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Distinct Pathologic Roles for Glycogen Synthase Kinase 3 β in Colorectal Cancer Progression

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1. Introduction

Colorectal cancer (CRC) is the third most frequent cancer type and the second leading cause of cancer-related deaths worldwide (Cunningham et al., 2010; Jemal et al., 2010). This is despite the recent trend of stabilizing or declining rates for CRC incidence and mortality in economically developed countries (Center et al., 2009; Edwards et al., 2010; Umar & Greenwald, 2009). Surgical intervention is the initial treatment for most CRC patients. Continuous efforts to optimize surgery for patients with localized CRC has resulted in markedly improved 5-year and 10-year survival rates (Cunningham et al., 2010; Wu & Fazio, 2000). Given the large number of CRC patients who undergo curative surgery, there is now a substantial number who are susceptible to recurrent or metastatic tumors and could therefore benefit from additional systemic therapies. An increasing array of options and protocols for chemotherapies and biologically targeted therapies is now available for use in the adjuvant setting and for the treatment of recurrent and metastatic CRC.

Based on a more detailed knowledge of the molecular characteristics of CRC (Markowitz et al., 2009; Walther et al., 2009), biologically-based therapeutics have been developed for the treatment of advanced stage CRC patients. Currently approved agents for the treatment of advanced and metastatic CRC include therapeutic monoclonal antibodies that target vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR). Despite a substantial biological rationale for the use of these new classes of therapeutic agents, large-scale clinical trials have observed only incremental clinical benefits for overall patient populations. Clearly, not all patients with recurrent and metastatic CRC benefit from these therapies. This is due to inherent and acquired resistance of tumors to the chemotherapeutic and biologically-based agents. Moreover, there are few reliable markers for predicting the therapeutic and adverse effects of these agents and that would allow patients who benefit from these systemic treatments to be identified. Therefore, new

therapeutic targets are urgently required to further improve the survival of patients with recurrent and metastatic CRC. One such target may be glycogen synthase kinase 3 β (GSK3 β), a serine/threonine protein kinase that has recently been implicated in various human cancers.

In this Chapter, we briefly summarize the scientific basis and current status of systemic treatments for CRC, including combinations of surgery, chemotherapy and molecular target-directed therapy. Based on our published and ongoing studies, we then focus on GSK3 β as an emerging therapeutic target in CRC and other cancer types. We describe the underlying biological mechanism that allows exploration of a novel therapeutic strategy for CRC involving the targeting of aberrant GSK3 β .

2. Molecular basis of colorectal cancer

2.1 Multistep and multiple molecular alterations

Colorectal carcinogenesis displays all the major biological hallmarks of cancer (Hanahan & Weinberg, 2011). CRC evolves and develops through orchestrated, multistep genetic and epigenetic alterations in oncogenes, tumor suppressor genes and DNA mismatch repair genes. These include frequent aberrations in certain chromosomes, such as allelic imbalance at several chromosomal loci (e.g., chromosome 5q, 8p, 17p, 18q) and chromosome amplification and translocation. Various combinations of somatic and germ-line alterations in these genes and chromosomes characterize the different genotypes and phenotypes of sporadic and hereditary forms of CRC (Cunningham et al., 2010; Markowitz & Bertagnolli, 2009; Walther et al., 2009). Among the genes involved in the molecular process of CRC development, several genetic markers have been reported to harbor diagnostic and prognostic information and to predict the benefit from or resistance to systemic therapy (Ellis & Hicklin, 2009; Markowitz & Bertagnolli, 2009; Walther et al., 2009).

Recent advances in DNA sequencing technology have allowed sequencing of the entire coding genome of human cancer to become a reality. The high throughput, next-generation sequencing of 18,000 genes in the Reference Sequence data-base of the National Center for Biotechnology Information in the USA has identified cancer-associated somatic mutations in 848 genes. Amongst these, 140 are considered as candidate genes responsible for the development and phenotype of CRC (Sjöblom et al., 2006; Wood et al., 2007).

2.2 Oncogene addiction

The unrestrained survival and proliferation of cancer cells relies on distinct oncogenic signalling pathways in which various oncoproteins, growth factor receptors and their ligands are aberrantly activated, leading to the concept of “oncogene addiction” (Sharma & Settleman, 2007; Weinstein, 2002; Weinstein & Joe, 2006). In theory, acute ablation of oncogene function should lead to the rapid dissipation of its pro-survival signal in cancer cells, thus resulting in apoptotic cell death. This “oncogenic shock” concept underlies the strategy of molecular targeting in cancer therapy (Sharma et al., 2006). The scientific rationale behind the development and application of therapeutic monoclonal antibodies targeting VEGF and EGFR for the treatment of CRC is based on these concepts. Intriguingly, however, the EGFR expression level in primary CRC determined by immunohistochemistry was not observed to correlate with the efficacy of therapeutic anti-EGFR antibodies in clinical trials of metastatic CRC (Hecht et al., 2010; commented by Grothey, 2010).

3. Systemic treatment: An overview

Surgery remains the cornerstone for the cure of localized CRC (Cunningham et al., 2010; Wu & Fazio, 2000). For colon cancer, total resection of the primary tumor with ample surgical margins and regional lymphadenectomy are the requisites for curative surgery. For rectal cancer, curative resection includes total excision of the mesorectum with adequate circumferential and distal surgical margins (R0) and lymphadenectomy along the inferior mesenteric vessels. Laparoscopic surgery has now become prevalent and safe, with long-term oncological outcomes of CRC patients undergoing this surgery reported as comparable to those treated by the open surgical approach (Lacy et al., 2008; The Clinical Outcomes of Surgical Therapy Study Group, 2004). Within 5 years after curative surgical resection, disease relapse (tumor recurrence or metastasis) occurs in 40 to 50% of patients with stage III CRC and in 20% of those with stage II CRC (Midgley & Kerr, 1999). Systemic therapy with

	Chemotherapeutic agents			Therapeutic monoclonal antibodies		
	5-FU Capecitabine	Irinotecan	Oxaliplatin	Bevacizumab	Cetuximab	Panitumumab
Target	TS	Topo- isomerase I	DNA cross- link	VEGF	EGFR	EGFR
Indication	PO adjuvant metastatic	metastatic	PO adjuvant metastatic	metastatic	metastatic	metastatic
Combination						
FOLFOX	+ LV		+	combined	combined	combined
FOLFIRI	+ LV	+		combined	combined	combined
FOLFOXIRI	+ LV	+	+			
Predictive markers	TS, DPD, TP	UGT1A1*	ERCC-1	VEGF? Tumor micro- vessels?	EGFR copy number**, K-ras, B-raf, PI3CA, AREG, EREG	K-ras, B-raf, PI3CA

