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Murine models of colorectal cancer

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Abstract

Colorectal cancer is one of the most prevalent cancers of humans. To experimentally investigate this common disease, numerous murine models have been established. These models accurately recapitulate the molecular and pathological characteristics of human colorectal cancer including activation of MYC, which has recently been suggested to be a key mediator of colorectal cancer development. This review focuses on the variety of murine models of human colorectal cancer that are available to the research community and on their use to identify common and distinct characteristics of colorectal cancer.

Keywords

murine models; colorectal cancer; review; WNT; TGFB

Introduction

Colorectal cancer (CRC) is expected to account for approximately 149,000 new cases and 50,000 deaths in the United States in 2008 (American Cancer Society statistics). Although overall five-year survival rates for CRC increased between 1975 and 2003, nearly 90% of individuals live longer than five years if diagnosis with localized CRC but only 10% if diagnosed with metastatic disease. A major clinical challenge that will improve survival from CRC is early detection. Similarly, improved treatments for metastatic CRC are needed for those cases not detected early. New approaches for CRC detection and treatment should be accelerated through insights gained from studying current and future murine models of human CRC.

Many genetic and carcinogen-based murine models have been developed that recapitulate human CRC through alteration of a variety of signaling pathways (Table 1). Most CRC models have been generated by mutating murine orthologs of human CRC genes or by discovering models that spontaneously develop cancers during unrelated studies. Two of the most highly studied signaling pathways implicated in human CRC are the WNT/CTNNB1 (wingless-related MMTV integration site/beta-catenin) and TGFB (transforming growth factor beta) pathways. The most commonly used models perturb the WNT/CTNNB1 (wingless-related MMTV integration site/beta-catenin) signaling pathway. Components of the WNT/CTNNB1 signaling pathway, originally discovered in *Drosophila* (Nüsslein-Volhard and Wieschaus 1980), are dysregulated in the majority of human CRCs. The predominant initiating mutation

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in human CRC occurs in the gene encoding the adenomatous polyposis coli (APC) tumor suppressor (Powell et al. 1992). Loss of APC function in the presence of active WNT signaling results in increased nuclear levels of the transcriptional co-activator CTNNB1. This in turn activates transcription of pro-cell cycle molecules like JUN resulting uncontrolled cell division (Mann et al. 1999).

The second most widely studied pathway implicated in the progression of CRC is the TGFB pathway. Upon activation of TGFB receptors (TGFBR1, 2 and 3), intracellular SMAD2 and SMAD3 signal mediators become phosphorylated, bind to SMAD4 and translocate to the nucleus where the complex interacts with other transcription factors to induce down stream targets (Blobe et al. 2000). In the normal colonic epithelium and in early stages of tumorigenesis, TGFB functions as a tumor suppressor by inhibiting the cell cycle through up-regulation of *CDNK1A* and *CDNK2B* coding for cyclin-dependent protein kinase inhibitors (Derynck et al. 2001). Unlike the WNT/CTNNB1 pathway, perturbation of TGFB signaling is a later event in the process of carcinogenesis; up-regulation of this pathway is associated with increased tumor invasion and metastasis (Grady et al. 1998).

Although CRCs are heterogeneous, similarities across CRCs with different etiologies and between species are becoming apparent. Comparison of WNT and non-WNT mediated murine models implicated MYC as a key mediator of CRC, thereby linking seemingly independent pathways (Hanada et al. 2006; Kaiser et al. 2007; Rigby et al. 2007; Sansom et al. 2007). A similar role for MYC during human CRC development is also suggested from its widespread up-regulation in human CRCs (Hanada et al. 2006; Kaiser et al. 2007; Rigby et al. 2007; Sansom et al. 2007). Although murine models have been established that model the early stages of CRC, less progress has been achieved in establishing models that accurately recapitulate the later stages of invasion and metastasis.

In keeping with the goal of providing a concise narrative, we have chosen to highlight a handful of pertinent examples of murine models which have provided insight into the mechanisms of CRC development and that hold promise in informing clinical intervention of human CRC.

