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Animal Models of Colorectal Cancer in Chemoprevention and Therapeutics Development

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1. Introduction

Considering the complexity of genetic and epigenetic events that occurs during colorectal carcinogenesis and the uncertainty in relying solely on extrapolation from cell culture models, it is essential to use animal models relevant to the molecular characteristics of colorectal cancer (CRC). Requirements for a mouse model of CRC are that the model has relevance to the molecular pathways involved in human CRC, that there are correlates with factors that affect the frequency of the disease in human populations, and that the chemopreventive/therapeutic agent-induced signal is sufficient to carry out the project with an affordable and statistically significant number of mice. In this chapter we will discuss how animal models have not only advanced our understanding of CRC initiation and progression but have also greatly facilitated the development of newer chemopreventive and therapeutic strategies to reduce mortality and incidence.

2. Animal models of colorectal cancer

Use of animal models could significantly expedite not only the delineation of molecular pathogenesis of colorectal carcinogenesis but could also aid in the development of newer preventive and therapeutic strategies. Animal tumor models can be classified as spontaneous and artificially transplanted systems. Spontaneous tumor models are now being widely considered for studying the biology of carcinogenesis and development of chemopreventive or chemosuppressive drugs.

Initial animal models of CRC involved use of chemical carcinogens in mouse, rat, as well as in guinea pig. In the last two decades genetically modified mice such as APC[Min/+] (Min: multiple intestinal neoplasia) with germline APC mutations at different sites have been extensively used for the investigation of therapeutic, chemopreventive and dietary factors for management of colorectal cancer (Hu et al., 2006; Gerner, 2007). Furthermore, studies to identify genetic modifiers of CRC are undertaken by generating mouse models representing molecular events involved in colorectal carcinogenesis like mismatch repair deficiency (MSH2-/-) and crossing

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them with APC$^{Min/+}$(Kwong & Dove, 2009). Other models for CRC targeting relevant pathway are also being developed to elucidate chemopreventive and chemotherapeutic response to newer molecules (Kwong & Dove, 2009). Because there is no ideal animal tumor model, which can mimic all the complexities associated with human CRC, the selection of an appropriate experimental model is crucial to study specific biologic end points towards the understanding of mechanistic, preventive and therapeutic aspects of the cancer.

2.1 Rat models

In the last few decades many murine models have been established that are useful for the investigation of initiation, expansion and progression of gastrointestinal (GI) cancers. In most of these models, Wnt signaling, mismatch repair, and TGFβ pathways are targeted not only to understand initiation and progression of CRC but also to evaluate various pharmaceutical and biological agents for prevention and treatment of CRC.

Normally CRC is not observed in rats (<0.1%) (Goodman et al., 1980) except the Wistar-Furth/Osaka strain that spontaneously develops adenocarcinomas in 30-40% of the animal (Miyamoto & Takizawa, 1975). The rat models of colon cancer are developed using common carcinogens like AOM (azoxymethane), DMH (dimethylhydrazine), or PhIP (2-amino-1-methyl-6-phenylimidazo [4,5-*b*]pyridine)(Corpet & Pierre, 2003, 2005). Most of the carcinogen-treated rat models develop tumors in the colon and often progress to adenocarcinomas. However, long latency period of tumor development is a distinct disadvantage. Efforts have been made to generate target-selected mutations, including nonsense alleles by several laboratories resulting into development of a rat strain carrying a nonsense allele in codon 1137 of APC (Corpet & Pierre, 2005). Interestingly, multiple intestinal neoplasms mostly in the colon were observed in F344 rats, commonly known as PIRC (polyposis in the rat colon) model, heterozygous for this allele and these animals survive for about one year (Zan et al., 2003; Smits et al., 2006; Amos-Landgraf et al., 2007). The rat models due to their size allows investigators to perform procedures like endoscopy, microCT (Computerized Tomography), and microPET (Positron Emission Tomography) imaging to evaluate chemoprevention or therapeutic interventions without sacrificing the animal.

2.1.1 Rat models in chemoprevention and therapeutics development

Although, dimethylhydrazine and its metabolites azoxymethane (AOM) and methylazoxymethanol are commonly used in the induction of colonic tumors in rat models, other carcinogens, like nitrosomethyl urea (MNU), specific nitrosamines and heterocyclic amines are also in frequent use. Many potential chemopreventive agents of colorectal cancer have been assessed in rat models. The effects of chemopreventive and therapeutic agents on initiation and progression of carcinogen-induced colonic tumors can be studied by varying the time of intervention. In rat models over 160 compounds have been screened for chemopreventive properties (Corpet et al., 2008) and the compounds found to be of chemopreventive and therapeutic importance are summarized in Table 1. Complete inhibition of cancer induction has been detected in ursodeoxycholic, polyethylene glycol (PEG), methylmethanethiosulfonate (MMTS) treated rats and in rats given exercise. Also, celecoxib, acetoxychavicol, selenium, p53 vaccination, piroxicam with difluoromethylornithine (DFMO), cellulose, aspirin, S-allylcysteine, obacunone, sulindac sulfone and hesperidin (flavanone glycoside) reduced the incidence of adenocarcinoma more than 78% (Corpet et al., 2008). Moreover, a DMBDD (7-hydroxy-7'-methoxy-4,4'-

