Targeting the tumor microenvironment as a potential therapeutic approach in colorectal cancer: Rational and progress

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Colorectal cancer (CC) is often diagnosed at a late stage when tumor metastasis may have already occurred. Current treatments are often ineffective in metastatic disease, and consequently late diagnosis is often associated with poor outcomes in CC. Alternative strategies are therefore urgently required. An interaction between epithelial cancer cells and their tissue microenvironment is a contributor to metastasis, and therefore recent studies are beginning to focus on the properties of the tumor microenvironment and the mechanism by which the metastatic cells exploit the tumor microenvironment for survival, immune evasion, and growth. We have reviewed the development of the combined therapeutic approaches that have focused on targeting the microenvironment of CC.

KEYWORDS
colorectal cancer, extracellular matrix, fibroblast, microenvironment

1 | INTRODUCTION

Colorectal cancer (CC) is a common condition that often has a poor prognosis (Bahrami, Hassanian, et al., 2017). CC is a heterogeneous disease, with many differences in its clinical manifestation, molecular profiles, and prognosis (Bahrami, Shahidsales, et al., 2017).

A large proportion of early-stage patients are successfully treated with aggressive surgical resection of the primary tumor (Bahrami, Aledavoud, et al., 2017). However, many patients with stage II/III disease have recurrent disease, and this is frequently associated with metastases (Gholamin et al., 2014). Patients with stage IV disease and...
metastases, and those with a high risk of relapse, receive cytotoxic chemotherapy (Bahrami, Khazaei, et al., 2017). A combination of folinic acid, 5-fluorouracil (5-FU), and oxaliplatin/irontecan is often used to treat CC (Bahrami, Hesari, et al., 2017). However, adjuvant chemotherapy is not very effective in metastatic disease, and may lead to drug resistance and disease progression (Bahrami, Amerizadeh, ShahidSales, et al., 2017).

In second-line treatment, targeted therapy is added to chemotherapy, to interrupt specific cellular mechanisms, or signaling pathways (Hosseini et al., 2016). For examples, in CRC, monoclonal antibodies to the epidermal growth factor (EGF) receptor may be used, as this is often involved in the proliferation of CC cells (ShahidSales, Mobarhan, Ghasemi, Gholamin, & Avan, 2015). Bevacizumab, afibercept, and regorafenib are anti-angiogenic drugs currently approved for the treatment of metastatic CRC (Table 1). However, drug resistance and the variable response to treatment are reasons for the need to better understand the mechanisms of disease and the development of predictive biomarkers (Bahrami, Hassanian, et al., 2017).

To improve patient classification and identify putative molecular targets for therapy, large collections of transcriptomic databases from tumor specimens have been generated (Mirzaei et al., 2016). Several CRC subtypes are now recognized, based on their unique global gene expression profiles (Felipe De Sousa et al., 2013).

Colorectal cancer tissues are characterized by a cellular/molecular heterogeneity, representing a mixture of normal epithelial ducts, invasive or in situ tumor cells, surrounding stroma, blood vessels, infiltrating cells of immune system, and the extracellular matrix (ECM) (Bahrami, Amerizadeh, Hassanian, et al., 2017). Moreover, tumor heterogeneity can also be mediated via genetic and epigenetic alterations in tumor mass (Kreso & Dick, 2014). Approximately 20% of cancer-related mortality is reported to be related to unresolved chronic inflammation, leading to cellular transformation and enhanced invasive condition of tumor cell (Rahmani, Avan, Hashemy, & Hassanian, 2017). It has also been shown that chronic tissue damaging can modulate cell growth, immune regulatory cytokines, and tissue-remodeling enzymes (Bahrami, Hesari, et al., 2017; Vatandoost et al., 2016).

An increased expression of mesenchymal genes in epithelial cancer cells has led to the suggestion that an epithelial-to-mesenchymal transition (EMT) relates to a poor prognosis in patients with CRC (Kalluri & Weinberg, 2009). However, the transcriptome of a tumor containing tissue represents the expression profile of the epithelial cancer cells as well as the mesenchymal cells that form the TME. This microenvironment, or stroma, comprises connective tissue, that has functional and structural roles in homeostasis and in pathological condition such as wounding or illness. The stroma consists of fibroblasts, immune cells, blood and lymphatic vessels, and ECM. The stroma has a complex, and dynamic composition which is transformed by cancer cells and can enhance malignant progression (Peddareddigari, Wang, & DuBois, 2010). In this review, we discuss the combined approaches to treatment that focus on targeting the microenvironment of colorectal tumors.

