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Molecular therapy of colorectal cancer: Progress and future directions

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Mini Review

Colorectal cancer (CRC) remains one of the most common types of cancer and leading causes of cancer death worldwide. Although the introduction of cytotoxic drugs such as oxaliplatin, irinotecan and fluorouracil has improved the treatment of advanced CRC, the individual response to chemoradiotherapy varies tremendously from one patient to another. However, recent progress in CRC molecular therapies may provide new insight into the treatment of this disease. Currently, components of the EGFR, VEGF, Wnt and NF-kB pathways are the most important targets for CRC therapy. This review chronicles the development of molecular CRC therapies over the past few decades. We also provide an update on the current progress of research concerning the molecular pathways leading to CRC and discuss the possible implications for CRC therapy.

Colorectal cancer (CRC) remains one of the most common types of cancer and leading causes of cancer death worldwide. Indeed, despite improvements in diagnostic and treatment modalities, more than 1 million people develop CRC each year, with over 600,000 patients dying of the disease annually.[1] Furthermore, surgery for CRC cannot always prevent the recurrence of advanced CRC and ~25% of CRC patients present with liver metastases at the time of the initial diagnosis. The 5-year survival rate is 10–20% for patients with distant metastatic disease, >80% for patients without lymph node metastasis and 70% even for those with lymph node metastasis without distant metastases.[2] Nonetheless, both surgical and nonsurgical treatments have improved during the past decades.[3]

The recent introduction of cytotoxic drugs, such as oxaliplatin, irinotecan and fluorouracil, has improved the treatment of advanced CRC. However, after the advent of these drugs, it was soon realized that the histopathological response to chemoradiotherapy varied tremendously among patients.[4] Currently, the therapeutic antibody cetuximab, an IgG1 chimeric monoclonal antibody (mAb) against epidermal growth factor receptor (EGFR) and bevacizumab, a mAb against vascular endothelial growth factor (VEGF), have ushered in a new era of targeted therapy against cancer-specific molecular pathways.[5–8]

Although the above improvements have reduced CRC mortality in the past few decades, there is sufficient evidence to suggest that the majority of patients undergoing drug therapy will not benefit and will instead experience severe and even lethal adverse drug events.[9] Therefore, new and better molecular targeted therapies are needed. This review chronicles the development of molecular CRC therapies over the past few decades and provides an update on the current progress of research concerning the molecular pathways leading to CRC, discussing the possible implications for CRC therapy.

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Therapy Targeting WNT Signaling in CRC

Extensive descriptions of the roles of Wnt signaling in development and disease can be found in recent reviews.[10,11] The canonical Wnt/α-catenin signaling pathway involves the sequestration of α-catenin in a complex called the destruction complex. This complex consists of adenomatous polyposis coli (APC), glycogen synthase kinase 3-α (GSK3α), casein kinase 1 (CK1) and Axin. The formation of the destruction complex leads to the sequential phosphorylation ofâ-catenin at serine 45, tyrosine 41 and serines 37 and 33 by CK1 and GSK3α, which in turn stimulates its binding and degradation by the proteasomal complex α-transducin repeat-containing protein (α-TRCP).[12] When Wnt proteins are secreted from

cells, they form a ternary complex with Fzd and LRP5/6, resulting in the activation of Disheveled (Dvl), which sequesters Axin and GSK3α from the cytoplasm to the membrane.[13] At this point, α-catenin cannot be trapped in the APC (destruction) complex and subsequently phosphorylated. This accumulation of α-catenin in the cytoplasm results in its translocation to the nucleus where it interacts with T-cell factor (TCF)/lymphoid enhancing factor to induce the expression of downstream target genes that regulate the cell cycle, proliferation and differentiation. The activation of Wnt/α-catenin signaling is important for both the initiation and progression of cancers of different tissues.[11] Therefore, the disruption of Wnt/α-catenin signaling represents an opportunity for rational cancer chemoprevention and therapy.[11,14] The numerous small molecule inhibitors of and antibodies against Wnt/α-catenin signaling are illustrated in Figure 1 and Table 1.

In CRC, 90% of all tumors have a mutation in a key regulatory factor of the Wnt/α-catenin signaling pathway, resulting in the activation of the pathway and up to 80% of tumors exhibit nuclear accumulation of α-catenin.[15–17] A growing number of bioactive compounds ranging from small molecules to targeted antibodies have proven effective at activating and inhibiting the Wnt/α-catenin pathway in experimental trials.