Table 1. Key agents and their combinations presently used for the treatment of CRC

Abbreviations: AREG, amphyregulin; DPD, dihydropyrimidine dehydrogenase; EGFR, epidermal growth factor receptor; ERCC-1, excision-repair cross-complementing-1; EREG, epiregulin; 5-FU, 5-fluorouracil; FOLFIRI, folinate, 5-FU and irinotecan; FOLFOX, folinate, 5-FU and oxaliplatin; FOLFOXIRI, FOLFOX and irinotecan; LV, leukovorin; PI3KCA, phosphoinositide 3 kinase (PI3K) p110 catalytic subunit gene; PO, postoperative; TP, thymidine phosphorylase; TS, thymidylate synthase; UGT1A1, uridine diphosphate (UDP)-glucuronosyltransferase 1A1; VEGF, vascular endothelial growth factor.

* The number of TA repeats in the TATA element in UGT1A1 gene predicts the drug toxicity and resultant adverse effects.

** EGFR copy number is measured by fluorescence *in-situ* hybridization (FISH).

either chemotherapy and/or targeted therapies have been demonstrated to provide benefit to these CRC patients in both the post-operative adjuvant and advanced disease settings (Inoue et al., 2006; Midgley et al., 2009). Table 1 summarizes the key chemotherapeutic agents and therapeutic monoclonal antibodies targeting VEGF and EGFR and the combinations currently prescribed as adjuvant therapy for relapse-prone CRC patients and patients with metastatic tumors (reviewed in Cunningham et al., 2010; Meyerhardt & Mayer, 2005; Midgley et al., 2009; Wolpin et al., 2007; Wolpin & Mayer, 2008). The putative predictive markers for response to the respective agents are also shown in Table 1 (Walther et al., 2009).

3.1 Adjuvant chemotherapy

The purpose of postoperative adjuvant chemotherapy for stage II or III CRC is to destroy residual tumor cells and/or micrometastatic foci that are latent at the time of curative surgery. The chemotherapeutic mainstay for CRC, 5-fluorouracil (5-FU), exerts its anti-tumor effect by inhibiting thymidylate synthase (TS), a critical enzyme for nucleic acid synthesis. Folinic acid (leucovorin: LV) is frequently used to enhance the anti-tumor effect of 5-FU. The clinical and pharmacological rationale for this combination derives from the biological role of LV in stabilizing the ternary complex between TS and fluoro-deoxyuridine monophosphate (dUMP), an active metabolite of 5-FU, thereby enhancing TS inhibition. Adjuvant treatment regimens consist of oral (capecitabine) or infusional fluoropyrimidine-based chemotherapy as a single agent with LV, or in combination with irinotecan (a topoisomerase I inhibitor), oxaliplatin (a DNA cross-linker) or both (Table 1) (Midgley et al., 2009; Wolpin et al., 2007; Wolpin & Mayer, 2008).

Adjuvant fluoropyrimidine-based chemotherapy reduces the risk of cancer-related mortality by 30% and increases the 5-year survival rate by 5-12% in patients with stage III (node-positive) CRC. Adjuvant chemotherapy for stage II (node-negative) CRC patients is controversial because it increases the 5-year survival rate by just 3-4%. It has been proposed that “high-risk” stage II CRC patients characterized by T4 tumor, luminal stenosis or obstruction, poor histological differentiation, extramural vessel invasion, inadequate lymphadenectomy or surgical margins (R1) should preferentially undergo adjuvant chemotherapy (Cunningham et al., 2010; Midgley et al., 2009). Tumor relapse after curative resection occurs mostly within 3 years, irrespective of adjuvant chemotherapy (Sargent et al., 2007). Several clinical trials have failed to show a survival benefit from combining molecular target-directed agents (e.g., bevacizumab, cetuximab) with adjuvant chemotherapy (reviewed in Cunningham et al., 2010). Improvement in the survival of patients at high risk of tumor relapse therefore depends on intensive surveillance for early diagnosis of metastatic lesions, as well as identification of patients who are susceptible to tumor recurrence and who could thus benefit from more aggressive adjuvant treatment.

3.2 Treatment of metastatic CRC

A series of systemic, fluoropyrimidine-based combinatorial chemotherapies (Table 1) has substantially improved tumor response to treatment and increased the duration of progression-free and overall survival in patients with metastatic CRC. The remarkable advance in treating metastatic CRC in recent years has been due to the emergence and clinical application of molecular targeted therapeutics (Cunningham et al., 2010; Midgley et al., 2009). As stated above, a number of therapeutic monoclonal antibodies that target

relevant oncogenic pathways have been tested in clinical trials for CRC. Among them, the most widely used agents are bevacizumab, a recombinant humanized monoclonal antibody against VEGF (Ellis & Hicklin, 2008a; Li & Saif, 2009), cetuximab, a chimeric monoclonal antibody against EGFR (Balko et al, 2010) and panitumumab, a fully humanized monoclonal antibody against EGFR (Davis & Jimeno, 2010). These therapeutic antibodies have been used as monotherapy for the treatment of patients with metastatic CRC, or in combination with systemic chemotherapy (Table 1). Many clinical trials have demonstrated the additive effect of these antibodies on tumor response rate and progression-free survival (reviewed in Cunningham et al., 2010; Midgley et al., 2009). However, the combination of each therapeutic antibody with systemic chemotherapy regimens produced incremental but not always robust benefits to overall survival when compared to chemotherapy alone (Fojo & Parkinson, 2010).

3.3 Obstacles to systemic therapy

3.3.1 Drug resistance and predictive markers

The major obstacles to systemic therapy for CRC include drug resistance (both inherent and acquired) and the lack of reliable biomarkers for predicting response or resistance to drugs in clinical use (Ellis & Hicklin, 2009). This has led to the recent trend of using intensive combinatorial regimens for advanced CRC patients. Surprisingly, some recent clinical trials have shown that combinatorial target-directed therapies resulted in decreased survival, inferior quality of life and unexpected detrimental effects (Douillard et al., 2010; Hecht et al., 2009; Li & Saif, 2009; Tol et al., 2009).