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<tr>
<th>Drug</th>
<th>Indication</th>
<th>Mechanism of action</th>
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<tr>
<td>Bevacizumab</td>
<td>First or second-line mCRC</td>
<td>Monoclonal antibody (mAb) binding to VEGF-A</td>
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<td>Regorafenib</td>
<td>Third-line mCRC as monotherapy</td>
<td>Multikinase inhibitor of VEGFR-2, PDGFR, TIE-2, FGFR, RET, and c-kit</td>
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<tr>
<td>Afibercept</td>
<td>Second-line mCRC+FOLFIRI</td>
<td>VEGF decoy binding to VEGF-A, VEGF-B, and PIGF</td>
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2. THE TISSUE MICROENVIRONMENT IN COLORECTAL CANCER

Normal cells can send negative and positive signals to tumor cells. Furthermore, cancer cells can modify cells within their microenvironment to produce and secrete different chemokines, growth factors, and matrix-degrading enzymes which increase the development and invasion of the tumor. Additionally, these recruited normal cells provide a support system for tumor cells to retreat after traditional cytotoxic therapies. The TME may stimulate transformations in the stroma, such as changes in blood flow and interstitial fluid pressure enhancement, and these changes may reduce the effectiveness of anticancer drugs. The composition of the TME during colorectal carcinogenesis and in advanced tumors is not fully understood. But it is clear that TME composition is different from normal intestinal stroma (Peddareddigari et al., 2010). It has been reported that the majority of genes that predict cancer relapse are amplified in cancer-associated fibroblasts (CAFs), but not in the tumor cells (Calon, Espinet, et al., 2012). The significant prognostic value of the TME comes from the opportunity to more precisely calculate the risk of recurrence of any given CRC patient at stages I–III. It also provides the way for developing further molecular stratifications that take regard of the composition of the microenvironment. Galon and others have established a relevant primary example of ecological stratification of colorectal tumor (Galon, Costes, et al., 2006; Galon, Mlecnik, et al., 2014). They reported that infiltration of the tumor mass by a subgroups of T cells can predict prolonged disease-free survival following chemotherapy. Furthermore, stratification of CRC according to the type and characteristics of stromal cells will be important for the classification of patients prior to treatments using TME targeting. Because CRC cells rely on stromal factors to proliferate and migrate, therapeutic agents that alter the CRC ecosystem may be effective in preventing or treating metastatic disease. An additional benefit of TME targeting is its genetic stability, leading to the development of less drug resistance (Joyce, 2005). Moreover, the commonality of the various stromal elements between cancer types offers the prospect of
a wider spectrum of applicability. Several treatment strategies based on the above concept have been developed for a handful of cancers and are now being used as discussed further.

2.1 | Target TME in clinical

2.1.1 | Anti-angiogenesis therapy

Angiogenesis is a process in which new blood vessels are formed from existing blood vessels. This process is important for the transportation of oxygen and nutrients (Gholamin et al., 2014). Angiogenesis is composed of five steps: (i) endothelial cell activation; (ii) basement membrane degradation; (iii) endothelial cell spread; (iv) blood vessel formation; and (v) angiogenic remodeling. Hypoxia enhances the transcription of cellular hypoxia inducible factor (HIF), causing the overexpression of pro-angiogenic proteins such as tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF); and platelet-derived growth factor (PDGF) (Mirzaei et al., 2016). The ability of tumors to advance from a nonangiogenic to angiogenic phenotype (angiogenic switch) is central to the development/progression of tumor cells (Gholamin et al., 2014; Vatandoost et al., 2016).