To identify Wnt pathway inhibitors, Chen and colleagues[18] performed screens using a luciferase-based α-catenin transcriptional readout in mouse L-cells and recognized two classes of inhibitors: IWP and IWR. IWP directly inhibits the activity of Porcupine (Porcupine regulates Wnt ligand maturation) and IWR has been shown to positively affect Axin stability and decrease the pool of free α-catenin that resides in the cytoplasm. Another group[19] has found that compound XAV939 exerts its function *via* a mechanism that is similar to that of IWR: stabilization of the Axin protein and a reduction in the levels of free cytoplasmic α-catenin protein. Furthermore, several compounds, including pyrviniumpamoate, CCT031374, CCT036477 and CCT7070535, have been shown to abrogate α-catenin activation.[20,21] In addition to the direct inhibition of α-catenin, Lepourcel *et al.*[22] found that PKF115–584, CGP049090 and PKF222–815 decreased α-catenin-TCF4 binding in a dose-dependent manner. Additionally, Emami *et al.*[23] reported that the compound ICG-001 competes with α-catenin by selectively binding to CBP. This interaction abrogates the expression of transcription targets of the Wnt pathway, including survivin, cyclin D1 and S100A4.

Recently, several new small inhibitors showed a promising inhibitory effect on Wnt pathway. Sphingadiene and Enigmal could reduce the expression as well as affect the translocation of non-p-β-catenin in colon cancer cells or Apc(Min/+) mice.[24,25] Published reports from other study groups revealed that candidates, including Magnolol,[26] berberine,[27] Lycopene[28] and Genistein[29] attenuates Wnt signaling by inhibiting the components of Wnt pathway in CRC cells or mouse models.

In addition to the direct inhibition of Wnt/α-catenin signaling, another promising new approach for cancer therapy involves specific antibodies against Wnt pathway components. Indeed, recent studies indicate that Frizzled-7 (Fzd7) is a potential therapeutic target in CRC, as it plays an important role in CRC development and metastasis.[30–32] Fzd7 can activate the canonical and/or the noncanonical Wnt signaling pathways in different types of cancers based on the availability of the cognate Wnt protein, the coreceptor and variation in the sequence homology between the different Fzd isoforms. Fzd may interact with various intracellular adaptor proteins in addition to Dvl,[33] and the siRNA-mediated knockdown of endogenous Fzd7 expression decreases the invasive and metastatic potential of colon cancer cells.[30–32]

Therapy Targeting the EGFR Pathway in CRC

EGFR is a 170 kD cell surface tyrosine kinase (TK) transmembrane receptor and member of the human EGFR (HEGFR)-ErbB family of receptor TKs.[34] There are two major pathways that depend on EGFR activation: the Ras/Raf/MEK/ERK pathway and the PI3K/PTEN/AKT/mTOR pathway.[35] Initial evidence for the important role of EGFR in CRC originated from studies showing its increased expression in 60–80% of CRC cases.[36] Furthermore, EGFR expression has been associated with metastasis and reduced survival rates in CRC.[37]

Because intracellular signaling comprises a vastly complex network, the rationale increasingly involves the targeting of more than one signaling pathway or multiple targets within a single pathway to effectively regulate cancer. EGFR is a cellular oncogene and preclinical studies have hypothesized that the blockage of EGFR binding sites with an "antireceptor" mAb would lead to the inhibition of cell growth, thereby constituting an effective anticancer therapy.[37] The inhibitors of and antibodies against the EGFR pathway are summarized in Figure 1 and Table 1. There are two FDA-approved monoclonal antibodies against EGFR, cetuximab and panitumumab and anti-EGFR therapy has become clinically routine since cetuximab was first approved by the FDA in 2004 for the treatment of advanced CRC. Cetuximab is a human-murine chimeric mAb that binds to EGFR, and it is thought to act through the inhibition of the ligand-induced phosphorylation of EGFR.[38] Indeed, the inhibition of natural ligand binding to EGFR results in several different downstream effects, all of which may contribute to the antitumor activity of cetuximab.[39]