WNT pathway-mediated models of CRC

APC models—The Apc^{Min} (multiple intestinal neoplasia allele of the adenomatosis polyposis coli gene) mouse model of human familial adenomatous polyposis (FAP) is the most widely used CRC model for studying tumor initiation and early progression. The Apc^{Min} model, originally induced and fortuitously identified in a mutagenesis program (Moser et al. 1990; Su et al. 1992), bears one functional copy of the tumor suppressor *Apc* gene. Upon loss of the remaining wildtype copy of *Apc*, CTNNB1 is stabilized and transported to the nucleus where it functions as a transcriptional co-activator with the LEF/TCF family of transcription factors to stimulate cell cycle progression (Morin et al. 1997). This loss of growth control results in the development of tens-to-hundreds of polyps in the small intestine and a small number of polyps in the colon, while a similar mutation in humans results in predominantly colonic polyps (Groden et al. 1991).

Since discovery of the Apc^{Min} allele, other mutant alleles have been described. Gene targeting was used to generate $Apc^{\Delta 716}$ and Apc^{1638} alleles that display polyp distributions similar to the Apc^{Min} mouse (Fodde et al. 1994; Oshima et al. 1995). However, the Apc^{1638} model develops significantly fewer polyps than Apc^{Min}, while the $Apc^{\Delta 716}$ model develops more. Liver metastasis has been reported using the APC^{1638} model, possibly due to the notably longer lifespan of these mice compared to other *Apc*-mediated models.

The observation that CRC predisposition in Apc^{Min} mice is strain dependent led to the discovery of genetic loci called ‘Modifiers of Min’ (*Mom*) that modulate CRC susceptibility (Dietrich et

al. 1993). The first *Mom* candidate gene cloned, secretory phospholipase A2 (*Pla2g2a*), was for *Mom1* (MacPhee et al. 1995). Subsequently, *Mom1* was found to be more complex, with at least two distinct genes contributing to the effect of *Mom1* on Apc^{Min} (Cormier et al. 2000). Since the discovery of Mom1, over a dozen additional *Mom* loci have been genetically mapped (McCart et al. 2008).

While the genes underlying most *Mom* loci have not been identified, other modifiers of Apc^{Min}-mediated CRC have been proposed using crosses with mice carrying engineered or spontaneous mutations in specific genes. Haploinsufficiency of the Krüppel-like factor 4 (*Klf4*) transcription factor or reduction in EGFR activity using the $Egfr^{wa2}$ hypomorphic allele combined with loss of *Apc* enhances and suppresses, respectively, multiplicity in the small intestine and colon while showing no role in subsequent tumor progression (Ghaleb et al. 2007; Roberts et al. 2002; Torrance et al. 2000). In contrast, Apc^{Min} mice carrying mutations in the *Pten* tumor suppressor gene or the *Ephb2* gene for a guidance receptor show enhanced tumor progression (Batlle et al. 2005; Shao et al. 2007). Loss of *Ephb2* in mice also coincides with a shift from small intestinal adenomas to advanced colon carcinomas, potentially providing clues to the disparity in tumor distribution between humans with FAP and mice carrying Apc^{Min} (Batlle et al. 2005).

Although *Apc* mutant mice have been invaluable in modeling human CRC, there remain several aspects of the human disease that are not recapitulated well with these models. Rodent colonoscopy, a technique gaining in importance since it permits longitudinal studies of colon tumors (Becker et al. 2006), is not well suited for *Apc* mutant mice since they develop tumors predominantly in the small intestine. Additionally, *Apc* mutant mice rarely develop metastases to distant organs, which is the most clinical important aspect of human CRC.

