Cellular Signalling 54 (2019) 81–90

Contents lists available at ScienceDirect

Cellular Signalling

journal homepage: www.elsevier.com/locate/cellsig

Review

Signal interaction between the tumour and inflammatory cells in patients with gastrointestinal cancer: Implications for treatment

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ARTICLE INFO

Keywords:
Cancer
Inflammation
Immune/inflammatory phenotypes

ABSTRACT

Over the last 15 years there has been a change in how we understand the impact of the interaction between the tumour and the host on cancer outcomes. From the simplistic view that the make-up of tumours cells largely determines their aggressiveness to a more complex view that the interaction between the products of tumour and host cell signal transduction pathways is crucial in determining whether the tumour cell is eliminated or survives in the host. Of the host cells, those with an immune/inflammatory function are most well documented to inhibit or promote tumour cell proliferation and dissemination.

It is only in the last few years that there has been greater recognition of the impact of intracellular, cellular and systemic immune/inflammatory phenotypes on patient outcomes independent of current tumour staging and that these phenotypes are useful in informing oncological research and practice. In the present review we will examine the importance of inflammatory phenotypes at the intra-cellular, cellular and systemic levels on outcomes in patients with gastrointestinal cancer with focus on colorectal cancer. Based on these phenotypes we will examine and discuss the prospects for therapeutic intervention.

1. Introduction

Over the past decade or so there has been a vast body of evidence focused on increasing our understanding of tumour-host interactions in colorectal cancer (CRC). The traditional view that CRC tumour progression stems from genetic alterations up-regulating pro-tumour genes and down-regulating tumour suppressive genes is out-dated. Instead, it has become clear that the interaction between the tumour and host immune cells plays a central role in determining disease progression [1,2,3].

In the more recent view it is recognised that numerous genes become altered during the development of a tumour, however, it is also recognised that these tumour cells are maintained by the deregulation of specific signalling pathways [4]. Therefore, these genetic events are part of a larger network that alters signal transduction pathways resulting in an increase in tumour cell proliferation and a decrease in tumour cell death. In this network, these intracellular pathways within tumour cells do not function in isolation but regularly interact with stromal and immune cells. Furthermore, this complex network of genetic events and signal transduction pathways result in growth factors and cytokines/chemokines that alter cellular behaviour at both local and systemic levels. Of the host cells, those with an immune/inflammatory function are most well documented to inhibit or promote tumour cell proliferation and dissemination [5]. Broadly these inflammatory responses have been considered as adaptive immune responses inhibiting tumour progression and innate immune responses promoting tumour progression [6].

Unravelling the mechanisms of the immune systems involvement in CRC is a complex process due to its heterogeneous nature. There is a degree of plasticity to inflammation in cancer and components of the inflammatory infiltrate can exert both tumour-promoting and anti-tumour actions. Immunoediting describes the progression of a tumour from elimination, equilibrium to escape, whereby immune cells can eliminate, tolerate or be unable to kill the cancer cells [7]. The main

Abbreviations: CRC, Colorectal Cancer; COX, cyclooxygenase enzyme; EMT, epithelial mesenchymal transition; NSAID, non-steroidal anti-inflammatory drugs; NF-κB, Nuclear Factor Kappa B; STAT, signal transducer and activator of transcription; JAK, janus kinases; TAMs, tumour-associated macrophages; ILCs, innate lymphoid cells; ILC3, innate lymphoid cell 3; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; CAFs, cancer-associated fibroblasts; BMP, bone morphogenic pathway

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https://doi.org/10.1016/j.cellsig.2018.11.013
Received 10 October 2018; Received in revised form 15 November 2018; Accepted 15 November 2018
Available online 17 November 2018
0898-6568/

cells involved in the elimination of the tumour are CD8 + T cells (CTLS) and NK cells, which produce anti-tumour cytokine IFN-γ that signals via STAT1 via JAK1/2 [8]. In contrast, those cells shown to actively promote tumour growth include macrophages, innate lymphoid cells (ILC2s, ILC3s) and neutrophils. The equilibrium phase describes a state of dormancy or senescence between the tumour and host that is currently poorly understood [7]. The escape phase is characterised by an immunosuppressive microenvironment, which allows the tumour to evade immunosurveillance and escape subsequent attack. For the purposes identifying potential therapeutic targets, this review will focus on detrimental effects of immune cells and their activation of signalling cascades that promote tumorigenesis.

These tumour and immune/inflammatory responses whether at the intra-cellular, cellular or systemic levels appear to be similar across gastrointestinal tumour types and have prognostic value. Therefore, indicating the importance of such inflammatory phenotypes in gastrointestinal tumours. The aim of the present review was to examine the relationships of inflammatory phenotypes at the intra-cellular, cellular and systemic levels in patients with gastrointestinal cancer and discuss the prospects for therapeutic intervention.

1.1. Intracellular inflammatory phenotypes

There are a number of signal transduction pathways that may be considered to be important in tumour cell maintenance and characterisation of an intracellular inflammatory phenotype. Historically, there is a great deal of both epidemiology and clinical evidence that the cyclooxygenase enzyme (COX), in particular COX2/ PGE2 pathway, plays a key role in the development and progression of intestinal cancers. Its activation results in many of the hallmarks of cancer and regulation of other signalling pathways [9,10,11]. For example, up regulation of COX-2 has been shown in the majority of gastrointestinal cancers and appears to promote WNT signalling, epithelial mesenchymal transition (EMT), angiogenesis, and resistance to chemotherapy induced apoptosis. Furthermore, the benefits of taking aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) that target this pathway on reducing the lifetime risk of gastrointestinal, especially colorectal, cancer have been well documented. As a consequence, many individuals with no evidence of disease now regularly take aspirin [12]. Although the basis of this protective effect is most probably by the regulation of immune/inflammatory responses at the intracellular, cellular and systemic levels, the molecular mechanism is not clear.

