

Systemic Inflammation – Impact on Tumor Biology and Outcomes in Colorectal Cancer

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Abstract

Inflammation is increasingly recognized as a major factor in cancer development and progression. While local inflammation, represented by higher density of tumor infiltrating immune cells, is associated with better outcomes, the presence of systemic inflammation is conversely associated with poorer outcomes. This has been studied extensively in colorectal cancer where surrogates of systemic inflammation, such as serum albumin, C-reactive peptide, neutrophils and lymphocytes, have been shown to have prognostic significance independent of traditional clinicopathological factors. Despite the strength of this clinical data, the biological mechanisms underlying the poor outcomes are not well understood. This review details the impact of systemic inflammation on outcomes in colorectal cancer and examines what is known about the underlying biology.

Keywords: Systemic inflammation; Colorectal cancer; GPS; mGPS; NLR

Introduction

Across several cancers, including colorectal cancer (CRC), there is a large body of work that links systemic inflammation to both oncogenesis and tumor biology [1]. Systemic inflammation results from biochemical pathways that govern the interplay between inflammatory cytokines, chemokines and their cellular targets. From a cancer perspective, the impact of systemic inflammation on the immune system, tumor stroma and tumor cells results in poorer outcomes across a number of tumor types [2,3], independent of traditional prognostic factors such as tumor stage. Subsequently, the tumor associated immune response is now recognized as a fundamental process in cancer [4]. While a tumor-promoting immune response can lead to systemic inflammation and poorer outcomes, an anti-tumor immune response can lead to local inflammation and better outcomes. Furthermore, the success of immune checkpoint inhibitors has demonstrated that the type of tumor-associated immune response can be manipulated [5-7]. In this review, we explore the effect that systemic inflammation has on tumor biology, the various markers used for its evaluation and the potential clinical utility of these markers in CRC. Additionally, we also draw a distinction between systemic inflammation and local inflammation associated with anti-tumor immune responses.

Immunology of systemic inflammation in cancer

Inflammation is now considered a hallmark of cancer [4]. However, inflammation is a doubled edged sword. The tumor associated immune response and the type of inflammatory response that follows can dictate both favorable and poor outcomes [8].

Favorable outcomes are associated with an anti-tumor immune response, which is characterized by a strong local inflammatory infiltrate dominated by a high density of T-lymphocytes within the tumor [9,10]. This is thought to be driven by a T-helper-1 (Th1) lymphocyte adaptive immune response, which leads to the release of interleukin 2 (IL-2), tumor necrosis factor alpha (TNF α), interferon gamma (IFN γ) and other cytokines that promote CD8⁺ cytotoxic T-lymphocyte (CTL) activation and subsequent cytotoxicity [11]. Additionally, an M1 driven innate immune response has also been implicated [12]. It is now understood that this type of anti-tumor immune response can be dampened or suppressed by surrounding tumor stroma [13], MHC down regulation and production of negative regulatory signals in the tumor microenvironment [14].

In contrast to the favourable anti-tumor immune response, a tumor-promoting immune response and the subsequent systemic inflammation that arises, has been associated with poorer outcomes in many cancers. The driving processes behind this are complex and not clearly defined but appear to be part of a system designed to sense pathogens, tissue damage and eliminate noxious stimuli. Some data suggests that it may be driven by a T-helper-2 (Th2) adaptive immune response and a M2 innate immune response [12]. What is well accepted is that this tumor promoting immune response results in the production of cytokines which result in systemic inflammation. Some important cytokines involved in systemic inflammation include interleukin-6 (IL-6), interleukin 1 β (IL-1 β) and transforming growth factor beta (TGF β) [1,15-17]. IL-6 is a key mediator of the systemic inflammatory response and activates STAT3 transcription [18], which has broad effects on the tumor itself, the composition of circulating white blood cells, and the production of pro-inflammatory cytokines and chemokines. IL-6 results in maturation of platelets in the bone marrow resulting in paraneoplastic thrombocytosis [19] and is responsible for the production of acute phase reactants in the liver such as C-reactive peptide (CRP) and a decreased level of serum albumin

[20]. As such, elevated CRP and low serum albumin are surrogate markers of a systemic inflammatory state, both represented by the Glasgow Prognostic Score (GPS) and modified GPS (mGPS) (Table 1) [20].

Glasgow Prognostic Score (GPS)	Points allocated
C-reactive protein >10 mg/L and albumin >35 g/L	0
C-reactive protein >10 mg/L	1
Albumin <35 g/L	1
C-reactive protein >10 mg/L and albumin <35 g/L	2
Modified Glasgow Prognostic Score (mGPS)	Points allocated
C-reactive protein <10 mg/L and albumin >35 g/L	0
C-reactive protein >10 mg/L	1
C-reactive protein >10 mg/L and albumin <35 g/L	2

Table 1: Shows the Glasgow prognostic score (GPS) and modified GPS (mGPS).

