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Therapeutic Targets in Colorectal Cancer

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1. Introduction

Colon cancer is common worldwide: nearly a million people develop the disease every year and in the United States, colorectal cancer ranks third for frequency of occurrence and mortality in both men and women, with projected estimates for 2011 for occurrence and mortality put respectively at approximately 140,000 and 49,000 (American Cancer Society, 2011; Jemal et al, 2005). The projection for total deaths from all cancers in 2010 was 569,490 (Aliperti et al, 2011).

Significant progress in understanding colon cancer has produced a wealth of information that has aided improvements in aspects of diagnosis and disease management, contributing in the process to reduced mortality rates. The mechanisms that facilitate colorectal carcinogenesis and sustain progression and metastatic spread have been extensively investigated. The cause of colorectal cancer is multi-factorial. Notwithstanding the various contributing elements to the disease, the primary manifestation of colorectal carcinoma is the relentless and uncontrolled proliferation of cells and tissues in the intestinal mucosal epithelium. This pattern of abnormal proliferation is a disruption of the normal balance between new cell production by the epithelial cells in the mucosal crypts, and the release and loss of epithelial cells into the intestinal lumen i.e. cell-producing proliferation is normally finely and properly counter-balanced by regulated apoptotic and physical cell loss (Raz, 2002).

Given the multistep, multifactor origins of colorectal cancer, the rationale for targeted therapies and the identification of therapeutic targets is that the disease can be (a) prevented prior to initiation (b) obstructed in its progression by blocking or inhibiting mechanisms that sustain progression and facilitate metastasis (c) reversed. The list of potential targets include microbes and bacteria that facilitate tumor initiation, molecular targets such as adenomatous polyposis coli (APC), and cancer stem cells (CSCs) where targeted destruction is thought to be central to preventing metastatic tumor spread.

As with all cancers, finding and delivering therapeutic targets in colorectal cancer is based on the premise that there is one originating cell type (van der Flier & Clevers, 2009). If this population of mutant originating cells is eliminated, the ability for new initiation, progression and distant seeding of tumor cells should be impaired and eventually abolished. Several therapeutic approaches have shown promising results in experimental

studies. However, this chapter will focus largely on molecular targets in Wnt signaling, the nuclear receptor peroxisome proliferator-activated receptor (PPAR), and cancer stem cells (also known as cancer initiating cells).

2. Colonic epithelial cell renewal

The colon is the distal part of the intestinal tract and is lined internally by a simple layer of columnar epithelial cells (colonocytes) that send tube-like extensions called crypts into the mucosal layer of the intestinal wall. The crypts provide a conducive environment for the regulation and renewal of the epithelial covering of the colonic mucosa.

The epithelial cells in the crypt divide continuously and rapidly, achieving a turnover rate of epithelial renewal of between 5-6 days in mammals, with much shorter cell kinetic data reported for rodents (Di Garbo et al, 2010; Hall et al, 1994; Heath, 1996; Giles et al, 2003; Li et al, 1994; Loeffler et al, 1986; Potten & Loeffler, 1990; Okamoto & Watanabe, 2004; Wright & Alison, 1984). In the small intestine, between 8-9 cells are produced by each crypt epithelium every hour in mice; 2-3 dividing cells per crypt support cell production in the proximal intestine while up to 5 dividing cells are required to maintain cell production in the distal intestine (McGarvey et al, 2007a, 2007b). The renewal mechanism is sustained by a hierarchical arrangement of epithelial cells within the crypts, exemplified by the model described by Tomlinson and Bodmer (1995), with stem cells thought to reside in the lower part of the crypts, while differentiated cells populate the upper part of the crypt. By dividing and supplying transit (semi-differentiated) cells that migrate up the crypts, the stem cells are capable of and responsible for producing the various cell types that are found in the colonic epithelium. Differentiated cells at the top of the crypt and colonic mucosal surface eventually undergo spontaneous apoptosis and are released into the intestinal lumen (Fig 1).