The generation of gene-specific mutations in rat by *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis provides a new avenue for modeling human CRC (Zan et al. 2003). Recently, the Pirc (polyposis in rat colon) rat model of human CRC was generated that has a mutation in *Apc* (Amos-Landgraf et al. 2007). Unlike the Apc^{Min} mouse model where the incidence of colon tumors is low, the Pirc model develops colon tumors with 100% incidence by four months of age. The Pirc model opens opportunities to perform experimental studies that are difficult in mice. *Apc* mutant mice can develop invasive cancer but typically have shortened life spans due to intestinal blockage (Boivin et al. 2003). Conversely, rats are less susceptible to intestinal blockage by tumors because of their larger intestinal diameters. In rats of at least six months of age, twenty percent of tumors in the Pirc model become invasive (Amos-Landgraf et al. 2007). Although no distant metastases were reported in the initial analysis of the Pirc model, metastasis of CRCs to the liver has been reported in a rat azoxymethane (AOM) carcinogen model (Nordlinger et al. 1991).

Mismatch repair (MMR) deficient models—Hereditary non-polyposis colon cancer (HNPCC) is an inherited condition in which inactivation of one of several DNA mismatch repair (MMR) genes, like *MLH1*, *MSH2*, *MSH6*, and *PMS2*, result in defective DNA repair (Lynch and de la Chapelle 2003). In humans this leads to the development of a variety of cancers including that of the colon, endometrium, ovary, and stomach (Lynch and de la Chapelle 2003). A number of mutant mouse lines have been generated to model the loss of function of MMR genes in humans. Mice deficient for *Mhl1*, *Msh2* and *Msh6* develop cancers of the stomach, small intestine and colon. However, due to the inherent nature of defective MMR machinery, these mice also develop cancers of the lymphatic system, skin, cervix and lung (Edelmann et al. 2000; Edelmann et al. 1999; Edelmann et al. 1997; Reitmair et al. 1996).

Analysis of MMR deficient mice carrying one functional copy of *Apc* showed that loss of normal MMR results in a high percentage of *Apc*-inactivating mutations and an elevated frequency of tumor development (Kuraguchi et al. 2001; Reitmair et al. 1996). Mice deficient for *Mlh1* and heterozygous for the Apc^{1638N} allele have a 40-fold increase in stomach and colon tumors compared to Apc^{1638N} mice alone (Edelmann et al. 1999). Similarly, mice lacking *Msh2* have accelerated development of tumors in Apc^{Min} mice, with increased colon adenoma number and size suggesting roles for MSH2 in both tumor initiation and progression. Although loss of *Msh3* does not lead to increased cancer predisposition until late in life, loss of *Msh3* and *Msh6* together results in an increase in gastrointestinal tumors at a much younger age, similar to mice deficient for either *Mlh1* or *Msh2* (Edelmann et al. 2000).

Carcinogen-induced models—While genetic models have proven useful in the investigation of cancer mechanisms, particularly for familial cancers such as FAP or HNPCC, most human CRCs are non-familial and occur sporadically. The colon-specific carcinogen dimethylhyrdrazine (DMH), as well as the down-stream metabolite AOM, has proven useful in the investigation of the molecular mechanisms underlying the development of non-familial CRCs (Druckrey et al. 1967). Mice exposed to DMH or AOM develop colorectal tumors that accurately recapitulate pathologies seen in human CRC (Kaiser et al. 2007; Uronis et al. 2007). Consistent with the Apc^{Min} model, AOM-induced tumors result from activation of the WNT/CTNNB1 pathway (Takahashi et al. 2000). Unlike *Apc*-mediated models, AOM-induced tumors are primarily caused by mutations in *Ctnnb1*, which results in ubiquitination-resistant CTNNB1 and development of colorectal adenomas with increased expression of the key cell cycle regulators cyclin D1 (*Ccnd1*) and *Myc* (Kaiser et al. 2007; Wang et al. 1998).

Similar to the *Apc*-based models, modifier loci have also been identified using the DMH or AOM carcinogen models. *Ptprj* (a receptor-type protein tyrosine phosphatase) was shown to modify susceptibility to DMH (Ruivenkamp et al. 2002), although the significance of the orthologous gene in human CRC has not be elucidated. Although no germline *PTPRJ* mutations have been reported, *PTPRJ* frequently shows loss of heterozygosity in human colon cancers (Ruivenkamp et al. 2002). Additionally, *Pref1*, up-regulated in response to AOM in the distal colon of tumor susceptible A/J mice but not resistant AKR/J mice, was identified using the AOM carcinogen model (Dong et al. 2004). A direct link to WNT/CTNNB1 signaling was suggested through a putative CTNNB1/TCF response element in the promoter of *Pref1* (Ruivenkamp et al. 2002).