In terms of the molecular mechanism, it is recognised that COX2 is a target gene of Nuclear Factor Kappa B (NF-κB) responsible for prostaglandin synthesis and that aspirin consumption induces phosphorylation and degradation of IKK-B, resulting in inhibition of NF-κB nuclear translocation and therefore a decrease in COX2 expression [13,14]. There are 5 members of the NF-κB family: p65/RelA, p105/p50, RelB, p100/p52 and c-Rel. These transcription factors are controlled by 2 signalling pathways termed the canonical and non-canonical pathways (Fig. 1). The canonical pathway is regulated by the IKKα/IKKβ/IKKγ complex, which induces degradation of IκB, allowing p65 and p50 to dimerise and translocate to the nucleus to act as a transcription factor. In contrast, the non-canonical pathway only involves IKKα that acts with NIK to phosphorylate p100, inducing proteolysis and formation of p52, which dimerises with RelB and translocates to the nucleus where it also acts as a transcription factor.

NF-κB signalling pathways are well established as promoting tumour growth and progression as well as controlling immune responses. Activation of the NF-κB pathway in tumour and stromal cells results in secretion of factors into the tumour microenvironment that co-ordinate innate and adaptive immune responses, induce angiogenesis, and promote tumour cell proliferation and invasion. Therefore, NF-κB is not only activated in response to inflammatory stimuli but also regulates the inflammatory response. It also enables the tumour cells to be pro-proliferative via inducing expression of many genes involved in many other cellular processes eg: Cyclin D1 in cell cycle and proliferation; Bcl-CL anti-apoptosis; VEGF regulation of angiogenesis; MMP-9 regulation of invasion and increased secretion of growth factors and cytokines.

In particular, it would appear that an activated canonical NF-κB pathway in colorectal tumours is associated with poor outcome. For example, increased expression of NF-κB/RelA has been shown to be activated in colorectal carcinoma tissues [15]. Sakomoto et al. observed activation of NF-κB in 40% of colorectal cancer tissues and 67% of cell lines. Higher levels of NF-κB activation in human colorectal carcinoma tissue have been correlated with tumour progression and a higher T-stage [16]. More specifically activation may contribute to tumour angiogenesis in colorectal cancer [15]. Expression of the p65 subunit is up-regulated at the invasive margin and in the mucinous tumour cells in colorectal cancer [17] and it is been widely reported that p65 expression is up-regulated in colorectal tumour tissue compared to matched normal, and that its expression increases in response to intervention and is associated with poor prognosis, particularly in rectal cancer [18,19].

The prognostic power of p65 can be increased by measuring the activated form NF-κB phosphorylated at Serine 536 and also by looking at cellular locations. Lewander and co-workers (2012) reported that, in a cohort of 203 patients with colorectal cancer, that phospho-p65 expression was associated with shorter patient survival [20]. We have recently observed that IKKβ expression (the catalytic component of the canonical NF-κB pathway) was associated with the tumour microenvironment and local inflammatory infiltrate and this was associated with cancer specific survival (Edwards et al. unpublished results). In addition, when patients were stratified by BRAF status, the association between cytoplasmic IKKβ and cancer specific survival was upheld in patients with wild type BRAF but negated in those with mutated BRAF, suggesting this could be a possible target for those patients not responding to chemotherapy or EGFR and BRAF inhibitors.

There is less evidence in the literature that the non-canonical pathway is involved in colorectal cancer, and the main focus is on the role of IKKα (the catalytic component of the non-canonical pathway) which is involved in both the canonical and non-canonical pathways. Perhaps a better marker for the activation of the non-canonical pathway would be RelB which dimerises with p52 to form the transcription factor. However, few studies have investigated the role of RelB with regards to patient outcome measures. We have observed that high RelB expression was associated with local inflammatory infiltrate, tumour stroma percentage and shorter cancer specific survival but not associated with the systemic inflammatory response in right sided colon tumours and rectal tumours. We have in our group observed that elevated IKKα is associated with reduced cancer specific survival in a cohort of 700 patients.

More recently, there is evidence that COX2/ PGE2 mediates the activation of the JAK/STAT pathway, in particular STAT3 [21]. Furthermore, upregulation of COX2 may promote tumour dissemination through activation of both NF-κB and STAT3 in tumour-associated fibroblasts rather than in the tumour cells (Fig. 1). In turn, it has been shown that tumour-associated fibroblasts and other stromal cells have elevated expression of COX2, NF-κB and STAT3 which stimulates increased secretion of IL-6 and TNFα to promote tumour cell proliferation.

The signal transducer and activator of transcription (STAT) pathways are of particular interest since they are primarily under the control of the janus kinases (JAK1, JAK2 and JAK3) and these are required for immune cell activation and have been therapeutically targeted in various myeloproliferative disorders. JAKs phosphorylate STATs to transmit information from the membrane to the cell nucleus, where STATs act as transcription factors to regulate many cytoprotective genes including anti-apoptotic genes such as MCL-1, BCL-XL, BCL-2, survivin, HSP90 and HSP70; proliferation regulatory genes such as cyclin D1, cyclin B, c-jun, and c-Fos and angiogenesis promoting genes

