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Chemokines and chemokine receptors in colorectal cancer; multifarious roles and clinical impact

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ABSTRACT

Colorectal cancer (CRC) is considered the second cause of cancer death worldwide. The early diagnosis plays a key role in patient prognosis and subsequently overall survival. Similar to several types of cancer, colorectal cancer is also characterised by drug resistance and heterogeneity that contribute to its complexity -especially at advanced stages. However, despite the extensive research related to the identification of biomarkers associated to early diagnosis, accurate prognosis and the management of CRC patients, little progress has been made thus far. Therefore, the mortality rates, especially at advanced stages, remain high. A large family of chemoattractant cytokines called chemokines are known for their significant role in inflammation and immunity. Chemokines released by the different tumorous cells play a key role in increasing the complexity of the tumour's microenvironment. The current review investigates the role of chemokines and chemokine receptors in colorectal cancer and their potential as clinical molecular signatures that could be effectively used as a personalised therapeutic approach. We discussed how chemokine and chemokine receptors regulate the microenvironment and lead to heterogeneity in CRC. An important aspect of chemokines is their role in drug resistance which has been extensively discussed. This review also provides an overview of the current advances in the search for chemokines and chemokine receptors in CRC.

1. Introduction

1.1. Colorectal cancer

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers and the second cause of cancer related death in men and women worldwide. It originates in the colon or in the rectum by the abnormal growth of cells that form a polyp. The polyps form and appear in the epithelial tissue that lines the colon or the rectum. The development of the cancerous polyps or colorectal carcinoma results from a series of accumulated somatic and germline genetic mutations [1]. The most commonly mutated genes in CRC are *APC, TP53, KRAS,* and *PIK3CA* with ~82%, ~55%, ~45%, and ~18% of CRC cases, respectively [2]. There are four stages of colorectal cancer (I, II, III, IV) classified according to the tumour severity with stage l being the least malignant and stage IV being the most malignant [1].

1.2. Epidemiology

CRC affects men more than women, as reported by the Global Cancer Observatory (23.4 in 100,000 men vs 16.2 in 100,000 women) [3]. In more detail, there are around one million cases diagnosed with colorectal cancer in men and 500,000 deaths every year worldwide. In women, the diagnosed and death related colorectal cancer cases account for around 865,000 and 418,000 cases, respectively [3]. Generally, colorectal cancer occurs in adults older than 50 years of age. The average age of men and women diagnosed with colorectal cancer is 68 and 72 years, respectively. However, CRC can also affect teenagers [3].

Furthermore, CRC is more common in high human development index (HDI) countries compared to lower HDI countries. Consequently, higher mortality cases have been reported in high HDI countries. Countries with high HDI generally follow a "westernized lifestyle", which includes a diet with more red and processed meat, refined sugar and grains, fewer fibres, and less physical activity. CRC is also

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considered a marker of the socioeconomic development of a country [4]. Ultimately, this suggests that the socioeconomic status and a lifestyle that includes an unhealthy diet, smoking, alcohol consumption and obesity could afford major risk factors of CRC. Other significant risk factors include age and family history/genetics. It was reported that the diagnosis of a relative before the age of 60 with CRC, significantly increases the risk of CRC development [4].

Additionally, the higher the number of affected relatives -regardless of their family relation degree, the higher the CRC development risk [4,5].

In about 2–8 % of colorectal cancer cases the main cause is inherited syndromes, including hereditary nonpolyposis colorectal cancer (HNPCC), which is also called Lynch syndrome, and familial adenomatous polyposis (FAP). Both HNPCC and FAP represent an autosomal dominant pattern of heredity [5].

The HNPCC is caused by mutations in mismatch repair genes *MLH1* and *MSH2* genes. Patients with HNPCC have 20% and 80 % risk of developing CRC by the age of 50 and 85, respectively. The FAP disease is caused by adenomatous polyposis coli (*APC*) gene defect and the protein encoded by the *APC* gene is a tumour suppressor. Patients with FAP syndrome have higher risk of 70–100 % of developing CRC by the age of 35 [4,6,7].

1.3. Diagnosis

The 5-year survival rate for early stage diagnosed colorectal cancer is reported to be 90%, while the later CRC stages have a 5-year survival rate of only 13%. Hence, early diagnosis plays a key role in the survival of the patients. The several diagnostic methods and approaches clinicians opt for the CRC screening include different types of endoscopies including colonoscopy, rectoscopy, and sigmoidoscopy. Endoscopy allows the detection and the sampling of the tumour and the inspection of the rest of the bowel. Yet, the diagnostic procedure with the highest sensitivity and specificity for colorectal cancer is colonoscopy. Colonoscopy allows the assessment and examination of the entire large intestine for any adenomatous or malignant polyps formation. It also allows the possibility of taking a biopsy for further evaluation by histopathology [8].

Fecal Occult Blood Test (FOBT) is another screening method for CRC. It comprises of analysing a collected stool sample. This method is both non-invasive and unexpensive and has several types, including the guaiac based FOBT (gFOBT) and immunochemical based FOBT (FIT). All types are used to analyse the stool sample for the presence of non-apparent blood that might potentially signify colorectal cancer [8,9].

