Apc-related models of intestinal neoplasia: a brief review for pathologists

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Abstract

Rodent models of intestinal cancer are widely used as preclinical models for human colorectal carcinoma and have proven useful in many experimental contexts, including elucidation of basic pathways of carcinogenesis and in chemoprevention studies. One of the earliest genetically engineered mouse models of intestinal cancer is the ApcMin/+ mouse, which has been used for over 25 years. This model carries a mutation in the Apc gene, which is responsible for the inherited colon cancer syndrome, familial adenomatous polyposis coli, in humans. In this review, we discuss the pathologic features of ApcMin/+ -type intestinal adenomas and carcinomas, and compare them to the analogous human lesions. Pitfalls of assessment of histopathology of the mouse such as non-invasive mucosal herniation in prolapse are also described.

Keywords: Genetically engineered mice, intestinal neoplasms, Apc, disease models, Min, colorectal cancer

Background

Colorectal carcinoma is a common cause of cancer mortality in the Western world. In many pathology practices, colorectal adenomas removed during screening colonoscopies constitute a high percentage of the daily workload, and thus the morphology of human colorectal carcinoma and adenomas, its precursor lesions, is familiar to surgical pathologists. In academic centers, surgical pathologists may be asked to interpret mouse models of neoplasia for investigators, and a basic understanding of similarities and differences between the morphology of human intestinal neoplasia and mouse models is necessary for accurate interpretation.

Genetically altered mouse models of tumorigenesis, while sometimes criticized for their imperfect modeling of human disease, are useful in assessing whether specific mutations can lead to tumor formation, for chemoprevention studies and for elucidating functionality of altered gene products. While there are many genetically engineered mouse (GEM) models of intestinal neoplasia described in the scientific literature, they can be broadly divided into 5 groups: Apc-related models with alterations in Wnt signaling, mismatch repair deficient models, carcinogen-treated models, models with alterations in transforming growth factor β, and colitis-associated neoplasia arising in immune-deficient models such as IL10−/− mice. This review will focus on the pathology of one of the first GEM models of intestinal neoplasia, the ApcMin/+ mouse and related models, with the goal of describing the morphologic features of the intestinal lesions, with comparison to human colorectal adenomas and carcinomas.

One of the most widely used models for human intestinal neoplasia is the ApcMin/+ model, developed in 1990 in the laboratory of William Dove (Moser et al., 1990). The ApcMin/+ mouse, the first germline mutant mouse model of intestinal neoplasia, carries an autosomal dominant loss of function mutation at Apc codon 850 generated by exposure to N-ethyl-N-nitrosourea (ENU), a highly potent mutagen. A number of other models with Apc mutation, many with truncating mutations, have since been generated (Table 1).

