Surgical and Experimental Pathology

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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 $Apc^{Min/+}$ mouse, which has been used for over 25 years. This model carriers 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 $Apc^{Min/+}$-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 $Apc^{Min+/-}$ 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 $Apc^{Min+/-}$ model, developed in 1990 in the laboratory of William Dove (Moser et al., 1990). The $Apc^{Min+/-}$ 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

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Table 1 *Apc*$^{Min+/-}$ and selected related genetically altered mouse models of intestinal neoplasia

Model	Predominant Tumor Locations	Neoplasm	Average number of tumors per mouse	Other lesions	Reference
Apc$^{Min+/-}$	Small intestine > colon	Adenoma	30		Moser et al. 1990 (Moser et al., 1995)
Apc$^{1638N/+}$	Small intestine and colon; more in colon compared to *Apc*$^{Min+/-}$	Adenoma, carcinoma; rarely, liver metastasis (Fodde et al., 1994)	4 (10-fold reduction over *Apc*$^{Min+/}$)	Fibromatosis (desmoid tumors); gastric carcinoma, duodenal adenomas, cutaneous cysts	Fodde et al. 1994 (Fodde et al., 1994)
Apc$^{\Delta 716/+}$	Small intestine > colon	Adenoma	254 (10-fold increase over *Apc*$^{Min+/}$)		Oshima et al. 1995 (Oshima et al., 1995)
Apc$^{1309/+}$	Small intestine	Adenoma	34		Quesada et al. 1998 (Quesada et al., 1998)
Δ*N131* β-catenin	Small intestine	Adenoma	1	Polycystic kidneys	Romagnolo et al. 1999 (Romagnolo et al., 1999)
Apc$^{\Delta 474}$	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)
Apc^{1322T}	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)
Apc^{580S}	Not applicable	None	None	No phenotype without further manipulation	Shibata et al., 1997 (Shibata et al., 1997)
Apc$^{\Delta 15/+}$	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)
Fabpl*Cre;Apc*$^{15lox/+}$	Colon> small intestine	Adenoma, 17% with high grade dysplasia; adenocarcinoma (18% of lesions)	14.9, small intestine; 25.6, large intestine		Robanus-Maandag et al., 2010 (Robanus-Maandag et al., 2010)
Apc^{1576}	Not applicable	None	None	Multifocal breast neoplasia, trichogenic skin tumors, osteomas mimicking Gardner syndrome	Toki et al. 2013 (Toki et al., 2013)
Apc$^{\Delta 14/+}$	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)

Table 2 *Apc*-related models, other species

Model	Predominant Tumor Locations	Neoplasm	Average number of tumors per animal	Other lesions	Reference
$Apc^{Pirc/+}$ (rat)	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 (Amos-Landgraf et al., 2007); Irving et al. 2014 (Irving et al., 2014)
Kyoto Apc Delta (KAD) (rat)	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)
$APC^{1311/+}$ (pig)	Colon	Adenoma, some with high grade dysplasia	> 100		Flisikowska et al., 2012 (Flisikowska et al., 2012)

signal transduction (Boman & Fields, 2013), and its germline 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 $Apc^{1638N/+}$ mouse has a reduced polyp burden and longer lifespan compared to the $Apc^{Min/+}$ mouse (Smits et al., 1998), In the Apc^{1322T} mouse, the mutant protein retains one 20-amino acid β-catenin binding/degradation repeat (in the $Apc^{Min/+}$, there are none); adenomas in these mice are detectable earlier, have more severe dysplasia, and are larger (Pollard et al., 2009) compared to $Apc^{Min/+}$ mice. Timing of Apc loss of function may also be important; for instance, step-wise Apc loss using $Apc^{(Min/CKO)}$ or $Apc^{(1638N/CKO)}$ 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 $Apc^{\Delta el\text{-}15}$ mouse yields more rapid tumor development compared to Apc truncation, with decreased survival, more severe polyposis, and more advanced colon tumors progression compared to $Apc^{Min/+}$ mice (Cheung et al., 2010).