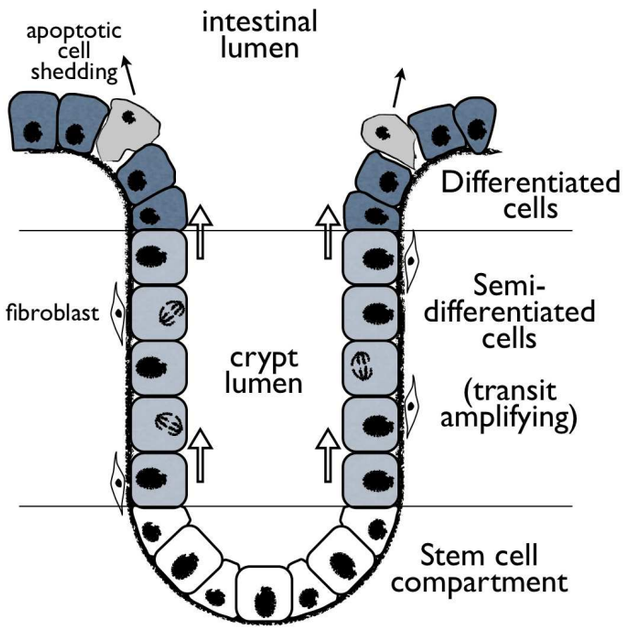

Fig. 1. Schematic diagram of colonic crypt, illustrating the three zones and cell categories that constitute the kinetic framework for cell production and regeneration.

The maintenance of functional and structural integrity and viability of the enteric mucosal epithelium depends on the preservation of the crypt cell renewing and emigration mechanisms for repopulating the continuously shedding epithelial cell cover (McGarvey et al, 2007a, 2007b). Several models for investigating the dynamics of colon cell regulation have been described (Boman et al, 2001; Hardy & Stark, 2002; Lander, 2009; Michor et al, 2004; Paulus et al, 1992; van Leeuwen et al, 2006; Wodarz, 2007). Many of these models have been employed in studies of the mechanisms that underlie normal colonic epithelial cell regulation and regeneration, as well as the dysregulated proliferation in colorectal cancer.

3. Apoptosis

All of the new cells that are produced by proliferation of the cells in the stem cell compartment of the crypt, and numerically amplified in the semi-differentiated compartment, are distributed to the colonic mucosal epithelium to provide functionally important roles in absorption and secretion as well as providing a selectively permeable surface cover (Hall et al, 1994). The supply of new cells towards the upper crypt and surface epithelium is designed to satisfy the losses caused by cell injury, loss and programmed death (apoptosis). Surface cover cells are therefore removed or shed by processes that are as controlled and as balanced as the crypt-mediated cell renewal mechanism, and involves a cessation of proliferative processes in conjunction with the initiation of disposal and cell loss pathways (Leblond, 1964; Wright & Alison, 1984; Hall et al, 1994). Because the enteric epithelium is associated with underlying connective tissue fibroblasts, the accompanying fluxes in these cells are also correspondingly regulated in a controlled manner for proliferation and for cell loss (Marsh & Trier, 1974a, 1974b; Parker et al, 1974; Pascal et al, 1968a, 1968b). Together, the careful balance of cell production and cell loss maintains homeostasis in the colonic epithelium. Apoptosis does not occur randomly, rather it is seen towards the distal end of the cell migration route up the crypt (Hall et al, 1994). In colon cancer, proliferation is elevated and apoptosis is dysregulated, making the restoration of apoptosis an attractive proposition for therapeutic control of colon cancer growth (Evan & Vousden, 2001, Johnstone et al, 2002).

A number of cyclooxygenase (COX) inhibitors induce apoptosis by activating mechanisms that are either upstream (via the lipid metabolite 13-S-hydroxyoctadecadienoic acid) or downstream (via 14-3-3ε proteins) of the nuclear hormone receptor PPAR∂ (Liou et al, 2007; Shureiqi et al, 2003), indicating that the pro-apoptotic effect of COX inhibitors on cancer cells is dependent on down-regulation of PPAR∂. In APC min mice, short-term treatment with nitric-oxide-donating aspirin (NO-ASA) induces apoptosis in differentiated intestinal epithelial cells while prolonged treatment with sulindac reverses the anti-apoptotic effect of APC (Mahmoud et al, 1998; Ouyang et al, 2006). In contrast, celecoxib administration produces no effect on apoptosis (Williams et al, 2000).

