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REVIEW – CANCER RESEARCH

The application of *Apc*$^{Min/+}$ mouse model in colorectal tumor researches

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Abstract

Purpose *Apc*$^{Min/+}$ mouse is an excellent animal model bearing multiple intestinal neoplasia, used to simulate human familial adenomatous polyposis and colorectal tumors. The key point of this model is the mutation of *Apc* gene, which is a significant tumor-suppressor gene in the Wnt signaling pathway. There are also some other possible mechanisms responsible for the development of colorectal tumors in the *Apc*$^{Min/+}$ mouse model, such as tumor-associated signaling pathways activation, the changes of tumor-related genes, and the involvement of some related proteins or molecules.

Methods The relevant literatures about *Apc*$^{Min/+}$ mouse model from PUBMED databases are reviewed in this study.

Results In recent years, increasing studies have focused on the application of *Apc*$^{Min/+}$ mouse model in colorectal tumor, trying to find effective therapeutic targets for further use.

Conclusion This article will give a brief review on the related molecular mechanisms of the *Apc*$^{Min/+}$ mouse model and its application in colorectal tumor researches.

Keywords *Apc*$^{Min/+}$ · Animal models · Colorectal tumor · Molecular targets · Application

Introduction

Colorectal tumor is one of the most commonly diagnosed tumors, while its malignant lesion, colorectal cancer (CRC), ranks third in males and second in females, with approximately 1.4 million incidences and 693,900 deaths in the year of 2012 (Jemal et al. 2010; Torre et al. 2015; Ji et al. 2016). As is all known, the mutations of tumor-suppressor gene *Apc*, responsible for the familial adenomatous polyposis (FAP) syndrome with a precancerous lesion, almost always stand for the initial step in most colorectal tumor (Morin et al. 1997). If not treated properly, the probability of FAP patients developing sporadic colorectal cancer is 100%. Currently, animal models of all stripes, including mouse, rat, pig, zebrafish, drosophila and *C. elegans*, have been generated to study *Apc*'s functions in tumorigenesis and development as required. Among them, characterized by multiple intestinal neoplasia, *Apc*$^{Min/+}$ mouse has been recognized as an ideal model for FAP researches. Meanwhile, few evidences can deny that it brings great benefits as an experimental vector to explore the deep-seated mechanism of CRC. This article will give a brief review on the characteristics of the *Apc*$^{Min/+}$ mouse model and its application in colorectal tumor researches.

Establishment and genetic characteristics of *Apc*$^{Min/+}$ mouse model

Background of *Apc*$^{Min/+}$ mouse model

Apc$^{Min/+}$ mouse develops numerous adenomas and is the first successful animal model employed to study the *Apc* gene involved in multiple intestinal tumorigenesis (McCart

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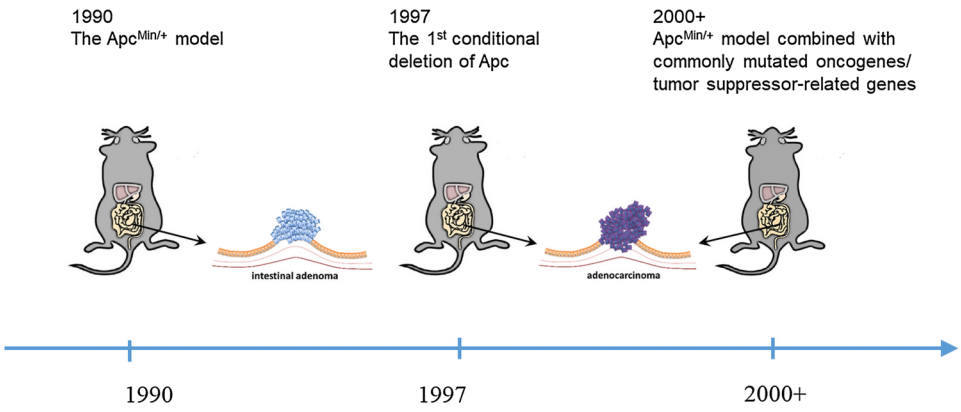

Fig. 1 Timeline of the development of $Apc^{Min/+}$ mouse models. Originally, $Apc^{Min/+}$ mouse, developed in 1990, recapitulates the disease observed in FAP patients. Later in 1997, the first conditional deletion of *Apc* performed in the colon led to colonic adenomas. To model more advanced diseases, the $Apc^{Min/+}$ model was combined with commonly mutated oncogenes or tumor suppressor-related genes (2000 onwards) (Jackstadt and Sansom 2016)

et al. 2008). The development of $Apc^{Min/+}$ mouse is briefly displayed in Fig. 1.