Rat model	Name of the compound	Reference
Azoxymethane (AOM) /Dimethylhydrazine model	Etoricoxib (selective COX-2 inhibitor)	(Kaur Saini &Nath Sanyal, 2010)
	Diclofenac (preferential COX-2 inhibitor)	(Kaur Saini &Nath Sanyal, 2010)
	Adlay bran ethanol extract (ABE-Ea)	(Chung et al., 2010)
	Soy isoflavones	(Min et al., 2010)
	Arabinoxylan-oligosaccharide	(Femia et al., 2010)
	Probiotic soy products	(Silva et al., 2009)
	Physical exercise	(Silva et al., 2009)
	Astaxanthine	(Prabhu et al., 2009)
	Soy isoflavones	(Raju et al., 2009)
	R-Flurbiprofen	(Martin et al., 2010)
	Copper-indomethacin	(Bonin et al., 2010)
	Naproxen	(Steele et al., 2009)
	Nitric Oxide-Naproxen	(Steele et al., 2009)
	CP-31398 (a p53 modulator)	(Rao et al., 2009)
	Celecoxib	(Rao et al., 2009)
	Symbiotic association of Bifidobacterium lactis and carbohydrate 'resistant starch	(Le Leu et al., 2010)
	Melatonin	(Tanaka et al., 2003)
	Prebiotic germinated barley foodstuff (GBF)	(Kanauchi et al., 2008)
	High amylose maize starch and butyrylated high amylose maize starch	(Clarke et al., 2008)
MNU model	TAC-101 (a retinobenzoic acid derivative)	(Nakayama et al., 2009)
DMBDD model	PJJ-34 (13 alpha, 14alpha-epoxy-3beta-methoxyserratan-21 beta-ol), a triterpenoid	(Doi et al., 2010)
Orthotropic model	Combined use of bevacizumab and irinotecan (CPT-11) as postoperative adjuvant chemotherapy	(Mizobe et al., 2008)
AOM model or Dimethylhydrazine model	Combinatorial therapy using HMG-CoA reductase inhibitor (HRI) lovastatin (LOV) and the selective apoptotic antineoplastic drug (SAAND) exisulind (EXS)	(Kim et al., 2004)
	Ursodeoxycholic acid (UDCA)	(Hess et al., 2004)
	Protective effect of Fullerenol on heart and liver toxicity induced by doxorubicin	(Injac et al., 2009)

Table 1. Rat models used in chemoprevention & chemotherapy.

bis(1,3-benzodioxole)-5,5'-dicarboxylic acid dimethyl ester) rat multiorgan carcinogenicity model has also been developed for carcinogen testing (Takahashi et al., 1992; Imaida et al., 2003). The DMBDD model can be used for prediction of intestinal carcinogenesis risk assessment as well as for chemoprevention studies.

2.2 Mouse models

2.2.1 APC related models

The first heritable mouse model of colon cancer, APC$^{Min/+}$, was reported in 1990 as a result of ethylnitrosourea (ENU)-induced germline truncating mutation at the codon 850 of APC (Moser et al., 1990, 1992; Su et al., 1992). In the C57BL/6J mouse background APC$^{Min/+}$ mice develop about 30 small intestinal polyps with occasional adenocarcinoma and essentially no tumor in the colon (McCart et al., 2008). Although this contrasts human FAP (familial adenomatous polyposis) where most of the adenomas are in the colon and these adenomas certainly progresses to invasive adenocarcinoma, the APC$^{Min/+}$ models due to their phenotypic and histopathological similarities to human intestinal neoplasm are used not only to test therapeutic and chemopreventive interventions but also to understand the role of APC gene in CRC (Fodde & Smits, 2001). The APC$^{Min/+}$ models also proved to be important for the study of genetic modifiers-of-Min (*Mom*) locus. When APC$^{Min/+}$ C57BL/6J mice were crossed to AKR and MA mice, only 6 to 7 intestinal adenomas were observed and backcrossing F1 hybrids to the C57BL/6J helped identify a number of loci modifying number and distribution of adenomas (Moser et al., 1992; Gould et al., 1996; Fodde & Smits, 2001). The adenomas in the small intestine of the APC$^{Min/+}$ mouse have dysplastic and hyperplastic crypts and villi but the colonic tumors are spherical and peduncular with dysplastic cells. Importantly, these adenomas display higher mitotic index than surrounding normal crypts (Kwong & Dove, 2009). The Min mice due to their many advantages have been extensively used by scientists to study molecular pathogenesis of CRC – i] Min mice contains a single genetic change that produces a organ-specific, consistent, and discrete tumor phenotype, ii] Adenomas in Min mice develop rapidly, with lesions visible as early as 60 days, iii] high tumor multiplicities (>100 /intestinal tract) providing strong statistical power, and iv] multiple pathways impacting tumorigenesis enable many entry points for basic or applied study (Kwong & Dove, 2009). Importantly, other mouse models with targeted genetic manipulations at different locations on APC have also been generated (summarized in Table 2). When heterozygous, the Δ474, Δ14, Δ716, lacZ, and Δ1309 mouse models show phenotypes similar to that of Min (Sasai et al., 2000; Oshima et al., 2001; Niho et al., 2003; Colnot et al., 2004). In contrast, heterozygosity for the 1638N allele results in 0-2 tumors (none in the colon) while the 1638T model is tumor-free and unlike any other truncating allele, 1638T homozygous is viable. The 1638N has only approximately 1-2% of the truncated protein and is referred to as leaky allele (Fodde & Smits, 2001). In contrast, 1638T has the full expression level of the truncated protein and is known as truncated allele. Furthermore, Li Q et al., (2005) inserted a neomycin cassette in either orientation (reverse (neoR) or forward (neoF)) into the 13th intron of APC to generate full-length hypomorphic (expression reduced to 10-20%) alleles and showed that these heterozygous mice developed fewer than two adenomas per mouse (Li et al., 2005). The Cre/*loxP* conditional gene targeting system is developed to generate additional APC models to induce tumors specifically in the colon (Shibata et al., 1997; Colnot et al., 2004; Gounari et al., 2005; Hinoi et al., 2007).