These Apc-related models are particularly useful because the most common driver mutation for colorectal carcinoma in humans is mutation in the tumor suppressor gene APC, leading to inactivation of APC and activation of the Wnt signaling pathway, with stabilization of β-catenin and its translocation of to the nucleus. The APC gene in humans encodes a 213 kilodalton protein involved in cell adhesion and motility, cell cycle regulation, apoptosis, and...
| Model          | Predominant Tumor Locations | Neoplasm                         | Average number of tumors per mouse | Other lesions                                               | Reference                                      |
|---------------|-----------------------------|----------------------------------|------------------------------------|------------------------------------------------------------|------------------------------------------------|
| \(\text{Apc}^{\text{Min+/-}}\) | Small intestine > colon    | Adenoma                          | 30                                 |                                                            | Moser et al. 1990 (Moser et al., 1995)          |
| \(\text{Apc}^{+538N/+}\)       | Small intestine and colon; more in colon compared to \(\text{Apc}^{\text{Min+/-}}\) | Adenoma, carcinoma; rarely, liver metastasis (Fodde et al., 1994) | 4 (10-fold reduction over \(\text{Apc}^{\text{Min+/-}}\)) | Fibromatosis (desmoid tumors); gastric carcinoma, duodenal adenomas, cutaneous cysts | Fodde et al. 1994 (Fodde et al., 1994)          |
| \(\text{Apc}^{\Delta716/+}\) | Small intestine > colon    | Adenoma                          | 254 (10-fold increase over \(\text{Apc}^{\text{Min+/-}}\)) |                                                            | Oshima et al. 1995 (Oshima et al., 1995)        |
| \(\text{Apc}^{1309/+}\)       | Small intestine            | Adenoma                          | 34                                 |                                                            | Quesada et al. 1998 (Quesada et al., 1998)     |
| \(\text{Apc}^{716}\) \(\beta\text{-catenin}\)          | Small intestine            | Adenoma                          | 1                                  | Polycystic kidneys                                         | Romagnolo et al. 1999 (Romagnolo et al., 1999) |
| \(\text{Apc}^{\Delta474}\) | Small intestine > colon    | Adenoma                          | 122; small intestine; 1.4 in large intestine | Adenomas in duodenum, stomach, mammary gland               | Sasai et al., 2000 (Sasai et al., 2000)        |
| \(\text{Apc}^{1227}\)      | Small intestine (location shifted towards proximal small intestine) | Adenoma, some with high grade dysplasia | 192; small intestine; 2, large intestine | Gastric adenomas                                             | Pollard et al., 2009 (Pollard et al., 2009)    |
| \(\text{Apc}^{905}\)       | Not applicable              | None                             | None                               | No phenotype without further manipulation                  | Shibata et al., 1997 (Shibata et al., 1997)    |
| \(\text{Apc}^{15/+}\)       | Small intestine > colon    | Adenoma, some with high grade dysplasia; adenocarcinoma | 176; small intestine; 8.3, large intestine |                                                            | Robanus-Maandag et al., 2010 (Robanus-Maandag et al., 2010) |
| \(\text{Fabpl}^{\text{Cre}}/\text{Apc}^{15\text{lox}/+}\) | Colon> small intestine     | Adenoma, 17% with high grade dysplasia; adenocarcinoma (18% of lesions) | 149; small intestine; 256, large intestine | Multifocal breast neoplasia, trichogenic skin tumors, osteomas mimicking Gardner syndrome | Robanus-Maandag et al., 2010 (Robanus-Maandag et al., 2010) |
| \(\text{Apc}^{1576}\)       | Not applicable              | None                             | None                               | Multifocal breast neoplasia, trichogenic skin tumors, osteomas mimicking Gardner syndrome | Toki et al. 2013 (Toki et al., 2013)            |
| \(\text{Apc}^{146/+}\)       | Distal colon and rectum    | Adenomas and carcinomas (50% of lesions) | 36; conventional housing; 65, specific pathogen-free conditions | Mammary gland tumors; rectal prolapse                     | Colnot et al. 2014 (Colnot et al., 2004)        |
signal transduction (Boman & Fields, 2013), and its germ-line mutation results in familial adenomatosis polyposis coli (FAP). This cancer predisposition syndrome is characterized by the development of hundreds of colorectal adenomas, leading to adenocarcinoma at a young age. Most mutations causing FAP are within the 5′ half of the gene and result in truncated polypeptides.

**Genetics of APC-related animal models**

Many of the Apc-related mouse models have been engineered to contain germline mutations in Apc that lead to expression of a truncated Apc protein; in most of these models, only heterozygotes are viable, as homozygosity is embryonic lethal. Loss of growth control upon loss of the remaining wild type copy of Apc leads to multiple intestinal adenomas. The specific location of the Apc mutation affects polyp multiplicity, location, and longevity of the mice (McCart et al., 2008). For example, the Apc<sup>1638N/+</sup> mouse has a reduced polyp burden and longer lifespan compared to the Apc<sup>Min/+</sup> mouse (Smits et al., 1998). In the Apc<sup>1322T</sup> mouse, the mutant protein retains one 20-amino acid β-catenin binding/degradation repeat (in the Apc<sup>Min/+</sup>, there are none); adenomas in these mice are detectable earlier, have more severe dysplasia, and are larger (Pollard et al., 2009) compared to Apc<sup>Min/+</sup> mice. Timing of Apc loss of function may also be important; for instance, step-wise Apc loss using Apc<sup>(Min/CKO)</sup> or Apc<sup>(1638N/CKO)</sup> results in grossly visible neoplasia in the intestine, while simultaneous loss leads to occult clonal expansion through crypt fission without morphologic transformation (Fischer et al., 2012). Deletion of the entire Apc gene in the Apc<sup>Δel-15</sup> mouse yields more rapid tumor development compared to Apc truncation, with decreased survival, more severe polyposis, and more advanced colon tumors progression compared to Apc<sup>Min/+</sup> mice (Cheung et al., 2010).

