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Mouse Models of Endocrine Tumors

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Abstract

Since the onset of the genomic era, there has been tremendous progress in identifying the genetic causes of endocrine tumors. Although this knowledge is valuable in its own right, understanding the molecular basis of tumorigenesis allows the development of new therapies targeted towards the causative defects. Understanding the connection between genotype and phenotype is a complex process, which can only be partially understood from analysis of primary tumors or from studies of cells *in vitro*. To bridge this gap, genetically modified mice have been developed in order to allow molecular dissection of the relevant defects in an intact organism. In this review, we will discuss the status of genetic modeling for hereditary and sporadic endocrine tumorigenesis with a goal towards providing a picture of how this technology will be of future benefit to clinicians developing specifically targeted therapies for endocrine tumors.

Keywords

Knockout mice; Transgenic mice; Tumor suppressor genes; Oncogenes; Endocrine Neoplasia syndromes

INTRODUCTION

With the advent of positional cloning strategies, it became possible to identify the genes responsible for inherited human diseases. These studies spurred further work in the identification of the genes responsible for inherited and sporadic endocrine neoplasia. Once these genes were identified, either as tumor suppressor genes or as oncogenes, molecular characterization required the generation of tissue culture model systems to verify their role in tumor formation. However, the need to understand the molecular basis of these pleiotropic syndromes necessitated the use of a more complex system in order to allow an appreciation of the biology of these diseases. In this review, we will describe the work done to date in the generation and analysis of mouse models of endocrine neoplasia. Although the scope of this

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review is somewhat limited, our goal is to provide a brief survey of the field, with references cited to point the interested reader to more detailed discussions of the respective topics.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)

Multiple endocrine neoplasia type I (MEN1), also known as Wermer syndrome (1), is an autosomal dominant tumor predisposition caused by mutations in the *MEN1* gene. *MEN1* is a tumor-suppressor localized to chromosome 11q13 (2) that codes for MENIN, a 610 amino acid protein found to interact with the JunD transcription factor in order to suppress cell growth (3–6). The major complications associated with MEN1 are tumors of the parathyroid, pancreatic islets, duodenal endocrine cells, and the anterior pituitary (7). Uncommon tumors include foregut carcinoids, lipomas, angiofibromas, thyroid adenomas, adrenocortical adenomas, angiomyolipomas, and spinal cord ependymomas (8).

Conventional Knockout (KO) Models of MEN1

To better understand the role of Menin in relation to endocrine tumorigenesis, *Men1* knockout (KO) mouse models have been generated. Crabtree *et al* (2001) generated a conventional KO mouse model for MEN1 that exhibited a phenotype similar to the human disorder. While homozygous-null ($Men1^{-/-}$) mice died embryonically due to defects in craniofacial development, heterozygotes developed tumors of various endocrine glands, including pancreatic islet cell tumors, pituitary and parathyroid adenoma, and adrenocortical tumors.

A second *Men1* conventional KO model confirmed that disruption of *Men1* causes 100% embryonic lethality at E11.5–E13.5, showing that Menin plays an important role in cell differentiation and/or senescence (9). Based on the findings from these two conventional models, and owing to the role of Menin in cell cycle regulation, it was hypothesized that the absence of Menin may arrest cell replication, thereby allowing cells to acquire genetic alterations that may predispose them to tumorigenesis.

Another KO mouse model that more closely resembled the human MEN1 syndrome was developed by deleting exon 2, including the translational start site of *Men1* ((10)). Like the others, this model also showed rare progression to carcinoma and metastasis. This mouse model developed tumors in pancreatic islets, pituitary, thyroid and parathyroid, adrenal glands, testes and ovaries. Loss of heterozygosity (LOH) at the *Men1* locus was seen in all tumors, albeit at a lower frequency in testicular tumors. Low Menin expression was detected in ovary, thyroid and testis; and uniform loss of nuclear Menin in all pancreatic islet adenomas and some hyperplastic islet cells was also observed. This suggested that complete loss of *Men1* is important for islet tumor progression in this model.