Endoscopy using narrow-band imaging (NBI) or blue light filters, and i-Scan technology, also known as image enhanced endoscopy (IEE) are two other diagnostic methods for CRC. Both methods provide a clear and enhanced visualization of the mucosal structure and microvascular patterns of colorectal polyps [8].

Despite the current advances in diagnostic and screening methods, the early detection of CRC is not feasible in a plethora of CRC cases, which results in high mortality rates associated with this type of malignancy.

1.4. Prognosis

The prognosis of colorectal cancer depends on several factors at the time of diagnoses, such as the stage and the degree of penetration of the tumour. The overall five-year survival rate decreases as the malignancy stage of colorectal cancer increases. Subsequently, it has been estimated that the overall five-year survival for stage 1 CRC is around 90 %, for stage II is 70 %, for stage III is around 58 % and stage IV, which is the most aggressive one, is < 15 % [2].

The late diagnosis and the secondary metastasis of the CRC, in which the liver is the most common site, as well as the unsuccessful resection of the whole primary tumour, comprise prognostic factors that have been associated with unfavourable outcomes and relapse. For instance, almost 50 % of stage III patients who undergo surgery are cured, whilst 30% will experience tumour relapse within two to three years [2].

Thus far, several biomarkers have been associated with CRC prognosis. For instance, the microsatellite instability (MSI) status. The MSI is a result of a deficient DNA mismatch repair (MMR), which is generally caused by the inactivation of the four mismatch repair genes (*MSH2, MLH1, MSH6* and *PMS*2). MSI-high colorectal cancer patients have highly unstable tumour cells that cannot escape the immune system easily. These patients have a better prognosis compared to MSI-low patients. Additionally, it has been previously suggested that the colorectal cancer patients with *KRAS* mutations have a 1.5 higher relapse and death risk compared to non-mutant *KRAS* patients [2,8].

Interestingly, it was. suggested that twelve signature chemokines could potentially be used in order to predict effectively any tumour recurrence s in CRC patients. The prediction is based on the high expression levels of tertiary lymphoid structures (TLSs) that prevent tumour progression [10].

1.5. Treatment

Colorectal cancer therapeutic interventions include surgery, chemotherapy, and radiotherapy. These therapies can be used either alone or combined which are also known as primary and adjuvant treatments. Surgery is the most typical treatment option for CRC, in which the aim is to achieve full resection of tumour and metastatic lesions [11]. However, metachronous metastases may develop in 20 % of CRC advanced stage cases leading to tumour relapse, secondary metastasis, and death [12]. In many cases, chemotherapy and radiotherapy might be applied before surgery as neoadjuvant treatment or following the surgery as adjuvant treatment in order to ensure maximum tumour reduction [11].

The chemotherapy approach for CRC includes single agent and multiple drug regimens, depending on the CRC stage and the patients' diagnostic data. For instance, 5-fluorouracil (5-FU), irinotecan (IRI), capecitabine (CAP), and oxaliplatin (OX) are first line chemotherapeutic drugs for CRC. The combinations like FOLFOX (5-FU+OX), CAPOX (CAP+OX), and FOXFIRI (5-FU+IRI) are mostly used in CRC treatment (Fig. 4). Nevertheless, administration of chemotherapy has been associated with several side effects and limitations, including resistance and cytotoxicity, due to untargeted delivery and low tumour selectivity [11].

Subsequently, targeted therapy is the approach by which curative agents like chemotherapeutic drugs and monoclonal antibodies can reach the tumour directly. Targeted delivery allows the reduction of random drug delivery and inhibition of cell proliferation, differentiation, and migration. For instance, cetuximab and bevacizumab are the first two Food and Drug Administration (FDA) approved targeted drugs for CRC [13]. Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor, which is also a monoclonal antibody. Cetuximab acts on inhibiting the EGFR downstream signalling pathways and ultimately inhibiting both cellular proliferation and tumour progression [11]. Conversely, bevacizumab is an anti-vascular endothelial growth factor inhibitor (VEGF) agent. It acts by selectively binding to VEGF and inhibiting the binding of VEGF to its corresponding cell surface receptor VEGFR. Targeting the VEGF pathway by bevacizumab results in the inhibition of the signalling cascade including the Ras/MAPK pathway that regulates cell proliferation and gene expression. Cetuximab, bevacizumab and other monoclonal antibodies are part of the targeted CRC immunotherapy [10,14].

Nanoparticles are also an approach to increase the treatment outcome by delivering the chemotherapy drugs in a targeted way. Currently, there are no FDA approved nanoparticle-based drugs for colorectal cancer. However, there are several studies that are working on developing nano-based therapies for more effective and targeted treatment in CRC. For instance, the delivery of fluoropyrimidine via Rapa liposomes showed a "synergistic antitumor effect" both *in vitro* and