More recently, the AOM model was used to investigate the etiology of CRCs with distinct morphologies. CRCs with flat morphologies more frequently escape detection during routine colonoscopies than their larger polypoid counterparts, and with this realization have become increasingly apparent in recent years (Owen 1996; Saitoh et al. 2001; Soetikno et al. 2006; Soetikno et al. 2008; Speake et al. 2007). The AOM model was used to show that flat and polypoid tumors arise independently, despite having a similar mutational spectrum (Uronis et al. 2007).

Non-WNT pathway-mediated models of CRC

TGFB models—The transforming growth factor beta (TGFB) signaling pathway functions in a variety of cellular processes including differentiation, growth suppression, deposition of extracellular matrix and apoptosis. CRCs often acquire resistance to TGFB signaling and at later stages of cancer progression, express increased levels of TGFB promoting invasion and metastasis (Blobe et al. 2000).

Several TGFB pathway-associated models have been used to dissect the complex role of this pathway during CRC development. *Tgfb1* deficient mice die around three weeks of age due to extensive inflammation (Kulkarni et al. 1993; Shull et al. 1992). However, on a *Rag2* deficient

background, lacking functional B and T-cells, *Tgfb1* deficient mice survive until adulthood (Diebold et al. 1995; Engle et al. 1999). Mice deficient for both *Tgfb1* and *Rag2* rapidly develop carcinoma of the cecum and colon suggesting that inflammation in combination with loss of TGFB1 results in predisposition to cancer (Engle et al. 1999). Interestingly, CRCs do not form with *Tgfb1* deficiency unless specific bacterial pathogens are present to induce inflammation (Maggio-Price et al. 2006). Mutations in *Smad2* and *Smad4*, but not *Smad3*, have been reported to occur in human CRCs (Eppert et al. 1996; Takagi et al. 1996; Thiagalingam et al. 1996). *Smad2* and *Smad4* deficient mice are embryonic lethal, while *Smad3* deficient mice are viable and develop highly invasive CRC, which metastasizes to lymph nodes by four-to-six months of age (Zhu et al. 1998). *Apc* is not lost in TGFB-mediated tumors, nor do they display nuclear localization of CTNNB1 suggesting the existence of non-WNT/CTNNB1-mediated mechanism for tumor initiation (Kaiser et al. 2007). Consistent with current models of CRC and with the growth suppressive role of TGFB, mice deficient for *Smad3* or heterozygous for a *Smad4* mutant allele combined with mutant *Apc* develop an increased incidence of invasive carcinoma of the distal colon (Sodir et al. 2006; Takaku et al. 1998).

Inflammation-mediated models—The inflammatory diseases ulcerative colitis (UC) and Crohn's Disease, collectively termed inflammatory bowel disease (IBD), result in chronic inflammation of the colon and predisposition to the development of CRC (Itzkowitz and Harpaz 2004; Itzkowitz and Yio 2004). In mice the role of chronic inflammation in CRC was demonstrated by the discovery that prolonged administration of dextran sulfate sodium (DSS) results in chronic colitis and formation of high-grade dysplasia (Okayasu et al. 1990). A single dose of AOM followed by administration of DSS enhances tumor development and progression (Tanaka et al. 2003). The AOM/DSS model was used recently to show that deficiency for *Sigirr* (single immunoglobulin and toll-interleukin 1 receptor domain) increases susceptibility to CRC (Wald et al. 2003; Xiao et al. 2007). Similar to *Tgfb1* deficient mice, bacteria-induced inflammation is probably important for SIGIRR-associated cancer.