However, Anti-EGFR monoclonal antibodies are effective only in a small subset (10%) of mCRC patients.[40] The reasons for such a limited success rate are that genetic alterations in oncoproteins modulating EGFR signaling including KRAS, BRAF, PIK3CA and HER2 contribute to the primary resistance to anti EGFR therapies.[41–43] A systematic review of cost-effectiveness of monoclonal antibodies for metastatic CRC showed that the treatment with cetuximab and panitumumab is mainly considered to be not cost-effective in

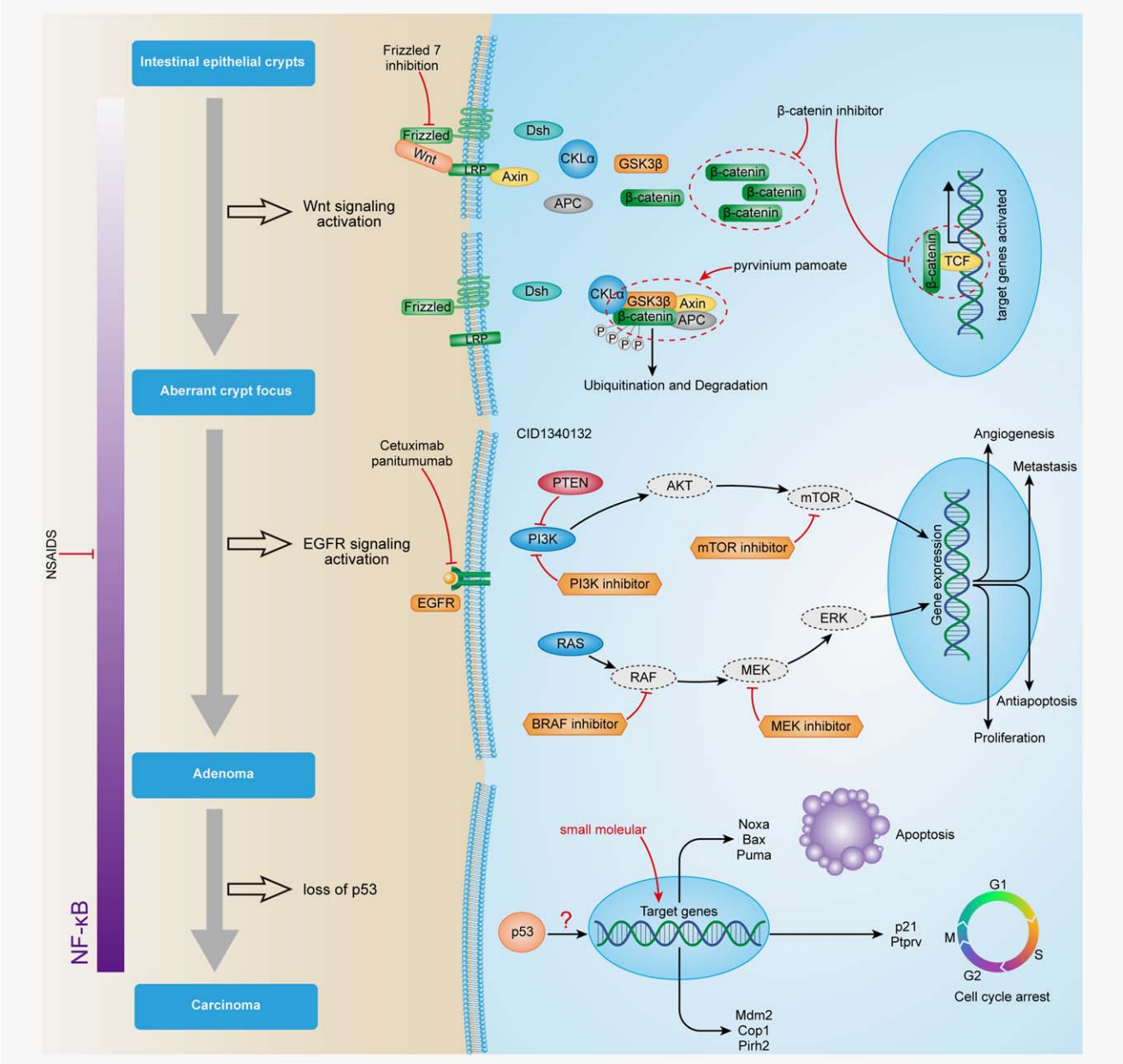

Figure 1. Schematic illustrating numerous antibody, small molecules and biological compounds identified in the literature that inhibit Wnt/β-catenin, EGFR or NF-κb signaling at various points in the pathway. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

patients with mCRC. However, testing for Kirsten ras (K-RAS) oncogene mutation prior to the treatment with cetuximab or panitumumab is found to be clearly cost-effective compared with no testing.[44] Therefore, US FDA approved cetuximab and panitumumab treatment are only for the subgroup of patients with ras oncogene (KRAS) wild-type tumors.

