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REVIEW

Systemic inflammation in colorectal cancer: Underlying factors, effects, and prognostic significance

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Abstract

Systemic inflammation is a marker of poor prognosis preoperatively present in around 20%-40% of colorectal cancer patients. The hallmarks of systemic inflammation include an increased production of proinflammatory cytokines and acute phase proteins that enter the circulation. While the low-level systemic inflammation is often clinically silent, its consequences are many and may ultimately lead to chronic cancer-associated wasting, cachexia. In this review, we discuss the pathogenesis of cancer-related systemic inflammation, explore the role of systemic inflammation in promoting cancer growth, escaping antitumor defense, and shifting metabolic pathways, and how these changes are related to less favorable outcome.

Key words: Colorectal cancer; Inflammation; Prognosis; Cytokine; Chemokine; C-reactive protein; Glasgow prognostic score; Cachexia; Metastasis

Core tip: Increasing evidence indicates that systemic inflammation has wide-ranging effects on colorectal cancer (CRC) pathogenesis, spanning from supporting primary tumor growth by promoting tumor cell proliferation to helping angiogenesis by enhancing the availability of pro-angiogenic molecules, to suppressing anti-tumor immunity by recruiting anti-inflammatory cell types, and to shaping pre-metastatic niches to promote subsequent metastasis. Systemic inflammatory biomarkers, such as circulating acute phase proteins, cytokines, exosomes, and leukocytes, may help to classify CRC patients into useful prognostic categories. However, further larger-scale

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studies are needed to determine optimal marker combinations for selecting patients to receive specific treatments.

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INTRODUCTION

Interactions between tumor and host are important regulators of tumor progression[1-3]. These interactions are mediated by a complex network of cytokines, chemokines, growth factors, and matrix remodeling enzymes[4], reaching beyond the local tumor microenvironment and evoking systemic responses[1,5] that have an effect on the course of the disease[6]. Therefore, cancer progression is not only determined by factors intrinsic for the tumor, but is largely directed by multifaceted systemic processes[5].

Colorectal cancer (CRC) is the third most common cancer in the Western World, and the second most common cause of cancer deaths[7]. Systemic inflammation is most common in poorly differentiated and advanced CRC[8,9], but despite that it is also an independent indicator of less favorable outcome in CRC [10,11] and associated with shorter survival[6,12,13]. In the case of resectable disease, 21%–41% of CRC patients have increased serum levels of acute phase proteins such as CRP (C-reactive protein), indicating a systemic inflammatory response to the tumor[8,9,14].

Cancer-associated systemic inflammation is characterized by numerous alterations in many organ systems distant from the site or sites of inflammation. Activation of systemic inflammatory response in the liver results in a rapid increase in the production of acute phase proteins, such as CRP[15]. Many disabling symptoms of cancer patients, such as fever, anemia, fatigue and loss of appetite can be attributed to the presence of systemic inflammation, and finally, metabolic changes such as loss of muscle and negative nitrogen balance manifest in cachexia, a cancer-associated wasting syndrome[16].

Many markers of systemic inflammation are based on counts, ratios, or scores of circulating white cells or acute phase proteins, such as neutrophil/lymphocyte ratio (NLR) and Modified Glasgow Prognostic score (mGPS), a measure based on elevated serum CRP level and decreased serum albumin level[17], but more recent studies have also evaluated the significance of alterations in circulating cytokine, chemokine, and growth factor milieu[18-20], platelet transcriptome[21], or the composition of tumor-derived extracellular vesicles[22]. Released by tumor cells or non-neoplastic cells in tumor-elicited host reaction, IL6 (interleukin-6) is one of the most important mediators of systemic effects of inflammation, such as the production of acute phase proteins in the liver[15] and in cancer cachexia[16].

In this review, we aim to provide an overview of the factors contributing to systemic inflammatory responses in CRC, of their downstream processes in the responding tissues, as well as of the prognostic significance of systemic inflammatory markers in CRC.

LITERATURE SEARCH

A literature search using PubMed was conducted to identify articles relevant to the topic, using search terms: ("colorectal cancer" or "colon cancer" or "rectal cancer" or "colorectal neoplasia") and ("systemic inflammation" or "CRP" or "Glasgow Prognostic Score" or "interleukin" or "chemokine" or "IL6" or "cytokine" or "CXCL*" or "CCL*" or "cachexia" or "inflammation" or "premetastatic niche"). The last search update was performed in March 2019. The titles and abstracts of the studies were screened for studies relevant to the review topic. Additional relevant publications were identified from the bibliographies of the included studies. Finally, this review was based on 196 publications identified during the search.

FACTORS UNDERLYING SYSTEMIC INFLAMMATION IN CRC

The hallmarks of systemic inflammation in cancer patients include an increased production of proinflammatory cytokines and acute phase proteins that enter the circulation. Indeed, many proteins regulating the function of immune cells, or produced in large quantities by immune cells or in inflammatory conditions, have been reported to show altered serum levels in CRC patients compared to controls (Table 1). For example, when evaluating serum profiles of 13 cytokines, chemokines, and growth factors in 116 CRC patients and 86 healthy controls, it was found that serum levels of five of these proteins showed statistically significant alterations, including increased serum IL6, IL7, CXCL8 (IL8), and PDGFB levels, and decreased serum CCL2 levels[18]. Increased serum IL6 and CXCL8 levels in CRC have been reported in many studies, also summarized in two recent meta-analyses[23,24]. Further highlighting the presence of systemic inflammatory markers in the sera of CRC patients, in a systematic review and meta-analysis of diagnostic and prognostic serum biomarkers of CRC[25], several of the most frequently reported diagnostic markers, such as CRP, VEGFA, and TIMP1, were related to the systemic inflammatory response.

The factors driving the systemic inflammatory response in CRC patients are complex and thereby not clear, but they are related to the interaction between neoplastic cells and the surrounding tumor microenvironment involving inflammatory cells, fibroblasts, extracellular matrix, and vasculature[5]. While tumor cells can variably express different cytokines and chemokines[26], immune cells and fibroblasts are capable of producing many of these factors at much higher levels[27-29].

Tumor cells produce inflammatory mediators

Cancer cells express highly variable amounts of different cytokines, chemokines, and growth factors *in vitro*[26,30]. These include IL6, CCL2, CXCL8, CSF1 (macrophage colony-stimulating factor, M-CSF), and CSF2 (granulocyte-macrophage colony-stimulating factor, GM-CSF) (Table 2). These molecules contribute to a variety of functions related to systemic inflammation and cancer progression. For example, IL6, a seminal proinflammatory cytokine, regulates the acute phase response through the induction of acute phase proteins in hepatocytes and the differentiation of monocytes to macrophages[31], whereas CCL2 is essential for the recruitment of bone marrow derived monocytes into peripheral organs and tumors[32]. CXCL8 is an important proinflammatory chemokine, recruiting granulocytes but also promoting angiogenesis[33]. Both CSF1 and CSF2 stimulate the proliferation, differentiation, and survival of monocytes and macrophages, but while CSF1 is involved in M2-like anti-inflammatory macrophage polarization, CSF2 contributes to M1-like pro-inflammatory macrophage polarization[34].

Tumor-derived extracellular vesicles have recently gained more and more interest as potential regulators of tumor cell-immune cell interactions[35,36]. They are a heterogeneous group of lipid bilayer-delimited particles released by tumor cells in the tumor microenvironment and into the circulation[35,36]. They have been implicated in a variety of functions in tumor progression, such as contributing to angiogenesis, vascular leakiness, regulation of immune responses, and reprogramming of stromal recipient cells in subsequent metastatic areas[35,36]. Based on their size and contents, they can be divided into subcategories, such as microvesicles, exosomes, ectosomes, and oncosomes.