Tissue specific KO of Men1

Since Menin plays an important role as a tumor suppressor, and somatic loss of the wild type allele is required for tumorigenesis in MEN1 tumors, it was important to determine its role in normal development or in sporadic tumors. Although $Men1^{+/-}$ mice showed evidence for parathyroid neoplasm, the exact consequences of homozygous deletion in somatic tissues could not be determined using this model. Thus, developing tissue specific KO of *Men1* was necessary to establish the direct effect of menin inactivation and endocrine tumor development.

In order to overcome homozygous lethality, a conditional KO model was developed which used cre-mediated recombination to cause deletion of exons 3–8 of *Men1* (11). After mating these mice with rat insulin promoter (RIP) cre mice which expressed low levels of cre, 80% of the mice developed multiple pancreatic islet adenomas by 60 weeks of age. Furthermore, these pancreatic KO mice showed high insulin levels with low blood glucose, indicative of pancreatic β-cell tumors. In contrast, a cre line with high expression in the islet cells caused

hyperplastic islets by the age of 2 months of age and insulinomas by 6 months. Hormonal dysregulation and insulinomas observed in these mice mimicked that seen in MEN1 patients. Down regulation of membrane expression of both E-cadherin and β-catenin in advanced insulinomas was also observed in this model. Interestingly, pituitary adenomas were also observed in these mice, and they were similar to the *Men1*$^{+/-}$ mice. Both models showed resemblance to human tumors in that they were derived from the pars distalis, expressed prolactin, and were more prevalent in females (11).

Tissue-specific loss of *Men1* in the parathyroid resulted in a mouse model of hyperparathyroidism (12). These mice developed abnormal parathyroid glands and elevated serum calcium levels, similar to MEN1 patients with hyperparathyroidism. Thus, this model helped to better define the pathophysiology of familial parathyroid neoplasia that results in hypercalcemia and primary hyperparathyroidism.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2)

Multiple endocrine neoplasia type 2 (MEN2), also known as Sipple Syndrome, is a dominantly inherited tumor syndrome that comprises three clinical subtypes: MEN type 2A (MEN-2A), MEN type 2B (MEN-2B), and familial medullary thyroid carcinoma (FMTC). Patients with MEN2 may develop benign or malignant tumors or overactivity of the endocrine glands (e.g. medullary thyroid carcinoma, pheochromocytoma, and hyperparathyroidism) and tumors of neuroendocrine tissues as well (e.g. mucosal neuromata).

MEN2 mutations convert the RET (REarranged during Transfection) protooncogene to a dominantly acting oncogene as a consequence of the ligand-independent activation of the tyrosine kinase. The MEN2A mutant form of RET is oncogenic in parafollicular C cells of the thyroid, and transgenic mice harboring this mutation served as an ideal model for FMTC (13). A second, constitutively active, form of RET (*RET*^{MEN2B}) was over expressed in mice under the control of dopamine-β-hydroxylase (*D*b*H*) promoter in the adrenal chromaffin cells, catecholaminergic neurons, and their precursor cells (14). These transgenic embryos developed profound neuroglial hyperplasia of their sympathetic ganglia and adrenal medullae, suggesting an important role for *RET* in the neuroendocrine system.

Finally, in another model of MEN2-related tumorigenesis, the c-mos protooncogene was overexpressed in transgenic mice (15). These mice developed severe neurological defects, multicentric pheochromocytomas, and medullary thyroid neoplasias consistent with the human disease, giving further insight into the molecular basis for MEN2.

