

## Mouse models for the discovery of colorectal cancer driver genes

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### Abstract

Colorectal cancer (CRC) constitutes a major public

health problem as the third most commonly diagnosed and third most lethal malignancy worldwide. The prevalence and the physical accessibility to colorectal tumors have made CRC an ideal model for the study of tumor genetics. Early research efforts using patient derived CRC samples led to the discovery of several highly penetrant mutations (*e.g.*, *APC*, *KRAS*, *MMR* genes) in both hereditary and sporadic CRC tumors. This knowledge has enabled researchers to develop genetically engineered and chemically induced tumor models of CRC, both of which have had a substantial impact on our understanding of the molecular basis of CRC. Despite these advances, the morbidity and mortality of CRC remains a cause for concern and highlight the need to uncover novel genetic drivers of CRC. This review focuses on mouse models of CRC with particular emphasis on a newly developed cancer gene discovery tool, the *Sleeping Beauty* transposon-based mutagenesis model of CRC.

**Key words:** Mouse models; Colorectal cancer; Cancer genes; Insertional mutagenesis; Transposable elements

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**Core tip:** Successful implementation of targeted therapy will require a much more sophisticated understanding of colorectal cancer genetics, including the ability to discern "driver" mutations from the more common "passenger" mutations. Interpreting causality from large human genomic datasets will benefit from data produced by animal models and will expedite clinical trials using targeted therapies. This review describes the benefits and limitations of both traditional and new mouse models that are being used to discover and define colorectal cancer driver genes.

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## INTRODUCTION

The cause of colorectal cancer (CRC), as with many malignancies, is the accumulation of genetic mutations and other genetic aberrations over an individual's lifetime. Several decades of genomic studies have revealed that colorectal tumors can be categorized into two general molecular categories known as the "mutator" phenotype and the "chromosome unstable" phenotype<sup>[1-3]</sup>.

It is estimated that fifteen percent of patients with CRC have mutations in the DNA mismatch repair system. Because these patients have tumors containing a significantly higher number of somatic mutations vs those with proficient DNA repair systems, their tumors are said to display the mutator phenotype. Sporadic CRC tumors displaying the mutator phenotype typically have a loss of *MLH1* expression due to promoter methylation<sup>[4]</sup>. The *MLH1* gene is highly conserved and its gene product functions in repairing DNA replication errors that result in mismatched nucleotide bases. Loss of *MLH1* function results in the accumulation of single nucleotide alterations across the genome but are especially apparent in regions of the genome displaying highly repetitive sequence<sup>[5]</sup>. The result of dysfunctional DNA mismatch repair is illustrated by that fact that *MLH1* knockout mice display increased susceptibility to cancer formation<sup>[5]</sup>. Individuals with Lynch syndrome, also known as Hereditary Non-polyposis Colorectal Cancer (HNPCC), have germline mutations in DNA mismatch repair genes causing a high mutation load and microsatellite instability. Those with Lynch syndrome are at high risk of developing CRC and typically account for 3%-5% of the total number of new CRC diagnoses<sup>[6]</sup>. For reasons that are not well understood, patients with CRC tumors that are genetically defined as the mutator phenotype generally have a better clinical prognosis vs their non-mutator phenotype counterparts<sup>[7,8]</sup>.

Inactivating mutations in the adenomatous polyposis coli (*APC*) gene, a tumor suppressor gene, is widely regarded as a key somatic mutation responsible for driving sporadic colorectal tumor formation<sup>[9]</sup>. This statement is supported by data from large-scale genomic studies that identified mutations in *APC* in approximately 80% of sporadic CRCs<sup>[10,11]</sup>. The protein encoded by the *APC* gene functions as a negative regulator of the Wnt signaling pathway, which is a highly conserved pathway responsible for controlling many cellular processes including cellular proliferation and differentiation<sup>[12,13]</sup>. Additionally, the Wnt pathway is critical for maintaining organ homeostasis and is particularly important in maintaining homeostasis in the intestinal epithelium. The consequences of

deregulated Wnt signaling, usually due to inactivating mutations in *APC*, are best exemplified in those affected by the relatively uncommon syndrome known as familial adenomatous polyposis (FAP). Individuals with FAP have germline mutations in *APC* and consequently develop hundreds to thousands of colon polyps by their teenage years. Furthermore, it is estimated that nearly all FAP patients are diagnosed with CRC prior to the age of 40<sup>[14,15]</sup>.