The contents of tumor-derived extracellular vesicles can be highly variable. For example, they have been reported to contain immunosuppressive proteins such as TGFB[37,38], protease enzymes such as MMP9[38], and growth factors such as IGF1[38]. Moreover, nucleic acids (micro RNAs, miRNAs; and long non-coding RNAs, lncRNAs) can be found in tumor-derived extracellular vesicles, and these can contribute to tumor cell and stromal cell proliferation and apoptosis, and the regulation of immune responses against the tumor[35,36]. For example, exosome-carried miR-21, miR-29a, and miR-222-3p have been associated with immunoregulatory functions in various tumor types[39]. However, current knowledge of miRNAs in the regulation of immune reactions is limited, and further investigation is required to show more clearly the significance of exosome-carried mRNAs in systemic inflammatory reactions, relative to other factors[35].

Tumor-infiltrating immune cells produce inflammatory mediators

CRCs are infiltrated by a heterogeneous population of immune and inflammatory cells, including proinflammatory cells, such as $CD8^+$ cytotoxic T cells, type 1 $CD4^+$ helper T cells (Th1 cells), NK cells, and M1 macrophages, anti-inflammatory cells such as regulatory T cells (Treg), type 2 helper T cells (Th2 cells), M2 macrophages, and

Table 1 Some systemic inflammatory markers showing altered circulating levels in colorectal cancer patients

Marker		Function	Detection method	Samples	Ref.
Acute phase proteins					
CRP (C-reactive protein)	↑	Acute phase protein	ELISA	serum	Gunter *et al*[157]
HP (haptoglobin)	↑	Hemoglobin-binding acute phase protein	ELISA	serum	Sun *et al*[158]
Ferritin	↓	Protein that stores iron	meta-analysis	serum	Feng *et al*[159]
Cytokines and chemokines					
IL6	↑	Proinflammatory cytokine	meta-analysis	serum	Xu *et al*[23]
IL7	↑	Cytokine involved in lymphocyte maturation	Multiplex magnetic bead assay	serum	Kantola *et al*[18]
IL17A	↑	Proinflammatory cytokine	meta-analysis	serum	Yan *et al*[160]
IL22	↑	Cytokine contributing to tissue homeostasis	meta-analysis	serum	Yan *et al*[160]
IL23	↑	Proinflammatory cytokine	meta-analysis	serum	Yan *et al*[160]
CCL2	↓	Recruitment of monocytes and macrophages	Multiplex magnetic bead assay	serum	Kantola *et al*[18]
CXCL5	↑	Recruitment of neutrophils	ELISA	serum	Kawamura *et al*[161]
CXCL8 (IL8)	↑	Recruitment of neutrophils	meta-analysis	serum	Jin *et al*[24]
CXCL10	↑	Recruitment of T cells and NK cells	ELISA	serum	Toiyama et el [162]
CXCL16	↑	Recruitment of T cells and NK cells	ELISA	serum	Matsushita *et al*[163]
SPP1 (secreted phosphoprotein 1)	↑	Leukocyte chemotaxis	streptavidin–biotin sandwich assay	serum	Werner *et al*[164]
Protease enzymes and their inhibitors					
MMP8	↑	Protease enzyme also cleaving cytokines	immunofluorometric assay	serum	Väyrynen *et al*[165]
MMP9		Degradation of extracellular matrix and regulation of neutrophil action	ELISA	serum	Wilson *et al*[166]
TIMP1	↑	Inhibitor of metalloproteinases	meta-analysis	serum	Meng *et al*[167]
Growth factors and their inhibitors					
ANGPTL2	↑	Growth factor contributing to the regulation of inflammation and angiogenesis	ELISA	serum	Toiyama *et al*[168]
ESM1	↑	Secreted angiogenic factor	ELISA	serum	Jiang *et al*[169]
PDGFB	↑	Proliferation of mesenchymal cells	Multiplex magnetic bead assay	serum	Kantola *et al*[18]
VEGFA	↑	Vascular growth factor	ELISA	serum	George *et el*[196]
VEGFC	↑	Vascular growth factor	ELISA	serum	Wang *et al*[170]
Markers of metabolism					
glucose (fasting)	↑	Energy source	G6PD	serum	Ferroni *et al*[171]
HbA1c		Oxygen carrier	HPLC Analyzer	serum	Ferroni *et al*[171]
insulin (fasting)	↑	Regulator of metabolism	ELISA	serum	Ferroni *et al*[171]
ECM/endothelium-derived signaling proteins					
Endostatin	↑	Angiogenesis inhibitor	ELISA	serum	Kantola *et al*[173]
POSTN (periostin)	↑	ECM protein	ELISA	serum	Ben *et al*[174]
VASTATIN	↑	Collagen VIII derived matrikine	ELISA	serum	Willumsen *et al*[172]

VCAM-1 (soluble)	↑	Multifunctional	ELISA	serum	Toiyama et el[175]
Other signaling molecules					
DAND5	↑	BMP inhibitor	ELISA	serum	Miao *et al*[176]
LRP (leptin)	↓	Regulator of metabolism	ELISA	serum	Kumor *et al*[177]
Resistin	↑	Regulator of metabolism	ELISA	serum	Kumor *et al*[177]

ECM: Extracellular matrix; G6PD: Hexokinase/glucose-6-phosphate dehydrogenase.

myeloid derived suppressor cells (MDSCs). Other cells include B lymphocytes, plasma cells, neutrophils, eosinophils and mast cells that co-operate with both immunoenhancing and immunosuppressing cells[40,41]. In contrast to systemic inflammatory response, which is associated with adverse outcome[12], an intense immune cell infiltrate, evaluated using hematoxylin and eosin stained sections[42-45] or by immunohistochemistry using antibodies to specific immune cell markers[46-50], has frequently been associated with improved survival in CRC, independent of tumor stage or other prognostic parameters. This has been attributed to the ability of immune cells to recognize transformed malignant cells and restrict tumor growth (immunosurveillance hypothesis)[3,51]. However, some types of immune cells such as Th17 cells, characterized by their production of IL17, a proinflammatory cytokine, have been associated with poor survival[52].

Immune cells are considered an important source of cytokines, chemokines, and growth factors in tumor microenvironment (Table 3), but a few recent studies have shown an inverse correlation or lack of correlation between local immune response and systemic inflammation. A recent study evaluated the relationships between serum levels of 13 cytokines and the densities of eight types of tumor-infiltrating immune cells ($CD3^+$, $CD8^+$, and $FOXP3^+$ T cells, $CD68^+$ macrophages, $CD1a^+$ dendritic cells, $CD83^+$ dendritic cells, $ELANE^+$ neutrophils, and $tryptase^+$ mast cells) in a cohort of 147 stage I–IV CRC patients. In that study, serum cytokines and tumor-infiltrating immune cells in CRC represented entities with high intra-group correlations but relatively weak positive inter-group correlations. High macrophage density was associated with increased serum CCL4 levels (which could reflect CCL4 production by macrophages or recruitment of $CCR5^+$ macrophages in tumors as a response to CCL4) and high densities of $CD3^+$ and $CD8^+$ T cells were associated with increased serum IL12 levels (which indicates that systemic IL-12 levels may contribute to or reflect tumor-associated Th1 response). Yet another study reported a trend towards an inverse relationship between local inflammation and systemic inflammation in a cohort of stage II colon cancer patients[53].