Another problem of cetuximab treatment is an increased risk of severe adverse events. Zhang *et al* performed meta-analysis to investigate severe adverse events in CRC patients. Nine RCTs, involving 8,520 patients with CRC were included. The most common severe adverse events were neutropenia, diarrhea and rash. However, cetuximab was not associated with increased risk of fatal adverse events.[45]

Nevertheless, several clinical trials showed that cetuximab could enhance the antitumor effect of chemotherapy. For example, the overall response rate of a combination of cetuximab and irinotecan, fluorouracil and leucovorin (FOLFIRI) in the treatment of patients with unresectable CRC liver metastases is ~40%, and the rate of conversion to resectable liver metastases is ~30%, thus showing a survival advantage.[46] Van Cutsem *et al.* also showed cetuximab enhanced the antitumor effect of (FOLFIRI) and reduced the risk of progression of metastatic CRC. However, the benefit of

Table 1. List of antibodies and inhibitors in the treatment of CRC

Signaling pathway	Molecular target	Antibodies/inhibitors	Reference
Wnt/b-catenin	Porcupine	IWP	18
	Axin	IWR	18
	Axin	XAV939	19
	β-catenin	Pyrvinium pamoate, CCT031374, CCT036477 and CCT7070535; Sphingadiene and Enigmal	20,21,24,25
	β-catenin-TCF4	PKF115–584, CGP049090 and PKF222–815	22
	β-catenin-CBP	ICG-001	23
	Frizzled-7	Fzd7 siRNA	30–32
EGFR	EGFR	Cetuximab	38
	EGFR	Panitumumab	44
	MEK	AS703026 and AZD6244 selumetinib	51,53
	KRAS	TPT and SC-D	52
	PI3K	XL147, PX866, BKM120	57,58
	Akt	Perifosine, GDC0941	59,61
	mTOR inhibitors	MK2206, VQD-0002, CCI-779 and RAD001	62,63
VEGFR	VEGFR	Bevacizumab Aflibercept	72–74,78
	Integrins and other receptors on endothelial cells	Angiostatin and endostatin	84
	Receptor TK inhibitors	Regorafenib	86
NF-κB	NF-κB	NSAIDs	102,103
	IL-6	Siltuximab	111

cetuximab was limited to patients with KRAS wild-type tumors.[47] Furthermore, a novel mixture of antibody Sym004 provide an alternative therapy force tuxiamab resistance CRC.[48] Sym004 is developed to direct against distinct epitopes on the extracellular domain of EGFR. Unlike cetuximab, Sym004 induces rapid and efficient removal of the receptor from the cell surface by triggering EGFR internalization and degradation.[49]

According to the adenoma-carcinoma sequence model, K-ras mutations that lead to a continuously active protein are involved in the next step of tumor development following APC and can be found in 30–50% of CRC cases.[50] However, as mentioned above, anti-EGFR-therapy with cetuximab has been shown to be ineffective in patients harboring KRAS mutations. Consequently, several strategies have been developed to directly prevent ras signaling. Yoon *et al.* investigated the ability of two MEK inhibitors currently in clinical trials, AS703026 and AZD6244, to address the challenge posed by the resistance of KRAS-mutated CRC to EGFR mAbs. They found that MEK inhibition by AS703026 or AZD6244 suppressed cetuximab-resistant CRC cells induced by K-ras mutations both *in vitro* and *in vivo*.[51] Torrance *et al.*[52] used high-throughput screening strategies with a pair of isogenic CRC cell lines that differ by a single mutation in the KRAS gene to identify four compounds with selective toxicity toward the cell line bearing the KRAS mutation. Among the 30,000 compounds screened, a novel KRAS pathway inhibitor, triphenyltetrazolium (TPT) and a sulphinylcytidine derivative (SC-D) were identified, and these compounds displayed selective activity *in vitro* and inhibited tumor xenografts containing mutant KRAS. In addition, recent studies reported the MEK1/2 inhibitor selumetinib and WNT pathway modulators cyclosporine A showed synergistic antiproliferative effects *in vitro* and *in vivo* models of CRC, suggesting a clinically effective rational combination strategy for patients with metastatic CRC.[53]