The vast majority of sporadic colorectal tumors (about 85%) are molecularly characterized as chromosome unstable<sup>[2]</sup>. Tumors in this category display major chromosomal aberrations including aneuploidy, loss of heterozygosity, gene fusions, and large insertions and deletions<sup>[2,16]</sup>. The root cause of chromosomal instability in colon cancer is unclear but many mechanisms have been proposed. These mechanisms include, but are not limited to, defects in the system responsible for faithful chromosome segregation during mitosis and inactivation of genes responsible for the repair of DNA damaged by genotoxic stressors (e.g., methylating agents)<sup>[2,17]</sup>. Regardless of the underlying cause of chromosome instability, it is likely that the accumulation of somatic mutations in tumor suppressor and oncogenes in combination with genome instability leads to the initiation and progression of CRC.

## EARLY ADVANCES IN CRC GENE DISCOVERY

During the 1970's researchers identified and defined a small number of cancer oncogenes and tumor suppressors based on the study of oncoviruses and recurrent chromosomal abnormalities. In the 1980's several groups used this knowledge to assay those known cancer genes in CRC and found that *RAS* mutations were present in 30% to 50% of patients<sup>[18,19]</sup>. Furthermore, recurrent allelic deletions were identified that eventually implicated *TP53*, *APC* and *SMAD4* as tumor suppressors in CRC<sup>[19-21]</sup>. By analyzing tumors at various stages along the continuum of adenoma-adenocarcinoma-metastasis, these researchers were able to hypothesize that certain mutations were early gatekeepers, such as *APC* and *KRAS*, while other mutations were only found at later stages, such as *SMAD4* and *TP53*.

In the early 1990s scientists used FAP and Lynch syndrome family cohorts to identify the causative tumor suppressor genes for these two syndromes. The *APC* gene was identified by positional cloning in FAP cohorts, while linkage analysis implicated mutations at chromosomal regions 2p16 and 3p21 in Lynch syndrome families<sup>[22-28]</sup>. At the same time it was discovered that a subset of CRC patients had novel microsatellite alleles in their cancers, indicating microsatellite instability. At the same time, microbiologists had recently identified mismatch repair (MMR) genes in yeast. This finding

lead to the hypothesis that mutations in human homologs of the yeast MMR genes may be the cause of Lynch Syndrome<sup>[29]</sup>. This hypothesis was strengthened by the discovery that one of the homologs, *MSH2*, was in the chromosome 2p region linked to Lynch syndrome<sup>[30]</sup>. Within the next few years mutations in several other MMR genes, including *MLH1*, *PMS1*, *PMS2*, and *MSH6*, were discovered in Lynch syndrome patients<sup>[31-35]</sup>.

## CURRENT ADVANCES IN CRC GENE DISCOVERY

New technologies, such as next generation sequencing, have allowed researchers to comprehensively analyze whole exomes, genomes and transcriptomes of large numbers of CRC patients. These datasets are then mined using various bioinformatic algorithms to identify putative CRC driver genes. In general, these algorithms detect genes that are recurrently mutated, amplified, deleted, or altered by other means and assign a rank or *P*-value to predict whether or not the gene is a driver of tumorigenesis. For example, a study of the entire exomes of 11 CRC patient tumors identified 140 putative cancer drivers based on frequency of recurrence<sup>[36,37]</sup>. More recently, 224 CRC patient tumors were assayed for mutations, gene expression, copy number, and methylation status by The Cancer Research Atlas (TCGA) Network. This study produced various lists of genes based on recurrent changes, including 31 genes recurrently mutated and a larger number of genes found in genomic regions that were recurrently amplified or deleted<sup>[38]</sup>. It is still unknown how many genetic mutations are necessary and sufficient for cancer initiation with estimates ranging from 3 to 14<sup>[37,39]</sup>.