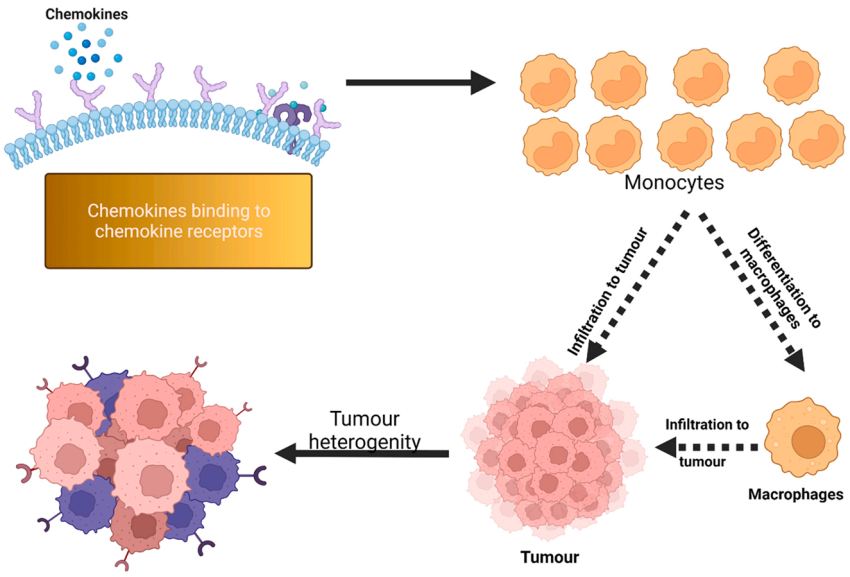


Fig. 1. Chemokines involved in CRC heterogeneity: Chemokine receptors are present on the surface of monocytes which can interact with chemokines released by other cells in tumour microenvironment. Upon binding the monocytes can differentiate into macrophage and infiltrate into tumour microenvironment. The tumour associated macrophages (TAMs) that infiltrate the tumour is one of the reasons for heterogeneity in the CRC.

in vivo [15].

1.6. Chemokines

Immunotherapy is one of the approved therapies for the treatment of several cancers, including colorectal cancer. Immunotherapy consists of helping the immune system fight the tumour using several approaches such as monoclonal antibodies, immune checkpoint inhibitors, vaccination, and cytokine administration. Chemokines are a large family of chemoattractant cytokines that play a crucial role in inflammation and immunity [14]. They are classified into four main subfamilies: CC, CXC, CX_3C and C. The subfamilies are defined based on the primary amino acid sequence of the chemokine and the arrangement of the structurally specific and important cysteine residues. The conserved cysteine amino acid residues are linked by disulfide bonds at the N-terminus within the mature protein, i.e., the chemokine ligand.

Biologically, the function of chemokines consists of binding to G protein-coupled receptors (GPCR) with the N-terminus outside the cell and the C-terminus with serine and threonine phosphorylation sites in the cytoplasm. The spatial and temporal expression of chemokines coordinates the proper movement of immune cells. In other terms, chemokine receptors trigger a flux of calcium ions intracellularly upon specific ligand binding, which leads to chemotaxis and the start of cell trafficking to the desired location [14,16].

Chemokines and their receptor can be either homeostatic or inflammatory, or both. Chemokines can bind and activate more than one

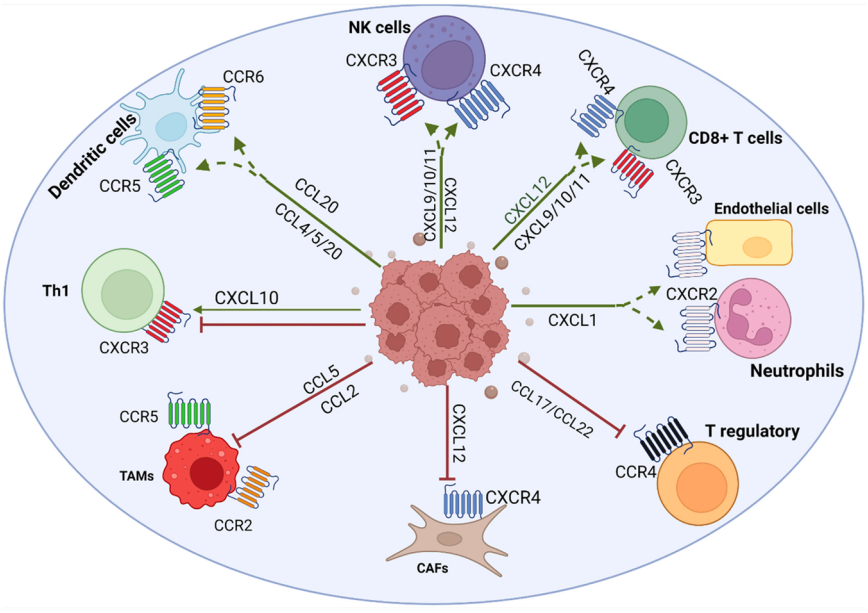


Fig. 2. Chemokines and chemokine receptors involved in immune activation and immune inhibition: The different cells in tumour microenvironment are infiltrated and activated by different chemokines. These cells can be immunoactivatory or immunoinhibitory in nature. A number of such chemokines and chemokine receptors are shown that affect the cancer immune response.