$Apc^{Min/+}$ mouse model was first established by Dove Lab of Wisconsin-Madison University (Moser et al. 1990). Initially, the researchers treated C57BL/6J male mice with the mutation agent ethylnitrosourea (ENU) and then hybridized it with the AKR/J female mice. They intriguingly found that some offspring were prone to intestinal tumors. Interestingly, further studies revealed that a non-sense mutation emerged in the 850th codon of one of the two chains in the *Apc* gene and finally formed a truncated protein. This kind of mouse model is, therefore, called multiple intestinal neoplasia (MIN) mouse or $Apc^{Min/+}$ mouse for it is prone to intestinal multiple adenomas. It is worth mentioning that the *Apc* mutant mouse specifically refers to C57BL/6K strain mouse that has a non-sense mutation (TTG to TAG) at the 850th codon of the *Apc* gene, while the other ones are not so called $Apc^{Min/+}$ mice (Westbrook et al. 2016). The studies of $Apc^{Min/+}$ mouse can further clarify the mechanism of colorectal cancer and provide ideas and methods for clinical propensity patients to prevent and treat colorectal tumors through prospective experiments (Fig. 2).

Genetic and phenotypic characteristics of $Apc^{Min/+}$ mouse model

The main genetic feature of $Apc^{Min/+}$ mice is the translocation of the 2549th base in the 850th codon occurs, and the leucine-encoding codon TTG converts to the stop codon TAG. As a result, the truncated proteins were produced to hobble *Apc* against its effective work. The intestinal tumors in $Apc^{Min/+}$ mouse are prone to loss of *Apc* heterozygosity, that is, the normal Apc^{+} is absent in the *Apc* allele, and only the Apc^{Min} band leaves. However, studies have shown that one tumor being developed derives not only from the loss of alleles of Apc^{+}, but also from other factors involved. $Apc^{Min/+}$ mice have a natural survival period ranging from 120 to 150 days and are often accompanied by characteristics of chronic anemia, manifested as increased reticulocytes and decreased red blood cell count, together with bloody stools, prolapse of the anus, splenomegaly, hyperlipidemia and other performances. In addition, some female mice can develop breast tumors (Sheng et al. 2008). Homozygous $Apc^{Min/+}$ mice are confronted with low survival and difficult reproduction. The mouse *Apc* gene is located on chromosome 18 and 90% homologous to the human *Apc* gene (Su et al. 1992). However, unlike humans, most tumor lesions in the mouse model are mainly distributed in the small intestine. Almost all tumors are benign adenomas at first. As the mice age, colon adenomas and adenocarcinomas can be observed in some older animals (Chandrakesan et al. 2017; Grill et al. 2015).

Possible reasons for the development of colorectal tumors in the $Apc^{Min/+}$ mouse model

$Apc^{Min/+}$ mouse model and tumor-associated signaling pathway activation

$Apc^{Min/+}$ mouse model and the Wnt signaling pathway

Commonly accepted, Wnt signaling is associated with tumor formation. Its activated mutations are principal genetic alterations in the premalignant lesions of the small intestine. Generally, *Apc* downregulates the Wnt signaling pathway by binding to β-catenin coupled with promoting its destruction (Liu et al. 2013a). In normal cells, the *Apc* gene degrades β-catenin, which is a key component of the Wnt signaling cascade and functions at the cell membrane to enhance intercellular adhesion (Wang et al. 2014). Deletion or mutation of the *Apc* gene makes β-catenin unable to be effectively degraded and accumulated, thereby resulting in abnormal activation of Wnt pathway in cells. Accumulated β-catenin in nucleus leads to transcription of some target oncogenes (Cheung et al. 2010; Hawkes and Alkan 2011). Meanwhile, studies have illustrated that mutations in one strand of the