CARNEY COMPLEX

Conventional KO Models of Carney Complex

Carney complex (CNC) is a rare endocrine neoplasia syndrome that has been described as the complex of spotty skin pigmentation, myxoma, endocrine overactivity and schwannoma (16). Mutations in one of the PKA regulatory subunit genes, *PRKAR1A*, causes the majority of CNC cases, although a second unidentified gene has been localized to chromosome 2 (17,18). In an effort to model the disease, mice were generated that harbored a targeted deletion of this gene, resulting in dysregulated PKA activity (19). *Prkar1a*$^{-/-}$ mice died early in embryogenesis, but *Prkar1a*$^{+/-}$ mice survived and exhibited tumor formation in a range of cAMP-responsive tissues. Over 80% of these animals developed tumors in the tail vertebrae that were pathologically similar to osteochondromyxoma, a rare feature of CNC (19). In terms of morbidity, most mutant mice required early euthanasia due to rapid progression of solid tumors found on the head, limbs, or rump (19). By one year of age, approximately one third of

Prkar1a$^{+/-}$ mice developed these neoplasms which were clinically characterized as schwannomas with divergent differentiation (19).

Thyroid neoplasia occurred in approximately 11% of the *Prkar1a*$^{+/-}$ mice over 1 year of age (19). Up to 60% of CNC patients may develop thyroid nodules which are histologically characterized as follicular adenomas in about 11% of patients, and in some cases carcinomas have developed (20). The thyroid tumors observed in *Prkar1a*$^{+/-}$ mice were characterized as either thyroid adenoma or carcinoma, and most had a solid or papillary pattern of growth. Of note, the generation of this mouse represented the first conventional genetic model of spontaneous epithelial thyroid cancer, which may serve as a useful tool for studying the role of PKA in thyroid cancer progression.

Tissue Specific KO of *Prkar1a*

Conditional *Prkar1a* knock-out mice were generated by adding *loxP* sites flanking the second exon of the gene (19). Using the α-Myosin heavy chain (αMHC) promoter as a Cre driver, selective knock-out of *Prkar1a* was achieved in the embryonic heart in an attempt to model cardiac myxoma, the most common neoplasm found in CNC patients (21). These cardiac knock-out (CKO) mice died *in utero* before embryonic day 12.5 due to specific defects associated with the ventricular wall. Because of excess PKA signaling in the embryonic heart, loss of cardiac-specific transcription factor expression occured, and subsequently resulted in decreased transcription of genes required for cardiac development. Reduced cardiomyocyte proliferation, thinning of the myocardium, ventricular dilation, and sarcomere disorganization all contributed to the inability for the CKO embryos to efficiently circulate blood; therefore causing growth retardation and lethality (21).

Even though the CKO mice died embryonically, all was not lost in the effort to model cardiac myxoma. Despite decreased proliferation in the CKO heart, about half of the animals displayed focal areas of myxomatous lesions adjacent to the left atrium; which is the same site as nearly three quarters of human cardiac myxomas (21) . The cardiomyocytes in these lesions underwent myxoid degeneration and developed a gland-like appearance which is indicative of myxoma and a diagnostic characteristic for human tumors. Owing to the fact that *Prkar1a*$^{+/-}$mice do not exhibit cardiac myxomagenesis, the CKO mice serve as the first model for cardiac myxoma that emulates early stages of the human condition seen in CNC.

To assess the role of PKA signaling specifically in the pituitary, the rat growth hormone releasing hormone receptor (rGHRHR) promoter was used to drive cre expression in the Pit1 lineage of anterior pituitary cells (22). Pit1 is a transcription factor that is expressed in a subset of pituitary cells that secrete growth hormone (GH), prolactin (PRL), and thyroid stimulating hormone (TSH). The *rGHRHR-Cre* mice were mated with *Prkar1a*-conditional animals to generate pituitary-specific knock-out mice (pitKO, (23)). Pituitary tumors were found in about 50% of pitKO mice at 18 months of age, compared to less than 20% in control animals. Tumors found in pitKO mice were characterized as non-prolactinomas and in most cases the tumor cells expressed GH, PRL, and TSH (23). These mice also exhibited significantly increased levels of GH in serum samples, even in the absence of a defined tumor. Overall, the data from this mouse model illustrated the importance for proper PKA regulation in the pituitary for both regulated cell growth and homeostasis.