Allele/truncation location	Average life-span	Genetic back-ground	Homozygous phenotype	Heterozygous phenotype	Average no. of spontaneous tumors	References
Min/850	4-6 months	C57BL/6J	Embryonic lethality	Multiple adenoma in GI-tract (mainly small intestine)	50-70	(Moser et al., 1990; Su et al., 1992)
Min/850	3-5	BTBR/Pas	Embryonic lethality	Multiple adenoma in GI-tract (mainly small intestine)	Up to 600	(Kwong et al., 2007)
Δ716/716	5-7 months	C57BL/6J	Embryonic lethality	Multiple adenoma in GI-tract	Up to 300	(Oshima et al., 1995)
580S/580* (based on Cre-LoxP recombination system)	N/A	Mixed	N/A	N/A	No tumor up to 1year of age	(Shibata et al., 1997)
580D/580*	N/A	Mixed	Embryonic lethality	Multiple adenomas at 4 week after conditional deletion	7-10	(Shibata et al., 1997)
1638N/1638	>1Year	C57BL/6J	Embryonic lethality	Adenoma and adenocarcinomas in GI-tract, desmoids tumors	3-4	(Fodde et al., 1994)
1638T/1638	Up to 2 Years	C57BL/6J	Viable	Normal	0	(Smits et al., 1999)
Δ474/474	<6 months	C57BL/6J	Embryonic lethality	Develops tumor mainly in small intestine, but also in colon and stomach	120	(Sasai et al., 2000)
Δ1309/1309	N/R	C57BL/6J	N/R		25-40	(Niho et al., 2003)
Δ14/580*	N/A	C57BL/6J	N/A	Multiple adenomas	40-50	(Colnot et al., 2004)
Δ468/468	N/R	N/R	Embryonic lethality	Polyps starting after 2 months of age	N/R	(Gounari et al., 2005)
Ex13NeoR/ Full-length	>15 months	C57BL/6J	N/R	Small microadenoma	1.1	(Li et al., 2005)
Ex13NeoF/ Full-length	>15 months	C57BL/6J	N/R	Small microadenoma	0.3	(Li et al., 2005)

*Conditional expression; N/A=Not applicable; N/R=Not reported

Table 2. Adematous polyposis coli (APC) based intestinal tumor models

Because APC$^{Min/+}$ mice rarely develop invasive cancer, efforts were made to develop compound mouse models by introducing alterations of genes known to be involved in CRC signaling pathways and produce invasive tumors mimicking human disease. The oncogene Kras, which is mutated in 40-50% of human CRC, is not altered in APC$^{Min/+}$ polyps and the APC$^{Min/+}$ mice with the introduction of Kras develop aggressive adenocarcinoma (Fodde & Smits, 2001). Loss of EphB receptor is an important event in the progression of CRC and APCMin/+ carrying a dominant negative EphB2 transgene showed 10 fold more tumor formation with greater number of invasive adenocarcinomas (Fodde & Smits, 2001; Batlle et al., 2005). The APC$^{Min/+}$ mouse model has been quite useful as an experimental system for studying colorectal tumorigenesis and CRC chemoprevention strategies (Moser et al., 1990) because Min mice have two distinct advantages i] numerous adenomas with the same inherited APC mutation are available for analysis and ii] these adenomas develop in animals of uniform genetic background (Luongo et al., 1994).