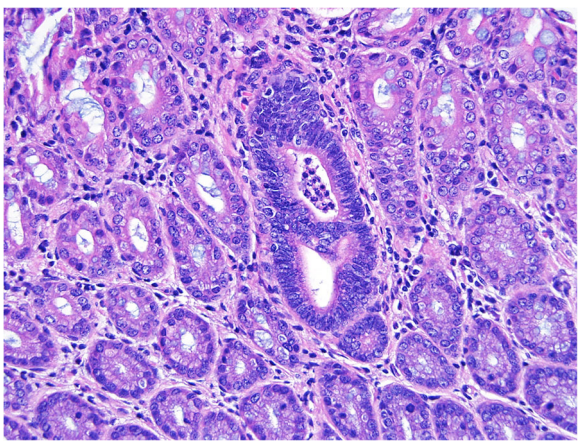

Fig. 1 A small adenoma in colonic mucosa in an $Apc^{1638N/+}$ mouse, similar to human colorectal adenomas. Note the increased nucleus-to-cytoplasm ratio and hyperchromatic, crowded pencillate nuclei

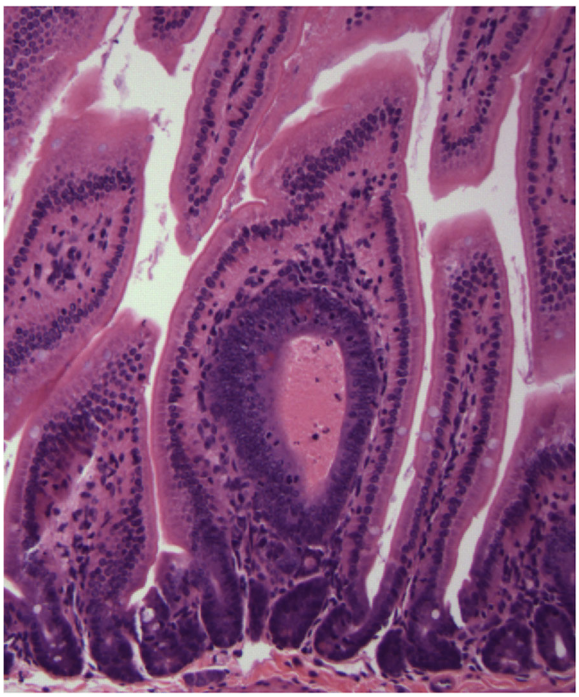

Fig. 2 A single adenomatous crypt in the small intestine of an $Apc^{Min/+}$ mouse, composed of a dilated cystic invagination into the villu

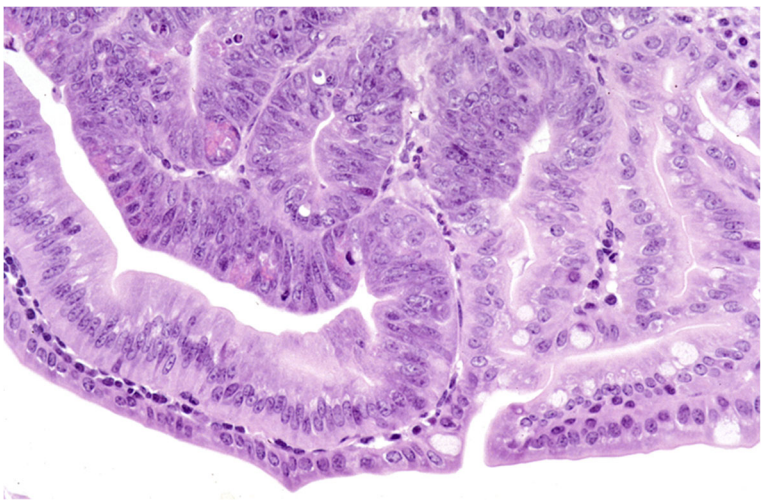

Fig. 3 Adenomas in *Apc*$^{Min/+}$ and related models are often covered by a single layer of normal overlying epithelium, unlike in human colorectal adenomas, where the surface mucosa is usually involved by adenomatous epithelium