GPCR, and they can be recognized by more than one GPCR. However, they both have distinct functions under different physiological conditions. Therefore, they have complex activities that allow them to cope with complex responses [16]. CC and CXC chemokines, for instance, play key roles in angiogenesis, leukocyte recruitment, and tumour growth and proliferation. The CC (CCL2, CCL3, CCL5) and CXC (CXCL1, CXCL2, CXCL5, CXCL6, and CXCL8) are inflammatory chemokines. At the tumour site, they recruit CC chemokine receptor 2 (CCR2 +) monocytes and CXC chemokine receptor 2 (CXCR2 +) neutrophils. Then, recruited CCR2 + monocytes and CXCR2 + neutrophils differentiate into tumour associated macrophages (TAMs) and tumour associated neutrophils (TANs), playing either pro- or anti-tumoral roles or both [14]. CXC chemokines have two different and opposing effects in angiogenesis based on the presence of the glutamic-leucine-arginine (ELR) motif at the N-terminal. Hence, ELR+ chemokines have an angiogenic effect that promotes angiogenesis, while ELR− chemokines have an angiostatic effect that inhibits angiogenesis [14,16]. Due to their versatile functionalities, chemokines can be used in cancer immunotherapy. An example of a chemokine /chemokine-receptor treatment that has already been approved by the FDA is the CCR4 antagonist Mogamulizumab (KW-0761, AMG761, Poteligeo). It is approved for the treatment of two main types of cutaneous T-cell lymphomas. The outcome showed improved overall survival rates and enhanced progression-free survival [17]. Colorectal cancer therapy based on chemokines and chemokine- receptors has not surpassed the clinical trials phase yet. Still, the antitumor effects of the CXCR4 inhibitor LY2510924 were reported to be clinically safe and well-tolerated in CRC in the phase I trial, with a primary response rate of 20% [18].

1.7. The tumour microenvironment and immune system in normal homeostasis – innate and adaptive immune system

The tumour microenvironment is highly heterogeneous in nature. Many types of immune cells are found in the tumour microenvironment, where they either inhibit or support tumour growth. Several of these immune cells show high plasticity in the tumour microenvironment, which means that they can polarize into many different differentiated states (Fig. 1). The T cells in the tumour could be either CD8 + cytotoxic T cells, T helper type 1 cells, T helper type 2 cells, TH17 cells and T regulatory cells [19]. Many of these cells have anti-tumour effects, and some are pro-tumorigenic. In addition, many immune cells have dual roles based on the cancer types, their differentiation status and the stage of cancer [20]. The most important immune cells that kill cancer cells are the cytotoxic T cells and the natural killer (NK) cells, while the tumour promoting immune cells are the tumour associated macrophages (TAM), the tumour associated neutrophils (TANs) and the myeloid-derived suppressor cells (MDSCs) [20]. Thus, the tumour microenvironment is highly complex, and the complexity is enhanced due to the secretion of chemokines and cytokines that are being released by the different cells in the tumour (Fig. 2) [21,22].

There are chemokines expressed by the cancer cells and other cells in the tumour microenvironment, which trigger the migration of immune cells that carry the respective chemokine receptors. Furthermore, the immune cells can also produce a number of chemokines and facilitate the migration of immune cells, creating a positive feedback loop [22]. There are many possible outcomes of the migration of immune cells. On the one hand, the chemokine release triggers the migration of anti-tumorigenic cells. In that case, it will lead to the elimination of cancer cells. In contrast, if it leads to the migration of pro-tumorigenic cells, it will facilitate the progression of CRC tumours [23,24].

There are certain chemokines that have mostly the anti-tumour effects, such as the XCR1 and CXCR3 axis, whereas CCR4 and CCR8 usually have pro-tumorigenic responses. The anti-tumorigenic chemokines are immunoactivatory in nature and are a suitable target in cancer therapy, while there are efforts ongoing to inhibit the immunosuppressive chemokines [22]. In the case of CAR-T cell therapy, researchers are transducing T cells with chemokine receptors that can facilitate deeper T cell mobility in solid tumours. This leads to better clearance of CRC tumour cells [25].

The bulk of the information on the role of chemokines and chemokine receptors is obtained from the field of infection biology. It was predicted that this information could therefore be extrapolated to the field of cancer biology as well, which did not seem to be the case. The tumour cells blunt/reduce the anti-tumour response of the chemokines and enhance the immunosuppressive pathways triggered by them [22,26,27].

1.8. The role of chemokines within colorectal cancer pathogenesis

There are many chemokines that are known to play a role in CRC progression and patients' prognosis. Here are some of the examples that show the role of chemokines and their receptors in CRC progression. In an in vitro assay using HCT116 and Caco2 cell lines, it was found that the transfection of CXCL8 (IL-8) led to more proliferation, migration, and invasion of CRC tumour cells. Moreover, in xenograft models using these cell lines, there is enhanced tumour growth with the IL-8 overexpression group as compared to the control [28]. In a cohort of 165 CRC patients enrolled at the National Cancer Centre Hospital, Tokyo, Japan, the CXCL12 expression was also shown to be associated with poor prognosis [29]. On the other hand, in a study on CXCL10 in a cohort of 64 stage II and stage III CRC patients, it was identified that low expression of the chemokine was associated with an unfavourable prognosis [30].

A study on CXCL5 using the biopsies of colonic adenoma patients, colorectal carcinoma patients, and normal colonic tissue samples identified with immunohistochemistry (IHC) that CXCL5 positivity was higher for CRC samples. Moreover, the serum levels of CXCL5 were also determined to be higher in CRC patients as compared to controls [31]. In a similar study with 314 CRC patients and 20 normal volunteers, the serum levels of CXCL16 were identified, and it was found that CRC patients have higher serum levels of CXCL16. Although the sample size of healthy individuals is small, the study inferred that CXCL16 was associated with a poor prognosis. The chemokine CCL20 is regulated by miR-21 and expressed by the tumour infiltrating immune cells in the CRC microenvironment [32]. Therefore, different chemokines have either favourable or unfavourableprognoses due to the heterogeneity of solid CRC tumours. The different prognoses can also be dependent upon the stage and grade of cancer.