2.2.2 Mismatch repair (MMR) deficient models

The HNPCC (hereditary nonpolyposis colorectal cancer) is an inherited condition with inactivated DNA mismatch repair (MMR) genes, like *MLH1, MSH2, MSH6*, and *PMS2* (Fishel et al., 1993; Lynch & de la Chapelle, 2003) and leads to the development of a variety of cancers including that of the colon (Lynch & Smyrk, 1996). Mouse models with loss of function of MMR genes have been generated and mice lacking *Mlh1, Msh2* and *Msh6* develop tumors in stomach, small intestine, and colon. However, these mice also develop cancers of the lymphatic system, skin and lung (Reitmair et al., 1996; Edelmann et al., 1997, 1999, 2000). Enhanced development of adenomas was observed in the APC$^{Min/+}$ mice lacking *Msh2* with increase in colonic adenoma numbers. Interestingly, these mice show normal growth and can reproduce but have reduced life span (Reitmair et al., 1996). Although loss of *Msh3* is not associated with increased tumors, loss of both the *Msh3* and *Msh6* leads to an increase in GI tumors at a younger age, similar to *Mlh1* or *Msh2-deficient mice* (Edelmann et al., 2000). Mice bearing mutations in the *Msh6* gene have a life span of 18 months and develop GI tumors within one year. The MMR mouse models carrying one functional copy of APC showed increasing mutation of APC and an enhanced frequency of intestinal neoplasia (Reitmair et al., 1996; Kuraguchi et al., 2001). Furthermore, mice lacking *Mlh1* in APC1638N model have a 40-fold increase in adenomas compared to APC1638N mice alone (Edelmann et al., 1999). Interestingly, the PMS2$^{-/-}$ mice are vulnerable to lymphomas but they do not develop GI tumors. However, the PMS2$^{-/-}$ mice in APCMin background showed an increased number of adenomas in the GI-tract compared to Min alone (Prolla et al., 1998; Prolla, 1998; Baker et al., 1995). In contrast, the Mlh1/APC1638N mice showed a greater percentage of tumors progressed to invasive carcinomas (Edelmann et al., 1999). The MMR models are useful for screening of agents known to interfere with DNA mismatch repair processes for their therapeutic or carcinogenic effects.

2.2.3 TGF-β models

The TGF-β (transforming growth factor-β) signaling pathway regulates a number of cellular processes including cellular differentiation, growth suppression, deposition of extracellular matrix and apoptosis (Figure 1). The TGF ligands through a heteromeric receptor mediate their effects on cells and dysregulation of the TGF-β receptor 2 (TGF-βR2) is the most common occurrence in the CRC (Bellam & Pasche, 2010; Grady et al., 1999). Although TGFβR2 has been suggested to have a tumor suppressor function in CRC, recent reports indicate that it could act as a tumor suppressor as well as a tumor promoter (Tang et al., 1998;
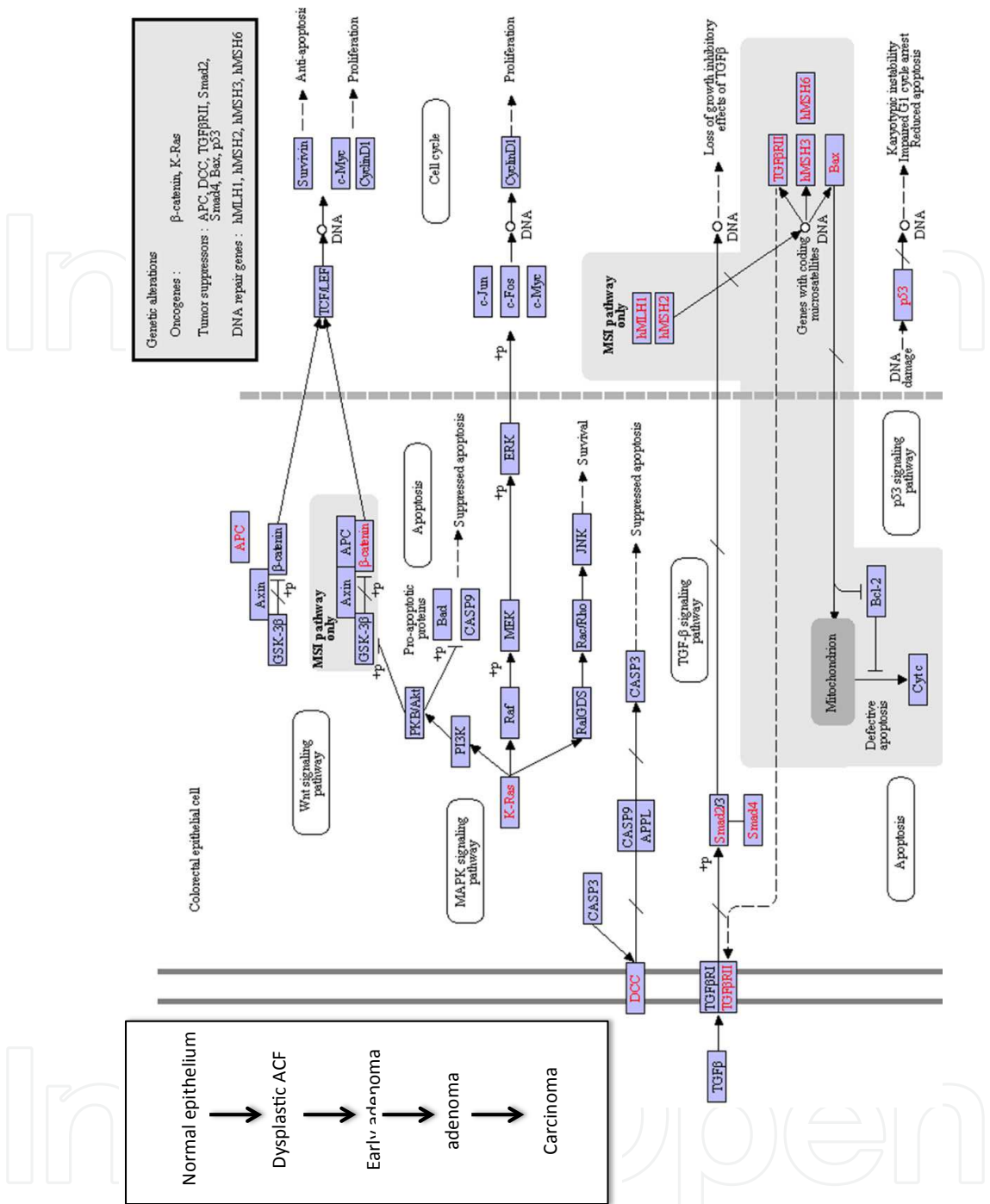
Fig. 1. Integrated molecular pathway implicated in development of colorectal cancer
(Courtesy: KEGG pathway, www.genome.jp/kegg). Alterations in Wnt signaling including
Wnt, APC, Axin and TCFs are associated increased β-catenin level and increased cell
proliferation. The MAPK signaling is associated with the oncogenic activation of RAS and
ERK signaling leading to increase cell proliferation). The TGF-β pathway is mainly a growth
inhibitory pathway and any perturbations leads to suppressed apoptosis and increased cell
proliferation. The mismatch repair (MMR) pathway maintains DNA homeostasis by
facilitating post-replication repair and dysfunction results in accumulation of potential
mutations and genetic instability implicated in the development of CRC. Important
candidate proteins altered in CRC are highlighted in red color.