The reasons underlying the relative weakness of the observed associations between tumor immune cell densities and serum levels of inflammatory markers are unclear. However, more precise definition of immune cell categories may be needed to show more closely defined associations with circulating inflammatory mediators. For example, general macrophage markers, such as CD68, do not adequately reflect the phenotypic diversity of macrophages, which can produce copious amounts of various cytokines depending on their polarization status (Figure 1)[28,54]. Also other immune cells, including T helper cells[55], B cells[56], neutrophils[57,58], produce different types and quantities of cytokines and chemokines related to the type of their activation. Based on this, for example, neutrophil categorization into proinflammatory N1 and anti-inflammatory N2 subsets has been suggested[59], but it is not as well established as T helper cell classification (Th1, Th2, Th17, Treg) or macrophage classification (M1 and M2)[60].

Cancer-associated fibroblasts produce inflammatory mediators

Cancer-associated fibroblasts (CAFs) contribute to proliferative signaling, invasion and metastasis, angiogenesis, and inflammatory reactions[1,27]. Cancer cells and fibroblasts may form a reciprocal positive feedback loop where tumor cells release growth factors activating fibroblasts and, in return, fibroblasts secrete growth factors, such as IGF1, which stimulate the proliferation of cancer cells. Recently, such an IGF1-dependent feedback loop, promoting disease progression, was demonstrated in radiotherapy-activated CAFs in CRC mouse model and human CRC samples[61].

CAFs also produce several factors contributing to tumor inflammatory reactions (Table 4). For example, two recent studies indicated that stromal fibroblasts are an important source of IL6 in CRC[29,62]. Nagasaki *et al*[29] found that stromal fibroblasts had higher IL6 production than tumor cells, and that colon cancer cells enhanced IL6 production by isolated stromal fibroblasts. Moreover, in a xenograft mouse model, anti-IL6R antibody targeting stromal tissue showed greater anti-tumor activity than

Table 2 Examples of inflammatory mediators reported to be expressed by colorectal cancer cells

Inflammatory mediator	Function	Detection method	Samples	Ref.
IL6	Proinflammatory cytokine	IHC, RT-PCR	FFPE CRC specimens	Zeng *et al*[178]
CSF1	Proliferation, differentiation, and survival of monocytes, macrophages, and bone marrow progenitor cells; polarization of pro-tumor M2 macrophages	IHC	FFPE CRC specimens	Nebiker *et al*[179]
CSF2	Proliferation, differentiation, and survival of monocytes, macrophages, granulocytes and bone marrow progenitor cells, polarization of anti-tumor M1 macrophages	IHC	FFPE CRC specimens	Nebiker *et al*[179]
CCL2	Recruitment of monocytes and macrophages	IHC, WB	CRC cell lines, FFPE CRC specimens	Hu *et al*[180]
CXCL1	Recruitment of neutrophils	IHC	FFPE CRC specimens	Oladipo *et al*[181]
CXCL8	Recruitment of neutrophils	IHC, IF, WB	CRC cell lines, FFPE CRC specimens	Xiao *et al*[30]
CXCL8	Recruitment of neutrophils	IHC	FFPE CRC specimens	Oladipo *et al*[181]
CXCL10	Recruitment of T cells and NK cells	IHC, RT-PCR	CRC cell lines, FFPE CRC specimens	Jiang *et al*[182]
CXCL12	Recruitment of lymphocytes and endothelial progenitor cells	IHC	FFPE CRC specimens	Akishima-Fukasawa *et al*[183]
VEGFA	Angiogenesis	IHC	FFPE CRC specimens	Tuomisto *et al*[184]

CRC: Colorectal cancer; FFPE: Formalin-fixed paraffin-embedded; IHC: Immunohistochemistry; IF: Immunofluorescence; RT-PCR: Real-time polymerase chain reaction; WB: Western blot.

anti-IL6R antibody targeting xenografted cancer cells. Huynh *et al*[62] also demonstrated that CAFs are a major source of IL6 in human CRC samples, and found that IL6 production was associated with tumor promoting Th17 immune response. De Boeck *et al*[63] performed secretome profiling of CAFs isolated from human CRC samples, and found that in these experimental conditions, CAFs represent a rich source of cytokines, chemokines, proteases, and growth factors, such as CXCL8 involved in neutrophil recruitment, CCL5 involved in T cell recruitment, VEGFA involved in angiogenesis, and various matrix metalloproteinases (MMPs) (Table 4). MMPs play an important role in extracellular matrix remodeling during tumor invasion, but can also contribute to inflammatory regulation by, for example, cleaving chemokines and cytokines[64,65].

TGFB signaling is a central immunosuppressive pathway in CRC progression[66,67]. Recently, Hawinkels *et al*[68] demonstrated a positive feedback loop, where the interaction of tumor cells with resident fibroblasts results in hyperactivated TGFB signaling in both cell types. *In vitro*, the treatment of CAFs with TGFB increased their expression of collagen-1, PLAU (urokinase type plasminogen activator), various matrix MMPs, including MMP2, MMP3, and MMP9, tissue inhibitors of matrix metalloproteinases (TIMPs), and TGFB itself[68]. Collectively, these data support the role of CAFs in the regulation of cancer associate inflammatory reactions.

The role of tumor necrosis in systemic inflammation

Necrosis, an uncontrolled process of cell death, provokes a rapid systemic inflammatory response that is necessary for the removal of dead tissues from the body by phagocytic cells like neutrophilic granulocytes and macrophages. Necrosis is also prevalent and represents an indicator of less favorable outcome in colorectal, renal, lung, and breast cancer[69-71]. Irreversible cell injury induces the systemic inflammatory response, when dying cells release proinflammatory molecules into the extracellular space, and this is further propagated when intracellular contents of the cells are exposed[72]. In trauma patients, mitochondrional damage-associated components released to the circulation are able to elicit systemic inflammation[73]. Richards *et al*[74] and Guthrie *et al*[75] found that increasing amount of tumor necrosis in CRC is associated with higher levels of markers of systemic inflammation, such as modified Glasgow Prognostic Score (mGPS) and serum IL6, supporting the role of tumor necrosis in the induction of systemic inflammatory response. In addition, further

Table 3 Examples of inflammatory mediators produced by different inflammatory cells

Cell type	Inflammatory mediators	Functions	Ref.
M1 macrophage	IL6, TNF, IL12A, IL12B, IL23A, CXCL5, CXCL9, CXCL10, CXCL11,	Activation of inflammation	Murray *et al*[178]
M2 macrophage	IL10, CCL4, CCL13, CCL17, CCL18, MMP1, TGFB1	Resolution of inflammation	Murray *et al*[47]
Th1 lymphocyte	IFNG, IL2	Activation of cytotoxic immune response	Zhu *et al*[55]
Th2 lymphocyte	IL4, IL5, IL10, IL13	Activation of humoral immune response	Zhu *et al*[55]
Th17 lymphocyte	IL17A, IL17F, IL21, IL22	Activation of neutrophils	Zhu *et al*[55]
Treg lymphocyte	TGFB	Immunosuppression	Zhu *et al*[55]
Plasma cell	IL10, IL35. TNF, IL17A, CSF2	Both pro- and anti-inflammatory mediators	Dang *et al*[156]
Neutrophil	IL1A, IL1B, IL1RA, IL6, IL12 CXCL8, CXCL9, CXCL10, CXCL11, CCL2, CCL3, CCL4, TGFB1, VEGFA	Activation of inflammation; depending on the type of polarization, also anti-inflammatory mediators are secreted	Tecchio *et al*[58]
Eosinophil	IL1A, IL2, IL4, IL6, IL12, CXCL1, CXCL8, CXCL10, CCL3, CCL5, CCL11	Th2 type immune responses	Davoine *et al*[185]
Myeloid derived suppressor cell	IL10, TGFB	Immunosuppression	Bronte *et al*[87]
Mast cell	IL4, IL5, IL6, TNF, CSF2	Th2 type immune responses	Amin *et al*[186]

supporting the association between hypoxia and systemic inflammation, Bousquet *et al*[76] showed that hypoxic conditions are related to a reduction of reactive oxygen species (ROS) production and increased damaged mitochondrial DNA (mtDNA) generation *in vitro* and that in rectal cancer patients with locally advanced disease, a low circulating ROS to damaged mtDNA ratio was associated with systemic inflammation. However, to our knowledge, the activation of systemic inflammation by tumor necrosis has not been demonstrated in more experimental studies.