In addition to the MAPK pathway, the activity of the PI3K/PTEN pathway is also stimulated by EGFR. Several studies have revealed an important role for the PI3K/PTEN pathway in the development of CRC,[54,55] suggesting that the agents targeting this pathway may be effective for the treatment of CRC. Data from http://clinicaltrials.gov revealed that several inhibitors of the PI3K pathway were being tested in clinical trials, including a PI3K inhibitor (XL147, PX866 and BKM120), an Akt inhibitor (perifosine, GDC0941) and mTOR inhibitors (MK2206, VQD-0002, CCI-779 and

RAD001), suggesting that these kinases may be potentially druggable targets in CRC.

PI3K inhibitors can be divided into two classes: pan-PI3K inhibitors, which target all class IAPI3Ks, and isoform-specific PI3K inhibitors. Since one isoform of PI3K is found to be predominant in driving tumor formation, using isoform-specificPI3K inhibitors would have the advantage of reduced toxicity and fewer off-target effect.[56] Recent studies have showed an essential role for p110β, but not p110α, in mediating PI3K signaling in some PTEN-loss cancers. Thus, these cancers would be more susceptible to p110β-specific inhibitors than cancers with intact PTEN.[57,58]

Perifosine is a well-known AKT inhibitor in the most advanced stage of clinical development. It has displayed evidence of antitumor activity in both *in vitro* and *in vivo* studies.[59–61] The mechanism of such drug is that perfosine binds to the PH domain of AKT and interferes with the binding of the PH domain to phosphoinositides, therefore, preventing recruitment of AKT to the cell membrane, where it would normally be phosphorylated.

mTOR inhibitors are the most clinically advanced class of PI3K pathway inhibitors currently in use. Rapamycin and analogs of rapamycin (RAD001/Afinitor; Novartis, CCI-779/Torisel; Wyeth) have been shown to have clinical activity for breast cancer, glioma and renal cell cancer.[62,63] These agents are currently being used in phase II studies for the treatment of CRC. However, mTORC1 inhibition can lead to feedback activation of the MAPK pathway in aPI3K-dependent manner.[64] The presence of feedback loops in cancer cells has posed challenges in targeting PI3K signaling for the treatment of CRC. Therefore, the use of combining therapies is necessary for the improvement of efficacy of PI3K signaling inhibitors. Recently, Dual PI3K/mTOR inhibitors have been developed to overcome mTORC1 inhibition induced feedback and showed a promising antitumor effect.[65–67] Dual PI3K/mTOR inhibitors, such asXL765 (Exelixis), NVPBEZ235 (Novartis) and SF-1126 (Semafore) are based on the structural similarity between the p110 subunit of PI3K and mTOR.[68] Dual PI3K/mTOR inhibitors became more effective therapy than single agents treatment. However, a key issue should be raised that PI3K/mTOR inhibitors may result in great toxicity in patients due to complete inhibition of PI3K/AKT/mTORC1/2 signaling in noncancerous cells. Therefore, dual PI3K/mTOR inhibitor should be used to cancer cells addicted to oncogenic PI3K signaling, which leads to preferential toxicity compared to noncancerous cells.

Antiangiogenesis in CRC Therapy

Angiogenesis is the process of new capillary formation from pre-existing blood vessels, and it plays an important role in the growth and spread of CRC.[69] Neovascularization promotes tumor growth by supplying nutrients and oxygen and releasing growth factors that promote tumor cell proliferation.[70,71] In humans, there are four VEGF family members, VEGF-A-D and PlGF. VEGF is a diffusible glycoprotein and a crucial positive regulator of both normal and tumor angiogenesis. The binding of VEGF to its receptor (VEGFR) induces cell proliferation and vascularization *via* a TK pathway. In response to ligand-receptor binding, VEGFR TKs activate a network of downstream signaling pathways to induce angiogenesis. Therefore, the VEGF/VEGFR pathway is an attractive target for anticancer drug design. The inhibitors of the VEGF/VEGFR pathway are summarized in Figure 2 and Table 1.