1.9. The role of chemokine receptors within colorectal cancer pathogenesis

In CRC patients, high CXCR4 chemokine receptor expression was found to be associated with cancer progression and liver metastasis [33]. In another study on Stage II-III colorectal cancer patients, the high expression of CXCR4 was observed to be a strong predictor of relapse. This chemokine receptor induces clonogenic growth due to the release of VEGF and Intercellular Adhesion Molecule 1 (ICAM-1) upregulation. Thus, pinpointing the crucial role in CRC progression and a potential target for cancer metastasis and relapse [34]. In a series of studies, the role of chemokine receptor CCR6 was deciphered in CRC progression. In a cohort of 30 CRC patients and 30 healthy controls, it was suggested that CCR6 expression was associated with enhanced liver metastasis [35,36]. In another study on patients with colorectal adenomas, colorectal adenocarcinomas and colorectal liver metastases whilst keeping healthy individuals as controls, it was determined that the CCR6/CCL20 axis showed upregulation of CCR6 and CCL20 in all observed tissues [37]. Another chemokine receptor, CXCR3 was important for lymph node metastasis and poor survival of CRC patients compared with non-expressing individuals or individuals expressing CXCR4 or CCR7 [38]. In a study on a CRC transgenic mouse model, CXCR2 knockout colon cancer cells were implanted in the syngeneic mice, and it was

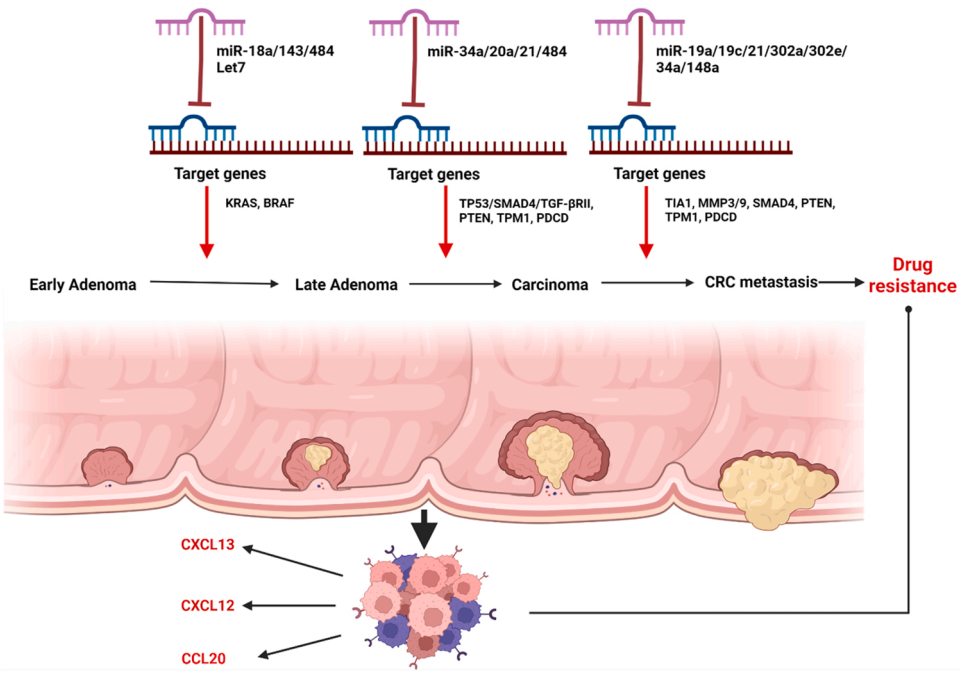


Fig. 3. miRNA affect different stages of CRC development: The different stages of CRC development is affected by the miRNA that affect several target genes and pathways.

observed that the mice had reduced angiogenesis and increased cancer cell necrosis [39]. Moreover, in another study, it was found that the small molecule antagonists for CXCR1 and CXCR2 can reduce the ability of CRC cancer cells to metastasize [40]. Using bioinformatics analysis, it was identified that CX3CR1 is a predictive biomarker for CRC where they regulate the infiltration and polarization of immune cells [41].