The AOM/DSS model has also been used to demonstrated the importance of the JAK/STAT (Janus kinase/signal transducers and activators of transcription) and NFKB (nuclear factor of kappa light chain gene enhancer in B-cells) pathways for inflammation-mediated CRC (Wirtz and Neurath 2007). Consistent with a role for the JAK/STAT pathway, loss of *Socs1* and *Socs3* (suppressors of cytokine signaling) expression results in increased activation of STAT1, STAT3 and NFKB and development of colorectal tumors (Hanada et al. 2006; Rigby et al. 2007). A direct link between SOCS signaling and *Myc* exists since AOM/DSS-induced adenocarcinomas from *Socs1* deficient mice have increased levels of nuclear CTNNB1 and *Myc* expression when compared to tumors from *Socs1* wildtype mice (Hanada et al. 2006). Intestinal epithelium-specific deficient for *Socs3* does not result in chronic inflammation or development tumors. However, when treated with AOM/DSS, these mice develop colon tumors preceded by inflammation suggesting that *Socs3* expression in neighboring stroma may be required to suppress chronic inflammation and subsequently tumor promotion (Hanada et al. 2006; Rigby et al. 2007). While colorectal tumors from *Socs3* deficient mice have not been shown to display high levels of nuclear CTNNB1 as is seen in tumors from *Socs1* deficient mice, *Socs3* deficiency has been shown to result in increased *Myc* expression in mammary tissue (Sutherland et al. 2006).

MYC as a central mediator of CRC

Recent evidence suggests that MYC functions as a global mediator of the oncogenic process, linking together a seemingly heterogeneous pool of molecular mechanisms underlying cancer development (Fig. 1) (Knoepfler 2007). The discovery that deletion of *Myc* rescues *Apc* deficiency elucidated a potential role of MYC as a key mediator of WNT/CTNNB1-initiated CRC (Sansom et al. 2007). Additionally, available evidence suggests that MYC is also involved

in mediating non-WNT/CTNNB1-initiated colorectal cancers. Although WNT/CTNNB1 and non-WNT/CTNNB1-mediated CRCs can be discriminated by unique gene expression signatures, all tumors from both classes display increased *Myc* expression (Kaiser et al. 2007). *Myc* is a direct transcriptional target of the WNT/CTNNB1 pathway, while TGFB signaling is associated with *Myc* repression through SMAD3 binding to a repressive SMAD binding element (RSBE) within the *Myc* promoter (Frederick et al. 2004).

A variety of genetic and carcinogen-induced murine models have provided important reagents for investigating the complexity of human CRC. While each model has provided unique insights into human CRC, it is becoming increasingly apparent that seemingly independent pathways converge upon similar transforming genes. Numerous lines of evidence indicate *Myc* as a central mediator of CRC, perhaps through its role in chromatin remodeling (Knoepfler 2007; Knoepfler et al. 2006). Mouse models have been used to show that decreased *Myc* expression leads to reduced numbers of CRCs (Yekkala and Baudino 2007), a result confirmed by *Myc* inhibition in human CRCs (Hao et al. 2008; Zhang et al. 2009).

While the exact role of MYC in the development of CRC is not fully understood, it is clear that increased attention on the role of MYC during CRC development and progression warrants further study and that murine models of human CRC will be essential to fully understand MYC function. Similarly, the development of new murine models with characteristics of metastatic CRC, possibly generated using new technologies like transposon-based screens in existing models (Starr et al. 2009), should greatly accelerate the discovery of new therapies to treat advanced human CRCs.