These landmark studies have provided cancer geneticists with a wealth of data regarding the genetic drivers of CRC and were the springboard for the creation of several animal models.

## MOUSE MODELS OF FAP

Moser *et al.*<sup>[40]</sup> developed the first mouse model of FAP in a forward genetic screen using N-Ethyl-N-Nitrosourea (ENU) as a germline mutagen. C57BL/6J (B6) were treated with ENU then crossed to AKR mice to generate progeny harboring ENU-induced germline mutations. The progeny from this breeding scheme exhibited an interesting circling trait that proved to be heritable in the offspring of AKR/B6 (f1) crossed to B6. Adult offspring from this cross were often anemic and frequently passed bloody stool. GI tract adenomas were observed in all anemic mice and tumors eventually progressed to adenocarcinomas in aging mice. Mice displaying these phenotypic features were said to carry the Multiple Intestinal Neoplasia (*Min*) gene. Further analysis demonstrated the *Min* mutation

was inherited in an autosomal dominant fashion and heterozygous offspring developed hundreds of GI tract tumors resulting in death at approximately 120 d. Su *et al.*<sup>[41]</sup> later identified the *Min* locus as the mouse homolog of the human *APC* gene. A thymine to adenine transversion mutation, creating a premature stop codon, was found at nucleotide 2549 (amino acid 850) of the *Apc* gene. With similar nonsense mutations often observed in FAP patients, it was determined that the *Apc*<sup>*Min*</sup> mouse was a suitable FAP model.

Several variations of the *Apc* mutant mouse have since been developed with the main differences being the location of the *Apc* truncating mutations. The most notable and well characterized of these variations are mice engineered with *Apc* truncated at amino acids 716 and 1638<sup>[42,43]</sup>. The development of Cre-lox technology has also enabled researchers to control the location and/or timing of *Apc* deletions. For example, expressing Cre recombinase from a tissue specific promoter (*e.g.*, *Fabpl*- and *Villin*-promoters) results in deletions of *Apc* specifically in the gastrointestinal (GI) tract epithelial cells<sup>[44-48]</sup>. Each *Apc* deletion mutant displays slight phenotypic variations but all develop GI tract adenomas that eventually develop to adenocarcinomas. For more detail on the various *Apc* mutants please refer to these excellent reviews<sup>[49-52]</sup>. Because *Apc* mutant mice rarely develop aggressive metastatic disease these models have been mostly helpful in studying the genetic events driving early CRC tumor formation.

## MOUSE MODELS OF LYNCH SYNDROME

Several attempts to create a mouse model of Lynch syndrome have been made but most are limited in their ability to faithfully recapitulate the early onset of CRC tumors. Early efforts to create a Lynch syndrome mouse model focused on deleting the murine homologs of *MSH1* and *MSH2*, as these genes are mutated in approximately 90% of Lynch syndrome patients<sup>[14]</sup>. *Msh2* knockout mice are viable and develop without abnormalities. Adult *Msh2*<sup>-/-</sup> mice have a reduced life span (6-12 mo) due to T-cell malignancies<sup>[53,54]</sup>. Gastrointestinal tract adenomas and adenocarcinomas are observed in 80% *Msh2*<sup>-/-</sup> mice that survive 8-10 mo<sup>[55]</sup>. The microsatellite instability observed in Lynch syndrome CRC tumors was also found in tumor tissues (T-cell and GI tract) from *Msh2*<sup>-/-</sup> mice. *Mlh1* knockout mice are phenotypically similar to *Msh2*<sup>-/-</sup> mice<sup>[56]</sup>. It has also been shown that mice deficient in the MMR protein *Msh6* develop GI tract tumors but, unlike *Msh1*<sup>-/-</sup> and *Msh2*<sup>-/-</sup> models, these mice do not display the microsatellite instability characteristic of Lynch syndrome CRC tumors<sup>[57]</sup>.