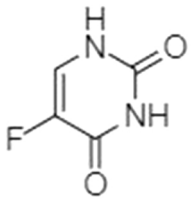
1.10. Chemokines and CRC immune response

Chemokines and their receptors are known to be involved in shaping the immune response against various cancers. We highlight here a few examples where chemokines and their receptors are involved in CRC progression. In an extensive bioinformatics-based study, the over-expression of CXCL1/2/3/4/5/8/9/10/11/13/14/16 was identified. Out of these, CXCL1/2/3/9/10/11 were associated with the tumour stage, while CXCL2/3/8/9/10/11/14 expression was associated with clinical outcomes. Moreover, the expression of CXCL8/9/10/11 was associated with the infiltration of immune cells [42]. Thus, predicting CXC chemokines as prognostic biomarkers for CRC. In an effort to find the relevance of the bacteria *Fusobacterium nucleatum* in the CRC TME, the CRC cell line was infected with the bacteria, and gene expression was investigated. Interestingly, there was an increase in the levels of CCL22 upon infection. The bioinformatics analysis showed that high CCL22 expression correlated with immunosuppression and antitumor immune response [25]. Another recent study found that Tumour necrosis factor-alpha (TNF-α) treatment, UV irradiation, and chemotherapeutic drugs trigger the release of IL-8 from primary patient cells and CRC cell lines. This IL-8 release further leads to chemotaxis of neutrophils which promotes an immunologically non-conducive tumour microenvironment [43]. Neutrophil infiltration in the microenvironment is associated with poor immune response. This is also evident from a recent study in which the KIAA1199 driven TGF-β pathway led to the release of CXCL1 and CXCL3, triggering the infiltration of immunosuppressive neutrophils [44]. The positive effect of a chemokine receptor was recently shown by CRISPR based overexpression of CXCR2 and cytokine IL-2 on the NK cell line NK-92. This genetically modified NK-92 cell line showed a better anti-tumour immune response in vitro and in vivo against CRC [45].

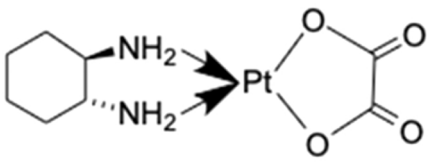
To understand the role of Sirtuin 1 (*SIRT1)* in the pathogenesis of CRC and its effect on the tumour microenvironment, a co-culture experiment was performed with monocytes, cytotoxic T cells and patient-derived tumour organoids (PDOs). The experiment showed that *SIRT-1*-hi CRC cells trigger the macrophages to reduce the anti-tumour activity of cytotoxic T cells. The mechanistic study showed that the migration of macrophages in this phenotype was dependent on the CXCL12/CXCR4 axis [46]. Additionally, in a study on atypical chemokine receptor 4 (ACKR4) on human CRC samples, CRC cell lines and transgenic animals, it was suggested that the loss of ACKR4 led to reduced immune infiltration in the tumour microenvironment. More importantly, a loss of ACKR4 on cancer cells led to reduced effects of immune checkpoint blockade [47]. In the case of colorectal neuroendocrine carcinomas (CRNECs), CCL5, which is usually considered an immunosuppressive chemokine, has been associated with high infiltration of CD8 + T cells and better long term survival of CRC patients [48]. Due to CRC genomic instability, cancer with DNA mismatch repair (dMMR) defect is highly abundant in tumour infiltrating lymphocytes. This has recently been shown that dMMR CRCs have a high abundance and activation of CD8 + T cells, which is dependent on the over-expression of chemokines such as CCL5 and CXCL10. Thus, targeting the upregulation of CCL5 and CXCL10 could be a viable strategy to enhance the TIL recruitment into CRC and thus maximise the anti-tumour immune response [49].

1.11. Chemokines and their role in the metastasis and drug resistance in colon cancer

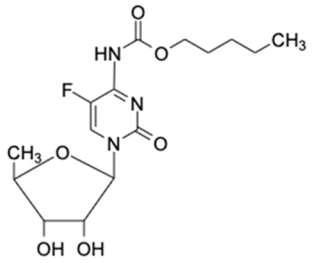
Since the initial identification of the link between leukocytes and the inflammatory processes taking place in the tumour microenvironment by Rudolf Virchow in 1863, chemokines have attracted a lot of attention [50]. Chemokines also referred to as chemotactic cytokines, are low-molecular-weight biomolecules (8–14 kDa) which have a prominent role in tumorigenesis by influencing the processes of angiogenesis, and proliferation, cancer stem cell migration and metastasis. Evidence also suggests that chemokines could directly influence the immune response of the tumour, leading to tumour immunity and thus drug resistance [51].



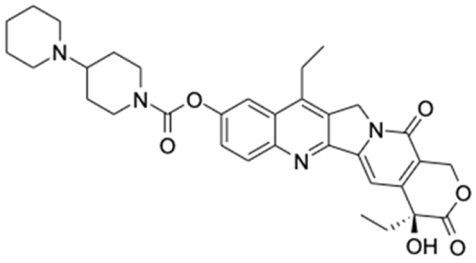
5-Fluorouracil



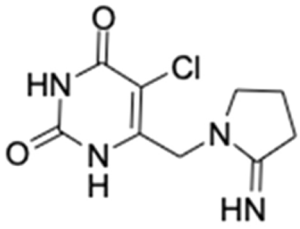
Oxaliplatin



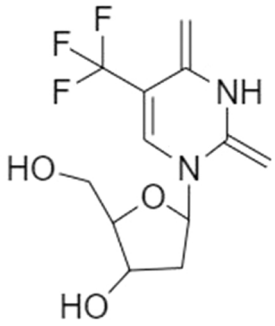
Capecitabine



Irinotecan



Tipiracil



Trifluiridin

Fig. 4. Chemical structure of the drugs used for CRC: The chemical structures and names of the approved drugs for CRC is denoted above.