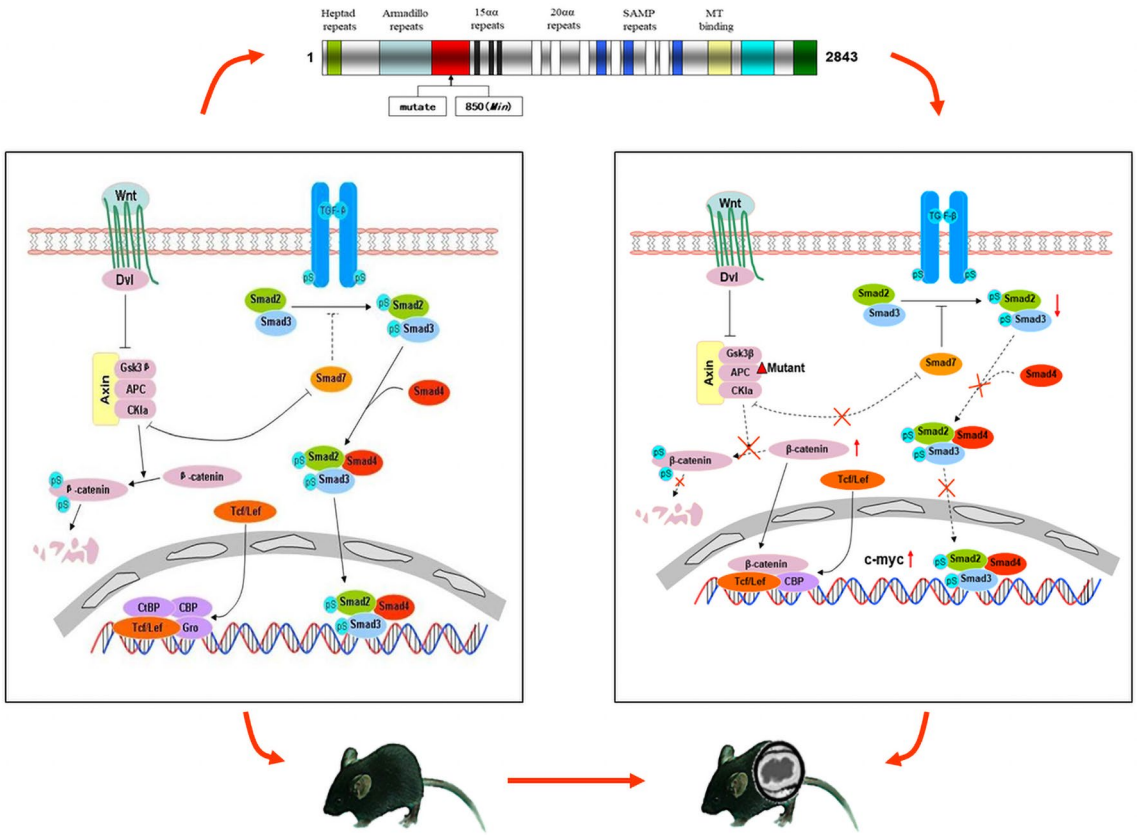

Fig. 2 *Apc* gene with Wnt signaling and TGF-β signaling pathways. As the *Apc* gene mutates at its 850th codon, the Wnt signaling pathway and the TGF-β signaling pathway are affected, eventually leading to an increase in tumor-associated genes such as *C-myc* in the downstream, which promotes the transformation of the mouse intestine from normal to adenoma and even adenocarcinoma

Apc gene are sufficient to affect the level of microtubule polarization, but not certainly cause dysregulation of the Wnt pathway, and may be necessary for the inactivation of both *Apc* alleles of the latter (Husoy et al. 2003).

$Apc^{Min/+}$ mouse model and the TGF-β signaling pathway

Loss of TGF-β signaling pathway is a common phenomenon during CRC progression. TGF-β pathway abrogation in CRC can generate through mutation of either TGF-β-receptor1 (TGFBR1) or TGFBR2 loss of heterozygosity (LOH) of chromosome 18q, where Smad2 and Smad4 are located, which are the two downstream mediators of TGF-β signaling pathway. In the mouse, *Apc* mutation in combination with inactivation of various components of TGF-β signaling (Tgfβr2, Smad2, Smad3 or Smad4) generally leads to the production of invasive adenocarcinoma, although apart from metastasis (Hamamoto et al. 2002; Munoz et al. 2006; Sodir et al. 2006; Takaku et al. 1998). Smad3 loss also alters tumor location in the $Apc^{Min/+}$ model, as more tumors arise in the distal colon. One of the postulated mechanisms for how the loss of TGF-β drives invasion, although it is required for processes such as EMT, is attributable to a protumorigenic microenvironment that mutations in the tumor bring about.