| Model                  | Predominant Tumor Locations                        | Neoplasm                              | Average number of tumors per animal | Other lesions | Reference                                      |
|------------------------|----------------------------------------------------|---------------------------------------|-------------------------------------|---------------|------------------------------------------------|
| Apc<sup>Min/+</sup>    | Small intestine and large intestine                | Adenoma, carcinoma                    | Small intestine: 1.5 to 22; large intestine: 7 to 26; depending on strain and sex. | odontomas     | Amos-Landgraf et al., 2007; Irving et al. 2014 (Irving et al., 2014) |
| Kyoto Apc Delta       | Colon (requires AOM/DSS treatment)                 | Treatment with AOM/DSS induces colorectal adenocarcinoma, invasive into submucosa | 9.5, males; 5.8, females            |               | Yoshima et al., 2009 (Yoshimi et al., 2009); Irving et al. 2014 (Irving et al., 2014) |
| Apc<sup>1311/+</sup>  | Colon                                              | Adenoma, some with high grade dysplasia | > 100                               |               | Flisikowska et al., 2012 (Flisikowska et al., 2012) |

**Table 2 Apc-related models, other species**

**Fig. 1** A small adenoma in colonic mucosa in an Apc<sup>1638N/+</sup> mouse, similar to human colorectal adenomas. Note the increased nucleus-to-cytoplasm ratio and hyperchromatic, crowded pencillate nuclei.

**Fig. 2** A single adenomatous crypt in the small intestine of an Apc<sup>Min/+</sup> mouse, composed of a dilated cystic invagination into the villus.
Fig. 3 Adenomas in $\text{Apc}^{\text{Min}/+}$ and related models are often covered by a single layer of normal overlying epithelium, unlike in human colorectal adenomas, where the surface mucosa is usually involved by adenomatous epithelium.

Fig. 4 Immunohistochemistry for beta catenin in $\text{Apc}^{\text{Min}/+}$ and related models is useful in identifying small single crypt adenomas, which show loss of the normal membranous pattern and accumulation of beta catenin in the nucleus due to alterations in Wnt signaling.

Fig. 5 a Small intestinal adenomas in $\text{Apc}^{\text{Min}/+}$ mice push into the intervillus spaces as they grow. Note preservation of normal epithelium over much of the adenoma. b A pedunculated colonic adenoma in an $\text{Apc}^{1638N/+}$ mouse.
Genetically altered rat models with Apc mutation are also available and are appealing based on the longevity of the models and the relative ease of performing colonoscopy, allowing for longitudinal experiments (Table 2). The most common are the Kyoto Apc Delta (KAD) rat and the Pirc rat. The KAD rat was derived via ENU mutagenesis and has a nonsense mutation in codon 2523 in exon 15 of Apc, yielding a truncated protein. These rats are viable in the homozygous state and do not develop intestinal tumors spontaneously. Treatment with azoxymethane and dextran sulfate sodium (AOM/DSS) is necessary to induce intestinal neoplasia. The Pirc rat, also produced via ENU-induced mutagenesis, has an Apc mutation at nucleotide 3409, producing a truncated protein. This mutation is embryonic lethal in the homozygote state. The mutation has 100% penetrance, with all rats developing colon polyps after age 4 months.

A genetically altered pig model carrying an APC 1311 mutation, orthologous to human APC 1309, has been developed. These animals develop aberrant crypt foci, single crypt adenomas, and multiple colorectal adenomas, similar to human FAP. The larger adenomas exhibit progression in the form of high grade dysplasia. Surface involvement, similar to human adenomas (Flisikowska et al., 2012), is characteristic.