In order to avoid early death from lymphomas, researchers have bred MMR gene knockout mice to immunocompromised strains (*tap1*<sup>-/-</sup>) that lack CD8+ T-cells. Such mice do not die early from lymphomas

allowing for the development of CRC tumors resembling those found in Lynch syndrome patients<sup>[58]</sup>. This approach has been improved upon using the Cre-lox system to restrict MMR gene deletion to the GI tract epithelial cells of immunocompetent mice<sup>[59]</sup>.

Although useful, genetically engineered mice (transgenic or gene, knockout/knockin) are typically designed to harbor only a few mutant alleles and are therefore, inherently limited in their ability to accurately model the complex genetic alterations of sporadic CRC tumors. Another deficiency is the difficulty of simultaneously altering multiple genes, including genes of unknown function. The next section describes models that can overcome these limitations.

## MODELS OF SPORADIC CRC

### **Chemically induced tumor models**

To mimic environmentally induced cancers researchers have used carcinogenic chemicals to generate sporadic CRC tumors. Methylazoxymethanol (MAM), 1,2-dimethylhydrazine (DMH), and azoxymethane (AOM) are examples of popular compounds used to generate CRC tumors in mice. Although the number of tumors varies depending on the strain, mice treated with these compounds quickly develop CRC tumors in the distal colon that moderately resemble human CRC tumors (*e.g.*, *KRAS* mutations). Although these models reliably produce sporadic CRC tumors, it is challenging to determine their mutational landscape. To do so, one must target previously identify cancer drivers for DNA sequencing or use a more unbiased method of analysis (*e.g.*, whole exome, RNA-seq, *etc.*), which can be cost prohibitive. For a comprehensive review of the many carcinogen-induced CRC models refer to these reviews<sup>[60-63]</sup>.

### **Insertional mutagenesis models for CRC gene discovery**

The advancement CRC therapeutics, specifically the development of molecularly targeted therapies, is critically dependent on the identification of novel CRC driver mutations. Insertional mutagenesis forward genetic screens are an excellent method to identify novel cancer genes. Retroviruses (*e.g.*, MMTV and MuLV) have long been used as insertional mutagens and their use has led to the discovery of several major cancer genes<sup>[64-67]</sup>. There are two flavors of retroviruses, the acute transforming and the slow transforming virus. Slow transforming retroviruses are often used as insertional mutagens because they do not carry viral oncogenes within their genomes. Instead, slow transforming viruses promote tumor formation by proviral insertional into oncogenes and tumor suppressors. Upon insertion next to, or within, a gene, elements within the viral genome can act in *cis* to alter the expression of cellular genes<sup>[68]</sup>. The identification of the virally disrupted genes is possible using PCR to amplify the viral-host genome DNA

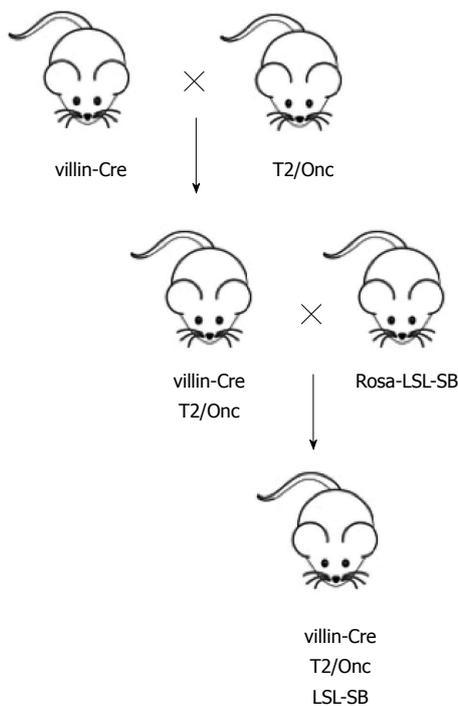
junction and subsequent sequencing. Due to tissue tropisms, the use of retroviruses has mainly been used to model mammary and blood cancers.