Previous studies have found that signaling by vascular endothelial growth factor A (VEGF-A) via the VEGF receptor-2 (VEGFR-2) is involved in the recruitment of myeloid-derived suppressor cells (MDSCs) precursors (Figure 1). In addition, once inside the tumor, MDSCs undergo further maturation, transforming into tumor-promoting macrophages. Other angiogenic factors, such as placental growth factor (PIGF), can either directly or indirectly induce angiogenesis by affecting a broad range of cell types, or through attracting macrophages and MDSCs into the TME (Giordano et al., 2014). PIGF activates pathological angiogenesis and inflammation by collaborating with alternative pathways through VEGFR-1 signaling (Figure 1). This is because myeloid cells are principally regulated by VEGFR-1 and not VEGFR-2, and PIGF has a complementary role, independent of VEGF-A (Fischer, Mazzone, Jonckx, & Carmeliet, 2008). It has been proposed for more than 40 years that targeting angiogenesis may be a potential therapeutic intervention in cancer treatment. More than 1,000 clinical trials have been undertaken using anti-angiogenic agents.

Endothelial cells and blood vessel formation have been extensively targeted by anti-angiogenic therapy (Carmeliet & Jain, 2011). A monoclonal antibody (mAb) against VEGF (i.e., bevacizumab) prevents angiogenesis and has been reported to improve survival in patients with stage IV CC (Table 1) (Mathonnet et al., 2014). Metronomic chemotherapy, targeting vascular endothelial cells, may forestall drug resistance and inhibit angiogenesis; it has shown promise for extending survival and lowering tumor spread in preclinical models. This approach is undergoing investigation in clinical trials (Pasquier, Kavallaris, & André, 2010). However, the results of antiangiogenic therapies have been contentious, with a lack of response in most patient groups. There have been some reports that suggest that anti-angiogenic drugs may lead to a switching on of an “vasoinvasion switch” of tumor cells, causing enhanced metastasis and a reduced life span in mice (Ebos & Kerbel, 2011; Páez-Ribes et al., 2009). These studies suggest a possible role of microenvironmental defense strategies in drug resistance, which may result in a more invasive and aggressive tumor phenotype. Phase III randomized studies in patients with CRC did not confirm the hypothesis that there may be an aggravation of cancer consequent of anti-VEGF therapy (Miles et al., 2010). These findings on the application of antiangiogenic compounds have resulted in the optimization of antiangiogenic drugs as adjuvant/neoadjuvant therapies combined with traditional cytotoxic treatments. It is notable that clinical trials using antiangiogenic compounds were mainly performed in advanced stages of tumor progression, whereas the most promising preclinical studies were conducted in animal models during early stages of tumor progression. Furthermore, antiangiogenic compounds used in the clinic mainly target the blocking of the VEGF cascade, while VEGF-independent angiogenic factors, such as PIGF, fibroblast growth factor, angiopoietins, ECM, and matrix metalloproteases (MMPs) molecules, are worth considering (Barker, Cox, & Erler, 2012). Also, new multitarget anti-angiogenic agents may have promise for the future of anti-angiogenic therapy. The expression of MMP-2 and MMP-9, and other family members, is elevated in advanced stage of CRC patients and is often associated with reduced survival (Hilska et al., 2007). Hence, MMP inhibitors (MMPIs) are also being assessed as potential tools to be applied in a clinical setting. The early studies used broad spectrum inhibitors that had off-target effects; so, more recent studies have used a more targeted approach to MMP inhibition (Roy, Yang, & Moses, 2009).

2.1.2 | Cancer stem cell therapies

There is growing evidence that there is an association between the presence of cancer stem cells (CSC) and resistance of tumor cell to chemotherapy or irradiation. It is also reported to be associated with
metastatic and aggressive behavior of tumor cells (Kelly, Dakic, Adams, Nutt, & Strasser, 2007; Rahmani et al., 2017; Tajbakhsh et al., 2017). Intratumor heterogeneity (e.g., CSC in tumor mass) related with heterogeneous protein function might perturbate tumor adaptation and therapeutic failure (Gerlinger et al., 2012). Other cell types that include stromal cells, immune cells, niche cells, and vascular derived cells, present in the tumor and its microenvironment, may also experience pathological alterations, serving as a “fertile soil” for CSCs (Egeblad, Nakasone, & Werb, 2010). These results suggest that the targeting of CSCs alone is inadequate; and targeting the TME is also necessary for effective treatment.