EFFECTS OF SYSTEMIC INFLAMMATION IN CRC

The effects of systemic inflammation span throughout the body; from primary tumors to metastases, liver, bone marrow, gut, skeletal muscle, and other organs (Figure 2). Recent studies have shown that even before metastatic disease, the systemic inflammatory response promotes tumor progression by modifying the interactions between neoplastic and non-neoplastic cells. The concept of pre-metastatic niche describes the process in which instead of being passive receivers of circulating tumor cells, the tissues and organs of a future metastasis are actively modified before the metastatic spread[77].

Liver

The liver participates in a large number of tasks, such as macronutrient metabolism, blood volume regulation, detoxification of chemicals and several metabolites, and regulation of immune responses[78]. The liver synthesizes the majority of serum proteins, such as albumin, fibrinogen, clotting factors, transport proteins, complement proteins, and lipoproteins. It maintains whole body homeostasis via metabolism of carbohydrates, lipids, amino acids and vitamins, and it also functions as an immune organ that mediates and regulates systemic and local innate and adaptive immunity. Digestion and nutrient absorption in the gastrointestinal tract provide a constant source of antigens (and a potential route for pathogens) that enter the body, and liver sinusoids are thereby rich in antigen-presenting cells, NK cells and NKT-cells that have a key role both in immunotolerance and in the immune defense against pathogens. Liver mediates immunotolerance *via* complex interaction of hepatocytes, liver nonparenchymal cells and immune cells[79].

One of the best-known mechanisms of the liver in immunoregulation is the production of acute-phase proteins in response to inflammation[15]. An acute-phase protein has been defined as one whose plasma concentration increases (positive acute-phase proteins) or decreases (negative acute-phase proteins) during inflammation. Examples of positive acute-phase proteins include ceruloplasmin, CRP, haptoglobin,

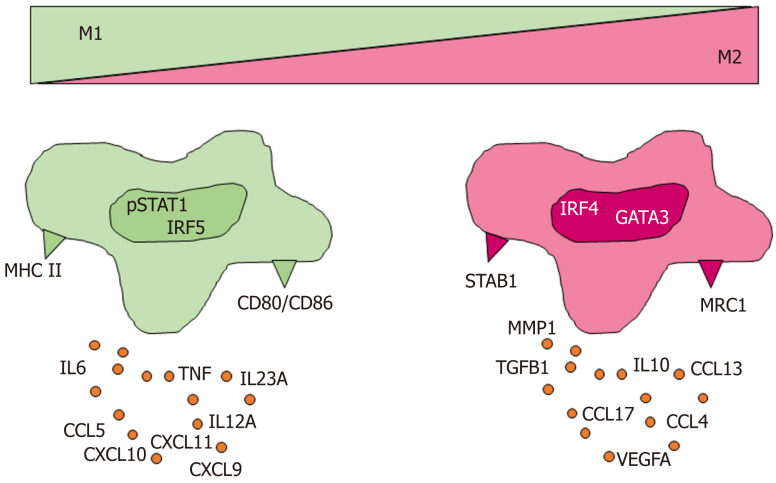

Figure 1 Phenotypic spectrum of macrophages. The illustration portrays the heterogeneity of immune cell main categories in producing inflammatory mediators and growth factors based on their activation state. The image illustrates the spectrum model of macrophage polarization based on the M1-M2 paradigm. Macrophage polarization describes the type of macrophage activation at a given point in space and time[155]. The polarization can be viewed as a continuum, with M1 (pro-inflammatory) and M2 (anti-inflammatory) as the extremes. The M1 and M2 designations are based on *in vitro* stimulation with either interferon gamma (M1) or interleukin 4 (M2) without environmental influence[54]; *in vivo*, stimulation of macrophages with multiple cytokines may result in mixed phenotypes. The image shows examples of transcription factors, cell surface molecules and inflammatory mediators commonly associated with M1 and M2 polarization states. Similarly to macrophages, different activation states have been associated with other immune cell types such as neutrophils[57,58], B cells[56], and plasma cells[156]. CCL: C-C motif chemokine ligand; CD80: CD80 molecule; CD86: CD86 molecule; CXCL: C-X-C motif chemokine ligand; GATA3: GATA binding protein 3; IL: Interleukin; IRF: Interferon regulatory factor; MHC II: Major histocompatibility complex, type II; MMP1: Matrix metallopeptidase 1; MRC1; Mannose receptor C-type 1; pSTAT1: Phosphorylated signal transducer and activator of transcription 1; STAB1: Stabilin 1; TGFB1: Transforming growth factor beta 1; TNF: Tumor necrosis factor; VEGFA: Vascular endothelial growth factor A.

hepcidin, and SAA, whereas negative acute-phase proteins include albumin, transferrin, transthyretin, and alpha-fetoprotein[15]. IL6 has been established as one of the most important contributors to altered protein production in the liver during the acute phase response. During response to infection, circulating IL6 levels quickly increase, propagating inflammatory signaling throughout the body[80]. Notably, IL6 is one of the cytokines showing the greatest increase in CRC patients relative to healthy controls, and a further increase in metastatic disease compared to non-metastatic disease[18].

IL6 also appears to be one of the main contributors to altered hepatic metabolism during systemic inflammation. In a recent study, Flint *et al*[81] showed that, in a mouse CRC model, tumor-induced IL6 caused systemic metabolic changes, such as suppression of hepatic ketogenesis, which triggered marked glucocorticoid secretion from the liver. In turn, this suppressed intratumoral immunity and caused failure of anti-cancer immunotherapy. The IL6-ketogenesis suppression-glucocorticoid pathway in the liver may represent one of the mechanisms by which immunosuppression in tumor tissue, often observed in CRC patients with advanced cancer[40], is coupled with changes in liver function and systemic metabolic changes.

Bone marrow

The immune system is governed by an appropriate balance of the lymphoid and myeloid responses. Hematopoietic stem cells (HSCs) reside in the bone marrow, producing different blood cell lineages in an highly organized manner[82]. HSCs respond rapidly to acute blood cell demand, such as injury or inflammation[83]. In patients with solid cancers, hematopoiesis is abnormal, leading to altered composition of hematopoietic progenitor cells, with myeloid-biased differentiation[84]. Accordingly, the systemic inflammation in cancer patients is widely reflected in hematological parameters, such as neutrophil-to-lymphocyte ratio, with neutrophil predominance over lymphocytes[85]. Together with CSF2, and CSF3, IL6 is among the leading myelopoiesis-driving cytokines[86].