Understanding the molecular mechanisms that underlie drug resistance and identifying predictive markers for drug sensitivity are *one and the same thing*. Pharmacogenomic approaches (Furuta et al., 2009; Walther et al., 2009) have identified a number of factors involved in drug metabolism and secretion, some of which (e.g., *UGT1A1* polymorphism) have been tested in clinical practice (Table 1). Several studies have suggested various biological mechanisms of resistance to VEGF-targeted cancer therapies (Bergers & Hanahan, 2008; Ebos et al., 2008; Ellis & Hicklin, 2008b), but to date there are no clinically useful predictive markers. Mutational activation of oncogenic pathways that lie downstream of EGFR signaling is known to cause intrinsic resistance to therapies that target this receptor. This has led to the identification of predictive markers (e.g., *K-ras*, *B-raf*, *PIK3CA*) that allow better patient selection for such treatments (Banck & Grothey, 2009; Cantwell-Dorris et al., 2011; De Roock et al., 2010a; Sartore-Bianchi et al., 2009). However, the complex pathways involved in tumor progression are often intercalated and therefore single markers cannot accurately predict the efficacy or outcome of CRC patients undergoing molecular targeted therapies (Baldus et al., 2010; De Roock et al., 2010b; Hecht et al., 2010).

Research into the mechanisms of acquired resistance to molecular targeted agents has generated new therapeutic strategies and agents aimed at counteracting the resistance mechanism (Bowles & Jimeno, 2011; Cidón, 2010; Dasari & Messersmith, 2010; Presen et al., 2010). Thus, improving the anti-tumor effects of molecular targeted therapies will depend on the identification of novel molecular pathways, development of new classes of rationally designed biological agents, and identification of predictive markers for response and resistance.

3.3.2 Economic issues

The high cost of developing the biologically-based therapeutic agents shown in Table 1 is a major issue in light of the modest clinical benefits, acquired drug resistance and lack of

suitable predictive markers. A recent study reported significantly higher hospital costs for CRC patients with recurrence compared to those without (Macafee et al., 2009). Outside of the United States, the high cost of molecular targeted drugs has restricted their use to patients with sufficient income and/or health insurance. This issue highlights the importance of accurate predictive markers that allow identification of patients who are most likely to benefit from targeted agents, thus improving the cost effectiveness.

4. GSK3 β as an emerging therapeutic target

4.1 GSK3 β biology

GSK3 was identified as a serine/threonine protein kinase that phosphorylates and inhibits glycogen synthase (GS), a rate-limiting enzyme in the regulation of glucose/glycogen metabolism in response to insulin-mediated signaling (Embi et al., 1980). In contrast to its original name and depending on its substrates and binding partners (Table 2) (Medina & Wandosell, 2011; Xu et al., 2009), GSK3 has been found to participate in many fundamental cellular pathways including proliferation, differentiation, motility, cell cycle and apoptosis (Doble & Woodgett, 2003; Harwood, 2001; Jope & Johnson, 2004; Nakada et al., 2011). The two isoforms of this kinase, GSK3 α and GSK3 β , are encoded by their respective genes. Their functions do not always overlap (Rayasam et al., 2009) and much recent attention has been directed towards the function of GSK3 β .

Unlike most protein kinases, GSK3 β is active in normal cells and this activity is controlled by its subcellular localization, differential phosphorylation at serine 9 (S9) and tyrosine 216 (Y216) residues, and different binding partners. A consensus motif and context-based computational analysis of *in vivo* protein phosphorylation sites indicate that GSK3 β is one of the kinases with the most substrates (Linding et al., 2007). In normal cells, multiple signaling pathways mediated by phosphoinositide 3 kinase (PI3K)-Akt, Wnt and mitogen-activated protein kinase (MAPK) are known to negatively regulate the activity of GSK3 β via S9 phosphorylation (Medina & Wandosell, 2011). The molecular structure and details of the functional and regulatory machinery of GSK3 β have been thoroughly described in many excellent reviews cited in this section and are not the focus of this Chapter.

4.2 GSK3 β in common chronic diseases

Accumulating evidence suggests pathological roles for GSK3 β in glucose intolerance due to inhibition of GS and other signaling cascades involved in the regulation of glucose homeostasis (Frame & Zheleva, 2006; Lee & Kim, 2007) and in neurodegenerative changes through accumulation of the neurotoxic substances amyloid A β and tau protein (Annaert & De Strooper, 2002; Bhat & Budd, 2002). Recognition that GSK3 β promotes inflammation also implicates this molecule in a broad spectrum of common diseases including type 2 diabetes mellitus and neuropsychiatric disorders involving an inflammatory reaction (Jope et al., 2007). GSK3 β has therefore emerged as a therapeutic target in these prevalent diseases (Cohen & Goedert, 2004; Kypta, 2005; Meijer et al., 2004; Phukan et al., 2010). Another line of studies has demonstrated an osteogenic function for the Wnt/ β -catenin signaling pathway (Hartman, 2006; Krishnan et al., 2006; Ralston & de Crombrughe, 2006). This suggests that GSK3 β may be a putative therapeutic target for osteoporotic bone disease, since under physiological conditions it is a well established member of a complex that destroys β -catenin

Categories	Substrates
Metabolism	glycogen synthase, ATP citrate lyase, PKA, PDH, acetyl-CoA, carboxylase, PP1, PP2A, PP2A inhibitor, cyclin D1, eIF2B, NGF receptor, axin, APP, Bax, VDAC, hexokinase II, presenilin, LRP5/6
Cell structure	tau, MAP1B, NCAM, neurofilament, CRMP2, dynein, dynein-like protein, maltose binding protein, APC, kinesin light chain
Signaling & Transcription	
Wnt	β-catenin, snail, smad1, Hath1, smad 3
Akt	SRC-3, B-cell lymphoma (BCL)-3, p21
PI3K-Akt	Mcl-1, c-Jun, phosphatase and tensin homologue (PTEN)
Ras-PI3K-Akt	c-Myc, cyclin D1
TNFα	nuclear factor (NF)-κB
Hedgehog	Ci (citrus interruptus), Gli-2
hypoxia	hypoxia inducible factor (HIF)-1α
insulin	glycogen synthase, SREBP
undetermined & others	cyclin E, AP-1, CREB, C/EBP, cdc25A, Notch, p53, p27 ^{Kip1} , NFAT, GR, HSF-1, FGD-1, FGD-3, c-Myb, mCRY2, NACα, MafA, IPF1/PDX1, presenilin 1 C-terminal fragment