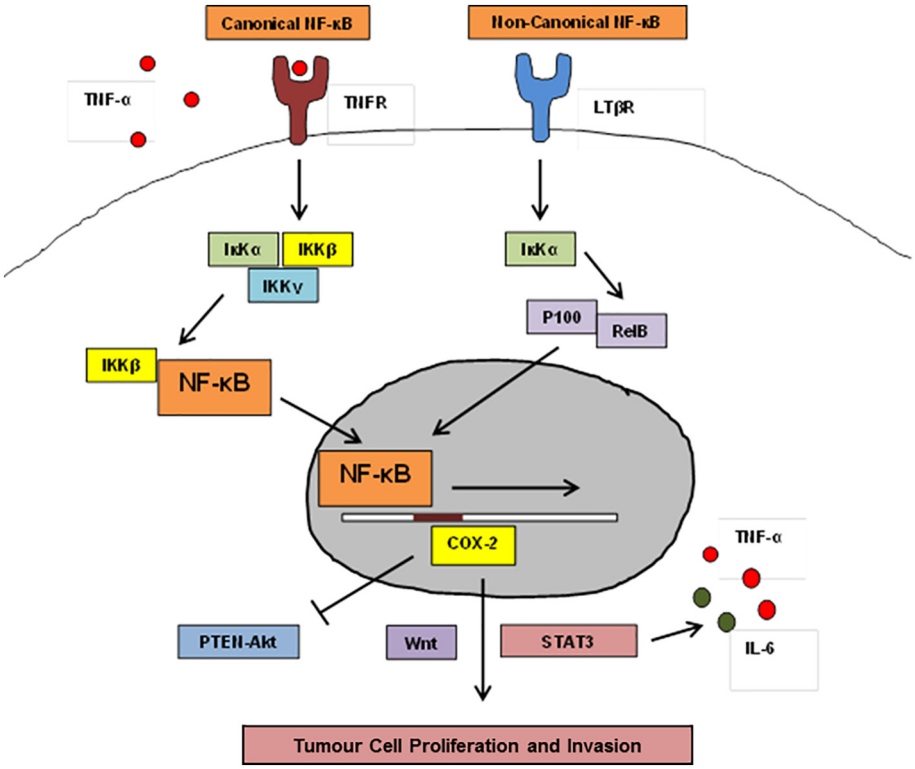

Fig. 1. Crosstalk of NF-κB Pathway in Colorectal Cancer.
The well-documented NF-κB canonical pathway can be initiated via TNFα binding its receptor, TNFR. This results in activation of the IκK complex causing IκBα phosphorylation and ubiquitination resulting in NF-κB translocating to the nucleus where it regulates gene transcription. The canonical or alternative pathway occurs via the lymphotoxin receptor activating IκKα, phosphorylation of p100 and translocation to the nucleus. COX2 is a main target of NF-κB, and its induction results in blockade of AKT pathway, initiation of Wnt signalling and activation of STAT3. IL-6 and TNF-α are produced via STAT3 signalling. The crosstalk of NF-κB with other pathways ultimately leads to tumour cell proliferation and invasion.

such as HIF1α and growth factors such as Il-6, FGF, EGF, and VEGF [22,23].

In mammalian cells there are seven members of the STAT protein family. STAT1, STAT3, STAT4 and STAT5 are the family members most commonly reported to be expressed in gastrointestinal cancers [24,25,26]. Cytokines and growth factors are the main ligands responsible for activating the STAT family members, however they may also be activated intrinsically via amplification of HER2, up-regulation of Src kinase or silencing of SOC3.

Activation of STATs via receptors and kinases results in phosphorylation allowing them to form homo/heterodimers and translocate to the nucleus where they act as transcription factors. Classically STAT1 has been associated with tumour suppression and STAT3 with oncogenesis, however both have been reported to have tumour promoting and tumour suppressive roles. For example, activation of STAT3 can result in activation of the MMPs that can promote tumour cell invasion and interactions with other tumour promoting pathways such as NF-κB and COX2. In general, persistent activation of these pathways in tumour cells and microenvironment results in the accumulation of stroma around the tumour cells and the loss of anti-tumour T-lymphocyte responses.

Taken together this emphasises the importance of the cross talk between the above signalling pathways and different cells in the tumour microenvironment to inhibit or promote tumour cell proliferation and invasion. Recently, it has been observed that there is further cross talk between COX2/PGE2 and the PTEN/Akt pathways [27]. An increased in expression of COX2 was observed to dampen the action of the PTEN/Akt pathway and it was only in the absence of COX-2 expression, that increased activation of PTEN/Akt was associated with poorer prognosis [28]. Therefore, it would appear that intracellular crosstalk between COX-2, NF-κB, STAT3, and probably other pathways is critical to the behaviour of the tumour cells and their microenvironment in patients with gastrointestinal cancer.

1.2. Cellular inflammatory phenotypes

There are a number of immune cells that can be considered to be important in characterising an inflammatory cell phenotype. In gastrointestinal cancers, neutrophils and macrophages (50:50) account for approximately 40% of inflammatory cells [29,30] with lymphocytes mainly constituting the remaining 60%. In contrast, lymphocytes only constitute approximately 30% of the circulating inflammatory immune cells with macrophages and neutrophils (85:15) being in the majority [31]. Therefore, there appears to be a disproportionately higher numbers of lymphocytes in the tumour microenvironment.

However, innate immune cells can influence the surrounding microenvironment to increase the amount of stromal tissue thus reducing the effectiveness of the adaptive immune system [32]. This would be consistent with the concept that the cytotoxic T lymphocytic infiltrate can be down-regulated and the immune competence of the host overridden by the presence of activated innate and humoral immune responses [33,34,35]. For example, in colorectal cancer, it is increasingly appreciated that as tumours invade there are changes in the tumour microenvironment facilitating adaptive immune cells to displace innate immune cells [36,37].