Class II transposable elements represents a novel insertional mutagen used for the discovery of novel CRC driver genes. Class II transposons are DNA elements that rely on the enzymatic activity of a transposase to be "cut" from one genomic location and "pasted" to another. Transposons have been used for decades to study gene function in a wide array of organisms but the use of transposons in vertebrates is a relatively new advancement<sup>[69,70]</sup>. Ivics *et al.*<sup>[71]</sup> (1997) were the first to construct a synthetic transposon, *Sleeping Beauty* (SB), and transposase that showed activity in vertebrate cells. Quickly after its introduction, the SB transposon system was engineered into the mouse genome and transposition was shown to occur *in vivo*<sup>[72,73]</sup>. Enhancements that increased the transposition frequency of the SB transposon lead to the development of the oncogenic transposon known as T2/Onc<sup>[74,75]</sup>. The T2/Onc transposon carries multiple mutagenic elements that make it an ideal tool for the discovery of candidate cancer genes. To mimic gain of function mutations, the T2/Onc transposon carries a strong viral promoter and a splice donor sequence. In the event of T2/Onc integration upstream of a gene and in the same transcriptional orientation, the strong viral promoter carried by the transposon will drive expression of the cellular gene. Similarly, if the transposon lands in an intron it can also produce an active truncated protein. T2/Onc also carries splice acceptor sites on both DNA strands and a bidirectional poly(A) signal. If T2/Onc integrates within a gene, in either orientation, the splice acceptors and poly(A) signal will terminate transcription effectively mimicking loss of function mutations (Figure 1). In separate publications Collier *et al.*<sup>[76]</sup> and Dupuy *et al.*<sup>[77]</sup> used the T2/Onc transposon and SB transposase to demonstrate the mutagenic potential of the T2/Onc transposon in somatic cells.

Soon after the debut of the T2/Onc transposon, Starr *et al.*<sup>[78]</sup> harnessed its mutagenic potential for the discovery of novel CRC driver genes. In this forward genetic screen, the authors created a triple transgenic mouse by crossing mice harboring a Cre-responsive SB transposase allele with double transgenic mice engineered to express the Cre recombinase only in the gut as well as carry a concatemer of T2/Onc transposons (Figure 2). In this model the T2/Onc transposon is mobilized by the SB transposase only after Cre recombinase (*villin-Cre*) removes the LoxP-STOP-LoxP cassette located upstream of the SB transposase. The results from this study revealed that triple transgenic mice become moribund at a faster rate than control mice (double transgenics) and that the vast majority of these triple transgenic mice developed intestinal lesions. Histopathology revealed the resulting GI tract growths to be intraepithelial neoplasias,



**Figure 1 Schematic of the T2/Onc transposon.** The central viral promoter and splice donor (SD) promote the expression of candidate oncogenes. The bidirectional splice acceptor (SA) sites and polyadenylation (pA) sites allow for the disruption of candidate tumor suppressor gene expression. The inverted repeat direct repeat (IR/DR) sites (in pink) serve as binding sites for the SB transposase.



**Figure 2 Breeding scheme used to generate triple transgenic mice.** Villin-Cre mice express the Cre recombinase enzyme from the gastrointestinal (GI)-specific villin promoter. T2/Onc mice carry a concatemer of T2/Onc transposons on Chromosome 1 or 15. Rosa-LSL-SB mice carry a knockin of the SB11 transposase enzyme downstream from a Lox-STOP-Lox (LSL) cassette at the Rosa locus. This design restricts T2/Onc transposition to the epithelial cells lining the GI tract.

adenomas, and adenocarcinomas. To identify the disrupted host genes, DNA was harvested from 135 tumors for linker-mediated PCR (LM-PCR) amplification of the transposon-host genome junction. Sequencing of the LM-PCR products revealed each tumor contained, on average, 124 T2/Onc insertions. Using statistical approaches to identify common insertion site (CIS) loci the authors were able to hone in on a list of 77 candidate CRC genes. The ability of this tool to model sporadic CRC was confirmed by the finding that *APC*, *PTEN*, and *SMAD4*, which are commonly disrupted in human CRC tumors, were also identified as T2/Onc CISs in mouse tumors. Of the 77 CIS genes, 17 were identified as novel CRC driver genes. One of these genes, *RSPO2*, has recently been identified as a tumor suppressor gene in human CRC tumors<sup>[79]</sup>.