Modifiers of Cancer Phenotypes
Strain differences have long been recognized as having a significant effect on the tumor burden in the ApcMin+/− model, which is usually maintained on a C57Bl/6J background. Crossing of B6 Min/+ mice to AKR and other inbred strains resulted in a decrease in average tumor number in the F1 mice (Shoemaker et al., 1997). Backcrossing experiments and other genetic analyses to map modifier loci have yielded a number of Modifier of Min (Mom) candidate genes (McCart et al., 2008). In addition, diet and intestinal microbiome of the mouse colony have important effects on polyp multiplicity, progression, and size. For instance, a high fat-low fiber western-style diet has been shown to increase polyp

| Table 3 | Cell types in adenomas in ApcMin+/− and related models |
|---------|--------------------------------------------------------|
| Cell Type                  | Proportion                      |
| Absorptive cells (enterocytes, colonocytes) | Majority of cells               |
| Goblet cells                | Second most common cell type    |
| Paneth cells                | Up to 10% in small intestinal adenomas; fewer in colonic lesions |
| Neuroendocrine cells        | Up to 5%                         |

Fig. 6 High grade dysplasia, characterized by cribriform architecture, in an Apc1638N/+ adenoma

Fig. 7 Multiple cell types are present in adenomas in ApcMin+/− and related models. Here, scattered Paneth cells can be identified by their red cytoplasmic granules, and a few goblet cells are present in the adenoma. The predominant cell type is an absorptive cell.
numbers and tumor progression in $Apc^{Δ716/+}$ mice (Hioki et al., 1997).

Pathology
The morphology of intestinal lesions in $Apc^{Min+/-}$ and related models is similar across the models although the age of onset, degree of dysplasia, and distribution in the gastrointestinal tract varies (Table 1). The earliest recognizable lesions consist of a single enlarged crypt or small cluster of crypts lined by crowded cells with increased nucleus-to-cytoplasm ratio and nuclear hyper-chromasia (Fig. 1). These early lesions are low grade dysplastic lesions similar to small tubular colonic adenomas seen in patients with FAP. In the small intestine, a small invagination develops in the lamina propria in the proliferative zone at the junction of the crypt and villus (Fig. 2). The adenomatous cells push into the lamina propria and up into the villus, forming a double layer of adenomatous epithelium underneath a normal surface mucosa (Fig. 3). In the colon, the early adenomas invaginate into the lamina propria between crypts, although single crypt adenomas may also be identified (Oshima et al., 1997). Immunohistochemistry for beta catenin can be used to help identify early adenomas, as even single crypt adenomas in $Apc^{Min+/-}$ and related models display accumulation of nuclear beta catenin (Fig. 4).

As the adenomas grow, they form polypoid, pedunculated or sometimes cup-shaped lesions with a depressed center (Fig. 5a and b). In many models, the adenomas do not progress beyond low grade dysplasia. However, in longer-lived models with fewer tumors, some develop high grade dysplasia characterized by cribriform architecture, in which not all cells are in contact with a basement membrane (Fig. 6). Numerous mitotic Figures and apoptotic bodies are common in adenomas at all stages of development.

The intestinal neoplasms arising in $Apc^{Min+/-}$ and related models contain multiple cells types but are primarily composed of absorptive type cells and goblet cells...
Table 4 Features helpful in distinguishing invasive adenocarcinoma from mucosal herniation (Boivin et al., 2003)

| Feature                                      | Favors Invasive Carcinoma                                                                 | Favors Herniated Epithelium                                                                 |
|----------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
| Comparison with overlying mucosa             | Invasive cells are different from overlying mucosa, with changes exceeding low grade dysplasia | Dysplasia is absent                                                                        |
| Desmoplasia                                  | Present; not associated with prominent inflammatory infiltrate.                           | Absent; lamina propria may exhibit fibromuscular obliterator changes in prolapse           |
| Crypt/gland profile                          | Irregular, pointed, angulated crypt profiles                                              | Rounded; may be cystically dilated                                                        |
| Spread relative to mucosal surface           | Invading crypts spread laterly                                                            | No lateral spread from overlying mucosa                                                   |
| Cell loss from leading edge                  | Present; crypts are incompletely lined by epithelium                                      | Absent; crypts are completely lined by epithelial cells                                    |
| Number of crypts in question                 | More than 2 invading crypts                                                               | Two or fewer crypts in question                                                            |
| Basement membrane                            | Discontinuous                                                                            | Continuous                                                                                 |
| Findings in other mice of the same genotype  | Evidence of progression to invasive cancer in other mice                                  | No invasive cancer in other mice                                                           |