Finally, there is accumulating evidence that innate immune cells such as neutrophils, monocytes/macrophages and myeloid derived suppressor cells promote the metastatic process [38,39,40]. Indeed, an increase or maintenance of neutrophils and a reduction of lymphocytes in the circulation are recognised prognostic features of cancer-associated inflammation [39]. The pathways through which inflammatory cells initiate their carcinogenic effects are complex and likely heterogeneous (Fig. 2). In neutrophils, activation of NF-κB via toll like receptors in a MyD88-dependant manner may be of importance (Fig. 2) [20]. Several studies have demonstrated that TLR-4 expression is increased in CRC patients, indicating a potential route for increased NF-κB activation in these patients [22,41]. Prolonged TLR-4 expression causes T cells to switch from a Th1 phenotype to a tumour-promoting regulatory phenotype [41]. A second signalling pathway linked to neutrophils and CRC pathogenesis is the IL-6/JAK1/2/STAT3 [42].

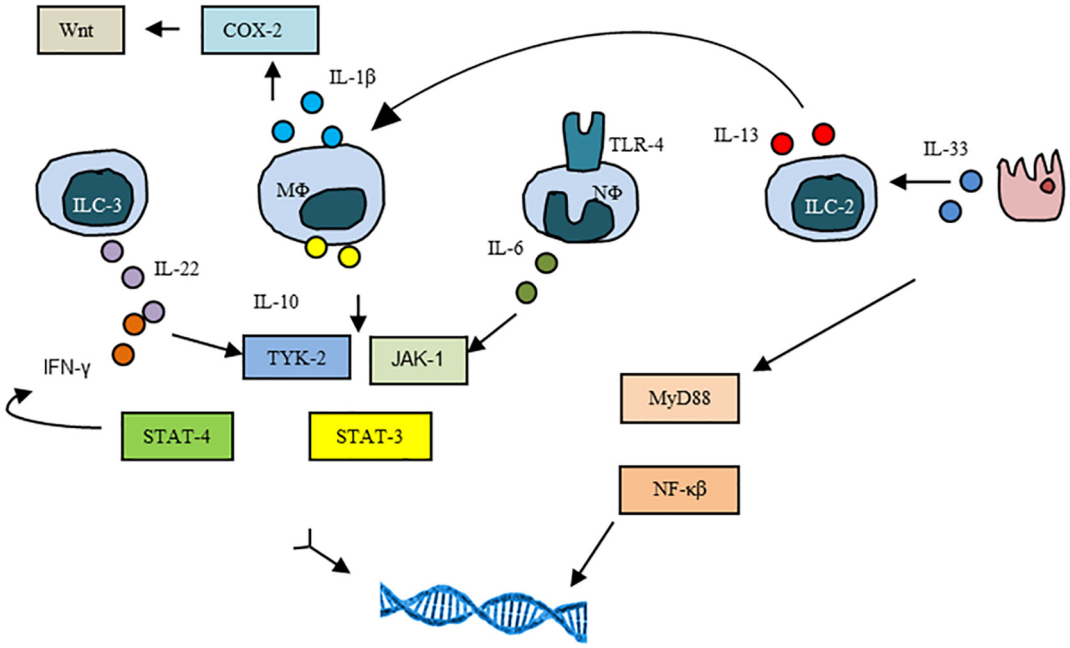

Fig. 2. A snapshot of inflammatory cell signalling in Colorectal Cancer.
Tumour infiltrating macrophages (TAMS, MΦ), innate lymphoid cells (ILC-3) and Neutrophils (NΦ) produce Il-10, Il-22 and Il-6 respectively, which result in induction of signal transducer and activator of transcription-3. TAMs also produce Il-1β, which causes upregulation of COX-2 and activation of the Wnt signalling pathway. ILC-2 s are activated by Il-33 from epithelial cells to produce Il-13 which activates TAMs to take on a pro-tumour phenotype. The Il-33 can also act independently of ILC-2 s to activate the NF-κβ cascade and promote tumorigenesis.

Tumour cells produce GM-CSF, which induces up-regulation of PD-L1 on tumour-infiltrating neutrophils via JAK-STAT3 [43]. PD-L1 causes immunosuppression via inhibiting Th1 cells and causing cytotoxic T cell anergy [43,44]. In addition, IL-6 activated STAT3 can crosstalk with EGFR signalling to promote tumour progression [45,46].

In addition to neutrophils, increased numbers of tumour-associated macrophages (TAMs) correlate with clinical factors such as tumour stage and lymph node metastasis [47]. There is evidence that TAMs promote tumorigenesis, in part, through the production of the anti-inflammatory cytokine IL-10 (Fig. 2). When bound to its receptor, IL-10 induces JAK-1 and TYK-2 activation, ultimately leading to STAT3 induction, which causes increased resistance of tumour cells to apoptosis [48]. Sustained STAT3 signalling is associated with an increase in anti-apoptotic markers Bcl-x and Mcl-1 [48]. In addition, increased STAT3 expression is an indicator of poor prognosis and is associated with systemic inflammation [49]. In CRC, another important function of TAMs is production of Il-1β, which induces up-regulation of COX2 [50]. This leads to phosphorylation of GSK- β, stabilization of β-catenin and induction of Wnt signalling to promote tumour progression [51].

In addition to traditional innate immune cells, a new subset of lymphoid-derived cells considered to function as part of the innate system, innate lymphoid cells (ILCs), have emerging roles in CRC (Fig. 2). Innate lymphoid cell 3 (ILC-3) is a subset of ILCs abundant at mucosal sites where they play a role in maintenance of intestinal integrity. From a signalling perspective, a member of the IL-10 family of cytokines, IL-22, acts with interferons to induce iNOS production via STAT3, and the source of IL-22 is thought to be ILC-3 s [52,53]. Dendritic cells in close proximity to the ILC3s produce IL-18, which induces the production of IL-22 [54]. This occurs via NF-κB signalling, with p65 binding to the promoter region of IL-22 [54]. Depletion of ILC-3 s in murine models has been shown to reduce circulating levels of IL-22 and reduce the incidence of adenocarcinomas [55]. Furthermore, iNOS expression associates with intratumour microvessel density and VEGF expression [56]. Therefore ILC3s may be involved in angiogenesis and promotion of a pro-tumour microenvironment. Another subset of innate lymphoid cells, ILC2s, are also found at mucosal sites, however, their involvement in tumorigenesis is somewhat limited. They have been shown to cause TAMs to switch from an M1 to an M2 phenotype via IL-13 production [56,57].