Other agents that have been shown to reduce colorectal cancer growth in vitro include CDDO-Me, an oleanane synthetic triterpenoid that achieves its apoptotic effect partly through the generation of reactive oxygen (ROS) and the activation of procaspases (Gao et al, 2011), green tea polyphenols that achieve their apoptotic effect through the induction of caspases (Oz & Ebersole, 2010), and tocotrienol, a member of the vitamin E family of compounds that induces morphological changes similar to apoptosis (paraptosis) and an accompanying reduction in Wnt signaling and its down-stream genes (Zhang et al, 2011).

4. Wnt and colorectal cancer

One of the primary regulators of epithelial cell proliferation is Wnt signaling (Di Garbo et al, 2010). This signaling pathway involves the intermediate elements beta catenin, glycogen synthase kinase 3 beta (GSK3β), casein kinase I (CKI), axin, adenomatous polyposis coli (APC) and T-cell factor/lymphoid enhancer factor (TCF/LEF). Inappropriate activation or disruption of Wnt signaling upsets the careful regulatory balance in epithelial kinetics, leads to disorderly proliferation, and is an important contributor to the process of colorectal carcinogenesis. Wnt signaling helps to control the levels of cytoplasmic beta catenin, between pools bound to APC and to the cell adhesion molecule E-cadherin. The APC-bound pool of beta catenin is held in a stable complex of axin, GSK3β, CKI and APC that serves to regulate its cytoplasmic levels via targeted ubiquitin-mediated proteasomal degradation (Kikuchi et al, 2003; Pinto & Clevers, 2005). Wnt ligand signaling via membrane receptor proteins triggers a cascade that alters the relationship between the scaffold protein axin and GSK3β, interrupts regulated destruction of beta catenin, and leads to accumulation of non-phosphorylated beta catenin in the cytoplasm that then reaches the nucleus. Translocation of beta catenin into the nucleus after binding with TCF/LEF leads to the activation of target genes that regulate proliferation, differentiation and apoptosis (Araki et al, 2003; Coghlan et al, 2000; DiGarbo et al, 2010; Fagotto et al, 1998; He et al, 1998; Kishida et al, 1999; Shtutman et al, 1999; Tetsu & McCormick, 1999; van der Flier & Clevers, 2009; Yamamoto et al, 1999; Yanagawa et al, 1995; Yost et al, 1996). Direct binding of TCF to regulatory elements in downstream genes have aided identification of target genes and suggest that Wnt-activated gene expression shows a gradient-wise concentration of activity in intestinal crypts with the highest expression in the bottom of the crypt (Gregorieff et al, 2005). Most of these target genes are expressed in normal crypts and in adenomas (van der Flier et al, 2007; van der Wetering et al, 2002).

5. Wnt and COX inhibition

Colon cancer is associated with dysregulation and overexpression of COX, a key enzyme in the biosynthetic conversion of arachidonic acid to eicosanoids (Botting, 2006). Increased levels of expression of COX-2 are seen in up to 85% of colorectal adenomas and carcinomas (Eberhart et al, 1994; Fujita et al, 1998; Rigas et al, 1993; Sheng et al, 1997).

COX inhibitors demonstrate an ability to disrupt proliferation in several CRC cell lines. In HT29 colorectal adenoma cell lines, suppression of proliferation is evident as early as 48 hours after treatment with naproxen and piroxicam and at later timepoints with aspirin, indomethacin, aspirin and NS398 (Shiff et al, 1996; Shureiqi et al, 2000). But in some studies, naproxen and salicylic acid showed no effect on proliferation in the same cell lines pointing to differing potencies for inhibition of COX as well as effects on growth and apoptosis (Piazza et al, 1997). Although anti-proliferative effects have been reported in studies using HCA7, HT115 and SW620 cell lines which all express COX, the non-COX expressing cell line HT116 also shows reduced growth when treated with celecoxib for 72 hours (Shureiqi et al, 2003). Most of the evidence allows the conclusion that the anti-proliferative effects of COX inhibitors on colon cancer cell lines are not related to COX expression or activity.