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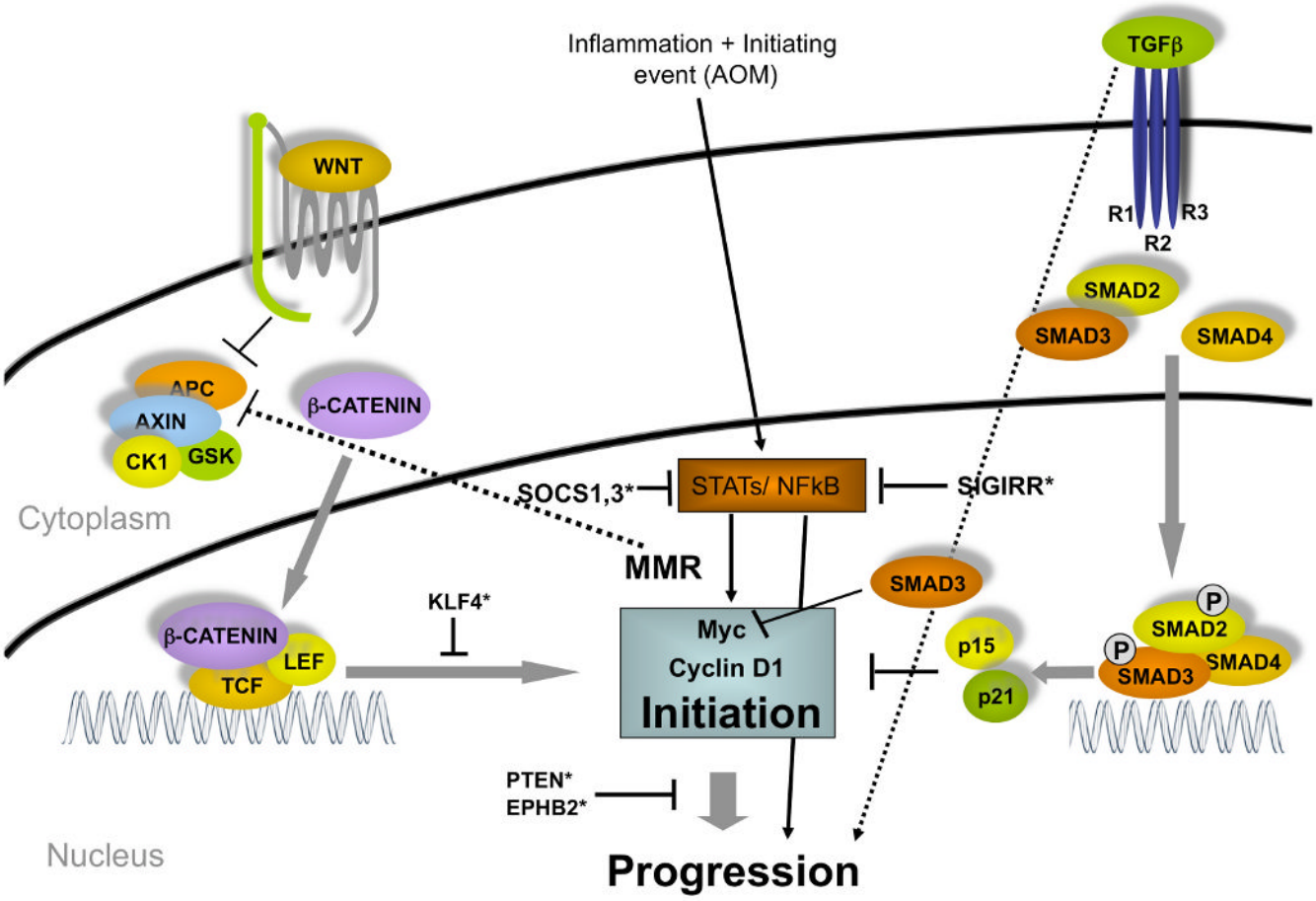

Fig. 1. Molecular pathways associated with colorectal cancer

Two major pathways, WNT and TGFB, converge in the nucleus to effect *Myc* expression. Murine models for human CRC have been developed by genetically altering many components of these two pathways. *, Modifiers of cancer initiation and progression.

Table 1

Murine models of human colorectal cancer.