A prolonged demand for myeloid cells – as in the case of a severe prolonged infection – results in sustained myelopoiesis that is characterized by the emergence of immature myeloid cells in the circulation and in peripheral tissues[87]. Many of these cells have been reported to harbor immunosuppressive functions, and this group of

Table 4 Examples of inflammatory mediators reported to be expressed by colorectal cancer associated fibroblasts

Inflammatory mediator	Function	Detection method	Samples	Ref.
IL6	Proinflammatory cytokine	IF	FFPE CRC specimens	Nagasaki *et al*[29]
IL6	Proinflammatory cytokine	LC-MS/MS	Cell culture (human cancer associated fibroblasts)	De Boeck *et al*[63]
IL6	Proinflammatory cytokine	ELISA	CAFs isolated from human CRC tissue	Zhang *et al*[187]
IL8	Proinflammatory cytokine	ELISA	CAFs isolated from human CRC tissue	Zhang *et al*[187]
IL11	Anti-inflammatory cytokine	qRT-PCR	CAFs isolated from human CRC tissue	Calon *et al*[188]
TGFB	Immunosuppression, inhibition of cytotoxic T cells and Th1 cells	IHC, WB	Cell culture (CRC cells, fibroblasts)	Hawingkels *et al*[68]
CXCL5	Recruitment of neutrophils	IHC, in situ hybridization	FFPE CRC specimens	Li *et al*[189]
CXCL8	Recruitment of neutrophils	LC-MS/MS	Cell culture (human cancer associated fibroblasts)	De Boeck *et al*[63]
CCL5	Recruitment of T cells	LC-MS/MS	Cell culture (human cancer associated fibroblasts)	De Boeck *et al*[63]
MMP1	ECM degradation	LC-MS/MS	Cell culture (human cancer associated fibroblasts)	De Boeck *et al*[63]
MMP2	ECM degradation	LC-MS/MS	Cell culture (human cancer associated fibroblasts)	De Boeck *et al*[63]
MMP3	ECM degradation	LC-MS/MS	Cell culture (human cancer associated fibroblasts)	De Boeck *et al*[63]
MMP9	ECM degradation	LC-MS/MS	Cell culture (human cancer associated fibroblasts)	De Boeck *et al*[63]
TIMP1	Inhibition of MMPs	LC-MS/MS	Cell culture (human cancer associated fibroblasts)	De Boeck *et al*[63]
TIMP1	Inhibition of MMPs	IHC, in situ hybridization	FFPE CRC specimens	Joo *et al*[190]
TIMP2	Inhibition of MMPs	LC-MS/MS	Cell culture (human cancer associated fibroblasts)	De Boeck *et al*[63]
TIMP2	Inhibition of MMPs	IHC, in situ hybridization	FFPE CRC specimens	Joo *et al*[190]
VEGFA	Angiogenesis	LC-MS/MS	Cell culture (human cancer associated fibroblasts)	De Boeck *et al*[63]

CRC: Colorectal cancer; ECM: Extracellular matrix; FFPE: Formalin fixed paraffin embedded; IHC: Immunohistochemistry; IF: Immunofluorescence; LC-MS/MS: Liquid chromatography with tandem mass spectrometry; MMP: Matrix metalloproteinase; RT-PCR: Real-time polymerase chain reaction; WB: Western blot.

myeloid progenitor cells with immunosuppressive activity has been named as myeloid derived suppressor cells (MDSCs)[87,88]. In the peripheral blood, human polymorphonuclear MDSCs are $CD11b^+CD14^-CD15^+$ and monocytic MDSCs are $CD11b^+CD14^+CD15^-HLADR^{-/low}$[87]. In addition to these gating criteria, functional suppression assays are required to precisely define MDSCs because of the overlap between their phenotype with that of more mature monocytes and granulocytes[87]. Besides peripheral blood, the presence of cells with MDSC-like phenotype has been reported in human CRC tissue[89].

The mechanisms by which MDSCs mediate immunosuppression and support tumor progression are complex and not fully understood[90]. However, several potential key pathways include the ARG1 pathway, IDO1 pathway, PD1/PDL1 pathway, and cytokine pathways (such as IL10 and IL6)[90,91] (Figure 3). L-arginine is an amino acid that is consumed by T cells and many other immune cells. MDSCs are characterized by high production of ARG1, which metabolizes L-arginine to L-ornithine and urea, resulting in L-arginine depletion and thus local immune suppression[92]. IDO1, expressed in a subset of MDSCs[87], converts tryptophan to kynurenine. The depletion of tryptophan suppresses activity in the mTORC1 signaling pathway, leading to autophagy in T cells and immunosuppression[93]. PD1 and PDL1 form an inhibitory immune checkpoint mechanism restricting excessive T cell activation[94]. The binding of PDL1, expressed on a subset of MDSCs[95], to PD1 causes T cell inhibition[96].

Besides myeloid immune cells, such as granulocytes, monocytes, and MDSCs, common myeloid progenitor cells can differentiate into megakaryocytes and red

