for the varying clinical expressions of mutations in different SDH subunits remain unclear, but speculations focus on possible effects on apoptosis pathways and on angiogenesis due to free radical formation (Eng et al., 2003).

von Hippel-Lindau disease (VHL)

VHL has an estimated birth incidence of 1/36,000/year and a penetrance of 95%–100% by age 65 (Nagy et al., 2004). PC in up to 20% of cases is the major endocrine manifestation, but islet cell tumors also occur. Retinal and cerebellar hemangioblastomas and renal cell cancer (all in up to 60% of cases) are the main nonendocrine features. Imaging for diagnosis and surgical treatment can be applied in a more targeted manner based on identification of loss-of-function mutations in the *VHL* gene as the cause of the disease, and the relatively specific phenotypes associated with particular *VHL* mutations (Clifford et al., 2001). The *VHL* gene encodes a subunit of a ubiquitin ligase complex that regulates degradation of the hypoxia-inducible transcription factor (HIF1). Type 1 disease, in which hemangioblastoma and renal cell cancer but not PC are common, is associated with truncation, deletion, and protein-folding mutations that impair regulation of HIF1. Resultant upregulation of assorted proangiogenic genes is thought to account for the associated tumors. Type 2 disease, in which PC is common, is associated with various missense mutations, and is further subdivided into 2A (renal cell cancer rare), 2B (renal cell cancer also), and 2C (PC only). In type 2C, mutated VHL protein may still downregulate HIF1, but abnormal extracellular matrix formation may account in ways yet unexplained for PC formation (Hoffman et al., 2001). Loss of VHL function has also been described in sporadic hemangioblastoma and renal cell cancer, but not PC. These interesting but still incompletely understood associations point to potential utility of angiogenesis inhibitors for at least some forms of VHL. The *VHL* gene pathway, its role in tumorigenesis, and opportunities for disease-specific

approaches to therapy are covered in an excellent recent review on kidney cancer (Linehan and Zbar, 2004).

Multiple endocrine neoplasia type 2 (MEN2)

Between 500–1000 kindreds with MEN2 have been reported. The incidence of its major component, MTC, is 1/million/year, with 25%–50% of cases being hereditary (Gertner and Kebebew, 2004). MEN2 is caused by germline activating mutations of *RET*, which encodes a transmembrane tyrosine kinase that binds members of the glial-derived neurotrophic factor (GDNF) family by associating with coreceptors for GDNF. As with other receptor-tyrposine kinases, agonist binding promotes receptor dimerization, transphosphorylation of key intracellular tyrosines, binding of intracellular adaptor proteins to phosphorylated tyrosines, and thereby stimulation of ras/mitogen activated protein kinase and PI3 kinase/AKT cascades.

The limited number of disease-causing missense mutations facilitates genetic diagnosis, and is associated with distinct phenotypes. Type 2A mutations most often involve extracellular cysteines, preventing intramolecular disulfide formation and leading instead to intermolecular disulfide formation, receptor dimerization, and constitutive activation. Mutations in cysteines at codons 609–620 may cause familial MTC only. Mutation of cysteine 634 is the most frequent cause of MEN2A: MTC associated with PC (50%) and hyperparathyroidism (15%–30%). Rarely, MEN2A may occur in association with Hirschsprung disease (loss of enteric ganglia). The latter is typically associated with germline loss-of-function mutations of *RET*. Codon 609–620 missense mutations simultaneously reduce cell surface expression while causing constitutive activation of those receptors that do reach the cell surface. The presumption is that development of enteric ganglia is more sensitive to reduced RET expression than thyroid C cells, explaining the combination of MTC due to constitutive RET activation and Hirschsprung disease due to RET loss of function. M918T is the most frequent type 2B mutation, and involves a conserved catalytic core residue that changes substrate specificity. How altered RET specificity leads to the Type 2B phenotype, with MTC, PC, mucosal, and intestinal neuromas, and a marfanoid habitus, is not clear, but MEN2B tumors have a different gene expression pattern than do MEN2A tumors (Santoro et al., 2004). Germline RET mutations may also be found in apparently sporadic MTC and/or PC.