Systemic inflammation can also contribute to altered myeloid differentiation; often, neutrophilia and increased immature myeloid cells such as myeloid derived suppressor cells (MDSC) are seen in the circulation as well as a relative lymphopenia [16]. This is the basis of the neutrophil-to-lymphocyte (NLR) score as a marker of systemic inflammation. MDSC and neutrophils also suppress lymphocyte function, shifting responses away from a CTL response [16] through upregulation of T-regulatory (T-reg) cells. Furthermore, the cytokine environment resulting from systemic inflammation promotes a M2 phenotype within macrophages [21], which promotes IL-6 production in a positive feedback loop that amplifies the whole process.

Systemic inflammation results in recruitment and amplification of cells and molecules that sustain growth, proliferation, invasion and neoangiogenesis whilst suppressing adaptive anti-tumor effects. In this way, cancer and inflammation initiate and sustain one another. At the extreme, excess cytokines and inflammatory molecules have wide ranging effects. Changes in energy metabolism, neurological and endocrine function, result in cancer syndromes such as fatigue, weight loss, cachexia and disease related fevers [16,20]. Markers such as NLR and GPS/mGPS reflect this systemic process and the associated poorer outcomes.

In a “chicken or the egg” type problem, it remains unclear whether systemic inflammation results in oncogenesis, or whether tumors themselves induce systemic inflammation in order to promote growth and survival. There is data to support both. Some data suggest that somatic mutations responsible for oncogenesis, such as KRAS or TP53, may directly induce transcription of key pro-inflammatory pathways [15,17]. Conversely, chronic inflammatory diseases, such as ulcerative colitis are associated with increased risk of colorectal cancer [22].

Markers of systemic inflammation and poor prognosis

As described, an elevated CRP, low serum albumin and high NLR are all commonly studied as surrogates of systemic inflammation and a tumor promoting immune response. There are also some novel markers being studied including IL-18 and others [17,23] (Table 2).

1.	An Anti-Tumour immune response is associated with favourable outcomes and a local inflammatory response represented by CD8+ cytotoxic lymphocyte infiltration within the tumour.
2.	A Tumour promoting immune response is associated with poorer outcomes and a systemic inflammatory response represented by markers such as elevated neutrophil-lymphocyte ratio, high C-reactive protein.

Table 2: Differing outcomes from the tumour associated immune response.

CRP is easily reproducible and cheap. It is not routinely ordered for cancer patients in institutions worldwide but reflects the increased cytokine state represented by systemic inflammation, as it induced by IL-1, IL-6 and TNF α . Multiple studies show an elevated CRP predicts for recurrence and death in CRC [24-27]. A retrospective analysis looking at various measurements and scores from large registry data suggested that scores consisting of CRP or other measures of acute phase proteins, were better predictors of survival than the circulating white cell counts alone [28]. In particular, in CRC, GPS, incorporating CRP better predicted cancer specific survival independent of age, sex and tumor stage.

Albumin is also a recognized acute phase reactant that drops in relation to systemic inflammation. Low albumin has been recognised for its value as an independent poor prognostic indicator in CRC [29]. However, albumin is better recognized as a component of inflammatory scores such as GPS and mGPS. The initial interest in albumin was due to its recognition as a reflection of nutritional status and lean body mass and hence its interest in combining with CRP to form the GPS or mGPS, both of which have been examined in a variety of cancers.

In early stage CRC, studies have consistently demonstrated that GPS/mGPS is associated with poorer prognosis, independent of TNM stage and co-morbidities [2]. Roxburgh et al. [30] studied 380 CRC patients undergoing curative resection and demonstrated that mGPS was an independent predictor of poorer cancer specific survival (CSS), with a hazard ratio (HR) of 1.56 (p=0.038) for colon cancer and 1.76 (p=0.033) for rectal cancer. Petrelli et al. recently published a pooled analysis of nine studies, examining 2,000 patients. They demonstrated that a high mGPS was associated with poorer overall survival (OS) (HR 1.69, p<0.00001) and CSS (HR 1.84, p<0.00001) [31].

An alternate marker of systemic inflammation is NLR, which was originally developed as a score in critically ill patients in order to predict poor prognosis [32]. It is calculated by dividing the absolute neutrophil count by the lymphocyte count and has been extensively used as a surrogate of systemic inflammation in cancer patients. Like GPS/mGPS, it has been studied in unselected populations and in specific tumor types. NLR can be calculated using blood tests routinely ordered in the care of cancer patients.