Yang et al., 2002a, b; Blobe et al., 2000). Mouse models related to the TGF-β pathway have been used to delineate the multifaceted role of this pathway during colorectal carcinogenesis. It has been reported that the *TGF-β1* deficient mice due to widespread inflammation die around three weeks of age (Shull et al., 1992; Kulkarni & Karlsson, 1993). Importantly, in the absence of *Rag2* the *TGF-β1*-deficient mice survive until adulthood (Diebold et al., 1995). Due to the significant incidence of carcinoma of the cecum and colon in these mice, the *Rag2/TGF-β1*-deficient mice remains a useful model to study the role of inflammation in CRC in relation to the TGFβ1 signaling (Engle et al., 1999; Maggio-Price et al., 2006). Mouse lacking TGF-β2 in the colonic epithelium showed increased adenoma and adenocarcinoma formation after carcinogen treatment. Apart from TGF-β, mouse models representing alterations in the other factors in this important pathway like SMAD2, SMAD4 and SMAD3 have been reported. (Eppert et al., 1996). Although mice lacking SMAD2 and SMAD4 are embryonically lethal, the SMAD3 deficient mice are viable and are a useful model of CRC (Zhu et al., 1998). Importance of the TGF-β related models lies in the fact that the APC remains intact in the adenomas of these mice and these models could serve as a valuable tool to investigate non-WNT/APC/β-catenin-mediated colorectal carcinogenesis (Kaiser et al., 2007). Interestingly, the TGF-β related models in the APC^Min/+ background showed increased incidence of invasive carcinoma specifically in the distal colon (Takaku et al., 1998; Sodir et al., 2006).

2.2.4 Inflammation mediated models

Inflammatory bowel diseases (IBD) like ulcerative colitis (UC) and Crohn's Disease are predisposing conditions of CRC (Itzkowitz & Harpaz, 2004; Itzkowitz & Yio, 2004). Prolonged administration of dextransulfate sodium (DSS) in mice resulting in chronic colitis and formation of high-grade dysplasia confirmed the involvement of chronic inflammation in colorectal carcinogenesis (Okayasu et al., 1990). Interestingly intestinal tumorigenesis was augmented by combined administration of AOM and DSS. (Tanaka et al., 2003). To demonstrate that deficiency of *Sigirr* (single immunoglobulin and toll-interleukin 1 receptor domain) along with bacteria-induced inflammation increases susceptibility to CRC investigators effectively utilized the combined AOM/DSS model (Wald et al., 2003; Xiao et al., 2007; Uronis & Threadgill, 2009). Furthermore, the combined AOM/DSS model was also an important instrument in defining the role 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 in inflammation-induced CRC (Wirtz & Neurath, 2007). The role of the JAK/STAT pathway in colorectal carcinogenesis was further confirmed by the fact that dysfunctional *Socs1* and *Socs3* (suppressors of cytokine signaling) leads to enhanced activation of STAT1, STAT3 and NFkB and subsequent growth of colorectal tumors (Hanada et al., 2006). Although lack of only *Socs3* in the intestinal epithelial cells is not associated with chronic inflammation or tumor formation, these mice when treated with AOM/DSS showed distinct inflammatory response followed by colonic tumors (Hanada et al., 2006; Rigby et al., 2007). In contrast to increased nuclear β-catenin in the *Socs3* deficient mice, the colorectal tumors in *Socs1* deficient mice display enhanced expression of *Myc* (Sutherland et al., 2006). In addition, the Muc2^-/- is an important animal model to study the role of inflammation in the colorectal carcinogenesis. This model specifically targets mucin-forming Muc2 and unlike other models tumor formation is also observed in the rectum (Mack & Hollingsworth, 1994; Yang et al., 2005; Femia et al., 2009).