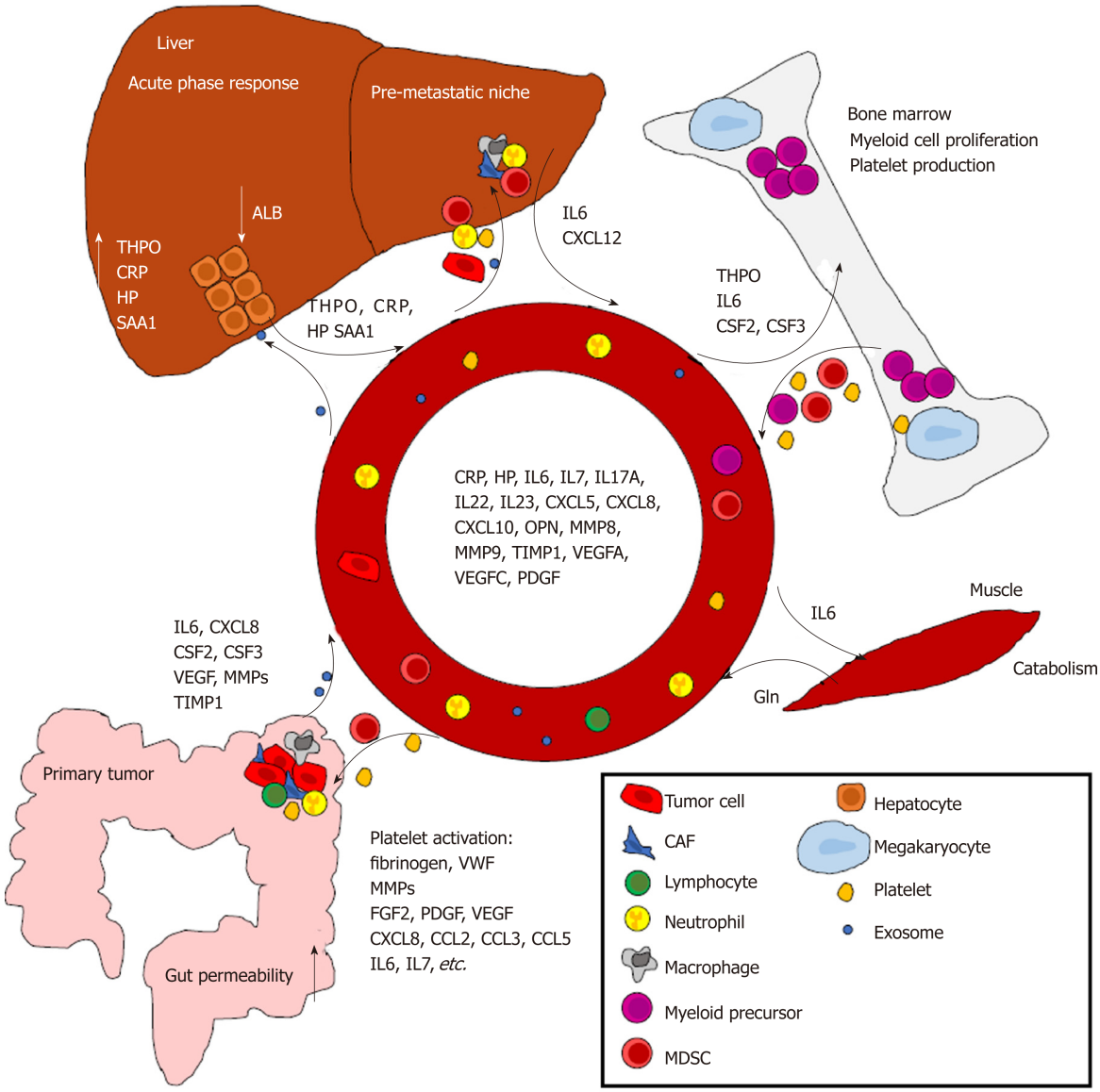

Figure 2 Overview of the effects of systemic inflammation in colorectal cancer. The illustration portrays some of the molecules and phenomena considered important in the pathogenesis of colorectal cancer associated systemic inflammation. Some markers showing increased circulating concentrations in colorectal cancer patients are listed in the center. ALB: Albumin; CCL: C-C motif chemokine ligand; CXCL: C-X-C motif chemokine ligand; CRP: C-reactive protein; CSF: Colony stimulating factor; FGF2: Fibroblast growth factor 2; Gln: Glutamine; HP: Haptoglobin; IL: Interleukin; MMP: Matrix metallopeptidase; OPN: Osteopontin; PDGF: Platelet derived growth factor; SAA1: Serum amyloid A1; THPO: Thrombopoietin; TIMP1: TIMP metallopeptidase inhibitor 1; VEGFA: Vascular endothelial growth factor A; VEGFC: Vascular endothelial growth factor C; vWF: von Willebrand factor

blood cells. However, instead of erythrocytosis (an increase in the number of red blood cells in the blood), CRC patients frequently have anemia (a decrease in the number of red blood cells or hemoglobin concentration), with a prevalence of 33%-43% in resectable disease[97-99]. Colorectal tumors frequently bleed into the lumen[100], explaining the iron deficiency associated with microcytic anemia in a subset of patients. However, systemic inflammation also appears to be one of the main determinants of low blood hemoglobin levels, and, in particular, normocytic anemia, in CRC patients[97-99]. There are several collaborating mechanisms linking systemic inflammation and anemia. First, hepcidin, an acute phase protein produced in the liver, limits iron absorption from small intestine[101,102] and iron availability for erythroid cells[102]. Second, pro-inflammatory cytokines directly inhibit the proliferation of erythroid progenitor cells[103]. Third, proinflammatory cytokines also inhibit erythropoietin synthesis in the kidney, resulting in decreased erythropoiesis[104]. In addition to the main symptoms associated with anemia such as fatigue, weakness, or shortness of breath, decreased availability of oxygen in anemic cancer patients may contribute to systemic metabolic changes, such as alterations in circulating and liver lipid levels, which have been shown to associate with hypoxia in animal models[105].

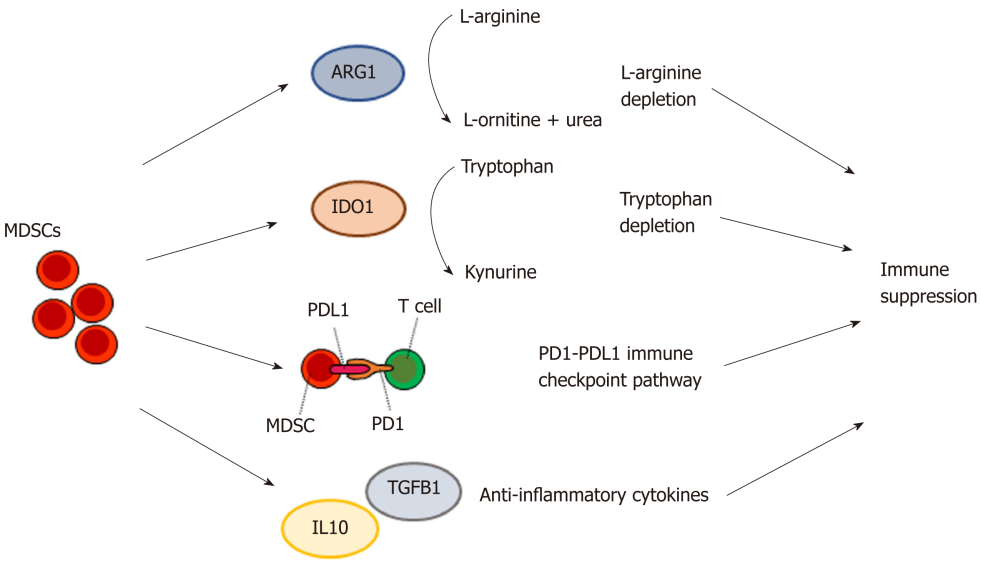

Figure 3 Overview of the potential pathways involved in the suppression of anti-tumor immunity by myeloid derived suppressor cells. ARG1: Arginase 1; IDO1: Indoleamine 2,3-dioxygenase 1; IL10: Interleukin 10; MDSCs: Myeloid derived suppressor cells; PD1: Programmed cell death protein 1; PDL1: Programmed death ligand 1; TGFB1: Transforming growth factor beta 1.

Platelets are anucleate cells generated in the bone marrow by the megakaryocyte. They contribute to hemostasis but also to cancer pathogenesis by releasing growth factors and cytokines[106]. Thrombocytosis (increased blood platelet count) is common in cancer patients. A recent prospective cohort study in the United Kingdom investigated 1-year cancer incidence in 40000 patients aged ≥ 40 years with thrombocytosis[107]. In that cohort, 11.6% of males and 6.2% of females developed cancer in 1-year follow-up, with CRC and lung cancer as the most common diagnoses[107]. The factors contributing to cancer-associated thrombocytosis include CSF2, CSF3, FGF2 (fibroblast growth factor 2, basic fibroblast growth factor), IL6, and THPO (thrombopoietin)[108]. In cancer patients with systemic inflammation, THPO production in the liver is increased in response to IL6 and other cytokines, resulting in increased platelet production[108,109].

Platelet granules contain a plethora of hemostatic factors (*e.g.*, fibrinogen, VWF), enzymes (*e.g.*, MMP1, MMP2), growth factors (*e.g.*, FGF2, PDGF, VEGF), chemokines (*e.g.*, CXCL8, CCL2, CCL3, CCL5), and cytokines (*e.g.*, IL6, IL7), which are released on platelet activation[110,111]. Reacting to the modified tumor vasculature, platelets can release these factors in the tumor microenvironment, promoting tumor progression. Although platelets lack nucleus, it has been demonstrated that the megakaryocyte packs them with a protein translation machinery that includes ribosomes, initiation and termination factors, miRNAs, and template messenger RNAs (mRNAs)[112]. Moreover, recent studies have indicated that platelets are capable of exchanging nucleic acids and proteins with tumor cells, leading to the concept of tumor-educated platelets, *i.e.*, platelets reflecting the properties of tumors and programmed to support tumor growth[21,106]. Highlighting the alterations in platelet mRNA profile in cancer patients, a recent study performed mRNA sequencing of 283 platelet samples and found that tumor-educated platelets distinguished cancer patients from healthy individuals with 96% accuracy, differentiated between six primary tumor types, including CRC, with 71% accuracy, and identified several genetic alterations found in tumors, such as *KRAS* mutation[113].