Overall, it is clear that the innate immune system plays a critical role in the development and progression of CRC. However, the nature of this involvement is complicated, with neutrophils, TAMS, ILCs, dendritic cells, and stromal cells amongst others involved in this orchestration of CRC tumorigenesis. It is still not clear if innate and lymphoid cells represent different points in immune cell evolution of fighting the tumour or if they represent a different type of carcinogenesis/tumour progression. However with the evidence emerging on checkpoint exhaustion and gamma delta T cells bridging the changes from adaptive to innate immune responses the evidence is weighted toward the first hypothesis, but additional evidence is required before this can be confirmed.

1.3. Systemic inflammatory phenotypes

It has long been recognised that humoral responses are activated in patients with gastrointestinal cancers [58]. It is only in the last 15 years the significance of this response and in particular the prognostic value of mediators of the systemic inflammatory phenotypes have been widely recognised. A large number of components of this humoral response have now been identified and include counter-regulatory hormones, complement, collectins, ficolins, pentraxins, cytokines, adipokines and chemokines. In the presence of cancer these mediators of the systemic inflammatory response are known to have complex interactions that are potentially detrimental to the host. There is also good evidence that IL-6 is directly associated with C-reactive protein (CRP) [59,60] and is increasingly recognised to have independent prognostic value [61]. Furthermore, CRP and its combination with albumin (GPS/mGPS) is now widely recognised to have independent prognostic value in patients with gastrointestinal cancer [62,63].

The composition of immune cells within the circulation can also be of prognostic value., For example, the neutrophil to lymphocyte ratio (NLR) is independently prognostic and neutrophilia is strongly

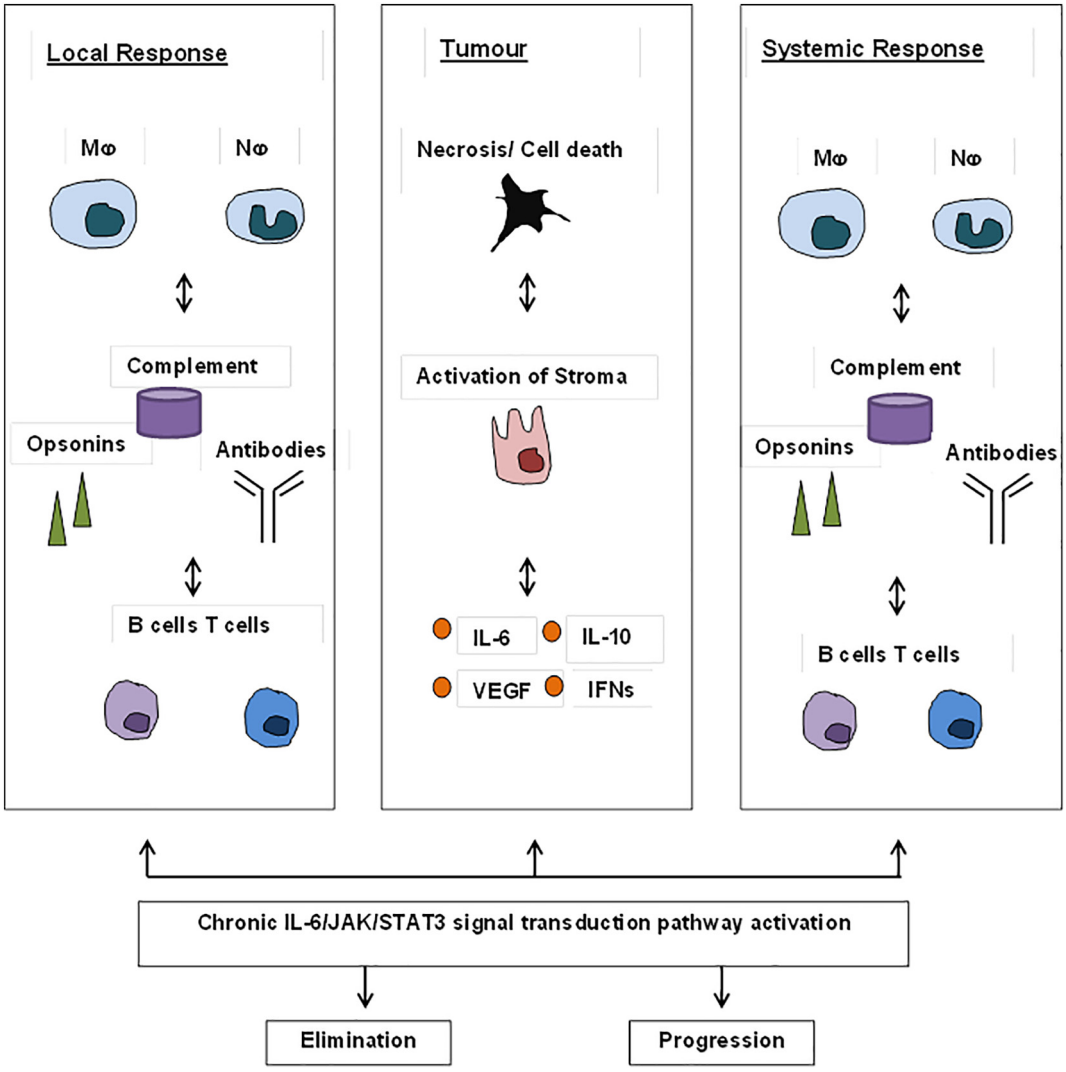

Fig. 3. Broad role of the Il-6/JAK/STAT3 Pathway in Colorectal Cancer.
Chronic Il-6/JAK/STAT3 signalling is an important aspect of both the local and systemic immune responses in colorectal cancer. Activation of the pathway in both adaptive and innate cells can cause complement induction, production of opsonins and antibodies. Within the tumour necrosis causes activation of surrounding stromal tissue such as epithelial cells and myocytes which results in production of IL-10, IL-6 VEGF and interferons. The Il-6/JAK/STAT3 can promote elimination or progression of the tumour.

