REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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Pathology of Rodent Models of Intestinal Cancer: Progress Report and Recommendations

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In October 2010, a pathology review of rodent models of intestinal neoplasia was held at The Jackson Laboratory. This review complemented 2 other concurrent events: a workshop on methods of modeling colon cancer in rodents and a conference on current issues in murine and human colon cancer. We summarize the results of the pathology review and the committee's recommendations for tumor nomenclature. A virtual high-resolution image slide box of these models has been developed. This report discusses significant recent developments in rodent modeling of intestinal neoplasia, including the role of stem cells in cancer and the creation of models of metastatic intestinal cancer.

Keywords: Intestinal Neoplasms; Pathology; Genetically Engineered Mice; Disease Models; Animal.

In 2000, a panel of 7 pathologists and 4 basic scientists met at The Jackson Laboratory in Bar Harbor, Maine. The group participated in a Mouse Models of Human Cancers Consortium–sponsored symposium focused on intestinal neoplasia and a workshop on techniques for modeling intestinal cancer in mice sponsored by The Jackson Laboratory. After reviewing 17 different models of murine intestinal cancer and comparing representative lesions with those of prototypical human colorectal cancers, the panel developed guidelines for nomenclature of intestinal tumors in rodents and criteria for distinguishing invasive carcinomas from herniations of non-neoplastic epithelium in rodent models. The findings and recommendations were published in a consensus report in GASTROENTEROLOGY in 2003.[1]

Since 2000, new developments in modeling human gastrointestinal (GI) cancers, including reports of convincing models of metastatic disease and new models derived from epithelial stem cell populations, have resulted in major advances in the field. The pathology of new rodent models of intestinal cancer was revisited in 2010 by a panel of pathologists and basic scientists. It was generally agreed that a "multiple pathways" hypothesis of intestinal cancer had largely replaced the sequential genetic model for human colorectal cancer.

The goals of the workshop in 2010 were to examine the pathology of new rodent models of intestinal neoplasia and reach a consensus among a group of expert pathologists regarding the findings, to gauge the progress made in the intervening decade toward modeling human intestinal cancer, to assess the utility of the original recommendations regarding nomenclature, and to explore the creation and ongoing curation of a digital slide box of rodent models that would be accessible to investigators worldwide.

The models reviewed at the 2000 meeting were summarized in Supplementary Table 3 of the 2003 report,[1] and the models reviewed at the 2010 meeting are summarized in Table 1. Not all existing mouse models of intestinal tumors were discussed at the 2010 meeting (many have been reviewed recently by Taketo and Edelmann[2]), and a number have since been developed. These include additional reports of mismatch repair– and phosphoinositide 3-kinase–induced tumors.[3–6] There was little discussion of the effects of the microbiome on tumorigenesis or the use of orthotopic or xenograft tumors. Reports on these topics have been recently published.[7–10]

Update on Mouse Pathology Nomenclature

Most of the nomenclature recommendations from the 2000 Mouse Histopathology Workshop[1] have been

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Abbreviations used in this paper: ACF, aberrant crypt foci; AOM, azoxymethane; DMH, 1,2-dimethylhydrazine; DSS, dextran sodium sulfate; GI, gastrointestinal; GIN, gastrointestinal intraepithelial neoplasia; IHC, immunohistochemistry; MDF, mucin-depleted foci; TGF, transforming growth factor.

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Table 1. Animal Models of Intestinal Cancer Reviewed at the Workshop