$Apc^{Min/+}$ mouse model and the NF-κB/COX-2 signaling pathway

Numerous studies have demonstrated that NF-κB/COX-2 signaling pathway plays an important role in the development of intestinal cancers. Among these, NF-κB/COX-2 interaction was reported to govern the stimulation of adenoma growth in intestinal polyps (Rao 2004; Yuan et al. 2008). NF-κB acts as 'first responder' of various types of cellular stress, induces COX-2 expression in response to cellular stress, and further stimulates Wnt signaling pathway. Finally, polyps expand and the tumorigenesis occurs. Increased COX-2 expression has been reported in intestinal tumors derived from human of multiple origins, and a

variety of animal models. All selective COX-2 inhibitors have the ability to narrow polyp frequency and size, which strongly highlights a causal role for COX-2 expression as a driver for FAP. While the reduction in intestinal tumor number and size in $Apc^{Min/+}$ mice (Chulada et al. 2000) with total COX-2 gene deletions provided conclusive proof that COX-2 expression, in some cell type(s), plays a pivotal role in tumor progression. Clearly, the causal role COX-2 expression has been recognized as an important role both in hereditary FAP patients with *Apc* gene mutated in the progression of intestinal cancer and in $Apc^{Min/+}$ mice (Cherukuri et al. 2014).

$Apc^{Min/+}$ mouse model and other signaling pathways

There are some other signaling pathways associated with $Apc^{Min/+}$ mouse model that contribute to the development of intestinal tumors as reported. Previous works showed that the inhibition of Delta-like 4/Notch signaling can repress tumor growth (Lopez-Arribillaga et al. 2015; Van Dussen et al. 2012; Zhao et al. 2011; Folkman 1990). Recently, the study by Badenes et al. determined the idea that Dll4/Notch signaling induced $Apc^{Min/+}$ tumor initiation through angiogenic and non-angiogenic dependent mechanisms (Badenes et al. 2017). The RP-MDM2-*p53* pathway has been shown to be important in preventing *C-myc*-induced lymphomagenesis (Macias et al. 2010), while another research unearthed that the RP-MDM2-*p53* pathway is a critical mediator of colorectal tumorigenesis with the loss of *Apc* gene (Liu et al. 2017). In addition, according to the result of Tippin, prostaglandin D2 signaling mediated by prostaglandin D_2 receptor (PTGDR) can suppress intestinal tumors in the mice of $Apc^{Min/+}$ (Tippin et al. 2014).

$Apc^{Min/+}$ mouse model and the alteration of tumor-related genes

$Apc^{Min/+}$ mouse model and low expression or inactivation of tumor suppressor genes

Normally, some genes are considered as a significant targets or suppressor in colorectal tumorigenesis, when they are with a low expression or inactivation in the tumor cells. Applied firstly in 1979 (DeLeo et al. 1979; Kress et al. 1979; Lane and Crawford 1979; Linzer and Levine 1979; Melero et al. 1979; Smith et al. 1979), the tumor suppressor *p53*, frequently mutated in many human cancers (Hollstein et al. 1991), has been broadly identified as an essential for the core functions of tumor suppression, such as cell cycle arresting, apoptosis, DNA repairing, and anti-angiogenesis (Menendez et al. 2009). Recently, the mitochondria-eating protein (Mieap) was identified as a *p53*-inducible protein. In a study of Mieap-deficient $Apc^{Min/+}$ mice, Nakamura and Arakawa discovered that tumor suppressor *p53* freshly controls Mieap-regulated mitochondrial quality, which is critical in tumor suppression (Nakamura and Arakawa 2017; Tsuneki et al. 2015). Mouse models of myeloid line-age-specific *p53* deletion or activation have been established, to unveil that the level of *p53* is correlated with the levels of inflammatory mediators in $Apc^{Min/+}$ mice and is more resistant to the development and invasion of colorectal tumors initiated by *Apc* mutations or carcinogens and promoted by colitis (He et al. 2015). Other than this, genetic disruption of β-catenin target gene immunoglobulin transcription factor 2 (*Itf2*) (Kolligs et al. 2002) on the $Apc^{Min/+}$ background has been reported to result in earlier death and a significant increase in tumor number and size in the small intestine. Based on these data, *Itf2* acts as a tumor suppressor gene of the intestinal tract that inhibits tumor initiation and growth (Grill et al. 2015). Meanwhile, as is proven that *Cables1* is an another tumor suppressor gene which located on chromosome 18q in $Apc^{Min/+}$ mouse model. After establishing a hybridization model between $Apc^{Min/+}$ mouse and the mouse with inactivation of the tumor suppressor gene *Cables1*, researchers concluded that the *Cables1* gene could exert in all probability a tumor suppressive effect in human colon cancer (Arnason et al. 2013).