2.1.3 | Immunotherapy

Another treatment directly targeting TME is immunotherapy. It has been suggested that several chemotherapies, such as 5-FU and platinum compounds, while not targeting immunity, depend on immune components. These conventional chemotherapies may act, in part, by supporting tumor immune-surveillance, particularly when they stimulate immunogenic cancer cell death (Zitvogel, Galluzzi, Smyth, & Kroemer, 2013).

Immunoablation is a well-known risk factor for gastrointestinal tumorigenesis. It includes different pathways involving various immune cells that appear to affect every stage of cancer proliferation and metastasis (Griwennikov, Greten, & Karin, 2010). Although the immune system may act as a strong tumor suppressor through the coordinated eradication of aberrant cells, tumors may evolve ways to survive, and there is evidence for immune-selection in many tumors, including CRC. For instance, the number of neoantigens in remaining cancer cell subclones is lower than would be expected according to the mutation rates. Tumor cells also acquire resistance to immunity, for example, by limiting antigen presentation (Schumacher & Schreiber, 2015). Furthermore, inflammatory mechanisms may also facilitate cancer progression (Griwennikov et al., 2010). An understanding of the mechanisms of progression, the antitumor response, and how cancer cells can subvert immune regulation to promote immune suppressor cells and generate pro-tumorigenic factors that support cancer cells may provide novel therapeutic approaches (Galluzzi et al., 2014). To achieve better outcomes, a therapy should reduce the cellular or molecular cross-talk of immune suppression as well as enhance T cell survival, infiltration, proliferation, and activation in the TME.

Regulatory T (\(T_{reg}\)) cells form part of the TME, and have varied immune modulatory functions in cancers. Under normal physiological conditions, \(T_{reg}\) cells modulate the proliferation and activation of B and T cells and have an important role in preserving the homeostasis of the innate cytotoxic lymphocytes (Gasteiger et al., 2013). Because of their complex regulatory functions in response to various environmental stimuli, it is likely that \(T_{reg}\) cells have different effects on tumorigenesis. In hepatocellular carcinoma and breast cancer, elevated numbers of \(T_{reg}\) cells are associated with decreased overall survival (Bates et al., 2006), while in other types, such as CRC, \(T_{reg}\) cells are correlated with an improved survival (Frey et al., 2010).

2.1.4 | Targeting CAFs

Cancer-associated fibroblasts (CAFs) or myofibroblasts are usually the predominant non-malignant tumor type in the cancer stroma. The origin of CAFs is not well understood; they may from epithelial cells via conversion from resident fibroblasts or through the EMT process, mesenchymal cells, adipocytes, or hematopoietic stem cells (Figure 2) (McDonald & LaRue, 2012). Transforming growth factor-\(\beta\) (TGF-\(\beta\)) is a tumor-derived factors that can mediate the transdifferentiation of normal fibroblasts into CAFs (Rønnov-Jessen & Petersen, 1993).

CAFs may be identified and quantified in patient tissue samples by staining for alpha smooth muscle actin (\(a\)-SMA), fibroblast-specific protein-1 (FSP-1/S100A4), or PDGF-\(\beta\) (Tommelein et al., 2015). CAFs stimulate cancer cell proliferation, survival, propagation, and invasion by secretion of different growth factors and cytokines, such as TGF-\(\beta\), HGF, stromal cell-derived factor-1\(\alpha\), and interleukin-6 (IL-6) (Bhowmick, Neilson, & Moses, 2004). Furthermore, CAFs secrete ECM and proteases including cathepsins, plasminogen activators, and matrix metalloproteases, consequently induce EMT and increase invasive growth of CRC cells (Tommelein et al., 2015). It has been shown that the 5-gene signature derived from CAF (CCL11, AMIGO2, ULBP2, SLC7A2, and PDLM3) predicts risk of recurrence in stage II patients precisely compared to conventional clinicopathological criteria alone (Berdiel-Acer et al., 2014). Interestingly, CAFs amplify the membrane-bound serine protease, fibroblast activation protein (FAP) which is not detectable in normal fibroblasts. The expression of FAP has been correlated with an overall worse prognosis in the several cancer types, such as CRC (Brennen, Rosen, Wang, Isaacs, & Denmeade, 2012). FAP is predominantly localized to the stroma surrounding tumor cells; but is not present in the stroma of normal tissue, and so it is an excellent candidate for cancer-targeted therapies (Xing, Saidou, & Watabe, 2010). However, several studies targeting FAP with sibrotuzumab (a humanized mAb) failed to show any clinical benefits in CRC.