To further investigate the role of PKA in schwannoma development, *Tyrosinase Expressing Cre 3* (*TEC3*) mice were mated with the *Prkar1a*-conditional animals to generate tissue-specific loss of the gene in the Schwann cells of the trigeminal nerve (*TEC3KO*; (19)). Nearly 80% of the *TEC3KO* animals developed solid myxomatous lesions, which bore similarity to those seen in *Prkar1a*$^{+/-}$ animals, either uni- or bilaterally on the face by 10 months of age (19,24). The tumors were pathologically classified as genetically engineered mouse (GEM)

schwannomas grade II or III, which signified that they were similar to human malignant peripheral nerve sheath tumors (MPNST; (24,25)). Despite this classification, no *TEC3KO* tumors became malignant, although there was clear remodeling of the cranial bones to accommodate the tumor. The generation of these mice represented a new model for Schwann cell tumorigenesis that did not involve mutations of the Neurofibromatosis genes, and brought unique insight to the molecular events leading to peripheral nerve sheath tumor development.

COWDEN DISEASE

Cowden Disease (CD) is an inherited autosomal dominant tumor syndrome characterized by tumor formation in multiple tissues, including the breast, intestine, skin, and thyroid; and macrocephaly is also often associated with CD. Inactivating mutations in the *PTEN* gene have been identified as the cause of CD, and *PTEN* deletions have been identified in sporadic tumors of these tissues as well (26).

Conventional KO Models of CD

In order to study tumorgenesis associated with CD, several mouse models have been generated. Of note, in no case have conventional $Pten^{-/-}$ mice resulted in viable offspring, however several groups have shown that heterozygotes may serve as good models of CD. In 1999, Podsypanina *et al* (27) described a mouse model in which exon 5 of *Pten* ($Pten^{\Delta 5/+}$)was deleted, effectively deleting the phosphatase doman of the gene. $Pten^{\Delta 5/+}$ mice developed thyroid, endometrial, and prostate neoplasias as well as numerous intestinal polyps, consistent with the human disease. Additionally, these mice exhibited lymph node hyperplasia and disorganized lymphoid tissues, however most CD patients do not exhibit this pathology. Importantly, no skin or breast tumors were observed in this model, despite increased susceptibility for CD patients to develop these neoplasms.

In another model, exons 3–5 of *Pten* were deleted ($Pten^{\Delta 3-5/+}$), thus deleting the phosphatase domain as well as a larger portion of the upstream gene (28). In this model, as well as the previously described model, the mice developed tumors in the endometrium, prostate, intestine, and lymphoid tissues. Additionally, $Pten^{\Delta 3-5/+}$animals exhibited a high incidence of breast tumors, as well as hyperplasia of the adrenal glands. While these mice did develop tumors of the breast, they did not exhibit thyroid neoplasia as seen in $Pten^{\Delta 5/+}$ animals. It was also found that tumors formed in these mice were accompanied by LOH of the *Pten* allele, suggesting that in order to facilitate tumor formation, a secondary inactivating event must occur to effectively delete *Pten* in these tissues.

A third model model, in which exons 4 and 5 were deleted ($Pten^{\Delta 4-5/+}$) developed tumors of the intestine, prostate, testes, thyroid, lymph nodes and skin (29). These mice, as well as those of both of the previously described models, developed some of the tumors seen in CD patients, but not all. This suggested that genetic background or type of *Pten* mutation may play a role in the variety of tumor spectrum seen in the mice as well as in human CD patients. The question of genetic background has been addressed, and it was shown that different mutations had no effect on tumor burden/onset in the same genetic background. However, the same mutation in differing genetic backgrounds showed a large difference in tumor incidence (30). These results suggest that differing genetic background and modifier genes may be important considerations, and could explain the broad spectrum of disease severity associated with CD.