$Apc^{Min/+}$ mouse model and tumor suppressor gene methylation or mismatch repair gene defect

Several studies have pointed out that the tumor suppressor gene CpG-island hyper-methylation, which leads to its inactivation and transcription inhibition, is one of the important causes of tumorigenesis (Sansom et al. 2003; Zhang and Wu 2006). The methyltransferase *Dnmt1* is an essential gene involved in methylation, whose increased expression may promote the methylation of the tumor suppressor gene. A study relating to $Apc^{Min/+}$ mouse model reported that reduction of methylated CpG islands caused by *Dnmt1* deficiency could suppress intestinal polyp formation (Eads et al. 2002).

Mismatch repair (MMR) gene defection has been confirmed as another important reason in colorectal tumorigenesis. Data from Lai and Cheng showed that microsatellite instability caused by defects in the mismatch repair gene could be demonstrated even at the early stage of CRC, and adenoma stage (Cheng et al. 2004). Basically, one of the major mismatch repair genes associated with CRC is *Msh2*. A study from Sohn group unveiled that the defect of the mismatch repair gene *Msh2* in $Apc^{Min/+}$ mouse can enhance the mutation of *Apc* gene and *p53* gene to generate the inactivation of tumor suppressor genes, thereby inducing a large number of intestinal tumors (Sohn et al. 2003).

Apc$^{Min/+}$ mouse model and tumor-promoting genes

Numerous studies generally confirm that overexpression of some genes is closely related to the poor prognosis of CRC and conversely the inhibition of these genes can reduce the incidence. For example, the high expressions of β-catenin and COX-2 were reported to promote tumorigenesis, while their selective inhibitors showed an opposite effect, that is, hobble intestinal tumors in *Apc*$^{Min/+}$ mouse model (Jacoby et al. 2000; Mohammed et al. 2011). These phenomena were attributable to the main mechanisms related to their relevant signaling pathways. Back to the clinic, it is well believed that multidrug resistance (MDR) of tumor cells is one of the key contributors in the failure of cancer chemotherapy. Replacing the *Mdr1* gene in the mouse model of *Apc*$^{Min/+}$ to achieve defect of *Mdr1*, the polypogenesis was significantly decreased in the new mouse model (Yamada et al. 2003). In addition, *Mdr1* is considered as one of the principal targets that Wnt pathway regulates and its expression increased by that pathway contributes to the development of tumor.

Apc$^{Min/+}$ mouse model and other related genes

During the development of multiple intestinal polyps or CRC in *Apc*$^{Min/+}$ model mouse, other related genes include and are directly involved in or indirectly affecting this process. Autophagy-related gene-5 (*Atg5*), an essential gene in autophagy, is lost in 23% of the patients with CRC (An et al. 2011). Recently, a study by *Apc*$^{Min/+}$ mouse model showed that heterozygous deletion of *Atg5* promotes intestinal adenoma growth and enhances the antitumor efficacy of interferon-gamma (Wang et al. 2015). For example, decreased expression of *EphB* gene can accelerate the development of intestinal tumor in mouse models (Batlle et al. 2005). And trefoil factor family 2 (*Tff2*) gene is a novel important factor capable of enlarging intestinal tumor size in *Apc*$^{Min/+}$ model mouse (Fujimoto et al. 2015). Other than that, after establishing a kind of hybridization model between *Apc*$^{Min/+}$ mice and *Mac-1* deletion mice, scholars pointed out that the loss of integrin *Mac-1* gene may inhibit the growth of adenomas in *Apc*$^{Min/+}$ mice and may be related to lipid metabolism (Zoller et al. 1996; McNally et al. 2006).

Altogether, the tumor-related genes in *Apc*$^{Min/+}$ mouse model as reported are summarized in Table 1.