Table 2. Known substrates for phosphorylation by GSK3β

Abbreviations: AP-1, activator protein 1; APC, adenomatous polyposis coli; APP, amyloid precursor protein; ATP, adenosine triphosphate; C/EBP, CCAAT (cytidine-cytidine-adenosine-adenosine-thymidine)-enhancer-binding protein; CREB, cyclic adenosine monophosphate (cAMP) response element binding protein; CRMP2, collapsin response mediator protein 2; eIF2B, eukaryotic protein synthesis initiation factor-2B; FGD, FYVE, RhoGEF and PH domain-containing protein; GR, glucocorticoid receptor; HSF-1, heat shock factor protein 1; IPF1, insulin promoter factor 1; LRP5/6, low-density lipoprotein (LDL) receptor-related protein 5/6; MafA, musculoaponeurotic fibrosarcoma oncogene homolog A; MAP1B, microtubule-associated protein 1B; mCRY2, mouse cryptochrome 2; NACα, nascent polypeptide-associated complex α subunit; NCAM, neural cell adhesion molecule; NFAT, nuclear factor of activated T-cells; NGF, nerve growth factor; PDH, pyruvate dehydrogenase; PDX1, pancreatic and duodenal homeobox 1; PKA, protein kinase A; PP, protein phosphatase; SREBP, sterol regulatory element-binding protein; TNFα, tumor necrosis factor α; VDAC, voltage-dependent anion channel.

(Fuchs et al., 2005). In this context, an orally bioavailable GSK3α/β dual inhibitor was generated and tested as a new drug for the treatment of osteoporosis (Kulkarni et al., 2006).

4.3 GSK3β in cancer

An increasing number of cellular structural and functional proteins have been identified as targets for GSK3β phosphorylation-dependent regulation (Table 2). However, this has also generated results that show conflicting roles for the signaling pathways regulated by GSK3β in either suppressing or promoting cancer.

4.3.1 GSK3β suppresses cancer

In physiologically normal cells, many of the substrates for GSK3β-mediated phosphorylation and subsequent ubiquitin-mediated degradation include oncogenic signaling and

transcription factors, cell cycle regulators and proto-oncoproteins (Table 2). A previous study showed that GSK3 β phosphorylates and stabilizes a major cell cycle regulator, p27^{Kip1} (Surjit & Lal, 2007). Recent studies have shown that inhibition of GSK3 β stabilizes snail and induces epithelial-mesenchymal transition (EMT), a morphological and phenotypic change closely associated with tumor cell invasion and metastasis (Bachelder et al., 2005; Zhou et al., 2004; reviewed in Doble & Woodgett, 2007; Schlessinger & Hall, 2004; Zhou & Hung, 2005). These findings are mostly observed in normal but not neoplastic cells and have led to the hypothesis that GSK3 β functions as a tumor suppressor (reviewed in Luo, 2009; Manoukian & Woodgett, 2003; Patel & Woodgett, 2008).

Consistent with this hypothesis, a number of studies in breast, lung and non-melanoma skin cancers have shown that GSK3 β is inactivated in tumor cells, but that its activation induces apoptosis (reviewed in Luo, 2009; Patel & Woodgett, 2008). It has been reported in several studies that GSK3 β renders cancer cells resistant to chemotherapeutic agents (reviewed in Luo, 2009). However, in contrast to the observations described in the next section (4.3.2), including our own, none of these studies addressed differences in the expression, activity and biological properties of GSK3 β between tumor cells and their normal cell counterparts. Furthermore, these studies did not investigate the direct consequences of GSK3 β inhibition for tumor cell survival, proliferation and chemotactic migration and invasion.

4.3.2 Deregulated GSK3 β promotes cancer

Wnt signaling plays a crucial role in embryonic development, the regeneration of adult tissues and in many other cellular processes. Aberrant activation of the Wnt pathway due to mutation or deregulated expression of its components mediates the multistep process of colorectal tumorigenesis (Kikuchi, 2007; Klaus & Birchmeier, 2008; Lustig & Behrens, 2003; Willert & Jones, 2006). Over 90% of CRC develops following activation of the Wnt signaling pathway in which β -catenin plays a central role (Fuchs et al., 2005; Giles et al., 2003). GSK3 β interrupts activation of the canonical Wnt pathway by phosphorylating β -catenin and recruiting it to ubiquitin-mediated degradation. GSK3 β is therefore believed to antagonize tumorigenesis that involves active Wnt signaling (Bienz & Clevers, 2000; Manoukian & Woodgett, 2002; Polakis P, 1999), as represented for example by CRC development. This notion is also supported by the frequent mutational activation of Ras and PI3K-Akt signaling (Markowitz & Bertagnolli, 2009; Parsons et al., 2005), since it is well established that Akt kinase phosphorylates the S9 residue of GSK3 β and inhibits its activity (Medina & Wandosell, 2011). However, few studies had focused on the biological properties of GSK3 β in cancer until we investigated a putative pathological role for this kinase in CRC, as described below.

Most CRC cell lines and primary CRC tumors in our studies have shown increased expression and activity of GSK3 β and deregulation of its activity due to imbalance in the differential phosphorylation of S9 (inactive) and Y216 (active) residues. This is in comparison to non-neoplastic cells (e.g., HEK293) and normal colon mucosa in which GSK3 β activity appears to be regulated by the differential phosphorylation. These tumor cell features are unrelated to the activation of β -catenin or Akt (Mai et al., 2009; Shakoori et al., 2005). A non-radioisotopic, *in vitro* kinase assay demonstrated an increased ability of GSK3 β derived from most CRC cell lines and primary CRC tumors to phosphorylate its substrate, as compared to non-neoplastic counterparts (Mai et al., 2006, 2009). These observations suggest that, in contrast to having hypothetical tumor suppressor function, GSK3 β may actually promote cancer.