Before RET gene discovery, prospective screening of at-risk family members involved calcitonin stimulation testing. Although this allowed identification of C cell hyperplasia as a pre-MTC lesion, it was insufficiently sensitive to identify mutation carriers early enough to prevent metastatic MTC in all. Studies using genetic diagnosis have documented the benefit of prophylactic thyroidectomy, notwithstanding risks of recurrent laryngeal nerve damage and hypoparathyroidism, in asymptomatic carrier children (Machens et al., 2003). Guidelines for management of MEN2 provide a paradigm for eventual management of other genetic forms of cancer (Cote and Gagel, 2003). Since MTC is relatively resistant to conventional forms of chemo- or radiation therapy, newer targeted therapies based on understanding of RET signaling are being tested (Santoro et al., 2004).

Future challenges

Although there has been dramatic progress in identifying the genetic basis for endocrine neoplasia syndromes, the challenge now is to translate this progress into more effective ways to treat and prevent these diseases. To do so will require defining the fundamental biologic roles for tumor suppressor gene products such as MENIN and PARAFIBROMIN, and the precise mechanisms responsible for tumorigenesis in all of the endocrine neoplasia syndromes. Only with a deeper understanding of such mechanisms can we hope to explain the basis for the unique phenotypic features of these diseases, such as tissue-specific tumor formation patterns. More robust methods for mutation identification and a clearer understanding of possible genotype-phenotype correlations are of obvious importance with regard to family screening and genetic counseling. Because conventional chemotherapy and radiotherapy are generally poorly effective in malignant forms of endocrine neoplasia, early genetic diagnosis and prevention are desirable goals. Prophylactic surgery, however, may only be warranted for endocrine glands such as the thyroid that can be removed relatively safely early in life, and for which there is adequate lifelong hormone replacement. That is one major reason why development of targeted therapies capable of safely and effectively blocking the specific pathways leading to endocrine neoplasia will be a high priority for future research.

Acknowledgment

I am grateful to many colleagues in NIDDK and NHGRI with whom I have participated in studies on MEN1 and McCune-Albright syndrome, and especially to Stephen Marx for helpful comments on the manuscript. I also apologize to the many authors whose work could not be cited because of space limitations.

References

Agarwal, S.K., Kennedy, P.A., Scacheri, P.C., Novotny, E.A., Hickman, A.B., Cerrato, A., Rice, T.S., Moore, J.B., Rao, S., Ji, Y., et al. (2004) Menin molecular interactions: Insights into normal functions and tumorigenesis. Horm. Metab. Res., in press.

Betea, D., Bradwell, A.R., Harvey, T.C., Mead, G.P., Schmidt-Gayk, H., Ghaye, B., Daly, A.F., and Beckers, A. (2004). Hormonal and biochemical normalization and tumor shrinkage induced by anti-parathyroid hormone immunotherapy in a patient with metastatic parathyroid carcinoma. J. Clin. Endocrinol. Metab. *89*, 3413–3420.

Bossis, I., Voutetakis, A., Bei, T., Sandrini, F., Griffin, K.J., and Stratakis, C.A. (2004). Protein kinase A and its role in human neoplasia: The Carney complex paradigm. Endocr. Relat. Cancer *11*, 265–280.

Carpten, J.D., Robbins, C.M., Villablanca, A., Forsberg, L., Presciuttini, S., Bailey-Wilson, J., Simonds, W.F., Gillanders, E.M., Kennedy, A.M., Chen, J.D., et al. (2002). HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat. Genet. *32*, 672–680.

Clifford, S.C., Cockman, M.E., Smallwood, A.C., Mole, D.R., Woodward, E.R., Maxwell, P.H., Ratcliffe, P.J., and Maher, E.R. (2001). Contrasting effects on HIF-1α regulation by disease-causing pVHL mutations correlate with patterns of tumourigenesis in von Hippel-Lindau disease. Hum. Mol. Genet. *10*, 1029–1038.

Cote, G.J., and Gagel, R.F. (2003). Lessons learned from the management of a rare genetic cancer. N. Engl. J. Med. *349*, 1566–1568.

Eng, C., Kiuru, M., Fernandez, M.J., and Aaltonen, L.A. (2003). A role for mitochondrial enzymes in inherited neoplasia and beyond. Nat. Rev. Cancer *3*, 193–202.