![FIGURE 2](origin_of_CAFs.png) Origin of CAFs. Schematic representation of cells may transit to CAFs in microenvironment. CAF, cancer-associated fibroblast; NF, normal fibroblast; MDSC, mesenchymal-derived stem cell; EMT, epithelial–mesenchymal transition; EC, endothelial cell; ASC, adipose tissue-derived stem cell.
2.1.5 | Targeting TGF-β

TGF-β is a multifunctional polypeptide that plays a crucial role in proliferation, differentiation, and embryonic development of normal tissues.

TGF-β is synthesized and secreted into the microenvironment by tissue cells and binds to unique TGF-β receptors for autocrine and paracrine signaling. TGF-β has a dual activity in CRC: tumor-suppressive roles in the early stages and increasing disease progression in advanced stage (Calon, Espinet, et al., 2012; Calon, Lonardo, et al., 2015). The pro-metastatic effects of TGF-β on the TME occur independently from the signaling in epithelial tumor cells since many tumors silence the epithelial pathway during progression. TGF-β signaling may be a tumor-suppressor cascade in colon tumorigenesis because it induces a strong cytostatic response within epithelial cells (Calon, Lonardo, et al., 2015). Indeed, nearly 40% of CRCs have loss-of-function mutations in the TGF-β pathway elements which lead to the adenoma–carcinoma transition (Cancer Genome Atlas Network, 2012). Initially, Kawata and colleagues found a positive effect of TGF-β signaling in disease development and reported that serum TGF-β1 levels predict recurrence in CRC patients (Tsushima et al., 2001). However, it was later shown that mRNA levels of TGFB1, TGFB2, and TGFB3 correlate with a reduced disease-free survival post-chemotherapy in stages I–III CRC patients. Increased TGFB1–3 regulation is associated with the TGF-β response gene signatures (TBRS) overexpression in cells of the TME, particularly in T cells, endothelial cells, macrophages, and most prominently CAFs. TBRSs have a strong predictive power for cancer relapse in CRC (Calon, Espinet, et al., 2012). Indeed, several proteins overexpressed in TGF-β–activated CAFs predict a high risk for relapse (Calon, Lonardo, et al., 2015). Moreover, comparison of molecular subtypes has demonstrated that the major signaling cascade deregulated in CRC is the TGF-β pathway (Guinney et al., 2015). Many genes are differentially expressed in CRCs that predict a high probability of relapse is related to the TBRSs and TGF-β-inducing genes in CAFs. The role of activated TGF-β in disease development has been demonstrated in advanced CRC experimental models, where induced TGF-β signaling in the TME putatively promotes metastatic burden (Calon, Espinet, et al., 2012). It has been found that increased TGF-β signaling in the TME correlates with a poor prognosis. The stromal TGF-β response leads to an increase of growth factors, cytokines, and ECM proteins. Many of them play important roles during disease development and metastasis in different cancer types. Among these potential therapeutic targets is interleukin-11 (IL-11), a cytokine secreted by TGF-β-activated fibroblasts and that induces a pro-survival response in CRC cells during tumorigenesis and metastatic colonization (Calon, Espinet, et al., 2012).

It has been observed that disseminated tumor cells develop as part of the TGF-β–activated environment, so this dependency could be applied in the clinical setting in order to patient treatment. The pharmacological suppression of stromal TGF-β signaling could potentially block metastatic colonization in mice (Calon, Lonardo, et al., 2015).

Several therapeutics targeting TGF-β pathway have been developed (Akhurst & Hata, 2012; Neuzillet et al., 2015). These include small-molecules that inhibit receptor kinase domains, antisense oligonucleotides (ASO) to TGF-β ligand mRNA, mAb against ligands or receptors, vaccines, and adoptive cell transfer strategies (Akhurst & Hata, 2012; Neuzillet et al., 2015) (Table 2). TGF-β inhibition may work as immunotherapy.