Similar screens have been carried out using the

T2/Onc transposon as an insertional mutagen in *Apc* mutant mice. This approach was used by Starr *et al.*<sup>[80]</sup> (2011) to identify novel CRC genes that cooperate with *Apc* mutations. T2/Onc transposition in *Apc*<sup>Min</sup> mice increased the polyp count from 112 (controls) to an average of 360 polyps per mouse. DNA analysis of 96 polyps from 12 mice revealed the presence of greater than 30 thousand transposon insertions. CIS analysis identified 37 genes in this set of transposon insertions. The remaining wild-type *Apc* allele of the *Apc*<sup>Min</sup> mouse was the most commonly mutated gene in this study, a result that further demonstrates the importance of *APC* mutations in CRC development. To validate some of the 37 CIS genes the authors used RNAi to decrease the expression of nine CIS genes (*CNOT1*, *PDE4DIP*, *PDCD6IP*, *ATF2*, *SF11*, *FNBP1L*, *MYO5B*, *SNX24*, and *STAG1*) *in vitro*. It was determined that knockdown of *CNOT*, *PDE4DIP*, *PDCD6IP*, *ATF2*, and *SF11* significantly decreased the proliferation of the SW480 CRC cell line<sup>[80]</sup>. Using a similar approach March *et al.*<sup>[81]</sup> also determined that SB transposition increased the morbidity and tumor burden of *Apc* mutant mice. CIS analysis of DNA from 446 transposon-induced tumors identified hundreds of CIS genes. Using pathway analysis the authors determined that genes from their CIS list were involved in 38 cancer related genetic networks (*e.g.*, K-Ras signaling pathway) and as many as 183 CIS genes were identified as Wnt pathway targets. A more recent publication by Takeda *et al.*<sup>[82]</sup> expanded upon this approach to include transposon based insertional mutagenesis on *KRAS*, *SMAD4*, and *TP53* mutant strains of mice. In human CRC tumors the loss of *APC* is a tumor initiating mutation followed by activating mutations in *KRAS* in early to intermediate adenomas and loss of function mutations in *SMAD4* and *TP53* occurring in later stages. By generating mouse models with initiating mutations in these three genes (*KRAS*, *SMAD4*, and *TP53*) the authors attempted to identify mutations that cooperate with these three genes. Using this strategy the authors discovered different sets of CIS genes that were unique to each genetic background suggesting that the initiating mutation influences which genes are mutated during CRC tumor development. One of their findings was that the gatekeeper *Apc* mutation was common in all backgrounds, while activating mutations in the Wnt pathway members *Rspo1* and *Rspo2* were only found in the *SMAD4* mutant mice.

## CONCLUSION

The ultimate goal of cancer gene discovery is to translate new knowledge into more effective therapies for treating CRC. Identification of recurrently altered genes is informative, but does not directly result in reduced mortality rates for CRC patients. The limited success of targeted therapies is likely attributed to tumor heterogeneity and the action of unidentified CRC driver genes. Mouse models continue to be an essential tool used to unveil novel CRC driver genes with therapeutic potential. One promising example is the identification of ion channel genes as candidate drivers of CRC. Both *KCNQ1* and *CFTR* were identified in multiple Sleeping Beauty insertional mutagenesis screens<sup>[80-82]</sup>. Based on these findings, Than *et al.*<sup>[83]</sup> reported that *KCNQ1* is a tumor suppressor in human CRC, while recent findings from cystic fibrosis patients support the hypothesis that *CFTR* is also a human tumor suppressor<sup>[84]</sup>. These findings suggest that ion channel modulators may represent a new class of drugs for treating a subset of CRC patients.

Eventually, clinical trials using approved and experimental therapies are required. Once the panoply of driver genes has been defined, we will need to develop clinical lab diagnostics capable of determining the exact drivers of each individual patient's cancer based on tumor biopsies. Such information will allow physicians to select drugs and therapies specifically designed to target those drivers.

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