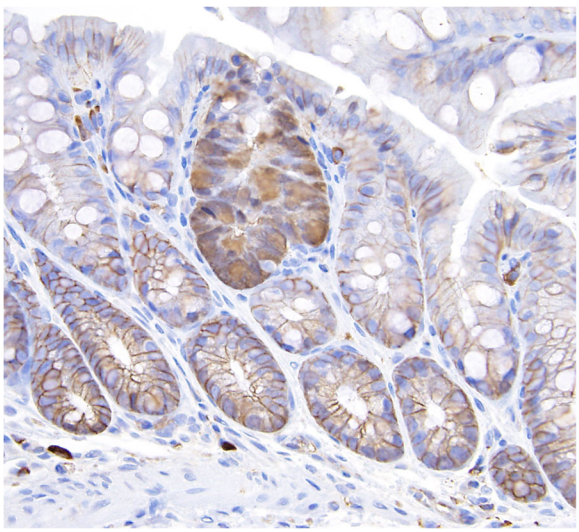

Fig. 4 Immunohistochemistry for beta catenin in *Apc*$^{Min/+}$ and related models is useful in identifying small single crypt adenomas, which show loss of the normal membranous pattern and accumulation of beta catenin in the nucleus due to alterations in Wnt signaling

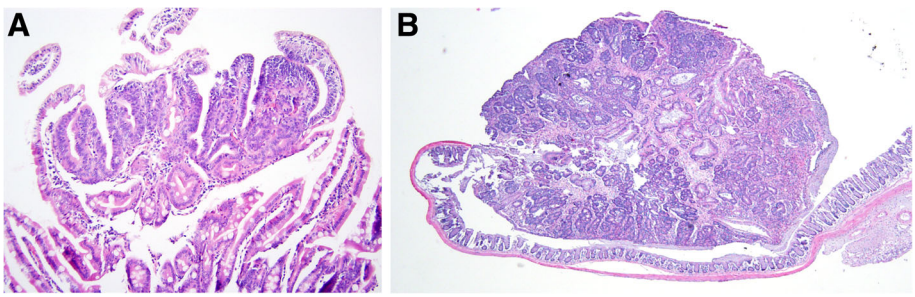

Fig. 5 a Small intestinal adenomas in *Apc*$^{Min/+}$ mice push into the intervillus spaces as they grow. Note preservation of normal epithelium over much of the adenoma. **b** A pedunculated colonic adenoma in an *Apc*$^{1638N/+}$ mouse

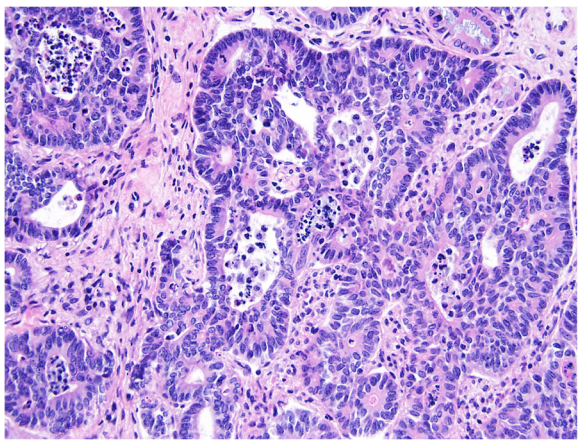

Fig. 6 High grade dysplasia, characterized by cribriform architecture, in an $Apc^{1638N/+}$ adenoma

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 at 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 animal 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.

Table 3 Cell types in adenomas in $Apc^{Min+/-}$ 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%

Modifiers of Cancer Phenotypes

Strain differences have long been recognized as having a significant effect on the tumor burden in the $Apc^{Min+/-}$ 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

