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Laboratory-Clinic Interface

Does interleukin-6 link explain the link between tumour necrosis, local and systemic inflammatory responses and outcome in patients with colorectal cancer?

Graeme J.K. Guthrie *, Campbell S.D. Roxburgh, Paul G. Horgan, Donald C. McMillan

Academic Unit of Surgery, School of Medicine, University of Glasgow, Royal Infirmary, Glasgow G31 2ER, UK

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ABSTRACT

Cancer-associated inflammation has been identified as a key determinant of disease progression and survival in colorectal cancer. In particular, it has been consistently reported that both the local and systemic inflammatory responses play an important role in determining outcome in colorectal cancer. Given the importance of cancer-associated inflammation, up-regulation or attenuation of these respective inflammatory responses may be important for progression and survival in colorectal cancer. Recent work has focused on the inter-relationships between the tumour and these key inflammatory processes. In particular, tumour necrosis has been reported to be associated with decreased local inflammatory infiltrate and with elevated markers of systemic inflammation in colorectal cancer and has been proposed as a potential link between the systemic and local inflammatory responses. Thus there is increasing interest in the potential biochemical mediators of this link. In this review we examine the evidence for IL-6 in the natural history of colorectal cancer and its relationship with tumour necrosis and the local and systemic inflammatory responses. There is now good evidence that tumour concentrations of IL-6 have been directly associated with increased necrosis, proliferation, differentiation and vascular invasion, while circulating concentrations of IL-6 are directly associated with T-stage, CRP concentrations and poorer survival. Also, interleukin-6 and down-stream pathways, such as the JAK/STAT pathway, have emerged as important factors in the modulation of cancer-associated inflammation. Therefore, IL-6 has emerged as a key mediator of the relationship between tumour necrosis, local and systemic inflammatory responses and outcome in patients with colorectal cancer.

Introduction

Colorectal cancer is the third most common cancer in males and females in the UK and the second most common cause of cancer death in both men and women.[1,2] Despite improvements in treatment, outcomes remain poor with approximately half of those undergoing curative surgery dying from the disease.

Since the advent of the Dukes' classification, prediction of outcome has been based on high-risk pathological criteria such as the tumour, node, metastasis (TNM) system, and this is widely accepted as the gold-standard. Despite this, it has become increasingly clear that within the Dukes staging system there is a wide spectrum of disease with survival being variable, reported to range between 50% and 85%, particularly in those with Dukes B2 or T3/4 node negative tumours.[3–5] In an attempt to improve the accuracy of prognostication pathological assessment has been refined. Using a simple, reproducible, cumulative score the Petersen Index combines four pathological factors: peritoneal involvement, venous invasion, spread involving resection margin, and tumour perforation to improve the accuracy of prognostication and this system has been validated in node-negative colorectal cancer. The Petersen Index provides prognostic information that identifies those patients at high-risk of recurrence that may benefit from adjuvant treatment.[6] Despite this, prognostication in colorectal cancer requires further refinement if those at high risk of recurrence are to be accurately identified.

The stratification of outcome in colorectal cancer is becoming increasingly important for several reasons: Firstly, the introduction of screening for colorectal cancer should bring about 'stage migration', with significant expansion of the node-negative group to approximately 75% of all cancers.[7] Secondly, patients with early stage disease and at high risk of recurrence may benefit from adjuvant therapies not currently approved for node negative disease.

It is therefore clear that there is a need for refinement of current staging systems for early stage colorectal cancer through the identification of reliable prognostic factors. In addition to improving outcomes such work may also provide further insight into the natural history of colorectal cancer.

* Corresponding author. Tel.:+44 141 211 5435; fax: +44 141 552 3229.
E-mail address: graemeguthrie@doctors.org.uk (G.J.K. Guthrie).

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Cancer-associated Inflammation

There is now persuasive evidence that cancer survival, especially in early stage disease, is dependent on the tumour–host interaction. In particular, inflammation is now thought to be key in tumourigenesis via DNA damage,[8] stimulation of angiogenesis and proliferation, and inhibition of apoptosis.[9] Indeed, the link between inflammatory bowel disease and development of colorectal cancer is well-established. For example, many epidemiological studies have reported high frequencies of CRC among patients with inflammatory bowel disease,[10] and animal models of colitis-associated CRC have been utilised to investigate models of cancer-related inflammation. In addition, it has been reported that IL-6 signalling is key to maintaining mucosal integrity and dysregulation of this key pathway may partly explain a link between inflammatory bowel disease and colorectal cancer.[11] Lastly, in recent years the risk of developing CRC on a background of inflammatory bowel disease appears to be reducing and this might be explained by improved treatments of colonic mucosal inflammation.[12]

Several studies have provided evidence for this crucial role for cancer-associated inflammation, both in resected colorectal tumours and in precursor lesions.[13] Indeed, cancer-associated inflammation has recently been identified as a key determinant of disease progression and survival in colorectal cancer and has been cited as the seventh hallmark of cancer.[14–16]