2.1.6 | Chromosomal instability in TME cells

Chromosomal instability (CI) is a result of aberrant segregation of chromosomes and aneuploidy (Rajagopalan, Nowak, Vogelstein, & Lengauer, 2003). Molecular mechanisms behind the CI are not well

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<th>Table 2: Clinical trials for TGF-β-targeted therapies in CRC</th>
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<td>Type</td>
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<td>Kinase inhibitors</td>
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<td>Kinase inhibitors</td>
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MAb, monoclonal antibody; ALK, activin receptor-like kinase; ASO, antisense oligonucleotides.

*From www.clinicaltrial.gov.
understood. Mitotic checkpoint proteins are disregulated in cancers with CI (Rajagopalan et al., 2003). Cancer cells unsuccessful in stopping the cell cycle since DNA repair can be executed. A CI signature related with tumor has been identified in which 29 of 70 included genes are mitotic regulators (Roschke et al., 2008).

Chemokines and growth factors expressed by inflammatory cells in the TME induce overexpression of c-Myc in tumor cells. c-Myc alters the expression of many target genes correlated to cell growth, development, apoptosis, and invasion. Although, c-Myc can trigger intrinsic mutation in tumoral cells. c-Myc accelerates double-strand break (DSB), and activate Ras (Halazonetis, Gorgoulis, & Bartek, 2008), leading to abnormal and incomplete DNA synthesis (Dominguez-Sola et al., 2007). Moreover, c-Myc drives abnormal DNA synthesis as a result of the overexpression of cyclin B1, specifically when combined with p53 deficiency (Taylor et al., 1999). Altogether, c-Myc delays prometaphase stimulating chromosomal mis-segregation through direct transactivation of checkpoint proteins (Menssen et al., 2007) and alleviates p53 function (Vafa et al., 2002). Inflammatory mediators modulate the effect of DSB repair systems. Bcl-2 is overexpressed in cancer cells by a different stimulus from the TME via NF-kB activation (Karin, 2006). Bcl-2 prevents DSB repair leading to elevated rates of inducible and spontaneous mutagenesis through post-translational modification (Saintigny, Dumay, Lambert, & Lopez, 2001). Different cytokines and growth factors can activate the signal transducer JAK-2 and mutated and wild type JAK-2 enhance the homologous recombination pathway leading to CI (Plo et al., 2008).

Inflammatory TME is involved in genome destabilization in cancer, alongside the microsatellite instability (MSI) and CI in non-cancer-associated inflammatory states. The mutation rate in the inflamed TME is higher compared to normal tissues (4 × 10^{-8} v.s. < 1 × 10^{-9} per base pair) (Bielas, Loeb, Rubin, True, & Loeb, 2006). MSI and p53 mutations have been identified in ulcerative colitis patients with negative dysplasia (Brentnall et al., 1996; Hussain et al., 2000).

Also, loss of heterozygosity (LOH) alterations in gene copy number of specific loci and somatic mutations in tumor suppressor genes, such as p53 and PTEN, are found in the genome of tumor-related stromal cells (Weinberg, 2008). Inconsistently, genetic alterations in CAFs of breast and ovarian cancers were not confirmed (Qiu et al., 2008). These contrasting results may be due to the technical differences, so more well-controlled researches are necessary to approve the idea of somatic mutations as well as coevolution of stromal cells in the TME (Weinberg, 2008).

### 2.1.7 Non-cellular properties of the TME

Interactions between host and cancer cell occur within a dense ECM framework that modulates and influences the features of both host and cancer cells. The non-cellular components of the TME are now known as major regulators of cancer development. Cross-talk between the non-cellular and cellular compartment of the TME was recognized as a major determinant in cancer proliferation and propagation. The non-cellular environment includes ECM compounds, and chemical and physical variables such as pH, interstitial pressure, oxygen tension, and fluid flux. The influences of ECM change as a part of the tumor ecosystem affect cancer cell behavior. For instance, hypoxia has been significantly associated with tumor metastasis and poor outcome for CRC patients. In fact, insufficient oxygen prevents tumor cell division while also selecting for malignant cells, and stimulating cell adaptations supporting for more invasive behavior. So, hypoxia is strongly linked with tumor progression and dissemination. This is because low oxygen tension is associated with an increased cell invasiveness, switching cells to anaerobic metabolism, enhance genetic instability, and increase angiogenesis (Michieli, 2009).