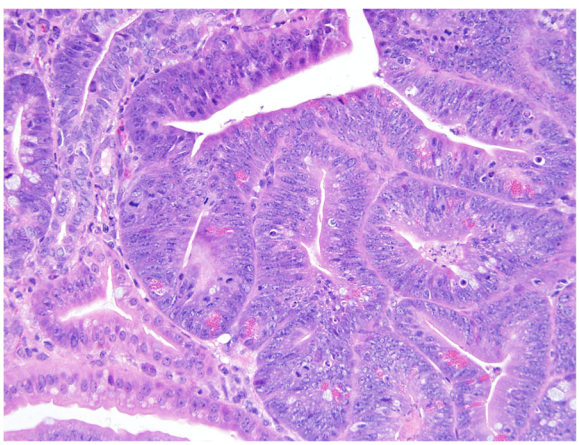

Fig. 7 Multiple cell types are present in adenomas in $Apc^{Min/+}$ and related models. Here, scattered Paneth cells can be identified by their red cytoplasmic granules, and a few goblet cells are present in the adenoma. The predominant cell type is an absorptive cell

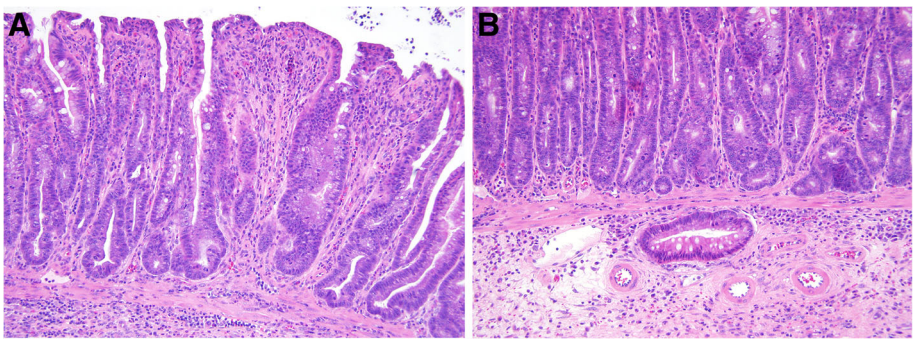

Fig. 8 a Rectal prolapse in mice may mimic adenomatous change, as in humans. Here, note thickened hyperplastic reactive-appearing mucosa, with fibromuscular changes in the lamina propria. **b** In areas of prolapse, displacement of non-neoplastic crypts may mimic invasive adenocarcinoma. Here, a single herniated crypt is present in the submucosa. Note the rounded crypt profile and resemblance to the overlying crypts

numbers and tumor progression in $Apc^{\Delta 716/+}$ 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 hyperchromasia (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

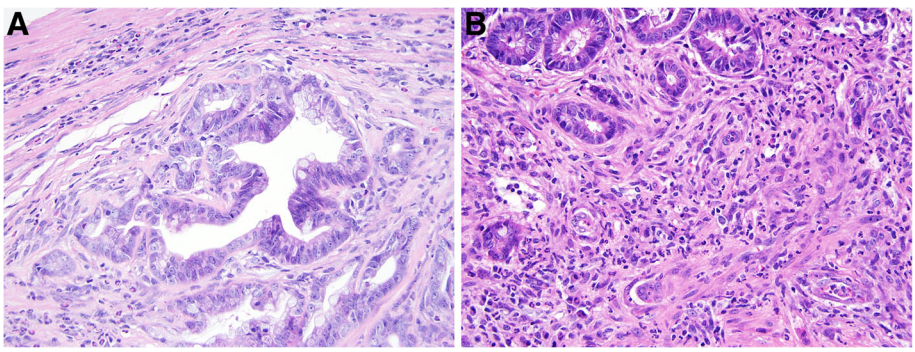

Fig. 9 a Invasive carcinoma may be seen in longer-lived $Apc^{Min/+}$-related models. In contrast to the smooth crypt profile of herniation, the invasive adenocarcinoma shown here has an angulated profile with infiltration of tumor cells into a desmoplastic stroma. **b** In this example from a $Apc^{1638N/+}$ mouse, adenocarcinoma cells infiltrate the lamina propria as small angulated glands with pointed profiles and elicit an inflammatory and stromal reaction

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 obliterative changes in prolapse
Crypt/gland profile	Irregular, pointed, angulated crypt profiles	Rounded; may be cystically dilated
Spread relative to mucosal surface	Invading crypts spread laterally	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