The mechanism by which *Pten* deficiency leads to tumorgenesis has also been examined using mouse models. In addition to LOH of *Pten* in CD-related tumors, the affected tissues also showed hyperphosphorlatyion and activation of Akt (28). Further supporting the activation of Akt as the mechanism of tumorgenesis in these tissues, mice deficient for both *Pten* and

Akt1 showed decreased tumor burden as compared with mice deficient for *Pten* alone, indicating that Pten's effects occur through activation of Akt (31).

Tissue Specific KO of PTEN

In addition to global deletion of *Pten*, thyroid-specific KO of the gene was accomplished in order to specifically study the role of *Pten* in thyroid development and tumorgenesis. These thyroid-KO mice developed goiters and exhibited marked proliferation in the thyroid (32). The dividing thyrocytes also showed activation of Akt, validating the role of Akt in thyroid tumorgenesis. Of note, invasive tumors were not observed in these animals, indicating that although deletion of *Pten* lays the groundwork for thyroid neoplasia and hyperproliferation, additional genetic changes must occur in order to potentiate the development of true malignant cancers.

The importance of *Pten* in the thyroid was also demonstrated in a model of sporadic thyroid cancer. Mice harboring mutations of the *thyroid hormone receptor β* (*TRβ*) develop follicular thyroid cancer, but when loss of *Pten* accompanied the *TRβ* mutation, the tumor phenotype was significantly enhanced and survival decreased (33).

MODELS FOR SPORADIC THYROID MUTATIONS

Genetic investigations of sporadic endocrine neoplasia have revealed a wide variety of genetic changes associated with the development of tumors. In order to confirm the role of specific alterations in tumor formation, genes with altered expression can be introduced into cell lines in order to determine their ability to stimulate growth.

Genetic analysis of sporadic papillary thyroid cancer (PTC) demonstrated fusion of the RET proto-oncogene to other sequences, which came to be known as PTC genes. In each of these cases, the C-terminal region of RET, carrying the tyrosine kinase domain, is fused to the N-terminus of a protein capable of dimerization. This leads to unregulated activity of the RET tyrosine kinase, the same gene mutated in MEN2 syndrome. To date, there have been 7 such fusion genes described, which are designated as RET-PTC genes. The most common of these are RET-PTC1, in which RET is fused to the H4 gene, and RET-PTC3, a fusion of RET to the ELE1 gene (34–36). Both H4 and ELE1 are located on chromosome 10, and the genes fuse by mechanism of an intrachromosomal rearrangement (37,38).

Transgenic mouse models for both RET-PTC1 (39,40) and RET-PTC3 (41) have been generated and used to study the role of this protein in thyroid cancer. In general, thyroid specificity has been achieved by using a thyroid-specific promoter such as that for Thyroglobulin (Tg) or Thyroid Peroxidase (Tpo) to target expression of the oncogene into the thyroid gland itself. These mice develop thyroid neoplasia and locally invasive thyroid cancer, although distant metastasis is quite rare. This approach has allowed investigations of specific components of the receptor required for oncogenic activity (42), as well as to identify other signaling pathways that may impact thyroid tumorigenicity (43). Although this experimental approach has not been taken to date, these models provide the opportunity to perform pre-clinical studies to examine drug effects in an endogenous model. Currently, such studies are performed either *in vitro* or in xenograft models using established thyroid cancer cell lines.

More recently, as the role of BRAF in sporadic thyroid cancer has become evident (44), a mouse model to explore this pathway has also been generated (45). By using a combination of inducible models and drug treatment, this model also has the chance of significantly enhancing our understanding of the signaling events in thyroid cancer.