Pre-metastatic niches

In CRC, metastasis is the major cause of death and the main target organ of metastasis is the liver[114]. The understanding of the biological mechanisms of cancer metastasis is still limited. During the past few decades, it has been established that before metastasis, primary tumors can create a favorable microenvironment, a pre-metastatic niche, at tissue sites for subsequent metastasis. Among the first to describe the phenomenon were Kaplan *et al*[115], who showed that in Lewis lung carcinoma and melanoma mouse models, VEGFR1$^+$ (vascular endothelial growth factor receptor 1) bone marrow-derived progenitor cells homed to tumor-specific pre-metastatic sites before the arrival of tumor cells, supporting the subsequent metastasis. The pre-metastatic niches are composed of stromal components of the distant organs, bone

marrow-derived cells including stromal cells and immunosuppressive immune cells, and tumor-derived secreted factors, such as cytokines, growth factors, and extracellular vesicles[5,116]. Liu and Cao recently proposed that six hallmark characteristics of pre-metastatic niche include inflammation supporting a proliferatory microenvironment; immunosuppression; angiogenesis; lymph-angiogenesis; metabolic, stromal, and epigenetic reprogramming; and organotropism.

Several studies have demonstrated pre-metastatic niches in CRC mouse models. Seubert *et al*[117] found that high systemic TIMP1 levels led to increased hepatic levels of neutrophil chemokine CXCL12, resulting in recruitment of neutrophils to the liver. Both inhibition of CXCL12-mediated neutrophil recruitment and systemic depletion of neutrophils reduced TIMP1-induced increased liver susceptibility towards metastasis. In another study, Shao *et al*[118] showed that CRC-derived small extracellular vesicles, also known as exosomes, are targeted to the liver where they promote the formation of premetastatic niche and CRC metastasis. Liver macrophages, Kupffer cells, engulfed these exosomes and their cargo, leading to Kupffer cell polarization toward proinflammatory phenotype and increased CSF3 and IL6 expression. An inflammatory microenvironment was created and expression of apoptosis and matrix remodeling related genes was altered, promoting cancer metastasis to the liver.

In a mouse model of pancreatic cancer, Lee *et al*[119] showed that IL6, produced by tumor-adjacent non-cancerous fibroblasts, traveled to the liver and mediated STAT3 signaling in hepatocytes, resulting in the secretion of acute phase reactants serum amyloid A1 and A2 (SAA proteins). SAA proteins attracted immunosuppressive myeloid cells to the liver, promoted hepatic stellate cell activation and production of extracellular matrix, creating a metastasis-prone environment in the liver. This study also reported enhanced hepatic SAA expression in CRC patients. All in all, more and more evidence supports the role of systemic inflammation in creating a tumor-favoring environment in distant organs, enabling metastatic tumor cells to survive after colonization.

Gut microbiome and systemic inflammation

The large bowel is the dwelling place for a vast set of commensal micro-organisms, mainly bacteria and fungi. Collectively, these are often described as intestinal microbiome or microbiota. Changes in the intestinal microbiota are observed in many situations, including CRC and cachexia[120,121]. The interplay between microbiota and the immune system has gained increasing interest, although our knowledge is still very limited. Still, recent studies have shown that the gut microbiota is able to modulate patients' responsiveness to PD1 and CTLA4 blocking immunotherapies[122,123]. Such findings give us a glimpse of the potential significance of microbiota to its host.

In normal circumstances, intestinal bacteria are barred from entering the circulation by several mechanisms, collectively known as the intestinal barrier. Increased permeability of the mucosa allows the entry of bacteria or bacterial components into the portal circulation and subsequently, the liver, where they elicit a succinct response[124]. In mouse cancer models, strong correlation exists between circulating IL6 levels and intestinal permeability[121,125]. Animal models of colon cancer have also indicated that areas adjacent to cancer present a disrupted barrier function[126,127], and that systemic inflammation may induce endotoxemia often associated with cancer. Besides bacteria or bacterial components, also bacterial metabolites such as short-chain fatty acids (SCFAs) can modulate peripheral immune response. SCFAs are capable of shifting the effector T to regulatory T cell balance by facilitating the differentiation of regulatory T cells, and thereby limit the systemic inflammation [128].

Skeletal muscle, cancer cachexia, and amino acid metabolism

The international consensus definition of cachexia is an ongoing loss of skeletal muscle mass – with or without loss of fat mass – that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment[129]. Systemic inflammation is a key driving factor in cancer-associated cachexia[16]. In CRC patients, the presence of systemic inflammation is associated with low skeletal muscle mass[130,131]. Cachexia not only reduces patient's quality of life and treatment response, but it is also an indirect cause of death in about 20% of patients who eventually die of cancer[16].

The $Apc^{Min/+}$ mouse is a widely used animal model of CRC and CRC-associated cachexia[132]. In this mouse line, the cachexia progression is associated with increased plasma IL6 levels, and cachexia does not progress in the absence of IL6 despite the presence of intestinal and colon tumors[133]. However, in control mice, the overexpression of IL6 does not induce cachexia[133], suggesting that IL6 is an indispensable but not sufficient factor in cancer cachexia pathogenesis. Systemic

inflammation in the absence of malignancy, such as in sepsis, is also able to induce severe muscle wasting[134], verifying that active inflammatory reaction is an important driver in muscle catabolism.

Active immune response is a highly energy-consuming process[135,136]. Thus, activation of systemic inflammation in cancer patients requires the utilization of stored energy and nutrients, especially as anorexia is a common symptom in cancer patients with advanced disease. A recent study investigated the relationships between systemic inflammatory markers and circulating levels of nine amino acids in 336 CRC patients and found that, of the studied factors, systemic inflammation was the main determinant of low serum glutamine level in these patients[137]. Glutamine is the most abundant amino acid in the body, and circulating glutamine is mainly derived from skeletal muscle, functioning as an inter-organ carbon, nitrogen and energy transporter to be utilized by rapidly dividing cells such as enterocytes and lymphocytes[138]. In healthy humans, circulating glutamine is mainly consumed in the gut and kidney[138]. Tumor tissue can either consume or produce glutamine, depending on tissue of origin and oncogene activation[139]. Patients with sepsis have decreased plasma glutamine levels[140] resulting from increased glutamine consumption[141]. Mouse studies have shown that tumor induces a decrease in circulating glutamine levels, stimulates glutamine release and decreases the glutamine content in skeletal muscle[142]. Accordingly, it has been suggested that altered interorgan glutamine homeostasis in cancer patients is an essential driver in cachexia.

PROGNOSTIC SIGNIFICANCE OF SYSTEMIC INFLAMMATION AND ASSOCIATED PARAMETERS IN CRC

The prognostic and predictive classification of CRC has mainly been based on tumor stage[143,144]. However, each patient and tumor is unique[145], and a more exact classification of the disease based on the features of the tumor and host could enable more personalized treatments. Indeed, patient selection for anti-EGFR treatment for metastatic CRC is currently based on *RAS* and *BRAF* mutation testing[146], and anti-PD1 antibody treatment has been approved for metastatic CRC with high-level microsatellite instability or mismatch repair deficiency[147]. Considering the impact of systemic inflammation in CRC progression, systemic inflammatory markers represent potential additional prognostic and predictive parameters (Table 5).