Early studies using NLR had no defined ratio defining high inflammation. Later studies have generally defined a NLR of above 5 as the critical number to represent the presence of clinically significant systemic inflammation. Consistently, a high NLR is associated with poorer outcomes in cancer patients. Li et al., recently conducted a meta-analysis examining the effect of high NLR in CRC [33]. The primary endpoints were OS and progression free survival (PFS). The authors included patients with both early stage and metastatic CRC. They demonstrated poorer OS (HR 1.813, 95% CI 1.499-2.193, p<0.001), and poorer PFS (HR 2.102, 95% CI 1.554-2.843, p<0.001) in

those with high NLR. However, there was considerable heterogeneity amongst the studies included. This meta-analysis is consistent with a larger meta-analysis conducted by Templeton et al. [34] who examined the prognostic role of NLR across all solid tumors. In this study, 22 CRC cohorts were analysed and the pooled HR for OS in CRC was 1.91 (95% CI 1.53-2.39).

As surrogates of systemic inflammation, elevated CRP, low albumin, GPS/mGPS and NLR have all been shown to be associated with poorer prognosis in both early stage and metastatic CRC, some studies have attempted to determine which marker is the better predictor of prognosis. Proctor and et al. examined the prognostic value of various inflammatory scores in an unselected cancer population [28]. Within the CRC cohort (n=374), only mGPS and Prognostic Index (a score involving CRP and white cell count) were significantly associated with poorer outcomes in the multivariate analysis, whereas NLR was only significant in the univariate analysis. Guthrie et al., conducted a similar study, involving a cohort of 326 patients with early stage CRC cancer. They demonstrated that pre-operative NLR and mGPS were both significantly associated with poorer cancer specific outcomes [35]. Despite these studies, it remains unclear which marker of systemic inflammation is the best predictor of poor prognosis in CRC or alternatively if a panel of markers may be more informative.

Relationship between systemic and local inflammation

The resurgence of cancer immunotherapy has led to an increasing recognition of the importance of the tumor microenvironment and the type of inflammatory cell infiltrate within a tumor, or local inflammation. In early stage CRC, it has long been appreciated that high levels of microsatellite instability (MSI-high) are associated with a higher density of CD8⁺ CTL infiltrate within tumor, and a better prognosis. The role of tumor infiltrating lymphocytes has been further explored in several studies, but most well studied in CRC by the group led by Jerome Galon; Pages et al., first described the Immune Score [36], which assesses the density of CD45RO⁺ (memory) T-cells and CD8⁺ CTLs at both the invasive margin and centre of the tumor. Patients with a high density of both cell types at both sites had the best prognosis, whereas conversely, those with a low density of both cell types at both sites had the worst prognosis. The Immune Score was highly prognostic, with a hazard ratio of 0.54 (95% CI, 0.43 to 0.69, p<0.0001) for OS.

While it is clear that the presence of systemic inflammation is associated with poor prognosis and the presence of local inflammation is associated with a good prognosis, the relationship between these two distinct types of inflammation remains unclear. Clinical evidence of a significant interaction between systemic and local inflammation has to date received limited attention. Our group recently examined the prognostic value of both a high NLR and intra-tumoral chronic inflammatory cell (CIC) infiltrate in a cohort of stage 2 colon cancer [37]. This retrospective study of recurrence free survival (RFS) in 396 patients confirmed the prognostic significance of both markers. The poorest outcomes were seen in patients who had a combined low CIC density (representing absent local inflammation) and high NLR (representing high levels of systemic inflammation) with a hazard ratio of 4.163 (95% CI 1.46–11.79, p<0.001). Furthermore, we identified a trend towards an inverse relationship between local inflammation and systemic inflammation (p=0.026), with only 10% of patients having evidence of both. Given systemic inflammation can occur as a result of multiple non-cancer related causes, it is possible that from a purely

oncological perspective, local and systemic inflammatory responses are mutually exclusive. Having said that, it is clear that for patients with cancer associated systemic inflammation, the mechanism linking local and systemic inflammation is complex and not well understood.

Clinical utility of identifying systemic inflammation

As described, there is extensive data demonstrating that systemic inflammation is associated with poor prognosis in cancer patients, including CRC. However, only few studies have examined the clinical utility of identifying systemic inflammation.

In stage II colon cancer, the risk of recurrence is low and benefit from adjuvant chemotherapy is limited [38], possibly greater in those patients with high-risk features, such as, T4 stage, less than 12 lymph nodes sampled and presence of lymphovascular invasion. Given the additional and independent prognostic information provided by markers of systemic inflammation, these might be incorporated into the algorithm used to make treatment recommendations for patients with stage II colon cancer. As described, our group demonstrated the combination of a high NLR and low CIC infiltrate identifies patients with stage 2 colon cancer who have significantly poorer outcomes, who may therefore gain the most benefit from adjuvant chemotherapy [37].