The role of proteins in *Apc*$^{Min/+}$ mouse model

Generally, multifarious proteins are involved in the process of tumor development in *Apc*$^{Min/+}$ model mice. Numerous reports confirm that epidermal growth factor receptor (EGFR) deficiency can inhibit the occurrence of colorectal tumors and treatment with EGFR tyrosine kinase inhibitors inhibits intestinal tumor growth in *Apc*$^{Min/+}$ mice (Goodlad et al. 2006). Meanwhile, prostaglandin D2 receptor

Table 1 Summary of tumor-related genes studied with *Apc*$^{Min/+}$ mouse model

Gene	Types	Comments	References
p53	Tumor suppressor gene	Cell cycle arresting, apoptosis, DNA repairing, and anti-angiogenesis, mitochondrial quality control	He et al. (2015); Nakamura and Arakawa (2017); Tsuneki et al. (2015)
Itf	Tumor suppressor gene	β-catenin target gene, tumor initiation and growth with its disruption	Grill et al. (2015); Kolligs et al. (2002)
Cables1	Tumor suppressor gene	Inactivation of *Cables1* results in activation of the Wnt signaling pathway	Arnason et al. (2013)
CpG-island	Tumor suppressor gene	Its hyper-methylation leads to tumor suppressor gene inactivation and transcription inhibition	Eads et al. (2002); Sansom et al. (2003); Zhang and Wu (2006)
Msh2	Mismatch repair gene	Enhance the mutation of *Apc* gene and *p53* gene, resulting in inactivation of tumor suppressor genes	Sohn et al. (2003)
Mdr1	Multidrug resistance gene	Important targets for the regulation of Wnt pathway, leading to failure of cancer chemotherapy, promoting the development of tumor	Yamada et al. (2003)
Atg5	Autophagy related gene	Lost in 23% of the patients with CRC, its heterozygous deletion promotes intestinal adenoma growth	An et al. (2011); Wang et al. (2015)
Tff2	Trefoil factor family gene	A novel important factor stably expressed in gastrointestinal mucosa to enlarge intestinal tumor size	Fujimoto et al. (2015)
Mac-1	Integrin gene	Inhibit the growth of adenomas through lipid metabolism	Fujimoto et al. (2015); McNally et al. (2006); Zoller et al. (1996)
EphB	Others	Accelerate intestinal tumor production	Batlle et al. (2005)

(PTGDR) can mediate PGD2 inhibition in intestinal tumors in mouse models (Tippin et al. 2014). As a member of the selectin family of cell adhesion molecules, P-selectin (CD62P) has been reported to play an important role in tumor growth and metastasis (Kim et al. 1998; Nash et al. 2002; Smyth et al. 2009; Varki and Varki 2002). By virtue of spontaneous intestinal tumor mouse models, researchers determined that the deletion of P-selectin suppressed intestinal tumor growth (Qi et al. 2015). In addition, the inhibitor of DNA-binding/differentiation (ID) proteins has been identified to regulate normal cell fate determination, proliferation and differentiation (Ruzinova and Benezra 2003). ID1 is overexpressed in numerous malignancies including CRC and modulates tumor cell behavior (Gumireddy et al. 2014; Norton 2000; Sikder et al. 2003). In the analysis of ID1 in $Apc^{Min/+}$ mouse models, Zhang et al. found that its deficiency played a significant reduction in the number of colorectal tumors in $Apc^{Min/+}$ mice and prolonged survival (Zhang et al. 2015). Olfactomedin 4 (OLFM4, also known as hGC-1 and GW112) is an evolutionarily conserved glycoprotein that belongs to the olfactomedin family (Zhang et al. 2002). It affects a diverse set of cellular processes, including proliferation, differentiation, apoptosis, adhesion and innate immunity against bacterial infections (Liu et al. 2006, 2010, 2012, 2013b). According to a latest study of $Apc^{Min/+}$ mice, systematic deletion of OLFM4 promoted colorectal tumorigenesis, conveying the view that OLFM4 could be used as a potential therapeutic target for malignant intestinal tumors (Liu et al. 2016). According to some researches, the status of some enzymes in colorectal polyps and tumors is also verified by the classical $Apc^{Min/+}$ mouse models. For example, DCLK1 (Doublecortin-like kinase 1), Wip1 (Wild-type P53-induced phosphatase 1), and SIRT1 can promote tumor growth (Chandrakesan et al. 2017; Leko et al. 2013; Suman et al. 2014), while PHLPP1 exerts an opposite effect on tumors (Li et al. 2014).