When COX inhibitors are administered to APC min mice, initiation and progression of intestinal and colonic polyps is inhibited and polyp load is reduced (Jacoby et al, 1996, 2000; Kohno et al, 2005; Mahmoud et al, 1998, Moorghen et al, 1988, 1998; Narisawa et al, 1983;

Rao et al, 1995, 2009; Reddy et al, 1993). Prevention of tumorigenesis or tumor load reduction reflects either decreased cell proliferation or increased cell death but findings from animal studies are inconsistent (Table 1). For example, celecoxib treatment reduces tumor numbers and inhibits cell proliferation but data from studies using various sulindac preparations point to a variability that may be rodent species dependent (Jacoby et al, 2000; Mahmoud et al, 1998; Moorghen et al, 1988, 1998; Rao et al 1995, 2009).

Model	Inhibitor	Dose & duration (wks)		Inhibition effect	Reference
APC					
mouse	sulindac	160ppm	10	none	*Shiff et al 1996*
mouse	sulindac S_2	20mg/kg	11	none	*Swamy et al 2006*
mouse	celecoxib	1500ppm	6	tumor number	*Han et al 2008*
DMH					
mouse	sulindac	5mg/kg	24	tumorigenesis	*Shureiqi et al 2000*
mouse	sulindac	5mg/kg	18	n/a	*Kim et al 2009*
AOM					
mouse	nimesulide	0.04%w/w	14	n/a	*Shureiqi et al 2003*
rat	celecoxib	300ppm	46	n/a	*Guo et al 2009*
rat	aspirin	200-400ppm	52	tumorigenesis	*Piazza et al 1997*
NMNU					
rat	indomethacin	10ppm	1-30	tumorigenesis	*Hanif et al 1996*

Table 1. Effect of COX inhibitors on initiation and progression of experimental colon cancer in vivo. S_2 = sulfide, NMNU = n-methyl-N-nitrosourea, AOM = azoxymethane, DMH = 1,2-dimethylhydrazine, APC = adenomatous polyposis coli, n/a = not measured

Some of the inconsistency in findings from animal studies is reflected in the results from clinical investigations in patients. Treatment with aspirin and celecoxib shows beneficial prevention of colorectal cancer in patients, and treatment with 150mg sulindac twice daily for nine months reduces number and size of colorectal adenomas. However, treatment with standard sulindac doses (25-150 mg twice daily) for 48 months did not prevent adenomas in patients (Giardiello et al, 1993, 2002; Giovannucci et al, 1994; Lanas & Fernandez, 2009; Thun et al, 1991).

6. PPAR and COX inhibition

Peroxisome proliferator-activated receptors (PPAR) are part of the nuclear hormone receptor superfamily. While PPARα and PPARγ have been shown to be involved in various aspects of dietary lipid and glucose metabolism, PPAR∂ is implicated in the control of cell proliferation, differentiation and colorectal carcinogenesis (Desvergne & Wahil, 1999; Michalik et al, 2003; Wang & Dubois, 2010). Ligand activation of PPAR∂ is associated with suppressed induction of colon cancer (genetic and chemical treatment models) in mice via mechanisms that are linked to colonocyte differentiation and apoptosis (Harman et al, 2004;

Marin et al, 2006). Conversely, inactivation of PPAR∂ in APC-min mice enhances predisposition to multiple intestinal and colorectal polyps (Harman et al, 2004; Reed et al, 2004). Such evidence suggests that PPAR∂ attenuates colon cancer. However, Park and colleagues found a reduction in the ability of PPAR∂-/-(null) cells to form tumors in nude mice and they concluded that PPAR∂ might function to assist the tumor-suppressing function of adenomatous polyposis coli (APC) protein (Park et al, 2001).