(Table 3). Adenomas arising in the small intestine of in the $Apc^{Min+/-}$ 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 $Apc^{Min+/-}$ 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 $Apc^{Min+/-}$ 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 $Apc^{Min+/-}$ 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 $Apc^{Min+/-}$ 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 (pseudoinvasion) 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 $Apc^{Min+/-}$ 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, $Apc^{Min+/-}$ 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: Kyoto Apc Delta, AOM, azoxymethane

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Competing interests

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References

Amos-Landgraf JM, Kwong LN, Kendziorski CM, Reichelderfer M, Torrealba J, Weichert J, et al. A target-selected Apc-mutant rat kindred enhances the modeling of familial human colon cancer. Proc Natl Acad Sci U S A 2007; 104(10):4036–4041. PubMed PMID: 17360473

Boivin GP, Washington K, Yang K, Ward JM, Pretlow TP, Russell R, et al. Pathology of mouse models of intestinal cancer: consensus report and recommendations. Gastroenterology. 2003;124(3):762–777. PubMed PMID: 12612914

Boman BM, Fields JZ. An APC:WNT counter-current-like mechanism regulates cell division along the human colonic crypt axis: a mechanism that explains how apc mutations induce proliferative abnormalities that drive colon cancer development. Front Oncol 2013;3:244. PubMed PMID: 24224156

Cheung AF, Carter AM, Kostova KK, Woodruff JF, Crowley D, Bronson RT, et al. Complete deletion of Apc results in severe polyposis in mice. Oncogene. 2010;29(12):1857–1864. PubMed PMID: 20010873. Pubmed Central PMCID: HHMIMS181538

Colnot S, Niwa-Kawakita M, Hamard G, Godard C, Le Plenier S, Houbron C, et al. Colorectal cancers in a new mouse model of familial adenomatous polyposis: influence of genetic and environmental modifiers. Lab Investig 2004;84(12):1619–1630. PubMed PMID: 15502862

Fischer JM, Miller AJ, Shibata D, Liskay RM. Different phenotypic consequences of simultaneous versus stepwise Apc loss. Oncogene. 2012;31(16):2028–2038. PubMed PMID: 21892206

Flisikowska T, Merkl C, Landmann M, Eser S, Rezaei N, Cui X, et al. A porcine model of familial adenomatous polyposis. Gastroenterology. 2012;143(5): 1173–5.e7. PubMed PMID: 22864254

Fodde R, Edelmann W, Yang K, van Leeuwen C, Carlson C, Renault B et al (1994) A targeted chain-termination mutation in the mouse Apc gene results in multiple intestinal tumors. Proc Natl Acad Sci 91(19):8969–8973

Hioki K, Shivapurkar N, Oshima H, Alabaster O, Oshima M, Taketo MM (1997) Suppression of intestinal polyp development by low-fat and high-fiber diet in Apc(delta716) knockout mice. Carcinogenesis. 18(10):1863–1865

Husoy T, Knutsen HK, Loberg EM, Alexander J. Intestinal adenomas of Min-mice lack enterochromaffin cells, and have increased lysozyme production in non-Paneth cells. Anticancer Res 2006;26(3A):1797–1802. PubMed PMID: 16827109

Irving AA, Halberg RB, Albrecht DM, Plum LA, Krentz KJ, Clipson L, et al. Supplementation by vitamin D compounds does not affect colonic tumor development in vitamin D sufficient murine models. Arch Biochem Biophys 2011;515(1–2):64–71. PubMed PMID: 21907701

Irving AA, Yoshimi K, Hart ML, Parker T, Clipson L, Ford MR, et al. The utility of Apc-mutant rats in modeling human colon cancer. Dis Model Mech 2014; 7(11):1215–1225. PubMed PMID: 25288683

McCart AE, Vickaryous NK, Silver A. Apc mice: models, modifiers and mutants. Pathol Res Pract 2008;204(7):479–490. PubMed PMID: 18538487

Moser AR, Dove WF, Roth KA, Gordon JI (1992) The Min (multiple intestinal neoplasia) mutation: its effect on gut epithelial cell differentiation and interaction with a modifier system. J Cell Biol 116(6):1517–1526