A putative pathological role for GSK3 β in cancer was demonstrated by subsequent observations that inhibition of GSK3 β activity using pharmacological (small-molecule) agents and of its expression by RNA interference reduced the survival and proliferation of CRC cells. Such inhibition also predisposed the cells to apoptosis *in vitro* and in tumor xenografts, suggesting that CRC cells depend on aberrant GSK3 β for their survival and proliferation (Mai et al., 2006, 2009; Shakoori et al., 2005, 2007). A series of studies by our group led us to propose that aberrant GSK3 β is a novel and potentially important therapeutic target in cancer (Miyashita et al., 2009b; Motoo et al., 2011; Nakada et al., 2011), thus allowing us to apply for domestic and international patents in this field (Minamoto). Following our studies on the antitumor effects of GSK3 β inhibition, similar observations were reported for CRC by other groups (Ghosh & Altieri, 2005; Rottmann et al., 2005; Tan et al., 2005; Tsuchiya et al., 2007) (Table 3). Similar results were also published for other cancer types with underlying biological mechanisms that included GSK3 β inhibition of several pathways involved in tumorigenesis (reviewed in Miyashita et al., 2009b; Nakada et al., 2011). A putative role for GSK3 β in cancer is still being debated (Luo, 2009; Manoukian & Woodgett, 2003; Patel & Woodgett, 2008) and was discussed in section 4.3.1. However, the overall results to date indicate that aberrant expression and activity of GSK3 β is likely to be a common and fundamental characteristic of a broad spectrum of human cancers.

4.3.3 Oncogene addiction and the effect of GSK3 β inhibition against cancer

As stated in section 2.2, the hypothesis of oncogene addiction has been proposed as a rationale for molecular targeting in cancer treatment. It refers to the observation that a cancer cell, despite its plethora of genetic alterations, seemingly exhibits dependence on a single oncoprotein or oncogenic pathway for its sustained survival and/or proliferation (Sharma & Settleman, 2007; Weinstein, 2002; Weinstein & Joe, 2006). This unique state of dependence by cancer cells is highlighted by the fact that inactivation of the normal counterpart of such proto-oncogene products in non-neoplastic cells is tolerated without obvious consequence. A profound implication of this hypothesis is that acute interruption of the critical oncogenic pathways upon which cancer cells are dependent should have a major detrimental effect (oncogene shock), while sparing normal cells that are not similarly addicted to these pathways (Sharma et al., 2006). In our series of studies, inhibition of GSK3 β had little effect on cell survival, growth, apoptosis or senescence in non-neoplastic cells (e.g., HEK293) and on major vital organs in rodents (Mai et al., 2006, 2009; Shakoori et al., 2005, 2007). This concurs with previous reports showing that GSK3 β inhibition does not influence the survival or growth of human mammary epithelial cells, embryonic lung fibroblasts (WI38) and mouse embryonic fibroblasts (NIH-3T3) (Kunnimalaiyaan et al., 2007; Ougolkov et al., 2005). With respect to the oncogene addiction hypothesis (Sharma & Settleman, 2007; Weinstein, 2002; Weinstein & Joe, 2006), the selective therapeutic effect of GSK3 β inhibition against cancer can be explained by differences in biological properties of GSK3 β between neoplastic and non-neoplastic cells (Mai et al., 2006, 2009; Shakoori et al., 2005).

5. GSK3 β and the hallmarks of colorectal cancer

Understanding the molecular mechanism behind a pathogenic role for GSK3 β in cancer is important for the development of treatment strategies that target this kinase. A current review highlights 8 hallmarks of cancer in which phenotypic properties are progressively

Authors	Study design	Types of GSK3β inhibitors	Pathological roles of GSK3β and underlying mechanism
Shakoori et al, 2005	<i>in vitro</i>	AR-A014418, SB-216763, siRNA	Deregulated GSK3β expression and activity are associated with CRC cell survival and proliferation by mechanism independent of activation of Wnt/β-catenin signaling and Akt. GSK3β inhibition attenuates survival and proliferation of colon cancer cells.
Mai et al, 2006	<i>in vitro</i>	AR-A014418, SB-216763, siRNA	NRIKA detected higher activity of GSK3β for phosphorylating its substrate (β-catenin) in gastrointestinal cancer cells including CRC cells than non-neoplastic HEK293 cells.
Shakoori et al, 2007	tumor xenograft	AR-A014418, SB-216763	GSK3β inhibition attenuates survival and proliferation of SW480 colon cancer cell xenografts with no detrimental effects on the major vital organs in the rodents.
Mai et al, 2009	<i>in vitro</i> , tumor xenograft	AR-A014418, SB-216763, siRNA	GSK3β inhibition attenuates survival and proliferation of colon cancer cells by decreasing hTERT expression and telomerase activity and inducing cell senescence.
Ghosh et al, 2005	<i>in vitro</i>	LiCl, TDZD8, SB-216763, siRNA	GSK3β functions against activation of p53-dependent apoptosis in colon cancer cells.
Tan et al, 2005	<i>in vitro</i>	LiCl, SB-216763, SB415286, LY2119301	GSK3β functions against activation of p53-dependent apoptosis through a direct Bax-mediated mitochondrial pathway in colon cancer cells.
Rottmann et al, 2005	<i>in vitro</i> , tumor xenograft	LiCl, siRNA	GSK3β functions against colon cancer cell apoptosis by inhibiting a TRAIL receptor-dependent synthetic lethal relationship between <i>Myc</i> activation and <i>FBW7</i> loss of function.
Tsuchiya et al, 2007	<i>in vitro</i>	BIO, LiCl, keupauillone	GSK3β inhibits colonocyte differentiation by destabilizing the transcription factor, Hath1.

Table 3. Pathological roles and functions of GSK3β in colorectal cancer

Abbreviations: hTERT, human telomerase reverse transcriptase; NRIKA, non-radioisotopic *in vitro* kinase assay; siRNA, small interfering RNA; TRAIL, tumor necrosis factor (TNF)-related apoptosis-inducing ligand.

acquired during multistep pathogenesis, thus allowing cancer cells to become tumorigenic and ultimately malignant (Hanahan & Weinberg, 2011). These hallmarks are sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, enabling of replicative immortality, induction of angiogenesis, activation of invasion and metastasis,

reprogramming of energy metabolism and evasion of immune destruction. The development of each hallmark involves multiple signaling pathways. In this section, we address how GSK3 β modulates some of these hallmark characteristics of CRC by referring to the studies shown in Table 3, including our own work.