$Apc^{Min/+}$ mouse model and other related factors

In addition to the above factors, there are other factors inseparable according to the $Apc^{Min/+}$ model study, such as stem cells, inflammatory cells and factors, and parasites. In *Apc*-deficient mice, inactivation of the *Apc* gene in intestinal stem cells causes abnormal Wnt signaling to activate downstream tumor-associated target genes, as described above, and further promotes intestinal stem cell-derived tumorigenesis (Barker et al. 2009; Tabrizian et al. 2017). Studies have found that in *Lgr5*-positive intestinal stem cells, the homeostatic conditions of the intestinal epithelium are damaged by inhibiting normal Wnt signaling, and tumor initiation is drove (Gregorieff et al. 2015; Yamamoto et al. 2003). It has conclusively been shown that IL-17A controls the ability of Treg (a functional thymus T cell) to inhibit intestinal tumorigenesis in $Apc^{Min/+}$ mice (Chae and Bothwell 2015). IL-17F deficiency inhibits small intestinal tumorigenesis in $Apc^{Min/+}$ mice (Chae and Bothwell 2011), while IL-6 may be responsible for obesity-related colorectal tumorigenesis (Yaoita et al. 2015). There is a relatively small body of literatures that emphasis that platelet adherent to tumor cells can promote tumor growth and metastasis (Qi et al. 2015), and platelet-activating factor (PAF) is a proinflammatory phospholipid that plays important roles in the control of immune cell functions (Wang and Chakrabarty 2003). Study from Xu et al. pointed out that PAF has bidirectional regulation of tumors, but suggests an anti-tumorigenic role in settings characterized by aberrant function of the tumor suppressor *Apc* (Xu et al. 2013). In addition, an interesting study showed that intestinal nematodes *T. muris* infection can be obviously conductive to tumor formation in a colon cancer model (Hayes et al. 2017).

Application of $Apc^{Min/+}$ mouse model in the prevention and treatment of colorectal tumors

Applications of $Apc^{Min/+}$ mouse model in chemical and drug prevention of colorectal tumors

Undoubtedly, the birth of $Apc^{Min/+}$ mouse model provides a reliable tool for humans to study prevention and treatment of FAP and CRC. And at present, mounting reports focus on its chemical and drug prevention. Being a component of the gum resin of Boswellia serrate, Acetyl-11-keto-beta-BA (AKBA) may exert its chemopreventive action through multiple mechanisms (Liu et al. 2013a). Besides that, the activity of AKBA is more effective than that of aspirin in the prevention of small intestinal and colonic polyps (Wang et al. 2014). And the combination of sulindac and atorvastatin significantly constrained microadenomas and tumors in model mice (Chang et al. 2018) while repletion of retinoic acid (RA) could reduce tumorigenesis in FAP patients (Penny et al. 2016). Resveratrol is a naturally occurring stilbenoid and has diverse biologic properties including anticarcinogenic, antioxidant, anti-inflammatory, anti-mutagenic, proapoptotic, and immuno-regulatory activities (Szekeres et al. 2011). Existing research recognizes that resveratrol mediates anti-inflammatory properties and suppresses intestinal tumorigenesis through miRNA modulation, potentially revealing an effective chemoprevention strategy (Huderson et al. 2013; Altamemi et al. 2014). As is known, glucocorticoids (GCs) are widely accepted as the most potent, endogenous, specific COX-2 inhibitors (Clark and Lasa 2003; Newton

Table 2 Measures used to prevent or treat colorectal tumors with $Apc^{Min/+}$ mouse model