With reference to the local inflammatory response, more than 100 studies over the last 40 years have reported that inflammatory/immune cells in the immediate tumour microenvironment play an important role in determining colorectal cancer outcome. Recently, Klintrup and co-workers determined, through assessment of the entire immune/inflammatory reaction at both the invasive margin and in the central part of the tumour, that local inflammation was an important prognostic marker predicting both enhanced survival and recurrence-free survival in both colonic and rectal tumours.[17] Recent work confirms that a pronounced tumour inflammatory infiltrate predicts good outcome and it has been proposed this may be used routinely to predict survival.[17–19]

With reference to the systemic inflammatory response, there is now good evidence that it is associated with poor outcome in patients with a variety of common solid organ tumours.[20–23] The systemic inflammatory response, measured as an elevated C-reactive protein and hypoalbuminaemia, has consistently been reported as a marker of poor prognosis in primary operable colorectal cancer.[24,25]

Thus the inflammatory response, both local and systemic, is intimately linked to colorectal cancer survival. Despite the strong evidence for the roles of these inflammatory processes in cancer survival, the mechanisms by which these two distinct inflammatory processes are activated, maintained, and interact are not clear. An interesting concept is that a cell-signalling mediator may be involved in the modulation of the systemic and local inflammatory responses.

The link between local and systemic inflammatory responses

A plausible hypothesis is that tumour necrosis may link the systemic and local inflammatory responses.[26,27] Indeed, there is good evidence that presence and extent of necrosis is important in determining outcome in many solid organ tumours such as lung,[28] urothelial,[29] and breast.[30] Studies in renal and breast cancer propose that tumour necrosis is associated with markers of systemic inflammation as well as recruitment of local inflammatory cells.[30,31]

With reference to colorectal cancer, some studies have reported the presence of tumour necrosis in more than 90% of colorectal cancers[32] thus strongly implicating tumour necrosis in the natural history of colorectal cancer. The importance of tumour necrosis in patients with colorectal cancer was reported in a study by Pollheimer and colleagues who demonstrated that necrosis was significantly associated with tumour-related factors including advanced stage, poor differentiation, venous invasion and larger tumour size.[32] Indeed it has been reported that necrosis stimulates the local recruitment of inflammatory cells and also is associated with unfavourable host responses such as increasing white cell count, and anaemia.[31,33,34]

Two recent studies have directly examined the relationship between tumour necrosis and survival. Both Pollheimer et al. and Richards et al. have reported that tumour necrosis is a negative prognostic marker in colorectal cancer.[32,27] In addition, Richards and co-workers reported an association between necrosis and well recognised high-risk pathological variables such as vascular invasion, peritoneal involvement and margin involvement in colorectal cancer.[27] They reported that tumour necrosis was directly associated with an increased systemic inflammatory response and decreased local inflammatory response, both of which were known to be associated with poor prognosis.[27] Although tumour necrosis was associated with both local and systemic inflammatory responses it did not have independent prognostic value, thus raising the issue of whether tumour necrosis plays a causal role in the systemic and local inflammatory responses and their relationship with survival in patients with colorectal cancer.

Cancer-associated inflammation and circulating cytokines in colorectal cancer

The clear association between tumour necrosis and the local and systemic inflammatory responses, but the lack of independent prognostic value suggests that necrosis although an important feature, reflects the production of a mediator of local and systemic inflammatory responses. One possibility is that necrosis may stimulate mediators that down-regulate the local inflammatory response and up-regulate the systemic inflammatory response. Therefore, the delineation of such a mediator of the relationship between tumour necrosis and these inflammatory responses may provide some unique insight into the natural history of colorectal cancer and provide potential therapeutic targets.

The molecular links between tumour necrosis and the inflammatory responses are likely to be very complex. However, it is recognised that tumour necrosis is likely to be the result of a tumour out-growing its blood supply, becoming relatively hypoxic and inducing the up-regulation of cellular stress genes in the tumour and the inflammatory cell infiltrate. Indeed, it has been postulated that the combination of inflammation and necrosis provides an environment in which the epigenetic regulation of genes, cell death, cell proliferation and mutagenesis occurs.[14] At sites of chronic inflammation, cells are continuously dying as a consequence of hypoxic stress, an event in turn promoting growth and proliferation of the local epithelium. The apoptotic to necrotic conversion that is associated with unscheduled cell death and the subsequent release of necrotic mediators is recognized not to be a 'clean' death, but instead stimulates inflammatory pathways.[14] These inflammatory pathways are now recognized to be important for angiogenesis, stromagenesis and the promotion of epithelial proliferation, all of which are required for tumour growth.[16]

An important hypoxic stress pathway is regulated by HIF-1 Alpha[35] that is, in turn, a potent stimulator of IL-6 production from the tumour and inflammatory infiltrate cells.[36] It is of interest, therefore, that the IL-6/JAK/STAT pathway has emerged as a key player in cancer-associated inflammation.[37–40]

Il-6 is a multi-functional pro-inflammatory cytokine that has crucial roles in tumour progression through growth-promotion, anti-apoptotic activity, and modulation of immune function and