5.1 Cell proliferation

Unrestrained cell proliferation is the most prominent feature of cancer. Our previous study showed that the effect of GSK3 β inhibition against the proliferative capacity of CRC cells was associated with decreased expression of cyclin D1 and cyclin-dependent kinase (CDK) 6 and phosphorylation of the Rb protein (Mai et al., 2009). These observations suggest that Rb function was restored, leading to the binding and inhibition of E2F transcription factor (reviewed in Classon & Harlow, 2002; Knudsen & Knudsen, 2008). This is consistent with a subsequent report that forced expression of exogenous GSK3 β promotes the proliferation of ovarian cancer cells by inducing cyclin D1 expression (Cao et al., 2006). Together, the results suggest that suppression of excess cancer cell proliferation via the inhibition of GSK3 β is partly due to negative regulation of cell cycling by cyclin D1. In normal or non-neoplastic cells, cyclin D1 is one of the primary targets of GSK3 β for phosphorylation and subsequent degradation in the ubiquitin-proteasome system (Diehl et al., 1998) (Table 2). The opposing role of GSK3 β in cyclin D1 expression may explain the lack of effect of GSK3 β inhibition on cell survival and growth of non-neoplastic cells found in earlier studies (Kunnimalaiyaan et al., 2007; Mai et al., 2009; Ougolkov et al., 2005; Shakoori et al., 2005).

5.2 Resistance to cell death via tumor suppressor pathways

A major mechanism by which cancer cells evade cell death is via the inactivation of tumor suppressor pathways mediated by p53 (Royds & Iacopetta B, 2006; Vousden & Lane, 2007; Zilfou & Lowe, 2009) and Rb (Classon & Harlow, 2002; Knudsen & Knudsen, 2008). The studies listed in Table 3 showed that inhibition of GSK3 β induced apoptosis in human CRC cell lines. This effect was associated with increased expression of p53 and of p21 in colon cancer cells with wild-type p53, and decreased Rb phosphorylation in colon cancer cells irrespective of their p53 status (Ghosh & Altieri, 2005; Mai et al., 2009; Tan et al., 2005). Another study showed that GSK3 β suppresses the apoptosis of colon cancer cells by inhibiting a tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptor-dependent synthetic lethal relationship between *c-Myc* activation and *FBW7* (a gene encoding a ubiquitin ligase receptor) loss of function (Rottmann et al., 2005). These studies suggest a putative pathological role for aberrant GSK3 β in mediating CRC cell resistance to apoptosis induced by a pathway involving tumor suppressor proteins, TRAIL and *c-Myc*.

One of the representative pathways for cell survival is mediated by nuclear factor- κ B (NF- κ B) (Inoue et al., 2007; Karin, 2006, 2009). Based on previous studies showing the potential involvement of GSK3 β in NF- κ B-mediated cell survival during mouse embryonic development (Hoeflich et al., 2000; Schwabe & Brenner, 2002), it was reported that GSK3 β sustains pancreatic cancer cell survival by maintaining transcriptional activity of NF- κ B (Ougolkov et al., 2005; Wilson & Baldwin, 2008). While these studies examined the activity of exogenous (transfected) NF- κ B, we previously observed no effect of GSK3 β inhibition on endogenous NF- κ B transcriptional activity in gastrointestinal cancer cells (including CRC) and glioblastoma cells (Mai et al., 2009; Miyashita et al., 2009a). Therefore, a role for GSK3 β in regulating NF- κ B activity in cancer is controversial.

5.3 Replicative cell immortality

Another critical mechanism used by cancer cells to evade cell death is replicative cell immortality. A close relationship exists in cancer cells between the molecular mechanisms for immortality and escape from replicative senescence (Finkel et al., 2007). Cancer cells acquire constitutive expression and activity of human telomerase reverse transcriptase (hTERT) and telomerase in order to circumvent telomere-dependent pathways of cell mortality (Harley, 2008).

We recently observed a decreased level of hTERT mRNA in colon cancer cells following inhibition of either the activity or expression of GSK3 β . Inhibition of GSK3 β attenuates telomerase activity and increases the β -galactosidase-positive (senescent) population in colon cancer cells. These effects were associated with increased expression of p53, p21 and c-Jun N-terminal kinase 1 (JNK1) and decreases in CDK6 expression and Rb phosphorylation (Mai et al., 2009). The findings are consistent with the known relationship between these proteins and cell senescence (reviewed in Kiyono, 2007) and with GSK3 β activity (Ghosh & Altieri, 2005; Kulikov et al., 2005; Liu et al., 2004; Mai et al., 2009; Qu et al., 2004; Rössig et al., 2002). Consistent with our observation, a recent study found that inhibition of GSK3 β suppressed hTERT expression and telomerase activity and shortened the telomere length in various cancer cell lines including HCT116 colon cancer cells, and attenuated cell proliferation and hTERT expression in ovarian cancer xenografts (Bilsland et al., 2009). The putative role for GSK3 β in protecting cancer cells from telomere-dependent senescence and mortality is attributed to its effects on hTERT expression and telomerase activity.

5.4 Influence on the cancer microenvironment and tumor invasion

In cancer, various events are orchestrated to produce a distinct tumor microenvironment that dictates the malignant potential. These include depletion of nutrients involved in cell proliferation, tumor cell invasion, tumor neovascularization in response to hypoxic condition, as well as stromal, inflammatory and immune reactions in the host (Joyce, 2005). The promotion of inflammation and immune response by GSK3 β (Jope et al., 2007) suggests a broad pathological role for this kinase in the cancer microenvironment.

The pro-invasive phenotype of cancer cells is characterized by EMT, enhanced cell motility and their ability to induce neovascularization. As discussed in section 4.3.1, inhibition of GSK3 β stabilizes snail and induces EMT (Bachelder et al., 2005; Zhou et al., 2004; reviewed in Doble & Woodgett, 2007; Schlessinger & Hall, 2004; Zhou & Hung, 2005). A hypoxic tumor microenvironment induces the expression of hypoxia-inducible factor-1 α (HIF-1 α), a transcription factor that controls oxygen homeostasis by regulating target genes involved in angiogenesis, glycolysis and cell proliferation (reviewed in Semenza, 2009). A previous study showed that under physiological conditions, GSK3 β inhibits angiogenesis by negatively regulating endothelial cell survival and migration in response to PI3K-, MAPK- and protein kinase A (PKA)-dependent signaling pathways (Kim et al., 2002). Another study demonstrated that hypoxia induces a biphasic effect on HIF-1 α stabilization in liver cancer cells. Accumulation of HIF-1 α occurs in early hypoxia and is dependent on an active PI3K/Akt pathway and inactive GSK3 β . In contrast, prolonged hypoxia results in the inactivation of Akt and activation of GSK3 β . This negatively regulates HIF-1 α activity by inhibiting its accumulation (Mottet et al., 2003). Collectively, it thus appears unlikely that GSK3 β participates in cancer cell EMT and in tumor angiogenesis.