The intracellular pH of cells in healthy tissues and tumors is resembled; however, tumors have a lower extracellular pH in proportion to normal tissues (6.0 and 7.0 v.s. 7.4) (Cardone, Casavola, & Reshkin, 2005; Van Sluis et al., 1999). An elevated rate of glycolysis in hypoxic tumor cells results in a lower pH and pO2 and ultimately tumor progress from in situ to invasive cancer (Fang, Gillies, & Gatenby, 2008).

Currently, ECM and their metabolites provide a dynamic component of the TME that regulates cell proliferation, invasion, migration, angiogenesis, and metastasis. For instance, Lysyl oxidase (LOX) cross-links elastin and collagen molecules in the ECM (Csizsar, 2001). At present, LOX is the only tumor-secreted factor found to directly contribute to the formation of pre-metastatic niche. Increased LOX expression related to metastasis form, propagation, and worse overall survival in many cancers (Erler et al., 2006). LOX expression is related to hypoxia and is increased in hypoxic tumors (Erler & Giaccia, 2006). Altogether, any distortion of ECM synthesis, density, degradation, and rigidity can significantly affect the capacity of the TME to increase cancer cell proliferation, dissemination, and invasion, as well as regulate inflammatory responses and lymphangiogenesis. Thus targeting the ECM may be a promising therapeutic target in future (Barker et al., 2012).

### 2.2 Improvement in tumor drug delivery

The achievement of many anticancer treatments, when they target the host or tumor cells, relies on effective drug delivery. One of the causes for the failure of many chemotherapeutic agents is the development of multidrug resistance, as well as microenvironmental influences, such as cell adhesion-mediated drug resistance (CAM-DR), and elevatins in interstitial fluid pressure (IFP). TME can impact on the efficacy and bioavailability of anticancer drugs (Morin, 2003). Anticancer drugs can only be therapeutically effective, if they are distributed widely in the tumor circulation, cross the vessel wall, and pass into the ECM. Many barriers exist that prevent drug transport, such as heterogeneous microenvironment within a tumor. One of these obstacles is an increase in IFP which is significantly higher within tumors than in normal tissues (Heldin, Rubin, Piertas, & Östman, 2004). Elevated IFP is caused by alterations in the ECM composition, contraction of the interstitial space mediated by fibroblast, and a nonfunctional lymphatic system within the tumor. Also, the chaotic nature of the tumor vasculature results in leaky, dilated, circuital tumor vessels (Carmeliet & Jain, 2000), which may further limit drug delivery.
Several strategies have been adopted to address these environmental blockages; decreasing IFP or "normalizing" the vasculature (Jain, 2005). Blood vessel normalization may selectively reduce the numbers of ineffective and immature blood vessels which can lead to reduced IFP and enhanced drug uptake. The introduction of VEGFR2-blocking antibodies, TGF β inhibitors, and PDGF antagonists can reduce IFP, resulting in enhanced drug uptake (Lammerts et al., 2002; Pietras et al., 2002). For instance, it has been reported that PDGF inhibitors or VEGF-specific antibody significantly affect vascular normalization, reduce IFP and tumor growth in preclinical and clinical models (Pietras et al., 2002; Winkler et al., 2004).

3 | CONCLUSIONS

In the last decades, there has been progress in the treatment of CC, although very little improvement has been observed in the overall survival for metastatic disease. The emerging evidence suggests a complex interaction between host cells, cancer cells, and the ECM. Modifications of the TME during cancer development facilitate the metastatic spread of tumor cells with malignant properties, which is the major cause of death in CRC patients. However, TME as a fundamental factor in determining metastatic disease presents an opportunity for gaining an insight into the biology of metastasis. While tumor cells have enormous differences in genetic alterations to elicit tumorigenesis, alterations in the TME may also be a common feature of many cancer types, providing the promises that targeted treatment of these events could be effective. Recognizing the most critical molecular players in the TME of each cancer type is the early step toward this goal. The complicated nature of cancer cell–host cell interactions and cell–ECM interactions in the tumor, an improvement of understanding about this complex ecosystem will be needed to promote cancer therapies. Therefore, selectively targeting the cells that have been modified within the TME may allow their unmodified precursors in the normal tissues to remain unaffected.

4 | DISCLOSURE

The authors have no conflict of interest to disclose.

REFERENCES