2.2.5 Immune system related models

Models have been developed to investigate the role of immune system in colorectal carcinogenesis. Immune cells are involved in inflammatory response and inflammation is intimately related to CRC. Therefore, the IL-2 (interleukin-2), IL-10, and TCRα knockout models were developed and used in studying role of diet and inflammation in colorectal cancer initiation and progression. (Rudolph et al., 1995; Kullberg et al., 1998; Mizoguchi et al., 2000; Seril et al., 2005).

2.2.6 Carcinogen-induced models

Although important information on familial and sporadic colorectal carcinogenesis was obtained from genetic animal models, it is the carcinogen-induced animal models that were instrumental in delineating molecular events specifically in the sporadic CRC. It is worth mentioning that the colon-specific carcinogen dimethylhyrdrazine (DMH) along with AOM has been useful in developing our current understanding of the molecular mechanisms underlying sporadic colorectal carcinogenesis (Druckrey et al., 1966). To its advantage the carcinogen-induced mouse model develops tumor which show much similarities to the pathophysiology of the human CRC (Kaiser et al., 2007; Uronis et al., 2007). The carcinogen-mediated tumors show alterations in the WNT/β-catenin pathway (Takahashi et al., 2000). Interestingly, the AOM-induced colorectal carcinogenesis, unlike in the APC$^{Min/+}$, is mainly due to the mutations in the *Ctnnb1 gene*, which encodes β-catenin protein. Mutations in the *Ctnnb1* results in ubiquitination-resistant stabilization of the β-catenin leading to growth of colorectal adenomas associated with upregulation of proliferation markers like cyclin D1 and c*Myc* (Wang et al., 1998; Kaiser et al., 2007). The carcinogen-induced model was also a key player in the identification of the modifier loci like the *Ptprj* (a receptor-type protein tyrosine phosphatase), which has been shown to modify susceptibility to DMH and has shown frequent loss of heterozygosity in human colon cancer (Ruivenkamp et al., 2002). Additionally, the carcinogen-induced models led to the recognition of *Pref1* as a modifier of CRC and the promoter of the *Pref1* is suggested to contain a β-catenin/TCF response element (Dong et al., 2004; Ruivenkamp et al., 2002; Uronis et al., 2007).

2.2.7 Mouse models in chemoprevention and therapeutics development

The genetic mouse models as well as the carcinogen-induced models of CRC (APC, TGF-β and mismatch repair based models) are used to evaluate the effect of diets and chemopreventive agents. The chemopreventive and dietary interventions are usually started between 3 and 6 weeks of age and invariably the principal biological endpoint is the number and grade of the tumors. It is important to note that in contrast to human CRC where no small intestinal tumors are observed, the tumors in the mutant models are mostly in the small intestine. However, the concept that the non-steroidal anti-inflammatory drugs (NSAID) have a chemopreventive role in the CRC was first established in these models showing reduction in tumor number in the small intestine. The chemopreventive properties of NSAIDs like celecoxib and piroxicam were also validated in the carcinogen-induced models showing decrease in polyp number and size. Due to commercial availability, the APC$^{Min/+}$ is the model of choice in many studies and a list of agents screened in APC$^{Min/+}$ mouse model is shown in Table 3. Most of the other CRC mouse models are used for specific biological end points. But a few of them such as APC1638N model because of its longer life span and good signal to noise ratio is used for carcinogen testing and is suggested to be more useful than APC$^{Min/+}$ mice (Trani et al., 2010).

Name of compound	References
Aspirin	(Barnes&Lee, 1998)
Piroxicam	(Ritland&Gendler, 1999)
Phenanthridinone derivative (PJ 34)	(Mabley et al., 2004)
Non-steroidal anti-inflammatory drugs (NSAIDs)	(Gescher, 2004)
DMU-135 (3-4 methylenedioxy-3'4'5'-trimethoxy chalcone), a potent tyrosine kinase inhibitor prodrug	(Sale et al., 2006)
Atorvastatin	(Swamy et al., 2006)
Celecoxib	(Swamy et al., 2006)
Sulforaphane (Isothiocynate compound)	(Khor et al., 2006)
Anthocyanin	(Bobe et al., 2006)
Difluoro methylornithine (DFMO)	(Telang&Katdare, 2007)
Epigallocatechin 3- gallate (EGCG)	(Telang&Katdare, 2007)
Dibenzoylmethane	(Tammariello&Milner, 2010)
PPAR ligand MCC-555	(Yamaguchi et al., 2008)
Metformin	(Tomimoto et al., 2008)
Alpha-phenyl-tert-butyl-nitrone (PBN) and 4 hydroxy-PBN	(Floyd et al., 2010)
Chafuroside	(Tammariello&Milner, 2010)
Sodium Taurocholate	(Smith et al., 2010)
COX-2 inhibitors	(Nakanishi et al., 2011)
Scopolamine butylbromide (muscarinic receptor antagonist)	(Raufman et al., 2011)
Curcumin	(Murphy et al., 2011)
Silibinin	(Rajamanickam et al., 2010)
Ellagic acid	(Mutanen et al., 2008)
Epigallocatechin gallate (EGCG)	(Telang&Katdare, 2007)
Dietary sphingolipids	(Symolon et al., 2004)
Dietary Folate	(Song et al., 2000)
Dietary isoflavones	(Sorensen et al., 1998)
Apple polyphenol extract (APE)	(Fini et al., 2011)
Grape Seed extract (GSE)	(Velmurugan et al., 2010)
Berries (bilberry, lingonberry, cloudberry)	(Mutanen et al., 2008)
Green tea	(Issa et al., 2007)
Orange peel extract (OPE)	(Fan et al., 2007)
Anthocyanin rich tart cherry extract	(Bobe et al., 2006)
Fermented brown rice and rice bran	(Phutthaphadoong et al., 2010)
Fish oil	(Bose et al., 2007)
Dietary /caloric restriction	(Tammariello&Milner, 2010)
Exercise/physical activity	(Baltgalvis et al., 2008)

Table 3. Use of APC$^{Min/+}$ mouse model in chemoprevention development.