Formation of lamellipodia, the characteristic cellular microarchitecture, is responsible not only for cell migration under physiological conditions (e.g., embryonic development,

wound healing) but also for cancer cell migration and invasion (Machesky, 2008; Small et al., 2002; Yilmaz & Christofori, 2009). A member of the Rho-GTPase family, Rac1, is known to participate in the formation of lamellipodia and may thus play an important role in cancer progression (Raftopoulou & Hall, 2004; Sahai & Marshall, 2002). It has been reported that GSK3 β participates in cell motility by facilitating the formation of lamellipodia (Koivisto et al., 2003) and by activating Rac1 (Farooqui et al., 2006; Kobayashi et al., 2006; Vaidya et al., 2006). Focal adhesion kinase (FAK) is also known to play a key role in regulating cell motility and migration and to be deregulated in cancer (McLean et al., 2005). Earlier studies reported that FAK is one of the downstream effectors in GSK3 β -mediated pathways (Kobayashi et al., 2006) and also regulates Rac1 (McLean et al., 2005). Consistent with a recent study for glioblastoma (Nowicki et al., 2008), our preliminary study has shown that inhibition of GSK3 β attenuates pancreatic cancer cell migration and invasion by negatively regulating FAK and Rac1 activities (unpublished observation). Therefore, in regard to cancer treatments that target GSK3 β , it is important to explore a possible role for GSK3 β in CRC cell invasion by investigating its effects on cellular microarchitecture, motility and migration.

5.5 Cancer cell stemness and metabolic traits

Cell stemness and the reprogramming of energy metabolism are primary cell characteristics that share distinct molecular pathways and allow cancer cells to survive, proliferate, invade their host tissues, metastasize and resist treatment. Here, we address future directions in our approach towards ascertaining the potential of GSK3 β as a therapeutic target in cancers including CRC.

5.5.1 Cancer cell stemness and GSK3 β

Arising from the concept of tissue stem cells, the notion of cancer stem cells has emerged and proposes that cancer initiating cells are a distinct subpopulation within a tumor that have the ability to self-renew and differentiate (Clarke et al., 2006; O'Brien et al., 2010). Similar to other cancer types, a small population of cancer initiating cells has been identified and characterized in CRC (Dalerba et al., 2007; O'Brien et al., 2007; Ricci-Vitiani et al., 2007; reviewed in Yeung & Mortensen, 2009). Current cancer treatments assume that all cancer cells in tumors are homogeneous and have a similar capacity to proliferate, invade and metastasize, as well as having similar susceptibility to chemotherapy and radiation. However, accumulating evidence suggests that cancer stem cells and cancer cells that are undergoing EMT share various biological traits (Polyak & Weinberg, 2009). These cells are also strongly resistant to current forms of therapeutics, thereby identifying this subpopulation of cancer cells as the ultimate target for cancer treatment (Lou & Dean, 2007). Consistent with the physiological roles of GSK3 β in Wnt, Hedgehog and Notch signaling (Foltz et al., 2002; Manoukian & Woodgett, 2002; Takenaka et al., 2007), GSK3 β inhibition by pharmacological means promotes embryonic stem cell pluripotency (Sato et al., 2004) and hematopoietic stem cell reconstitution (Trowbridge et al., 2006). Conversely, recent studies have demonstrated that GSK3 β sustains the respective molecular pathways leading to tumor cell stemness in a specific type of leukemia and in glioblastoma (Korur et al., 2009; Wang et al., 2008). Although the underlying molecular mechanisms are not well understood, these differential roles for GSK3 β in normal and cancer stem cells could ultimately benefit cancer treatment strategies by allowing this kinase to be targeted with little harm to patients. As addressed in the next section (5.5.2), anaerobic glycolysis and the presence of a distinct niche are thought to be characteristics of cancer stem cells, in addition to their extreme

resistance to drug treatment. Therefore, clarification of a putative role for GSK3 β in regulating CRC cell stemness is of great interest. This could lead to a new strategy for treatment that targets the biology of cancer cell stemness.

5.5.2 Distinct metabolic traits of cancer cells and GSK3 β

Production of excess energy is thought to provide an intrinsic and selective pressure that allows cancer cells to expand clonally and to acquire immortalized and destructive phenotypes. Even under normoxic conditions, most cancer cells depend on increased glucose uptake and aerobic glycolysis to produce their energy source, adenosine triphosphates (ATP) (Kim & Dang, 2006; Vander Heiden & Cantley, 2010). This is known as the Warburg effect and involves truncated oxidative phosphorylation in the tricarboxylic acid (TCA) cycle, thus resulting in mitochondrial uncoupling (Samudio et al., 2009). These properties allow cancer cells to survive and invade host tissues in a microenvironment where the supply of both oxygen and nutrients is deficient, as well as conferring resistance to apoptosis-inducing therapeutic stimuli (Smallbone et al., 2007). Therefore, the glycolytic phenotype of cancer cells is a potential target for cancer diagnosis and treatment (Gatenby & Gillies, 2007; Kroemer & Pouyssegur, 2008). For example, enhanced glucose uptake by cancer cells can be used to visualize cancer by positron emission tomography (PET) using the radioisotope-labeled glucose analogue 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG). FDG-PET in combination with computed tomography (PET-CT) enables the detection of metastatic lesions for most cancers with sensitivity and specificity both greater than 90% (Mankoff et al., 2007).