Finally, aberrant TSH signaling plays an important role in benign thyroid tumorigenesis, including in hyperfunctioning models. There is also a growing body of evidence suggesting that enhanced TSH signaling is associated with thyroid carcinogenesis (46). This concept can be modeled *in vivo* using various means to activate the PKA signaling pathways, which is downstream from the TSH receptor, among others. This pathway has been explored in transgenic mice by ectopically expressing the Adenosine A2 receptor in the thyroid, by expressing a mutated (activated) form of the Gsα subunit (47), or by expressing the cholera toxin A1 subunit (48). In each of these models, enhanced GPCR signaling through adenylate cyclase and PKA was associated with biochemical hyperthyroidism and thyroid gland hyperplasia, although no cancers were observed.

MODELS FOR SPORADIC PITUITARY TUMORIGENESIS

Although pituitary tumors are the most commonly encountered intracranial neoplasms in the general population (39), genetic alterations occurring in sporadic pituitary tumors are much less well characterized than those occurring in the thyroid. The most common genetic change in pituitary tumors are activating mutations of *GNAS1*, the same mutation that causes these tumors in association with McCune Albright syndrome. Activating *GNAS1* mutations are observed in over 25% of pituitary tumors, although no mouse model of this phenomenon has yet been observed. One genetic change that has been observed is the overexpression of the Pituitary Tumor Transforming Gene (*PTTG1*, also known as Securin). This gene was isolated using differential display techniques from a rat pituitary tumor cell line (49), and subsequently shown to be overexpressed in human pituitary tumors (50). A mouse model of PTTG overexpression targeted to the pituitary by the α-glycoprotein subunit promoter showed hyperplasia of pituitary lineages where the transgene was expressed (51), an effect which was enhanced by loss of the Rb gene (52). It was recently reported that mutations in the *AIP* gene predispose to familial pituitary tumors (53). Mice homozygous for mutations in this gene die *in utero* (54), and a tissue-specific mouse model has not yet been produced.

MOUSE MODELS FOR ADRENAL TUMORIGENESIS

Causative mutations associated with adrenocortical tumors are not well defined, although tumors are observed in association with Carney Complex, MEN1, APC, Li-Fraumeni syndrome, and Beckwith-Wiedeman syndrome (55). This latter is important, because overexpression of IGF2, which is located at the BWS locus at 11p15, is the most common molecular feature associated with adrenocortical carcinoma (ACC). However, no mouse models for this condition are yet available.

There are a number of mouse models that spontaneously develop adrenocortical tumors. The oldest of these is a strain-specific model which develops adrenocortical tumors in response to gonadectomy. These primitive adrenal tumors appear to represent persistence or transdifferentiation of adrenogenital tissue into a gonadal phenotype. This phenotype is also echoed in mice with a KO of the TGF-β family member, Inhibin, that have undergone gonadectomy (56). Although mutations in the phosphodiesterase genes PDE11A (57) and PDE8B (58) and β-catenin (59) appear to cause adrenal hyperplasia and/or tumors in humans , the corresponding mouse phenotype has not (yet) been described.

TUMOR SUPPRESSOR MODELS OF PITUITARY TUMORIGENESIS

Several classic cell cycle regulators – such as retinoblastoma (Rb), cyclin dependent kinases (CDKs), or cyclin-dependent kinase inhibitors (CDKIs) – have demonstrated prominent neoplastic impact in some endocrine tissues, such as the pituitary gland, as identified by several mouse models with deregulation of the cell cycle.

The initial linkage between pituitary tumors and cell cycle regulation was provided by the seminal genetic analysis of *Rb* in the mouse. Homozygous disruption of the *Rb* gene in mouse models was lethal during embryonic development. Transgenic mice in which one of the two germline *Rb* alleles was disrupted failed to develop retinoblastoma, but some displayed pituitary tumors arising from LOH of the wild-type *Rb* allele, indicating a second *Rb* "hit" as the basis for pituitary tumor development in this model (60). Moreover, loss of E2F1 and E2F4, transcription factors inhibited by *Rb*, interfered with the pituitary tumor incidence that occurred in *Rb*-deficient mice. This resulted in reduced frequency of pituitary tumors, thereby extending the lifespan of the animals and suggesting the relevance of the *Rb/E2F* cell cycle pathway in pituitary tumorigenesis (61,62).