2.3 Xenograft models of colon cancer

Colon cancer xenograft models are created by implantation of cells subcutaneously, intrasplenically, or into the renal capsule. It is important to implant the xenograft into the immunocompromised mice and commonly the T-cell deficient "nude" mice or NOD-SCID (non-obese diabetic/severe combined immunodeficiency) mice are used (Rygaard & Povlsen, 1969). The xenograft models of CRC are commonly used to assess newer therapeutics and understand the pathogenesis of human disease. Indeed, subcutaneous xenografts have found an important place in CRC research due to the fact that anesthetics are not required and the tumors are accessible for external measurement. Some of the disadvantages of the subcutaneous model are i] lack of tumor microenvironment representative of the CRC, and ii] in contrast to the >50% hepatic metastatic incidence of CRC, no metastasis is observed in the subcutaneous xenograft models. However, xenograft models involving intrasplenic or intra-renal-capsule, although have shown metastasis similar to human CRC, does not represent tumor microenvironment of CRC and signaling pathway could be different than the human disease (Furukawa et al., 1993; Fidler, 1991a, b, c). Consequently, implantation of CRC xenografts into mouse colon, the orthotopic model, is much preferred by the investigators due to their similar characteristics of the human ailment.

2.4 Orthotopic mouse model

An orthotopic mouse model involves placing of colorectal cancer cell or tumor tissue into the intestinal sub-mucosa (Tseng et al., 2007). The orthotopic model, unlike the subcutaneous model, is associated with all of the components of the tumor microenvironment as well as all of the angiogenic and growth factors, and cytokines. In addition to mimicking the human CRC in terms of metastasis and microenvironments, the orthotopic model also allows assessment of the alterations in the microenvironment on tumor initiation and progression. From a technical point of view, generation of orthotopic models demands specific expertise and more time than subcutaneous models. Because of technical difficulties in the physical measurement of the tumors, the orthotopic model also requires that an appropriate reporter like luciferase be in place for measuring tumor growth to determine the efficacy of a drug treatment. As with any animal model of human diseases there are inherent shortcoming and the orthotopic animal model is no exception. Because the tumors are in the colon, the orthotopic model requires sacrifice of the animals at a predetermined time for quantitative and qualitative analysis of the tumor. However, the orthotopic model has the advantage of mimicking human CRC including tumor microenvironment.

3. Zebrafish – A non-murine model of colorectal cancer

Signaling pathways involved in colorectal carcinogenesis are conserved across species and zebrafish, a well-characterized simple model system for human disease, are widely used to understand the molecular basis of cancer including CRC. Water borne carcinogens induce a wide variety of benign and malignant tumors in many organs of zebrafish. Zebrafish due to its easy maintainence and breeding along with conservation of human cancer-relevant oncogenes, and tumor suppressor and cell cycle genes makes it a useful model to study carcinogenesis. Interestingly, the zebrafish mutants display phenotypes similar to many human disorders, including cancer, cardiovascular disease, and neurodegeneration. Zebrafish carrying a mutation in the region representing most of the observed human APC

mutations were identified recently and like murine models the heterozygous fish develop intestinal adenomas (12%), which resembles its murine counterpart (Goessling et al., 2007). The APC-heterozygous fish when exposed to dimethylbenzanthracene, showed significant increase in the tumor number with 44% developing liver tumors and 35% developing intestinal tumors and could serve as an important model system to screen carcinogens (Goessling et al., 2007).

3.1 Zebrafish model in chemoprevention and therapy

Zebrafish model is in use for the target selection, bioactive compound screening as well as in the drug toxicity and efficacy studies (Lieschke & Currie, 2007). Angiogenesis supports cancer progression including CRC and anti-angiogenic therapy inhibits cancer growth. On the contrary anti-angiogenic therapy has been implicated in inflammation a known risk factor of colorectal carcinogenesis. Our understanding of the correlation between tumor angiogenesis, inflammation, and metastasis was much enhanced by studies in the zebrafish model (Moshal et al., 2010). Furthermore, the zebrafish model has been used to study potential therapeutic agents like SKLB610 (inhibitor of angiogenesis related tyrosine kinase), which was reported to inhibit angiogenesis in zebrafish sub-intestinal veins (Cao et al., 2011). The zebrafish model was useful in determining the role of DNA demthylase in maintaining intestinal epithelial cells lacking APC in an undifferentiated state (Rai et al., 2010). Additionally, it has been reported that the zebrafish expressing a truncated form of APC with either retinoic acid or a selective COX-2 inhibitor decreased β-catenin in the cell. Curcumin-loaded biodegradable polymeric micelles (Cur/MPEG-PCL) has been shown to efficiently block angiogenesis in transgenic zebrafish model (Gou et al., 2011). Similarly, the incorporation of doxorubicin in MPEG-PCL micelles enhanced the anticancer activity and decreased the systemic toxicity of doxorubicin in Zebrafish and has implications for CRC treatment (Lee et al., 2006).