The association between a glycolytic phenotype (*i.e.*, TCA cycle defects) and resistance to apoptosis is attributed to decreased mitochondrial hydrogen peroxide production and cytochrome C release (Samudio et al., 2009; Vander Heiden & Cantley, 2010). Pyruvate dehydrogenase (PDH) plays a crucial role in triggering the TCA cycle by converting pyruvate to citric acid. PDH kinase 1 (PDK1), which phosphorylates and inactivates PDH, is frequently over-activated in cancer cells, resulting in an impaired TCA cycle and mitochondrial hyperpolarization. Thus, inhibition of PDK1 would re-activate PDH and restore mitochondrial membrane polarity, thereby facilitating cancer cell apoptosis in response to chemotherapeutic agents and radiation. Dichloroacetate (DCA), an orally bio-available small molecule, is a well characterized PDK1 inhibitor. The ability of DCA to inhibit lactate production by stimulating PDH and the TCA cycle has long been used to treat lactic acidosis, which is a complication of inherited mitochondrial disorders (Stacpoole, 2003, 2006). A recent study demonstrated that DCA induces cancer cell apoptosis by selectively inhibiting PDK1 in cancer cells, leading to metabolic remodeling from glycolysis to glucose oxidation and the normalization of mitochondrial function (Bonnet et al., 2008). A clinical trial of oral DCA in children with congenital lactic acidosis reported that DCA was well tolerated and safe (Stacpoole, 2006). Thus, orally administered DCA is a promising and selective anticancer agent.

The primary role of GSK3 β is to control GS activity (Table 2). It thus acts as a checkpoint at the bifurcation between glycogenesis and glycolysis, the two major pathways of glucose/glycogen metabolism (Lee & Kim, 2007). We recently found that inhibition of GSK3 β in colon cancer cells increased GS expression and decreased its S640 phosphorylation (unpublished observation), suggesting that GSK3 β inhibition may switch cancer cells from a glycolytic to a glycogenic phenotype. It was previously reported that GSK3 β phosphorylates and inactivates PDH (Hoshi et al., 1996) (Table 2), a key enzyme for the TCA cycle in

mitochondria. This suggests that deregulated GSK3 β contributes to truncation of the TCA cycle and mitochondrial uncoupling in cancer cells, resulting in resistance to chemotherapy and radiation. It has also been reported that the distinct metabolism of cancer cells involves not only anaerobic glycolysis but also other metabolic pathways such as the pentose phosphate pathway, amino acid and nucleic acid synthesis and glutaminolysis (DeBerardinis et al., 2008). GSK3 β has a number of key metabolic enzymes as substrates (Table 2), suggesting this molecule could have broad control over various pathological metabolic pathways in cancer cells.

6. Perspectives

Biologically-based therapy of cancer holds great promise, particularly for patients who are refractory to existing forms of therapy. Current paradigms reviewed in the earlier part of this Chapter (**3. Systemic treatment: an overview**) include the targeting of growth factor receptor-type protein tyrosine kinases and angiogenic factors. Such therapies are directed against cancer cell survival, proliferation and tumor angiogenesis; however they are unable to completely eradicate cancer, as demonstrated by most large-scale clinical trials.

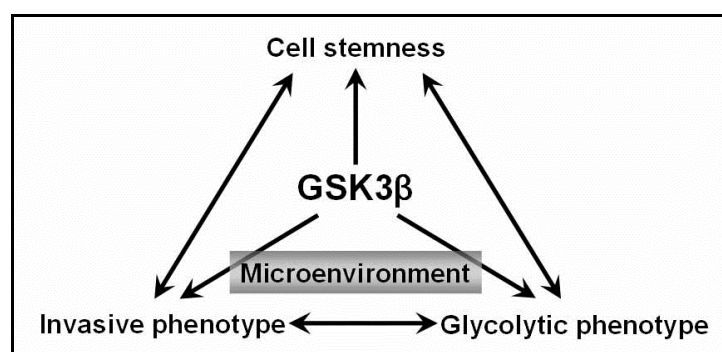


Fig. 1. GSK3 β promotes cell stemness, invasive capacity and excess glucose metabolism that interact to produce a distinct cancer microenvironment.

The distinct pathologic properties of GSK3 β in cancer described here highlight its potential to be an innovative target for the radical treatment of this disease, including CRC. GSK3 β can potentially promote cancer cell stemness, invasive capacity and glucose metabolism, thus creating the selective pressures that allow cancer cells to persist in a distinct microenvironment (Figure 1). Understanding the complex biological mechanisms for the multiple roles of GSK3 β in promoting cancer should allow elucidation of novel molecular pathways that lead to cancer development and progression. This will also provide a detailed scientific basis for the development of cancer treatment strategies that target aberrant GSK3 β .

Concerns regarding the therapeutic use of GSK3 β inhibitors remain because these may activate oncogenic (e.g., Wnt) signaling, thus promoting cell proliferation (Manoukian & Woodgett, 2003). However, this issue has not deterred preclinical studies of GSK3 β inhibitors for the treatment of many cancer types (reviewed in Miyashita et al., 2009b) or Phase II clinical trials for the treatment of neurological diseases (Chico et al., 2010). Currently, two clinical trials are being undertaken to test a pharmacological GSK3 β inhibitor (LY2090314) for enhancement of the anti-tumor effect of chemotherapeutic agents for advanced solid cancer (phase I: <http://clinicaltrials.gov/ct2/show/study/NCT01287520>) and leukemia (phase II: <http://clinicaltrials.gov/ct2/show/study/NCT01214603>). Such

trials targeting GSK3 β should complement, enhance or substitute the current front line therapies that target growth factor receptors and angiogenic factors in refractory colorectal cancer.

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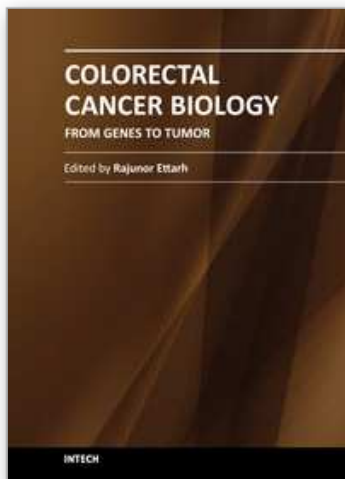
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Colorectal cancer is a common disease, affecting millions worldwide and represents a global health problem. Effective therapeutic solutions and control measures for the disease will come from the collective research efforts of clinicians and scientists worldwide. This book presents the current status of the strides being made to understand the fundamental scientific basis of colorectal cancer. It provides contributions from scientists, clinicians and investigators from 20 different countries. The four sections of this volume examine the evidence and data in relation to genes and various polymorphisms, tumor microenvironment and infections associated with colorectal cancer. An increasingly better appreciation of the complex inter-connected basic biology of colorectal cancer will translate into effective measures for management and treatment of the disease. Research scientists and investigators as well as clinicians searching for a good understanding of the disease will find this book useful.

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