associated with poorer outcomes [64]. NLRs prognostic ability is likely related to factors such as leptin, PrTH, albumin and CRP, which lead to cachexia, pain and reduced metabolism of drugs [64]. Furthermore high NLR is associated with metastasis and increased NF-κB and STAT3 signalling within the tumour [64,65,66].

Circulating IL-6 may provide another link between systemic inflammation and tumorigenesis (Fig. 3). The main source of elevated IL-6 within the tumour is cancer-associated fibroblasts (CAFs) [67]. IL-6 acts to promote tumour growth via phosphorylation of gp130 on STAT3, causing translocation to the nucleus of the tumour cell, where STAT3 acts as a transcription factor to promote a tumorigenic environment and angiogenesis [67,68] Cytoplasmic STAT3 within tumour cells has been shown to correlate with mGPS and reduced survival [68].

Another link between systemic inflammation and the tumour microenvironment is the strong association between mGPS and both FoxP3+ regulatory T cells and CD1a positive dendritic cells within the tumour [69]. Serum levels of cytokines and chemokines such as IL-12 and CCL4 also associate with intra-tumour changes. Increased systemic IL-12 correlates with an overall increase of CD3+ T lymphocytes, in particular CD8+ cytotoxic T cells, and increased neutrophils [69]. Whereas, elevated systemic CCL4 correlates with increased CD68+ macrophages at the invasive margin of the tumour [69]. Although the translational potential of such associations is currently unclear, this highlights a strong link between systemic inflammatory phenotypes and cellular inflammatory phenotypes. Furthermore, the systemic changes associated with tumour progression may provide us with a tool to easily and non-invasively predict patient prognosis.

1.4. Therapeutic intervention for inflammatory phenotypes

From the above it is clear that there is potential for the modification of inflammatory phenotypes at the intracellular, cellular and the systemic levels. Furthermore, there are networks that appear central to these inflammatory phenotypes at all levels. In particular, the modification of the COX2/ PGE2 pathway has been extensively investigated in-vitro and in-vivo and NSAIDs moderating this pathway have been shown to have clinical efficacy. Likewise, the IL-6/JAK/STAT3 pathway can activate the JAK/STAT pathway in inflammatory and stromal cells to modulate the tumour microenvironment and effect systemic level responses. Indeed, this pathway is central to the regulation of innate immune/inflammatory responses [65,70] as it is recognised to stimulate neutrophils and macrophage production from myeloid tissue and

CRP secretion from hepatocytes [65]. Inhibitors for this pathway are now emerging and present an interesting therapeutic for gastrointestinal tumours.

Much of the above information describes associations of inflammatory phenotypes and outcome in patients with cancer. However, this may not be a cause and effect relationship. Indeed, a rational conclusion from the present review is that it would be important to explore the moderation of the intracellular, cellular and systemic inflammatory phenotypes. With this perspective it may be concluded that much of current clinical management of gastrointestinal cancer needs to utilise a variety of approaches to moderate such inflammatory phenotypes whether it be by minimising the tissue injury associated with surgery, radiotherapy and chemotherapy treatments or the concurrent use of anti-inflammatory agents. For example, surgery is the primary treatment modality for many gastrointestinal cancers including CRC and its magnitude is likely to exacerbate immune/inflammatory phenotypes. In such an acute injury, circulating IL-6, neutrophils and CRP show quantitatively the most significant increases [66] and these are recognised to be important in tissue repair and remodelling. Furthermore, activated granulocytes can produce growth factors (EGF, TGFβ, VEGF, Il-6, TNFα and chemokines) that can act directly on cancer cells and confer mitogenic and angiogenic capabilities [3,71].

However, to date, moderation of such inflammatory phenotypes have been carried out empirically (eg. laparoscopic/robotic approaches to speed up recovery from surgery) and not by specifically targeting inflammatory phenotypes. Therefore, there is a need to examine what approaches may be useful to moderate intracellular, cellular and systemic inflammatory phenotypes. These will encompass pharmacological approaches that may be classified according to those already established in clinical practice and those with novel therapeutic benefit.

2. Established anti-inflammatory agents

2.1. NSAIDs

NSAIDs have long been recognised to be useful in prevention and treatment of patients with gastrointestinal cancer [72]. Aspirin and other NSAIDs are effective in inducing apoptosis in tumour cells through COX2 and COX2-independent mechanisms. Furthermore, the down regulation of the IL-6/ JAK/ STAT3 pathway has repeatedly been shown to be important in such apoptosis (Fig. 4) [73]. Moreover, NSAIDs appear to be effective in enhancing various aspects of anti-tumour immunity and immunotherapy [74]. This would again indicate the pre-eminence of the COX2/PGE2 and IL-6/JAK/STAT pathways as well as related cytokines and growth factors on gastrointestinal cancer outcomes. Furthermore, if efficacy for suppressing the IL-6/JAK/STAT pathway was also proven their use would further increase in clinical oncological practice.