Gertner, M.E., and Kebebew, E. (2004). Multiple endocrine neoplasia type 2. Curr. Treat. Options Oncol. *5*, 315–325.

Hoffman, M.A., Ohh, M., Yang, H., Klco, J.M., Ivan, M., and Kaelin, W.G., Jr. (2001). Von Hippel-Lindau protein mutants linked to type 2C VHL disease preserve the ability to downregulate HIF. Hum. Mol. Genet. *10*, 1019–1027.

Howell, V.M., Haven, C.J., Kahnoski, K., Khoo, S.K., Petillo, D., Chen, J.,

Fleuren, G.J., Robinson, B.G., Delbridge, L.W., Philips, J., et al. (2003). *HRPT2* mutations are associated with malignancy in sporadic parathyroid tumors. J. Med. Genet. *40*, 657–663.

Linehan, W.M., and Zbar, B. (2004). Focus on kidney cancer. Cancer Cell *6*, 223–228.

Luccio-Camelo, D.C., Une, K.N., Ferreira, R.E., Khoo, S.K., Nickolov, R., Bronstein, M.D., Vaisman, M., The, B.T., Frohman, L.A., Mendonca, B.B., and Gadelha, M.R. (2004). A meiotic recombination in a new isolated familial somatotropinoma kindred. Eur. J. Endocrinol. *150*, 643–648.

Machens, A., Niccoli-Sire, P., Hoegel, J., Frank-Raue, K., van Vroonhoven, T.J., Roeher, H.-D., Wahl, R.A., Lamesch, P., Raue, F., Conte-Devolx, B., et al. (2003). Early malignant progression of hereditary medullary thyroid cancer. N. Engl. J. Med. *349*, 1517–1525.

Marx, S.J. (1999). Contrasting paradigms for hereditary hyperfunction of endocrine cells. J. Clin. Endocrinol. Metab. *84*, 3001–3009.

Nagy, R., Sweet, K., and Eng, C. (2004). Highly penetrant hereditary cancer syndromes. Oncogene *23*, 6445–6470.

Neumann, H.P.H., Pawlu, C., Peczkowska, M., Bausch, B., McWhinney, S.R., Muresan, M., Buchta, M., Franke, G., Klisch, J., Bley, T.A., et al. (2004). Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. JAMA *292*, 943–951.

Santoro, M., Melillo, R.M., Carlomagno, F., Vecchio, G., and Fusco, A. (2004). RET: Normal and abnormal functions. Endocrinology, in press.

Segev, D.L., Umbricht, C., and Zeiger, M.A. (2003). Molecular pathogenesis of thyroid cancer. Surg. Oncol. *12*, 69–90.

Shapiro, S.E., Cote, G.C., Lee, J.E., Gagel, R.F., and Evans, D.B. (2003). The role of genetics in the surgical management of familial endocrinopathy syndromes. J. Am. Coll. Surg. *197*, 818–831.

Shattuck, T.M., Valimaki, S., Obara, T., Gaz, R.D., Clark, O.H., Shoback, D., Wierman, M.E., Tojo, K., Robbins, C.M., Carpten, J.D., et al. (2003). Somatic and germ-line mutations of the HRPT2 gene in sporadic parathyroid carcinoma. N. Engl. J. Med. *349*, 1722–1729.

Sidhu, S., Sywak, M., Robinson, B., and Delbridge, L. (2004). Adrenocortical cancer: Recent clinical and molecular advances. Curr. Opin. Oncol. *16*, 13–18.

Simonds, W.F., Robbins, C.M., Agarwal, S.K., Hendy, G.N., Carpten, J.D., and Marx, S.J. (2004). Familial isolated hyperparathyroidism is rarely caused by germline mutation in HRPT2, the gene for the hyperparathyroidism-jaw tumor syndrome. J. Clin. Endocrinol. Metab. *89*, 96–102.

Spiegel, A.M., and Weinstein, L.S. (2004). Inherited diseases involving G proteins and G protein-coupled receptors. Annu. Rev. Med. *55*, 27–39.

Thakker, R.V. (2004). Genetics of endocrine and metabolic disorders: Parathyroid. Rev. Endoc. Metab. Disorders *3*, 37–51.

Vogelstein, B., and Kinzler, K.W. (2004). Cancer genes and the pathways they control. Nat. Med. *10*, 789–799.