4. Animal models in chemoprevention and chemotherapeutics development

Rodent models have been used for CRC research providing insight into the complex oncogenic events contributing to the loss of cell growth and differentiation control. These models also offer prospects to identify and study both therapeutic and chemopreventive agents. In general, almost all popular human colorectal cancer prevention strategies, from dietary manipulations (such as folate or calcium supplementation), to drug testing (such as (NSAIDs) have been evaluated in both carcinogen-induced and genetically modified animal models. In most cases, suppression of polyps has demonstrated the preventive effects of these strategies, and in some cases, investigators have been able to dissect pathways where these agents block the development of aberrant crypt foci (ACF). Moreover, approaches that are effective in preventing the early stages of colorectal tumorigenesis have been shown to actually promote tumor growth in later stages of the adenoma-carcinoma sequence. This type of observation in mice is important in polyp prevention studies in humans where folate supplementation may actually be harmful in subjects already predisposed to colorectal neoplasia. Although it is important to note that caution has to be exercised in extrapolating animal model data to human, at least studies with NSAID have shown similar protective effects both in human and animal. However, some differential response of chemopreventive drugs has been observed between animal studies and human response. This could be because of higher genetic homogeneity of mice compared to humans, physiologic differences

in gut motility, hormones and immune surveillance, and differences in genetic events in somatic cells during adenoma to carcinoma transition in mouse compared to human colorectal neoplasia.

5. Comparison of human data with animal model data

With few exceptions, a significant correlation was observed between animal and human studies. Both the AOM rat model and the mutant mouse models supported the chemopreventive effects of the NSAID. This is supportive of the epidemiological studies proposing that, NSAIDs might reduce the colorectal cancer incidence by at least 45% in humans. Also supportive is the effects of celecoxib and sulindac shown to decrease the number of polyps in FAP patient trials. Similar to human data, rats and mice fed a high-fat diet showed increased adenomas than those fed a low-fat diet thus establishing the relationship between the colon cancer incidence and the intake of fat. Fatty diets with high linoleic acid content and n-6-polyunsaturated fatty acids seem to increase the number of tumors in rodents. Moreover, caloric reduction is a strategy that seems very efficient in animals. A reasonable agreement is observed between the results of these animal studies and the more limited clinical studies with few differences (Corpet & Pierre, 2003).

6. Limitations of animal models

Currently a number of animal models are available to dissect various facets of CRC and to undertake risk estimation studies. Mutant mouse models provide a unique opportunity in studying numerous adenomas under defined experimental conditions and uniform genetic background. However, use of animal models in studying human disease has its own limitations. For example, in carcinogen-induced models of CRC, the tumor incidence and latency period could be modulated by amount of carcinogen used – higher amount of carcinogen leading to higher incidence of tumors. However, high ethanol consumption reduced carcinogen (DMH)-induced tumorigenesis suggesting that DMH model is not useful in determining the role of alcohol in CRC. This discrepancy was resolved using the APC$^{Min/+}$ mice model where ethanol consumption was observed as a risk factor for CRC (Roy et al., 2002). Careful consideration is essential for the selection of animal model to study a particular agent and requires validation is two or more models for the unequivocal demonstration.

7. Conclusions

Future advances in animal model development will require combinations of dietary and genetic manipulation of rodents or other inexpensive animals to more accurately mimic the various factors that contribute to colorectal neoplasia in humans. As epidemiologic and molecular studies demonstrate the heterogeneity of colorectal tumor development in diverse populations (e.g. the microsatellite instability or CIMP pathways), it is expected that any one model will not answer all the questions about the CRC chemoprevention or therapeutic intervention strategies under investigation.

8. Acknowledgment

9. References

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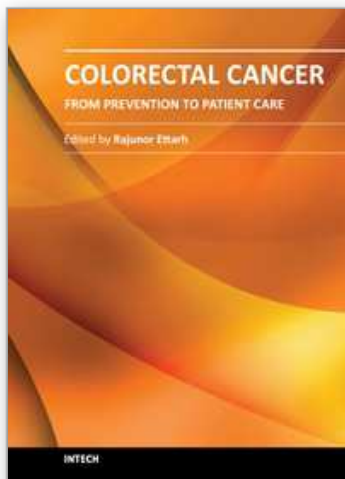
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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements and better solutions in patient care becomes evident. This volume, organized in five sections, represents a synopsis of the significant efforts from scientists, clinicians and investigators towards finding improvements in different patient care aspects including nutrition, diagnostic approaches, treatment strategies with the addition of some novel therapeutic approaches, and prevention. For scientists involved in investigations that explore fundamental cellular events in colorectal cancer, this volume provides a framework for translational integration of cell biological and clinical information. Clinicians as well as other healthcare professionals involved in patient management for colorectal cancer will find this volume useful.

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