(Tables 3). Adenomas arising in the small intestine of in the Apc\textsuperscript{Min−/−} and related models contain Paneth cells that are easily identified on hematoxylin and eosin stain (Fig. 7) and highlighted with immunohistochemistry for lysozyme. They are been shown to comprise 10% or less of the cells in small intestinal adenomas (Moser et al., 1992). The mouse colon does not contain Paneth cells but lysozyme-expressing cells lacking PAS positivity have been identified in colonic adenomas in these models, suggesting Paneth cell-like differentiation even in colonic lesions (Moser et al., 1992; Husoy et al., 2006). Neuroendocrine cells comprise a small proportion of the cells in Apc\textsuperscript{Min−/−} type adenomas, but the specific cell type reflects the neuroendocrine cells found in normal intestinal mucosa at the site of the adenoma (Moser et al., 1992). For instance, serotonin-expressing cells are the most common neuroendocrine cells in mouse intestine and are found throughout; such cells comprise up to 5% of Apc\textsuperscript{Min−/−} adenoma cells, in lesions from small bowel and colon (Moser et al., 1992). PYY-positive cells, in contrast, are found only in adenoma from the distal colon, reflecting the distribution of these cells normally. Neuroendocrine cells are diffusely scattered throughout the adenomas, and do not form small clusters as do the lysozyme-positive cells (Moser et al., 1992).

Dysplasia in intestinal adenomas in mouse models should be graded using the same terminology (low grade dysplasia, high grade dysplasia, intramucosal carcinoma) and criteria as for human colorectal adenomas (Washington et al., 2013). Most adenomas in the Apc\textsuperscript{Min−/−} mouse and related models show low grade dysplasia but many become progressively larger as the mouse ages, and a few progress along the adenoma-carcinoma sequence. Invasive carcinoma is rare, as most mice die of anemia or intussusception before progression. However, a few of the longer-lived models with fewer adenomas develop adenocarcinoma invasive into the submucosa (Colnot et al., 2004; Fodde et al., 1994; Robanus-Maandag et al., 2010). Metastasis does not occur in Apc\textsuperscript{Min−/−} mice and is exceedingly rare in related models (Fodde et al., 1994).

Surgical pathologists asked to analyze intestinal specimens should be aware of a pitfall in assessing tumor invasion in mouse models. Because the layers of the mouse intestine are thin and delicate, herniation of benign epithelium into submucosa is a common occurrence (Boivin et al., 2003), especially in the setting of rectal prolapse and in inflammatory conditions (Fig. 8a and b). Similar displacement of adenomatous mucosa (pseudo-invasion) occurs in pedunculated colorectal adenomas in humans and in colitis cystica profunda. Consensus guidelines for distinguishing between herniation and invasive adenocarcinoma were developed at a Mouse Models of Intestinal Neoplasia Workshop at Jackson Laboratories in 2000 by a panel of scientists and pathologists (Boivin et al., 2003) and are summarized in Table 4. It may not be possible to diagnose invasive carcinoma with certainty, especially in inflammatory models or areas of prolapse, and evaluation of older mice with better developed lesions may be necessary for a conclusive determination of invasion.

Invasion into the lamina propria is characterized by the development of angular crypt profiles with individual infiltrating cells and may be accompanied stromal alterations such as desmoplasia and increased inflammatory cell density (Fig. 9a and b).

Conclusions

The Apc\textsuperscript{Min−/−} mouse was developed over 25 years ago and has been reported in countless publications since that time. While the its limitations as a model for all aspects of human colorectal cancer are well recognized, Apc\textsuperscript{Min−/−} and related models remain useful, particularly in analyzing the biology of Apc, phenotype-genotype...
modeling comparison with familial adenomatous polyposis coli, and chemopreventative studies. Given their knowledge of morphology of human disease, surgical pathologists are well suited to assess and describe the pathology of these models, but should be aware of pitfalls in the interpretations of histology changes in the mouse.

Abbreviations

APC: adenomatous polyposis coli; DSS: dextran sulfate sodium; ENU: N-ethyl-N-nitrosourea; FAP: familial adenomatous polyposis; GEM: genetically engineered mouse; KAD: Kyotaro ApDelta, AOM, azoxymethane

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