Project	Measure type	Comments	References
AKBA	Chemical and drug prevention	A derivative of boswellic acid, modulates the Wnt signaling pathway, and functions as anti-proliferation, apoptosis induction, anti-inflammation and anti-angiogenesis	Liu et al. (2013a); Wang et al. (2014)
Sulindac and atorvastatin	Chemical and drug prevention	The combination of nonsteroidal anti-inflammatory drugs (NSAID) and statins can inhibit microadenomas and adenocarcinomas by suppressing some signaling pathways	Chang et al. (2018)
RA	Chemical and drug prevention	Plays a critical role in cell differentiation, maintaining immune homeostasis in the intestine and reducing tumorigenesis	Penny et al. (2016)
Resveratrol	Chemical and drug prevention	A kind of polyphenol which has anti-inflammatory, antioxidant, anti-allergy, and anti-cancer properties and suppresses intestinal tumorigenesis through miRNA modulation	Huderson et al. (2013); Szekeres et al. (2011); Altamemi et al. (2014)
GCs	Chemical and drug prevention	Potent, endogenous, specific COX-2 inhibitors	Zhang et al. (1999); Newton (2000); Clark and Lasa (2003); Benbrook et al. (2013)
Denervation	Surgical prevention	Interrupted vagal innervation inhibits tumor growth	Jin et al. (2017)
Cranberry, black raspberry, blueberry dietary fiber	Dietary prevention	Affect the colon polyps and CRC mainly by regulating intestinal flora	Jeyabalan et al. (2014; Kostic et al. (2013); Ray (2011); Sancho et al. (2016); Pan et al. (2015)
Aerobic exercise	Exercise prevention	May reduce the progression of CRC by immunomodulation or other way, and the mechanism is not yet clear	McClellan et al. (2014)

2000; Zhang et al. 1999). Possibly, uplifting the activity of GCs realizes to inhibit tumor growth and, therefore, achieve chemoprevention against CRC. Other than above, data from several research findings have demonstrated that SHetA2 by virtue of modulating biomarkers in colon polyps prevents colon and small intestinal tumorigenesis and identifies potential pharmacodynamic endpoints for its clinical trials (Benbrook et al. 2013).

Application of *Apc*$^{Min/+}$ mouse model in other measures for colorectal tumors prevention

Apart from chemical and drug prevention, there is a growing body of views and findings to outline additional methods for prevention and treatment, such as surgery, exercise and diet. In the aspect of surgery, clinical scholars concluded that extrinsic innervation of the small bowel was likely to modulate tumor development in *Apc*$^{Min/+}$ mouse. Interrupted vagal innervation, but not sympathetic denervation, seems to inhibit tumor growth (Liu et al. 2015). In terms of diet, more and more people think that dietary ingredients are linked to the prevention of CRC. Cranberry (Jin et al. 2017), black raspberry (Pan et al. 2015), blueberry (Jeyabalan et al. 2014) and certain dietary fiber (Sancho et al. 2016) have been identified to show certain preventive effects on tumor growth of *Apc*$^{Min/+}$ model mice. However, different diets on *Apc*$^{Min/+}$ model mice do not work necessarily the same. Most researchers substantiate the belief that diet can affect the colon polyps and CRC by regulating intestinal flora (Ray 2011; Kostic et al. 2013). Meanwhile, as exercise of kinds, the newest study shows that aerobic exercise can reduce the progression of colon tumors in mice of *Apc*$^{Min/+}$ by immunomodulation (McClellan et al. 2014; Hamasaki 2017). This conclusion undoubtedly gives a new insight into the clinical prevention of CRC. We believe that similar methods will continuously emerge to further power the basis for the clinical application.

All the applications of *Apc*$^{Min/+}$ mouse model in the prevention and treatment of colorectal tumors, as stated above, are summarized and listed in Table 2.

Discussions

As the mouse model of *Apc*$^{Min/+}$ becomes grown in sophistication, mounting valuable researches concentrate on the mechanisms concerned with the development of colorectal tumors from novel perspectives of kinds. As a result, the applications of *Apc*$^{Min/+}$ model for preventing and treating colorectal tumors have advanced most, among which are mainly chemical and pharmaceutical preventive measures. However, there are little published data on those primitive effective measures, such as dietary and aerobic exercise. Intriguingly, the current research frontier suggests that the intestinal flora plays an important part in the occurrence and development of colon polyps and colorectal tumors (Hale et al. 2017). We consider whether it is possible to find out the influences of diet or aerobic exercise on the intestinal flora and furthermore to explore its effects on colorectal diseases. Considering all of these evidences, we believe that applications of *Apc*$^{Min/+}$ mouse model in more broad fields will finally come. In summary, the *Apc*$^{Min/+}$ mouse model could help us to have a better understanding about the potential mechanisms in the course of tumor development, contributing to its further application in the prevention and treatment of colorectal cancer.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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