Model	MGI allele	Contributor	Strain	Tumor location	Tumor type	No. of tumors/mouse	Age when analyzed	Other lesions	Metastasis	Reference
gp130Y757F(AOM/DSS)	Il6st^{tm1Ern}	Ernst	C57BL/6	LI	AD and ACA	8	3 mo after challenge	Gastric ACA	No	Bollrath et al, 2009[32]
MDF in colon of DMH-exposed rats	N/A	Caderni	F344	Distal LI	MicroAD	7 MDF/LI (DMH dosage: 300 mg/kg)	3 mo after DMH	No	No	Caderni et al, 2003[21]; Femia et al, 2008[23]
Lrig1$^{CreERT2/CreERT2}$	Lrig1$^{tm1.1(cre/ERT2)Rjc}$	Coffey	129/SV X C57BL/6	Duodenum (atop Brunner's gland)	AD and ACA	1	6 mo	NR	No	Powell et al, 2012[31]
Lrig1^{CreERT2};Apc$^{flox/+}$	Apc$^{tm2.1Cip}$ Lrig1$^{tm1.1(cre/ERT2)Rjc}$	Coffey	129/SVX C57BL/6	SI and LI	AD	40 (SI); 12 (distal LI)	3–4 mo after tamoxifen	NR	No	Powell et al, 2012[31]
Sleeping Beauty transposon mutagenesis in Apc$^{Min/+}$ and WT mice	Apc^{Min}	Cormier	C57BL/6	SI and LI	AD and ACA	In WT screen, 3 tumors in SI and 1 tumor in LI; in Apc^{Min} screen, 350 in SI and 15 in LI	In WT screen, 10-12 mo; in Apc^{Min} screen, 3 mo	Thymic lymphomas, intestinal myeloid leukemias, liver adenomas	No	Starr et al, 2009[40]; Starr et al, 2011[41]
Apc$^{Pirc/+}$	N/A	Dove	F344XNTac	SI and LI	AD and ACA	Male, 22 in SI and 14 in LI; Female, 4 in SI and 7 in LI	7–13 mo	Jaw osteomas, benign epidermoid cysts	No	Amos-Langraf et al, 2007[28]
Apc$^{Pirc/+}$	N/A	Dove	F344/Tac X ACI/Hsd	Predominantly LI (some SI)	AD and ACA	Male, 13 in SI and 26 in LI; Female, 1.5 in SI and 8 in LI	5–6 mo	NR	NR	Irving et al, 2011[30]
CDX2P^{Cre};Apc$^{flox/+}$	Apc$^{tm.1Tno}$/+ Tg(CDX2-cre)101Erf	Fearon	C57BL6X SJL/J	Predominantly LI	AD and ACA	11	6 mo	NR	No	Hinoi et al, 2007[44]
Apc$^{Min/+}$;Rab25$^{-/-}$	Apc^{Min}/+ Rab25^{tm1Jrgo}	Goldenring	C57BL/6	SI and LI	AD	175 (SI); 4.7 (LI)	4 mo	NR	No	Nam et al, 2010[43]
Smad3$^{+/-}$;Rab25$^{-/-}$	Rab25^{tm1Jrgo} Smad3^{tm1Par}	Goldenring	129/J	LI	AD and ACA	5.75	10 mo	Squamous carcinoma of the vagina	No	Nam et al, 2010[43]
Apc1638N;Villin^{Cre}; Tgfbr2$^{flox/flox}$	Apc^{tm1Rak} Tg(Vil-cre)997Gum Tgfbr2$^{tm1.2Hlm}$	Grady	C57BL/6	Intestine (not specified)	AD and ACA	5	12 mo	NR	No	Munoz et al, 2006[35]
Villin^{Cre};LSL-K-ras$^{G12D/+}$; Tgfbr2$^{flox/flox}$	Tg(Vil-cre)997Gum K-ras^{tm4Tyj} Tgfbr2$^{tm1.2Hlm}$	Grady	C57BL/6	SI and LI	AD and ACA	2.4	6 mo	NR	Lymph nodes and lung	Trobridge et al, 2009[36]
LSL-K-ras$^{G12D/+}$; Ink4a/Arf$^{-/-}$	Cdkn2a^{tm1Rdp} K-ras^{tm4Tyj}	Greten	129X C57BL/6	Proximal LI	Serrated lesions and malignant spindle cell tumors	NR	12 mo	NR	Reportedly, lung	Bennecke et al, 2010[13]
Villin^{Cre};LSL-N-ras$^{G12D/+}$	N-ras^{tm1Tyj} Tg(Vil-cre)20Syr	Haigis	C57BL/6		No phenotype		4–6 mo			Haigis et al, 2008[65]
Fabpl^{Cre};Apc$^{flox/+}$;LSL-K-ras$^{G12D/+}$	K-ras^{tm4Tyj}/+ Tg(Fabp1-cre)1Jig	Haigis	C57BL/6	LI	AD and ACA	NR	4–6 mo	LI mucosal hyperplasia in K-ras$^{G12D/+}$ mice	No	Haigis et al, 2008[65]
Apc$^{flox/+}$;LSL-K-ras$^{G12D/+}$; adeno-Cre after colonic abrasion	Apc^{tm2Rak} K-ras^{tm4Tyj}	Hung	C57BL/6	Distal LI	AD and ACA	3.6	1 to >6 mo	Liver metastases	Liver	Hung et al, 2010[37]; Jackson et al, 2001[38]
Apc$^{Min/+}$;Smad3$^{-/-}$	Apc^{Min} Smad3^{tm1Par}	Laird	129/SV	Distal LI	AD and ACA	15	2 mo	NR	No	Sodir et al, 2006[34]
Csf1r-iCre$^{+/-}$;Stat3$^{flox/flox}$ (Stat3-IKO)	Tg(Csf1r-iCre)jwp$^{+/-}$ Stat3^{tm1Dlv}	Lin	FVBX C57BL/6	LI	Hyperplasia, dysplasia, and ACA	NR	2–10 mo	Colitis	No	Deng et al, 2010[33]

LI, large intestine; AD, adenoma; ACA, adenocarcinoma; MDF, mucin-depleted foci; NR, not reported; SI, small intestine; WT, wild-type; IKO, inducible knockout.