Despite significant insights into the role of PPAR∂ in colorectal cancer, the physiological role of PPAR∂ in epithelia is still not completely understood. The unresolved nature of the available data has not prevented studies that have explored the possibility of targeting PPAR∂ therapeutically in colorectal cancer. Prostacyclin I_2 can act as a natural ligand for PPAR∂ (Gupta et al, 2000), and because COX-2 inhibitors can suppress carcinogenesis and reduce intestinal polyposis (Hollingshead et al, 2008; Jacoby et al, 1996; Mahmoud et al, 1998), a number of studies examined the use of COX inhibtion to influence PPAR∂ activity. Sulindac and indomethacin inhibit colorectal carcinogenesis in vitro by rapidly downregulating transcriptional activity of PPAR∂ via disruption of DNA binding to PPAR∂-response elements (He et al, 1999). A similar effect on PPAR∂ is also observed following administration of sulindac and celecoxib but this is preceded by induction of the enzyme 15-lipoxygenase-1 (Shureiqi et al, 2003). Administration of nitric-oxide-donating aspirin reduces PPAR∂ expression and intestinal polyp numbers in mice but neither nimesulide nor GW0742 (a PPAR∂ ligand) has an effect on PPAR∂ mRNA levels, despite the fact that both agents reduce intestinal polyp numbers (Gupta et al, 2004; Hollingshead et al, 2008; Kohno et al, 2005).

COX-2 inhibitors and PPAR∂ ligands can separately attenuate cancer growth, however combinatorial protocols have so far failed to produce potentiated inhibition of colon cancer indicating that COX-inhibitory and PPAR∂ pathways are mechanistically separate (Hollingshead et al, 2008). In addition, concurrent expression of PPAR∂ and COX-2 in colorectal tumors has poor prognostic implications for patients (Yoshinaga et al, 2011).

Ligand activation of PPARγ is also anti-neoplastic in several tissues, but the data regarding its role in colorectal cancer is just as conflicting as the data for PPAR∂. PPARγ activation inhibits colon cancer cell growth in vitro whereas a mutation-dependent pro-tumorigenic effect has been reported in vivo (Girnun et al, 2002; Yoshizumi et al, 2004). The mechanistically interrelated and inter-dependent nature of colorectal cancer is illustrated by the finding that PPARγ agonists induce apoptosis by suppressing activation of NFκB and GSK3β (Ban et al, 2010). Other investigators have shown that PPARγ induces apoptosis via inactivation of survivin and activation of caspase-3 in colorectal cancer cell lines and were able to inhibit PPARγ-ligand induced apoptosis by activating PPAR∂ (Wang et al, 2011).

7. Clones and stem cells

The crypt structure of the colonic epithelium is maintained by the putative presence of pluripotent intestinal crypt stem cells (Schmidt et al, 1988). Initially crypts are polyclonal and subsequently become monoclonal. Two kinetic models of the stem-cell-sustained intestinal crypt have been described. In the classic model, intestinal stem cells are thought to reside in the 4th cell position from the bottom of the crypt (the +4 cell). These stem cells supply daughter cells to the proliferative, transit-amplifying zone of the crypt; stem cells can be replaced by these daughter cells if necessary (Marshman et al, 2002; Pottten, 1977; Potten et al, 1974, 2002). The zone model localizes stem cells to the bottom of the crypt; these cells are proposed to be the undifferentiated crypt base columnar (CBC) cells (Bjerknes & Cheng

1981a, 1981b, 1999, 2006). On the basis of modelling studies, it is proposed that stem cells and crypts can suffer losses and be replaced (Cairnie & Millen, 1975; Nicolas et al, 2007; Yatabe et al, 2001).

Unequivocal stem cell identification has long remained elusive but, using genetic lineage tracing experiments, Barker et al (2007) showed that Lgr5, a G-protein-coupled receptor, is expressed in CBC cells. The study followed Lgr5-positive daughter cells up intestinal crypts and on to the intestinal villous epithelium, where all differentiated epithelial cell types could be demonstrated. The ability of Lgr5-positive stem cells in the crypt to give rise to crypt-villus units appear to be dependent on proximity to CD24+ cells at the bottom of the crypt (Sato et al, 2011). Stem cells have also been identified in mammalian epidermal hair follicles where they express Lgr6 (Snippert et al, 2010). Deletion of the APC gene in crypt stem cells in Lgr5 knock-in mice facilitates intestinal microadenoma growth; deletion of APC in transit-amplifying, semi-differentiated crypt cells in Lgr5 knock-in mice significantly reduces the growth of intestinal adenomas. Together this suggests that APC loss needs to be stem cell specific to propagate unrestrained tumor growth (Barker et al, 2009). The finding that single isolated Lgr5-positive stem cells can give rise to self-organizing crypt-villus units (Sato et al, 2009) raises the possibility that these cells may be useful in treatment strategies that aim to repopulate enteric epithelia.