Most chemokines associated with CRC are part of the CXC and CC subdivisional families of this type of secretory ligands. The CXC chemokine stromal-cell derived factor 1, CXCL12, plays an important role in CRC metastasis via two different routes: the CXCL12-CXCR4 axis and the CXCL12-CXCR7 axis [18]. The five-year survival rate for patients with metastatic CRC is severely reduced to 27 %– 50 %, compared to non-metastatic cases, 80 %– 90 %, with more than 1,148,000 new CRC cases diagnosed for the year 2020 [3]. The role of CXCL12 in metastasis has also been established in different types of tumours, such as breast, kidney, lung, brain, and ovarian tumours [52]. The CXCL12-CXCR4 interaction promotes epithelial to the mesenchymal transmission of colon cancer cells and their metastasis via the direct influence on the Wnt- β -catenin signalling pathway. High levels of the CXCR4 receptor have been associated with poor prognosis and overall survival in CRC [53]. This statement is supported by the research of Yang and colleagues (2018), who demonstrated the potential importance of microRNA (miRNA)-CXCR4 regulation [54]. Further to their findings, Yu and researchers (2019) demonstrated that miR-133a-3p might act as a potential oncomir, inducing inflammatory colorectal cancer via the increased transcription of CXCR4 [53]. However, the full implication of miRNA regulation processes in CXCR4 is still to be elucidated, and their role as potential therapeutic agents will be discussed below [55]. The upregulated levels of CXCL12-CXCR4 interaction also correlate with the occurrence of liver metastasis in patients with CRC due to the increased levels of CXCL12 found in the hepatocytes of patients with CRC. The instant metastasis of colon cancer cells is aided via the TGF-β pathway, which promotes distant migration and invasion, leading to the differentiation of hepatic stellate cells into cancer-associated fibroblasts [56]. Even though the evidence of metastatic CRC cells keeps building up, the clear role of secreted CXCL12 and its action upon PI3K/Akt cascade still needs to be elucidated [57].

The way the CXCL12-CXCR7 axis aids CRC metastasis differs from the pathways associated with the CXCL12-CXCR4 axis. Evidence has suggested that interaction with the CXCR7 receptor, which is mainly expressed in the cytoplasm of CRC cells, induces TLR4 and β-arrestin signalling, promoting cancer cell growth and metastasis [58]. CXCR4 could promote tumour growth independently of its ligand, CXCL12. However, the association between the ligand and the receptor is essential for inducing metastasis [59] (Fig. 3). The most common sites of CRC metastasis associated with CXCL12-CXCR7 interaction occur in the lungs and lymph nodes [60]. Even though CXCR7 induces metastasis, this process might be indirectly inhibited by cell adhesion mechanisms

also associated with the action of the receptor. Overexpression of the CXCR7 receptor increases neovascular activities identified in colon cancer cells. The induced activity of the ERK and Akt pathways via the action of CXCL12-CXCR7 interaction leads to the overproduction of VEGF by endothelial cells, thus leading to the formation of new blood vessels and angiogenesis [59].

The co-expression of the chemokine CXCL10 and its receptor CXCR3 has been associated with a poor prognosis for patients with CRC. The increased transcription of CXCL10 via the action of TNF-α leads to the overexpression of the ligand in colon cancer cells, which in turn are triggered to metastases by small GTPases [61]. During this research, it was also identified that the CXCL10-CXCR3 interaction enhances epithelial to mesenchymal transition by the PI3K/Akt pathway. Another team of researchers have demonstrated that the migration abilities of $CD8^+$ cells in colorectal cancer is highly dependent on the interaction between CXCL10 and CXCR3. Increased levels of CXCR3 cease the migration of these cells to the tumour site, which in turn ensures immune evasion and cell survival [62]. The CXCR3 receptor also recognises another ligand named CXCL9. High levels of CXCL9-CXCR3 have been found in lymph nodes of patients with metastatic CRC, showing the potential of the chemokine to induce distant migration of cancer cells [63].

The CX3CL1 chemokine and its interaction with the CX3CR1 receptor have demonstrated the accumulation of mesenchymal stem cells in the hypoxic microenvironment of colon cancer. Once present in the TME, the mesenchymal stem cells differentiate into cancer-associated fibroblasts, which, as mentioned above, have the potential to induce CRC metastasis to distant sites [64]. The overexpression of the CX3CR1 receptor on tumour-associated macrophages could lead to their aggregation in TEM, which has been linked to the initiation of angiogenesis via the CX3CL1-CX3CL1 axis [65]. This formation of new blood vessels is a potential way through which CRC cells might metastases to distant tissues. However, the CX3CR1 receptor has also been found to be expressed on the surface of natural killer cells and cytotoxic T lymphocytes, introducing the doubt whether the CX3CL1-CX3CR1 axis is tumour suppressive or tumour initiative, or both [66].

CCL2, also known as monocyte chemotactic protein 1, is another chemokine that is strongly associated with the accumulation of macrophages within the hypoxic microenvironment of CRC. The CCL2-CCR2 axis has demonstrated its potential to initiate the aggregation of macrophages at the tumour site of mouse models, which in turn reduced the spread of CRC and led to a better prognosis [67]. However, the CCR2 receptor is also expressed on colon cancer myeloid cells which have been found in liver metastasis in CRC patients. The activation of the JAK2-Stat5 and p38MAPK pathways in CRC endothelial cells promotes extravasation from the blood vessels and thus enhances metastasis in CRC [68]. The overall survival rate for patients possessing $CCR2^+$ myeloid cells has been demonstrated to be reduced in comparison to cohorts not resembling this expression [69].