Bevacizumab (Avastin, Genentech) is a humanized mAb that specifically binds to and inhibits the biologic activity of VEGF by preventing its binding to VEGFR-1 and VEGFR-2. On February 26, 2004, the FDA approved bevacizumab as a first-line treatment for patients with metastatic CRC and numerous trials have demonstrated that the addition of bevacizumab improves clinical outcomes in metastatic CRC.[72–74] A meta-analysis of 5 randomized controlled trials showed that the addition of bevacizumab to first-line chemotherapy significantly increased both the progression free survival (PFS) and overall survival (OS) by 17.1 and 8.6%. Female and patients with primary rectal tumors seemed to benefit most.[75] However, there was controversy regarding the aforementioned findings in two large III trials. NSABP PROTOCOL c-08 trial showed that the addition of bevacizumab to modified FOLFOX6 as adjuvant treatment for 1 year did not significantly prolong disease free survival stages II and III colon cancer.[76] AVANT trial showed that Bevacizumab does not prolong disease-free survival when added to adjuvant chemotherapy in resected stage III colon cancer. Furthermore, OS data suggest a potential detrimental effect (including neutropenia, diarrhea and hypertension) with bevacizumab plus oxaliplatin-based adjuvant therapy in these patients. Serious adverse events were more common in the bevacizumab groups than in the FOLFOX4 group.[77] Therefore, serious side effects and complications should be considered before bevacizumab was used.

Aflibercept (Regeneron), a novel recombinant fusion protein, is an angiogenic factor trap that blocks the binding of VEGF-A, VEGF-B and placental growth factor (PIGF). The fusion protein consisting of the extracellular domains of human VEGFR-1 and -2 fused to the Fc portion of human IgG1.[78] Aflibercept has a higher VEGF-A binding affinity than bevacizumab. Furthermore, aflibercept also has the ability to bind to VEGF-B and PIGF, in contrast to bevacizumab in which binds VEGF-A only, providing more complete blockade of angiogenesis.[79,80] Phase I/II clinical trials have demonstrated effective activity in mCRC, with acceptable safety and tolerability. A recent phase III randomized double-blind trial in patients previously treated with oxaliplatin reported significant improvement in OS, PFS and RR with aflibercept compared to placebo when administered in combination with irinotecan and fluorouracil.[81] Interestingly, cost-effectiveness analysis compared treatment with bevacizumab with aflibercept in combination with chemotherapy was conducted using the Bucher method using hazard ratios from