Other studies have examined whether dynamic changes to inflammatory scores can predict for benefit from differing treatment options. Chua et al., conducted a retrospective study that analyzed the dynamic effects of NLR pre and post administration of 1 cycle of palliative chemotherapy in advanced CRC [39]. This study demonstrated that patients who had a conversion from high to low NLR after 1 cycle of chemotherapy had significantly better PFS (median 5.8 months versus 3.7 months, p=0.012) and OS (12.0 months versus 9.4 months, p=0.053). While this study was small and needs validation, these results suggest that changes in NLR may be an early indicator of treatment response and failure of the NLR to normalize may potentially predict reduced treatment benefit. In another study, examining patients with CRC and liver only metastases, Kishi et al. examined NLR prior to neoadjuvant chemotherapy and prior to liver resection [40]. In a subset of patients who had conversion from high to low NLR after neoadjuvant chemotherapy, there was improved OS compared to those who had a persistently high NLR (3 year OS 63% versus 42%, p=0.021). However, the numbers were small. Finally, our group examined the role of NLR in a cohort (n=145) of patients with *de novo* metastatic CRC cancer who underwent primary tumor resection [41]. In this specific cohort, we demonstrated that a conversion from high to low NLR following resection of the primary tumor, resulted in improved OS compared to patients who maintained a high NLR (HR 0.37, 95% CI 0.09-0.69, p-value=0.011). ECOG performance status and large primary tumor bulk were associated with NLR reversal and we hypothesized that these factors may help predict which patients with metastatic CRC might derive benefit from resection of their primary tumor. However, like the other studies, given the small numbers, this finding needs to be validated in larger trials.

It is clear that the presence of systemic inflammation in CRC, using NLR or GPS/mGPS, is associated with poor prognosis. Its role as a prognostic marker may help clinicians stratify patients for adjuvant chemotherapy in stage II disease. Furthermore, these markers may have a role, if validated further, in monitoring response and predicting who is unlikely to benefit from particular treatment options.

Future Directions

Given the association between systemic inflammation and poorer outcomes in CRC (and other tumor types), treatment strategies targeting the inflammatory response have been proposed.

One non-specific way of inhibiting inflammatory pathways is via cyclooxygenase (COX) inhibition. COX-1 and COX-2 are enzymes that catalyze arachidonic acid into various mediators. COX-1 is responsible for various homeostatic prostaglandins whilst COX-2 is inducible and the various mediators are associated with inflammation. Aspirin and non-steroidal anti-inflammatory drug (NSAIDs) have been shown in large epidemiological studies to be associated with decreased cancer risk, particularly in CRC [42]. Smaller retrospective studies have been reported primarily focusing on CRC cohorts but the evidence is contradictory: Liao et al. reported that aspirin reduced the risk of death in mutated PIK3CA CRC cancer [43]. Subsequent studies by both Reimers and our group showed no benefit in patients with PIK3CA mutations [44,45]. Given the conflicting results, outcomes from large prospective trials are awaited [42].

Targeting various cytokines has been trialed with monoclonal antibodies. Thus far, targeting IL-6 and other cytokines has produced modest benefits. For example, siltuximab, which is a monoclonal antibody to IL-6, has been tested in a number of solid tumors with mixed results [46,47]. Given the broad impact and complex interactions of these molecules, along with the poorly understood interdependency of the tumor microenvironment, local and systemic inflammatory response, this is not surprising. Better understanding of each of these should lead to more clearly defined therapeutic targets and optimized treatment, alone or in combinations with other strategies.

Encouragingly, there is evidence of benefit through targeting IL-1 α , which was initially targeted as a component of cancer cachexia. In a phase I study of MAPb1, a monoclonal antibody against IL-1 α , 8 patients had stable disease and 1 had a partial response by RECIST criteria. In addition, the expected gains in lean body mass were seen in patients as assessed by dual energy X-ray absorptiometry. The antitumor effects demonstrated in this small study suggest a potential role for targeting IL-1 α , not only the management of cancer related cachexia but in the treatment of the cancer itself [48]. A phase 3 placebo-controlled trial in treatment of refractory metastatic CRC is now recruiting.

Finally, given the weight of evidence for systemic inflammatory markers and tumor microenvironment, introducing a standardized way of scoring these markers, for incorporation into prospective clinical trials, will help advance the field further.

Conclusion

The presence of systemic inflammation is associated with poorer outcomes in CRC. This is likely to be driven through a tumor promoting immune response that produces cytokines such as IL-6. A dominant systemic inflammatory response can be easily identified in patients, using NLR or GPS/mGPS. While the clinical utility of identifying systemic inflammation in patients with CRC lies in its prognostic value, small studies suggest that early changes seen whilst on treatment may also have a predictive role.

With greater understanding of the complex mechanisms behind the systemic inflammatory response and the local immune infiltrate,

targeting the immune response is increasingly recognized as an important new approach to treating CRC.

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