Acute phase proteins, including CRP, albumin, and their composite mGPS (mGPS0: serum CRP ≤ 10 mg/L and serum albumin ≥ 35 g/L or < 35 g/L; mGPS1: serum CRP > 10 mg/L and serum albumin ≥ 35 g/L; mGPS2: serum CRP > 10 mg/L and serum albumin < 35 g/L), are among the best-studied systemic inflammation-based prognostic parameters in CRC[10]. Numerous studies have reported that high circulating CRP levels, low albumin levels and high mGPS are associated with adverse patient outcome (Table 5). In addition, blood differential leukocyte count parameters have well-established prognostic value in CRC. Myeloid cell proliferation, associated with systemic response to CRC, leads to an increase in circulating neutrophil and monocyte counts, relative to lymphocytes, which has been associated with adverse outcome[148,149]. Indices based on relative counts of these cell types represent promising prognostic parameters. Preoperative anemia, reflecting systemic inflammation in a subset of patients, has also been associated with adverse outcome[150]. Platelet count and platelet-to-lymphocyte ratio can also provide potentially clinically relevant prognostic information[151-153], with high platelet counts associated with poor survival. In future, more sophisticated analyses of platelet composition and function, such as platelet RNA sequencing, may complement these parameters to provide more nuanced information of the status of platelet activation and education during systemic inflammation[21].

Several studies have indicated that circulating cytokine concentrations provide prognostic information in CRC. Recently, using proximity extension assays, Birgisson *et al*[20] analyzed plasma levels of 92 oncology-related proteins, including an assemblage of cytokines, chemokines, and growth factors, in a cohort of 261 stage II-IV CRC patients. Many of these molecules, including CSF1, CXCL10, CXCL9, HGF (hepatocyte growth factor), IL6, osteoprotegerin, PGF (placental growth factor), and VEGFA, were significantly associated with survival in univariable analysis, and of these, osteoprotegerin was the best in predicting survival in multivariable survival models[20]. Analyzing multiple markers in one sample may improve the prognostic power relative to measuring the levels of a single marker. However, caution needs to be employed when interpreting the results of such studies because of the well-known risk of multiple hypothesis testing, necessitating confirmation of the findings in

Table 5 Selected systemic inflammation based prognostic markers in colorectal cancer

Marker	Ref.	Study design	Study population	Outcome, HR
Acute phase proteins				
CRP	Woo *et al*[191]	Meta-analysis, 21 studies	3934 CRC patients, stage I-II	OS, HR 2.04 (1.45–2.86); CSS, HR 4.37 (2.63–7.27); DFS, HR 1.88 (0.97–3.67)
Albumin	Gupta *et al*[192]	Systematic review, 12 studies	3644 CRC patients, stage I-IV	Low albumin associated with worse survival (no meta-analysis conducted)
Albumin	Ghuman *et al*[193]	Case-case study within a prospective cohort study (AMORIS)	4764 CRC patients, stage I-IV	OS, HR 0.57 (0.29–1.14); CSS, HR 0.36 (0.16–0.85)
mGPS	Lu *et al*[194]	Meta-analysis, 41 studies	9839 CRC patients, stage I-IV	OS, HR 2.20 (1.88–2.57); CSS, HR 1.86 (1.59–2.17)
HP (haptoglobin)	Ghuman *et al*[193]	Case-case study within a prospective cohort study (AMORIS)	4764 CRC patients, stage I-IV	OS, HR 1.28 (1.08–1.51); CSS, HR 1.17 (0.95–1.45)
Blood cell count parameters				
Neutrophil-to-lymphocyte ratio	Li *et al*[148]	Meta-analysis, 16 studies	5897 CRC patients, stage I-IV	OS, HR 1.66 (1.36–2.02); CSS, HR 2.27 (1.75–2.96); DFS, HR 1.54, (1.18–2.02)
Lymphocyte-to-monocyte ratio	Tan *et al*[149]	Meta-analysis, 15 studies	11783 CRC patients, stage I-IV	OS, HR 0.57 (0.52-0.62); CSS, HR 0.55 (0.32-0.95); DFS, HR 0.77 (0.70-0.84)
Platelet count	Rao *et al*[152]	Meta-analysis, 9 studies	3413 CRC patients, stage I-IV	OS, HR 2.11 (1.68-2.65); DFS, HR 2.51 (1.84-3.43)
Platelet-to-lymphocyte ratio	Tan *et al*[153]	Meta-analysis, 15 studies	3991 CRC patients, stage I-IV	OS, HR 1.53 (1.24–1.89), DFS, HR 1.68 (1.07–2.62)
Anemia	Wilson *et al*[150]	Meta-analysis, 12 studies	3588 CRC patients, stage I-IV	OS, HR 1.56 (1.30-1.88), DFS, HR 1.34 (1.11-1.61)
Cytokines, chemokines, and their receptors				
IL6	Xu *et al*[23]	Meta-analysis, 10 studies	860 CRC patients, stage I-IV	OS, HR 1.76 (1.42–2.19); DFS, HR 2.97 (1.76–5.01)
TNFRSF11B (Osteoprotegerin)	Birgisson *et al*[20]	Prospective cohort study	261 stage II-IV CRC patients	OS, HR 3.33
Protease enzymes and their inhibitors				
TIMP1	Lee *et al*[195]	Meta-analysis, 10 studies	1477 CRC patients, stage I-IV	OS, HR 2.25 (1.56-3.25)

CRC: Colorectal cancer; CSS: Cancer-specific survival; DFS: Disease-free survival; HR: Hazard ratio; OS: Overall survival.

independent study populations. As indicated by a recent meta-analysis[154], a few multiple cytokine array studies have been conducted in CRC, but mainly in fairly small populations, with varying markers and methods, making further larger scale studies necessary to draw more convincing conclusion about the prognostic significance of the reported marker combinations.

During the past decade, increasing effort has been directed towards the investigation of circulating tumor-derived extracellular vesicles as potential prognostic and diagnostic biomarkers in CRC and other tumors. Based on this approach, several promising results have been reported. For example, Liu *et al*[22] recently studied circulating exosomal miRNA content from 369 stage I–IV CRC patients. They found that exosomal miR-27a and miR-130a predicted survival. However, as for multiplex cytokine arrays, the selection of optimal combination of markers as well as independent validation studies would be required to establish circulating exosomal miRNA signatures as clinically relevant prognostic parameters in CRC.

CONCLUSION

The research conducted during the past few decades indicates that systemic inflammation has wide-ranging effects on CRC progression, including supporting primary tumor invasion, proliferation, angiogenesis, and metastasis, as well as suppressing anti-tumor immunity. Several systemic inflammation-based prognostic

parameters, such as neutrophil-lymphocyte ratio, modified Glasgow Prognostic Score, and platelet-lymphocyte ratio, have been found to have impressive prognostic value in a large number of studies and are widely available in clinical laboratories worldwide. However, larger-scale multi-institutional studies of their predictive value for the response to specific adjuvant therapies are needed. Moreover, these markers only begin to scratch the surface of the potential of systemic inflammation-based biomarkers in predicting patient survival. In future, additional tests, such as multiple cytokine-chemokine-growth factor assays, analysis of tumor-derived extracellular vesicles, and profiling of tumor-educated platelet transcriptome may translate into improved prognostic and predictive parameters, ultimately enabling accurate identification of patients who might benefit from specific adjuvant therapies, as well as into improved methods of non-invasive disease monitoring. Factors regulating the formation of pre-metastatic niches in CRC, suppression of anti-tumor immunity, tumor-platelet interactions, and CRC-associated cachexia also represent potential targets for drug development.

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