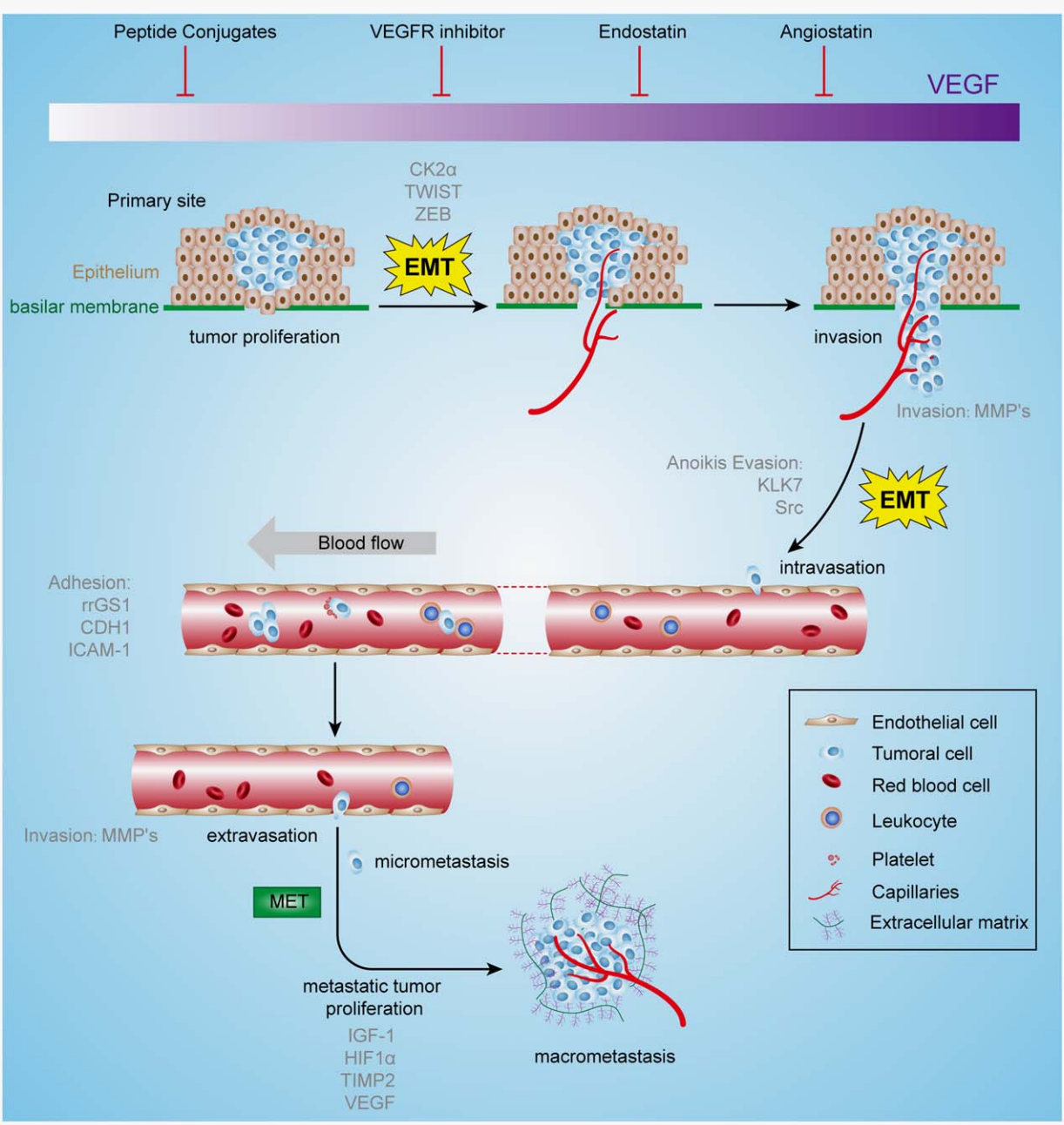

Figure 2. Angiogenesis is crucial for tumor survival. Bevacizumab or other inhibitors play an important therapeutic role in the treatment of patients with metastatic cancer. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

ML18147 and VELOUR.[82] The studies showed that the effectiveness of addition of bevacizumab to chemotherapy was similar to aflibercept, but adverse event rates and costs were higher for aflibercept compared with bevacizumab plus chemotherapy.

Angiostatin and endostatin are the best known endogenous inhibitors of angiogenesis.[83] Angiostatin and endostatin bind to a plethora of cell surface, soluble and matrix-associated targets. By binding to integrins and other receptors on endothelial cells (ECs), angiostatin and endostatin inhibit EC proliferation, migration, invasion and vascular morphogenesis *via* a variety of pathways.[84] Zhou *et al.*[85] evaluated the efficacy and safety of the combination of Endostar (a novel recombinant human endostatin) and chemotherapy in patients with metastatic CRC and concluded that the combination was well tolerated in patients with metastatic colorectal and gastric cancers and that it was relatively effective as a first-line therapy.

Additionally, small molecule RTKIs (receptor TK inhibitors) targeting VEGF and other signaling pathways have recently been developed. Some of the most clinically relevant RTKIs include sunitinib, pazopanib, sorafenib, vandetanib,

cabozantinib and most recently, axitinib, tivozanib and linifanib. Notably, the Phase III study has showed improved outcome in patients with metastatic CRC who were heavily pretreated when they received regorafenib.[86] Regorafenib (BAY73-4506) is an active multikianse inhibitor targeting abroad range of angiogenic, stromal and oncogenic kinases.[87] In preclinical studies, CRC xenograft exhibited a decreased vascular formation and tumor growth *in vivo* after treatment with regorafenib.[87] The Phase III trial showed that median OS was 6.4 months in the regorafenib group versus 5.0 months in the placebo group (hazard ratio 0.77; 95% CI 0.64–0.94), suggesting a potential new line of therapy with survival benefits in metastatic CRC, which has progressed after all standard therapies.[86]