Moser AR, Luongo C, Gould KA, McNeley MK, Shoemaker AR, Dove WF. ApcMin: a mouse model for intestinal and mammary tumorigenesis. Eur J Cancer 1995;31A(7–8):1061–1064. PubMed PMID: 7576992

Moser AR, Pitot HC, Dove WF. A dominant mutation that predisposes to multiple intestinal neoplasia in the mouse. Science. 1990;247(4940):322–324. PubMed PMID: 2296722

Oshima H, Oshima M, Kobayashi M, Tsutsumi M, Taketo MM (1997) Morphological and Molecular Processes of Polyp Formation in *Apc*Δ716 Knockout Mice. Cancer Res. 57(9):1644–1649

Oshima M, Oshima H, Kitagawa K, Kobayashi M, Itakura C, Taketo M. Loss of Apc heterozygosity and abnormal tissue building in nascent intestinal polyps in mice carrying a truncated Apc gene. Proc Natl Acad Sci U S A 1995;92(10): 4482–4486. PubMed PMID: 7753829

Pollard P, Deheragoda M, Segditsas S, Lewis A, Rowan A, Howarth K, et al. The Apc 1322T mouse develops severe polyposis associated with submaximal nuclear beta-catenin expression. Gastroenterology. 2009;136(7):2204–13.e1–13. PubMed PMID: 19248780

Quesada CF, Kimata H, Mori M, Nishimura M, Tsuneyoshi T, Baba S. Piroxicam and acarbose as chemopreventive agents for spontaneous intestinal adenomas in APC gene 1309 knockout mice. Japanese journal of cancer research : Gann 1998;89(4):392–396. PubMed PMID: 9617344

Robanus-Maandag EC, Koelink PJ, Breukel C, Salvatori DC, Jagmohan-Changur SC, Bosch CA, et al. A new conditional Apc-mutant mouse model for colorectal cancer. Carcinogenesis. 2010;31(5):946–952. PubMed PMID: 20176656

Romagnolo B, Berrebi D, Saadi-Keddoucci S, Porteu A, Pichard AL, Peuchmaur M et al (1999) Intestinal dysplasia and adenoma in transgenic mice after overexpression of an activated β-catenin. Cancer Res 59(16):3875–3879

Sasai H, Masaki M, Wakitani K. Suppression of polypogenesis in a new mouse strain with a truncated Apc(Delta474) by a novel COX-2 inhibitor, JTE-522. Carcinogenesis. 2000;21(5):953–958. PubMed PMID: 10783317

Shibata H, Toyama K, Shioya H, Ito M, Hirota M, Hasegawa S, et al. Rapid colorectal adenoma formation initiated by conditional targeting of the Apc gene. Science. 1997;278(5335):120–123. PubMed PMID: 9311916

Shoemaker AR, Gould KA, Luongo C, Moser AR, Dove WF. Studies of neoplasia in the Min mouse. Biochim Biophys Acta 1997;1332(2):F25–F48. PubMed PMID: 9141462

Smits R, van der Houven van Oordt W, Luz A, Zurcher C, Jagmohan-Changur S, Breukel C, et al. Apc1638N: a mouse model for familial adenomatous polyposis-associated desmoid tumors and cutaneous cysts. Gastroenterology. 1998;114(2):275–283. PubMed PMID: 9453487

Toki H, Inoue M, Motegi H, Minowa O, Kanda H, Yamamoto N, et al. Novel mouse model for Gardner syndrome generated by a large-scale N-ethyl-N-

nitrosourea mutagenesis program. Cancer Sci 2013;104(7):937–944. PubMed PMID: 23551873

Washington MK, Powell AE, Sullivan R, Sundberg JP, Wright N, Coffey RJ, et al. Pathology of rodent models of intestinal cancer: progress report and recommendations. Gastroenterology. 2013;144(4):705–717. PubMed PMID: 23415801. Pubmed Central PMCID: NIHMS450747 PMC3660997

Yoshimi K, Tanaka T, Takizawa A, Kato M, Hirabayashi M, Mashimo T et al (2009) Enhanced colitis-associated colon carcinogenesis in a novel Apc mutant rat. Cancer Sci 100(11):2022–2027