2.2. Glucocorticoids

Glucocorticoids have long been recognised to have benefit in the treatment of cancer-associated symptoms. They are known to also down regulate COX2/PGE2 and IL-6/JAK/STAT pathways as well as related cytokines and growth factors, They further decrease production and activity of neutrophils and macrophages as well as reduce complement and pentraxin synthesis (Fig. 4) [75,76]. Glucocorticoids interact with specific intracellular receptors in target tissues to alter the expression of corticosteroid-responsive genes. Specifically, glucocorticoid-specific receptors in the cell cytoplasm bind with steroid ligands to form hormone-receptor complexes that eventually translocate to the cell nucleus. There, these complexes bind to specific DNA sequences and alter their expression.

Cell line work has demonstrated that glucocorticoids such as dexamethasone may prove useful in reducing tumour cell growth, increasing apoptosis and sensitivity to chemotherapy [77]. The actions of dexamethasone may involve NF-κB signalling, as p65 correlates with the alpha portion of the glucocorticoid receptor in CRC cell lines (Fig. 4) [77].

2.3. Statins

It has recently become apparent that statins, in addition to their lipid lowering effect, also have effects on inflammatory phenotypes [78,79]. Statins have also been shown to have anti-tumour and anti-inflammatory activity in the AOM-DSS colon carcinogenesis mouse model [80]. As such there has been increasing interest in their use in patients with CRC. Furthermore, there is evidence that simvastatin can exert anti-tumour effects by suppressing IL-6-induced phosphorylation of JAK2 and STAT3 (Fig. 4) [81]. One other pathway thought to be

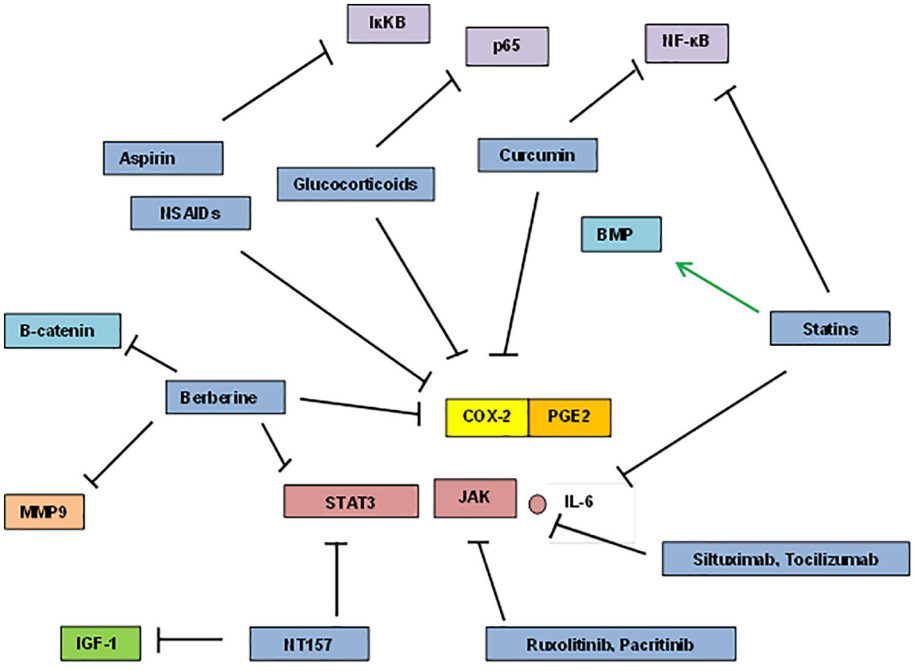

Fig. 4. Targeted therapy in colorectal cancer.
There are a number of therapeutics, some established and some novel, which target signalling pathways associated with colorectal cancer. COX2-PGE2 is a major target of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, curcumin and Berberine. Other than Berberine, these drugs also target aspects of NF-κB, which is also targeted by statins. Upregulation of bone morphogenic signalling and blockade of Il-6 represent two other functions of statins. Berberine additionally targets β-catenin, MMP9 and Stat3. NT157, small molecule inhibitors and monoclonal antibodies can target the Il-6/JAK/STAT pathway. NT157 can also inhibit IGF-1. The vast network of signalling pathway dysregulation associated with CRC makes for a variety of targets and a complex task.

involved in statins ability to block tumour growth is the bone morphogenic pathway (BMP) (Fig. 4). BMP2 is silenced by promoter hypermethylation in many gastric cancers including CRC, and statins can release BMP-2 from this silencing and induce downstream signalling [82]. Moreover, naturally derived stains such as simvastatin have also been shown to have an inhibitory effect on NF-κB signalling [83]. However, further study is still required to determine if statins show efficacy in suppressing the detrimental inflammatory phenotypes, and establishing through which signalling pathways they exert their effects. However, with their well-established safety profile, they could be readily incorporated into clinical oncology practice.

3. Novel anti-inflammatory agents

3.1. COX-2 and NF-κB

Oral supplementation with curcumin, a component of the curry spice, has been implicated as a potential anti-cancer therapeutic option in many cancers (Fig. 4) [84,85]. During a phase 1 clinical trial, in a patient cohort unresponsive to traditional chemotherapy, daily administration of curcumin reduced plasma levels of PGE_2 [86]. As upregulation of the COX-2 gene is observed in CRC and results in overproduction of PGE_2 [87] this suggests the mechanism through which curcumin exerts its anti-cancer is via the COX2 gene [86,87,88,89]. In a similar study, curcumin has also been shown to decrease plasma TNF-α and increase expression of intra-tumour p53 to promote apoptosis [90].