	Strain	Tumor Type	Location	Multiplicity	Reference
WNT pathway					
Apc					
Apc^{Min}	C57BL/6J	adenoma	small intestine	3-58	(Moser et al. 1990)
Apc^{Min}	BTBR/Pas	adenoma	small intestine	600	(Kwong et al. 2007)
Apc^{1638}	C57BL/6J	adenoma/carcinoma	small intestine, colon	4	(Fodde et al. 1994)
Apc$^{\Delta 716}$	C57BL/6J	adenoma	small intestine, colon	254	(Oshima et al. 1995)
Azoxymethane	A/J	adenoma/carcinoma	distal colon	36.4	(Papanikolaou et al. 1998)
Azoxymethane	SWR/J	adenoma/carcinoma	distal colon	16.3	(Papanikolaou et al. 1998)
Azoxymethane	AKR/J	adenoma/carcinoma	distal colon	0.12	(Papanikolaou et al. 1998)
Apc^{Min}	C57BL/6J	adenoma	small intestine	5.7	(Shao et al. 2007)
Apc^{Min}, *Pten*$^{+/-}$	129/C57/BL6	adenoma/carcinoma	small intestine	22	(Shao et al. 2007)
Apc^{Min}	C57BL/6J	adenoma	small intestine	18	(Ghaleb et al. 2007)
Klf4$^{-/+}$, *Apc*^{Min}	C57BL/6J	adenoma	small intestine	29	(Ghaleb et al. 2007)
Apc^{Min}	C57BL/6J	adenoma	small intestine	39	(Batlle et al. 2005)
Ephb2$^{\Delta cy}$, *Apc*^{Min}	C57BL/6J	carcinoma	small intestine	13	(Batlle et al. 2005)
Apc^{Min}	C57BL/6J	adenoma	colon	1	(Batlle et al. 2005)
Ephb2$^{\Delta cy}$, *Apc*^{Min}	C57BL/6J	carcinoma	colon	11	(Batlle et al. 2005)
Pirc	F344/NTac	carcinoma	small intestine, colon	36	(Amos-Landgraf et al. 2007)
Mismatch repair					
Mlh1$^{-/-}$	C57BL/6J/129/Ola (mixed)	adenoma, carcinoma	stomach, small intestine, colon	1.1	(Edelmann et al. 1999)
Mlh1$^{-/-}$, *Apc*$^{1638/N}$	Ola	adenoma, carcinoma	stomach, colon	45.1	(Edelmann et al. 1999)
Msh2$^{-/-}$	C57BL/6J/129/Ola (mixed)	adenoma, carcinoma	small intestine, colon	2.6	(Reitmair et al. 1996)
Msh2$^{-/-}$, *Apc*^{Min}	C57BL/6J/129/Ola (mixed)	adenoma	small intestine, colon	333	(Reitmair et al. 1996)
Msh6$^{-/-}$	C57BL/6J/129/Sv/SJL/J (mixed)	adenoma, carcinoma	small intestine	0.6	(Edelmann et al. 1997)
Msh3$^{-/-}$, *Msh6*$^{-/-}$	C57BL/6J/129/Sv/SJL/J (mixed)	adnoma, carcinoma	small intestine, colon	2.75	(Edelmann et al. 2000)
Non-WNT pathway					
Tgfb					
Tgfb1$^{-/-}$, *Rag2*$^{-/-}$	129S6 × CF1	adenoma/carcinoma	cecum, colon	NR	(Diebold et al. 1995)

	Strain	Tumor Type	Location	Multiplicity	Reference
Smad3$^{-/-}$	129/Sv	carcinoma	colon	3.8	(Zhu et al. 1998)
Inflammation					
DSS	CBA/J & BALB/C	high grade dysplasia	colon	NR	(Okayasu et al. 1990)
AOM/DSS	CD-1	adenoma/carcinoma	distal colon	5.8	(Tanaka et al. 2003)
Modifiers of inflammation					
Socs1$^{-/-}$	NR	adenoma/carcinoma	proximal colon	NR	(Garlanda et al. 2007; Hanada et al. 2006)
Socs3$^{-/-}$	C57BL/6J	adenoma	colon	NR	(Rigby et al. 2007)
Sigirr$^{-/-}$	C57BL/6J × 129/SvJ	adenoma/carcinoma	distal colon	17	(Xiao et al. 2007)

NR, not reported