Inflammation and CRC Therapy

In recent years, several studies have revealed the connection between inflammation and carcinogenesis.[88,89] In chronic inflammation, cytokines and chemokines produced by inflammatory cells propagate the localized inflammatory response and enhance the survival of premalignant cells by activating the NF-kB pathway. The core nuclear factor of inflammation NF-kB has been shown to be activated in all cells, and it regulates the expression of a diverse array of target genes that promote cell proliferation and contribute to the pathogenesis of various diseases, including cancer.[90,91] Cyclin D1 and cMyc, two target genes of NF-kB, have important roles in cell growth and proliferation.[92,93] Key angiogenesis factors, such as VEGF and interleukin-8, are also downstream effectors of NF-kB.[94] Furthermore, NF-kB can inhibit apoptosis by regulating such anti-apoptotic proteins as inhibitor of apoptotic proteins (IAPs)[95] or by inhibiting prolonged c-Jun N-terminal kinase activation and the accumulation of reactive oxygen species.[96]

NF-kB is aberrantly activated in 50% of CRC patients and those with colitis-associated tumors, and mouse studies have established that NF-kB plays a role in the development of colitis-associated cancer.[97,98] As the NF-kB signaling pathway plays a pivotal role in apoptosis, tumor promotion and tumor maintenance, inhibitors of this signaling pathway (summarized in Figure 1 and Table 1) would be useful in CRC therapy.

NSAIDs exhibit antineoplastic activities in the colon,[99] and several studies suggest that NF-kB is an NSAID target.[100] Stimulation of NF-kB expression may be inhibited by various NSAIDs,[101] indicating that NSAIDs may be chemopreventive agents for cancer treatment. Several studies, including randomized trials, have shown that the regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with decreased CRC incidence and mortality.[102,103] However, traditional NSAIDs, such as aspirin, inhibit both isoforms of cyclooxygenase (COX-1 and COX-2). The inhibition of the COX-1 enzyme induced by nonselective NSAIDs mediates their gastrointestinal tract toxicity. A variety of adverse events have now been associated with long-term use of NSAIDs. Symptomatic ulcers and ulcer complications associated with the use of conventional NSAIDs may occur in ~1% of patients treated for 3–6 months and in 2–4% of patients treated for 1 year.[104] Compared with traditional NSAIDS, Coxibs (celecoxib, rofecoxib) have higher COX-2 selectivity and have been shown to have less gastrointestinal toxicity than traditional NSAIDs.[105] Furthermore, an population-based case-control study indicated selective COX-2 inhibitors may reduce the development of CRC by at least 10% based on the medication possession ratio evaluated, suggesting chemopreventive effects of selective COX-2 inhibitors against cancer in individuals at no increased risk of CRC.[106]

Another promising anti-inflammation target is proinflammatory cytokinesIL-6. IL-6 seems to take a center stage in human cancer development. Knüpfer *et al.* demonstrated that IL-6 expression can be associated with tumor stage, size, metastasis and survival of patients with CRC.[107] In fact, several therapeutics inhibiting the IL-6 have been developed for the treatment of human disease. Anti-IL-6 antibodies were among the first therapeuticsin clinical studies on human cancer during the 1990s.[108,109] However, the antitumor effect is limited and this murine original antibodies induce severe immune response against this therapy.[110] Therefore, chemic human-murine anti-IL-6 monoclonal Siltuximab was developed to improve the Efficacy of anti-IL-6 antibody.[111] A clinical trial analyzing efficacy of Siltuximab (CNTO 328) with solid tumors (Ovarian, Pancreatic, Colorectal, Head and Neck and lung Neoplasms) was just completed. However, the study results are still awaited. (http://clinicaltrials.gov/ct2/show/study/NCT00841191).

Conclusions

The promising developments in CRC molecular therapy and the current progress of research concerning the molecular basis of the disease over the past few decades clearly demonstrate that CRC is an excellent platform for oncology research. EGFR, VEGF and Wnt pathway components currently constitute the most important targets of CRC therapy. However, to our knowledge, no therapeutic strategy has thus far been able to provide more than a delay of disease progression, a situation that has been largely attributed to the ability of cancer cells to adapt to their changing microenvironment and the expansion of resistant cell clones. Thus, the development of combinatory therapies in addition to new techniques, including RNA silencing, functional genomics and nanomedicine, should be introduced into CRC therapy. Moreover, new drugs specifically designed to target the relevant signaling pathways are still needed. For example, mutations in TP53 are among the most frequent genetic alterations in CRC; thus, drugs targeting the p53 pathway may protect cells from uncontrolled proliferation. As further details regarding the pathways involved become available, new therapeutics will be developed and, in turn, contribute to the study of oncology and the treatment of other cancers.

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