In addition to the well-established anti-cancer action of Aspirin, several other NSAIDs have been investigated for their efficacy in treating CRC. In a recent phase 1b clinical trial, COX-2 inhibitor Naproxen given at a dose of 440 mg for 6 months decreased CRC-associated inflammation in patients with Lynch Syndrome [91]. However in contrast, treating patients with selective COX-2 inhibitor, celecoxib, in addition to current chemotherapy (Irinotecan, 5-Fluorouracil, and Leucovorin) in a phase II clinical trial, showed no increased efficacy in stage IV patients [92].

As well as its effects on the COX2/PGE2 and IL6/JAK/STAT3 pathways, Aspirin has been shown to inhibit a component of the NF-κB pathway, IKK-β (Fig. 4). In the absence of IKK-β, phosphorylation of IKB is reduced, rendering NF-κB unable to carry out its function as a transcription factor [14]. Inhibiting IKKs directly has repeatedly shown promise in depleting cancer in vitro and in vivo. Drugs targeting IKKs specifically, as opposed to broad anti-inflammatory agents are a huge focus in current CRC research [93].

One alternative to NSAIDs, shown to have potential as an anti-CRC agent via COX2 signalling is Berberine, a plant-derived isoquinoline (Fig. 4). It acts via blockade of β-catenin, thereby inhibiting Wnt signalling, and reducing COX2/PGE, JAK2 and STAT3 [19,95]. In CRC cell lines, Berberine reduces MMP9 expression and prevents metastasis [21]. A clinical trial investigating the role of Berberine as a recurrence prevention method began in 2017 and will provide valuable insight into Berberine's efficacy and safety in CRC patients.

Another novel therapeutic is NT157, which targets both insulin growth factor 1 (IGF-1) and STAT3 simultaneously (Fig. 4). In murine models of CRC, dual blockade of IGF-1 and STAT3 using NT157 results in inhibition of IL-6, Il-11, Il-23, CCL-2, CCL-5 and TGF-β as well as tumour cell migration [95]. NT157 represents a promising anti-cancer agent; however its effects are still to be determined in humans.

3.2. IL-6/JAK/ STAT blockade

There is increasing interest in the selective down regulation of the components of this pathway in a variety of common cancers [96,97]. In particular, the inhibition of the production of CRP, measured by a fall in circulating concentrations, has proven to be reliable surrogate marker of anti-IL6 therapy efficacy. IL-6 blockade is thought to produce a profound reduction in systemic inflammatory phenotypes such as anorexia and cachexia [98]. There are two clinically registered drugs siltuximab [99] and tocilizumab [100] that have been shown to have moderating effects on systemic inflammatory phenotypes (Fig. 4).

As in other ubiquitous signalling cascades, activation of the JAK/STAT pathway is tightly controlled at multiple levels with influence from other signalling cascades. Nevertheless, it is clear that the JAK/STAT pathway is activated in a variety of solid tumours contributing to an aggressive inflammatory phenotype. In particular, this pathway would appear to have a global role in adaptation of cancer cells to a hypoxic environment [101]. Therefore, it makes an attractive therapeutic target in patients with cancer and is currently the subject of intense research. To date, there are two clinically registered JAK1/JAK2 inhibitors, Ruxolitinib and Pacritinib, and these are the subjects of on-going clinical trials in patients with cancer (Fig. 4). The clinical utility of Ruxolitinib has been established in myelofibrois (a myeloproliferative neoplasm) in a series of landmark studies [102]. Furthermore, Hurwitz and co-authors (2014) recently reported the results, of a randomized double-blind phase 2 study of ruxolitinib or placebo with capecitabine as second-line therapy in patients with metastatic pancreatic cancer [103]. They showed that the combination was associated with improved survival particularly in those patients with an elevated circulating CRP concentration [103]. There are now a number of randomized clinical trials of Ruxolitinib ongoing in variety of solid tumours. In one particular phase 2 clinical trial, administration of Ruxolitinib in combination with anti-VEGF agent Regorafinib, in stage IV CRC patients showed no improvement to overall survival when compared to Regorafinib treatment alone [104]. To date, the clinical use of Pacritinib has been reported exclusively in myeloproliferative neoplasms. In terms of CRC, one trial investigating the safety of Pacritinib in metastatic disease reported no benefit to patients and administration was stopped before the study end-point [105]. Finally, blockade of the inhibitory molecule PD-1 (Nivolumab, Pembrolizumab) expressed on numerous immune populations including Th1 cells has proven useful in treating non-small cell lung cancer and MSI-high CRC. However a large proportion of CRC patients do not respond to anti-PD-1 monotherapy which is surprising given the improved prognosis associated with an increased inflammatory infiltrate in CRC as defined by the Immunoscore [106,107]. The limited efficacy of anti-PD1 in CRC may be explained by the immune evasion stage of Immunoediting [108]. One function of anti-PD1 is to increase the effector functions of T cells, but if the tumour cells develop mechanisms to evade the immune response then the T cells would be unable to recognise the tumour and exert these effector functions [108]. Alternatively, due to the heterogeneity of pathogenesis observed in CRC, other routes to tumourogenesis may out-compete the actions of anti-PD1. The gut harbours a unique combination of different cell types, which may account for why PD-1 blockade is unsuccessful in most CRC cases but successful in other cancer types (non-small cell lung cancer) [109]. ILCs represent a cell population likely to account for a poor response rate to anti-PD1. They are abundant in the gut and can have pro-tumour functions such as the production of IL-10 [52]. Despite the disappointing results of anti-PD1 in CRC so far, the use of Nivolumab and/or Pembrolizumab may still harbour benefits if used in combination with other therapies that can prime the immune response.

4. Conclusion

Targeting the host intracellular, cellular and systemic inflammatory phenotypes has considerable potential to improve outcomes in patients with gastrointestinal cancer. For such a strategy to work there is a need for a well-characterised network of intracellular, cellular and systemic inflammatory phenotypes.

Funding

This work was supported by the Medical Research Council.

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