There is experimental evidence for several proposed colon cancer stem cell markers including CD133, CD44, CD166, the extracellular matrix protein olfactomedin-4 (OLFM4), aldehyde dehydrogenase (ALDH1A1), Lgr5, and pleckstrin homology-like domain family A member 1 (PHLDA1). Some of these markers are associated with IL6-STAT3-JAK2 signaling (Becker et al, 2008; Dalerba et al, 2007; O'Brien et al, 2007; Ricci-Vitani et al, 2007; Sakthianandeswaren et al, 2011; Sanders & Majumdar, 2011; Shmelkov et al, 2008; Tsai et al, 2011; Uchida et al, 2010; van der Flier et al, 2009).

In contrast to the idea that carcinogenic mutations can occur in any cell, the cancer stem cell model (first described in 1997 for hematologic malignancies) proposes that tumor transformation, progression and metastatic initiation is driven by the acquisition of oncogenic self-renewal properties by tissue stem cells, contributing to differentiation and the cellular heterogeneity of tumors (Chen et al, 2011; Sanders & Majumdar, 2011). This has led to the idea that conventional cancer therapies that target only proliferating cells in tumors may not necessarily be effective against cancer stem cells that mediate metastasis (Abdul Khalek et al, 2010, Sanders & Majumdar, 2011; Soltanian & Matin, 2011), and that these therapies may therefore be ineffective in producing long-term remissions. CSCs have greater DNA repair capacity and expression of ABC transporter genes, both of which contribute to relatively higher resistance to chemotherapy and radiation (Bao et al, 2006; Cho & Clarke, 2008; Hirschmann-Jax et al, 2004; Zhou et al, 2009). GO-Y030, a curcumin analogue has been shown to inhibit STAT3 phosphorylation signaling in colon cancer stem cells, offering the possibility of targeting STAT3 signaling in colon CSCs (Lin et al, 2011). The clonogenic and proliferative properties of CSCs are significantly interrupted by histone deacetylase (HDAC) inhibitors and this effect is associated with apoptotic cell death and modified Wnt signalling (Sikandar et al 2010).

8. Conclusion

1. When applied to colorectal cancer, the concept of hierarchical compartmentalization (as described in crypt kinetic models) offers target environments for stemness, proliferation

and differentiation. Potential targets in each compartment include dividing cells, apoptotic mechanisms and cancer stem cells.

2. Wnt signalling has been targeted for inhibition because of its relationship with proliferation. Activity in this pathway is highest in the stem zone which provides the source of new cells.
3. COX inhibitors have variable effects on proliferation that may be related to differing potencies, and the evidence suggests that these effects may not be due to any inhibitory action by the compounds on COX. Inconsistencies remain in trying to reproduce in patients the experimental outcomes on tumor loads seen following treatment with COX inhibitors.
4. A range of compounds, including nutritional and synthetic substances, induce apoptosis in colorectal cancer cell lines. Not all COX inhibitors induce apoptosis.
5. Some COX inhibitors down-regulate PPAR∂, other inhibitors do not. However, combination treatments do not produce the expected potentiation effect. The conflicting evidence of the roles of PPAR∂ and PPARγ in colorectal cancer remains unresolved.
6. Stem cells markers are increasingly being identified and involvement in signalling pathways such as IL6-STAT3 point to new targets that may be modulated using therapeutic agents or genetic manipulations.

9. References

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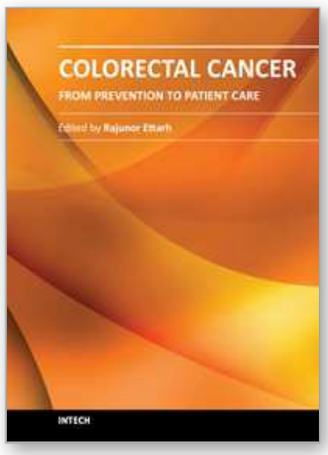

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The projections for future growth in the number of new patients with colorectal cancer in most parts of the world remain unfavorable. When we consider the substantial morbidity and mortality that accompanies the disease, the acute need for improvements 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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