The relationship between pituitary tumors and cell cycle regulation is not limited to *Rb* proteins. Previous reports showed a series of novel phenotypes including increased body size, multiple organ hyperplasia, and pituitary tumors in mice deficient for $p27^{KIP1}$(63–65). Deletion of $p27^{KIP1}$, like that of *Rb*, caused neoplastic growth of the intermediate pituitary, indicating that $p27^{KIP1}$ and *Rb* may function in the same regulatory pathway. Nevertheless, *Rb*-null and $p27^{KIP1}$-null pituitary tumors were significantly different in both their genetic and pathological characteristics (66). More recently, germline mutations in *CDKN1B*, which encodes the $p27^{KIP1}$ protein, have been reported to predispose human patients to the development of pituitary tumors (67,68).

In addition to the *Rb* and $p27^{KIP1}$ models, mice lacking $p18^{INK4c}$, a member of the INK4 family of CDKIs, displayed tumors of both the anterior and intermediate pituitary by 15 months, although the intermediate lobe was more severely affected in most cases (69). Approximately 40% of $p18^{INK4c}$-deficient mice died before 18 months of age due to the presence of large pituitary tumors, most of which were chromophobe adenomas of the intermediate lobe of the pituitary.

The implication of the cell cycle regulators in pituitary tumorigenesis is validated by the mouse models discussed above; however, the results from the combined deletions of some of these mutations in the mouse may put forward a more convoluted molecular network. For example, the combination of *Rb* and $p27^{KIP1}$ deletions accelerated the formation of pituitary tumors in mice, suggesting cooperation of these pathways in pituitary tumorigenesis (70). Moreover, $p27^{KIP1}$ mRNA expression was decreased in pituitary tumors arising in $Rb^{+/-}$ mice, indicating that Rb may participate in the regulation of $p27^{KIP1}$. Similarly, the simultaneous loss of both $p27^{KIP1}$ and $p18^{INK4c}$ exaggerated the phenotype caused by deficiency of either gene alone, indicating that these two genes mediate two separate pathways to collaboratively regulate cell growth (69). Additionally, growth suppression by $p18^{INK4c}$ combined with the wild-type *Rb* function may suggest that *Rb* is the common theme of both $p27^{KIP1}$- and $p18^{INK4c}$-mediated tumor suppression in the pituitary (69–71)

Similar to the models of CD, the interpretation of the findings in these pituitary tumor models may be complicated by strain-specific effects. It has been reported that the 129Sv background significantly enhanced both the initiation and progression of tumorigenesis in the intermediate lobe of the pituitary in $Rb^{+/-}$ mice, while a *Rb*-null mutation bred in to the C57 background resulted in highly-penetrant tumor formation in the anterior lobe of the pituitary (72). Furthermore, the 129S4 background decreased the latency of pituitary tumors and survival time in $p27^{KIP1}$-deficient mice. These data indicate the presence of genetic modifiers in pituitary tumor development.

CONCLUSIONS

Mouse models for the major endocrine neoplasia syndromes have been developed, as well as many models suitable for analyzing the genetic changes in many of the major sporadic endocrine tumors. These models should provide valuable models for the future as they allow researchers to identify downstream targets affected by these tumorigenic mutations. This will be important not only from a biological standpoint, but also will allow the development of newer therapies targeted toward these aberrant pathways that may impact tumor behavior.

RESEARCH AGENDA

- Use mouse models to identify signaling pathways aberrantly activated or shut down in endocrine tumors
- Use this information to develop new therapeutic modalities for endocrine tumors
- Use mouse models for pre-clinical testing of endocrine-targeted therapies

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