One of the important players in the development of drug resistance in CRC is β-catenin. The properties of β-catenin in inducing drug resistance have also been observed in glioblastoma tumours, where PHF19 promotes β-catenin's signalling, subsequently leading to resistance towards doxorubicin [70]. In colon cancer, β-catenin signalling has been shown to be regulated by the secretion of CCL2 chemokines and its interaction with the CCR2 receptor. The chemokine also enables excessive extravasation of colon cancer endothelial cells in the blood and lymph nodes. The ectopic overexpression of CRC2 in the colon cancer cell lines SW480 and HCT116 has led to resistance toward regorafenib. This in-vivo study also demonstrated that CRC cells have a poor response to therapies with regorafenib [71]. Resistance to regorafenib is induced in a β-catenin manner, as evidence from Ou and colleagues has demonstrated that the signalling mediator is a direct transcriptional factor for the CRC2 receptor, which in turn leads to its overexpression and promotes drug resistance [71].

In addition, CCL20 has been associated with chemoresistance in CRC. The ligand has been shown to induce resistance toward Folfox chemotherapy via a complex FOXO1/CEBPB/NF-kB signalling model. A team of researchers identified that the serum concentrations of CCL20 found in CRC patients were significantly higher in Fulfox-resistant individuals when compared to non-resistant cohorts. This was also the case when the serum levels of CCL20 have measured in a time-dependent manner for the resistant and non-resistant groups. To further validate the secretion of CCL20 from colon cancer cells, the study implicated immunofluorescence staining and identified that $CD326^+$ are the main secretory source of the chemokine [72]. Furthermore, to identify the specific chemotherapeutic drugs which might lead to resistance, the researchers assessed the levels of CCL20 in serum levels of CRC patients and identified that upregulation of the chemokine was sufficiently induced by the 5-FU drug alone. However, another drug in the chemotherapeutic cocktail, named L-OHP, can also induce higher expression of CCL20 but only when combined with 5-FU [72]. The findings suggested that the FOXO1/CEBPB/NF-kB axis might be a useful target for impairing drug resistance in CRC patients treated with the Folfox chemotherapy, as by targeting the axis, the overexpression of CLL20 might be ceased. However, further investigation is needed to introduce this hypothetical concept in practice.

The chemokine CXCL13 has also shown its potential as a resistance inducer towards 5-FU. For the purposes of investigating the role of CXCL13 in the initiation of drug resistance, a team of researchers used two 5-FU resistant CRC cell lines (DLD-1 and HCT116) and demonstrated that the IC_{50} of both cell lines increased when they were treated with recombinant CXCL13. Thus, they concluded that the chemokine acts as an autocrine factor in the induction of 5-FU resistance in these CRC cells when oversecreted [73]. Further validation of the cancerogenic properties of CXCL13 came from the patients' samples, where the levels of the chemokine were detected in increased quantities. Those patients presented with decreased overall survival rates, proposedly induced by the negative correlation between the increased level of the chemokine in serum and post-treatment with 5-FU [73]. These results are supported by previous research, where similar CXCL13 serum presence and 5-FU resistance were observed [74]. However, Zhang and colleagues (2020) concluded most of their findings from the treatment of 5-FU CRC resistant cell lines and xenograft mice models. The only assessment of patient samples performed was to measure the CXCL13 levels in serum. The researchers considered the limited patient sample size and suggested the use of PDX models for studying chemotherapy resistance in CRC patients [73].

The chemokine CCL2 has also been associated as a potential player in introducing chemoresistance towards 5-FU and paclitaxel. The CCL2 chemokine interacts with the CCR8 receptor and leads to anti-apoptotic activities and cell proliferation [75]. Alongside the cancerogenic properties of the chemokine, a study using the CRC cell line CT26 demonstrated that when the cells were cultured alongside 3T3-Snail fibroblasts, the chemoresistance of CRC cells overtly increased. The researchers proposed that the pathway by which CCL2 induces 5-FU/paclitaxel resistance involves the phosphorylation of ERK/AKT/NF-kB and Smad2 leaded by 3T3-Snail fibroblasts [76]. Existing evidence of the involvement of the TGF-beta and NF-kB pathways in drug resistance towards antiandrogens has already been demonstrated before within prostate cancer studies [77]. Thus, the importance of CCL2 in phosphorylating the TGF-beta and NF-kB pathway might be a potential target for drug resistance which should be considered for further investigation. Further research in assessing the chemokine's properties in this process is needed to validate their findings.

1.12. Cytokines and chemokines as CRC prognostic biomarkers

Several cytokines have been investigated as potential prognostic markers. IL-6 and TNF-α have been found to activate the NF-κB and STAT3 signalling pathways and induce the expression of genes that are involved in the invasion of cancer cells and angiogenesis [78]. IL-6 is a

pleiotropic inflammatory cytokine produced by T helper cells, synovial fibroblasts, monocytes and macrophages [79]. IL-6 is considered to act as a protector of cancer cells against oxidative stress and apoptosis, promoting repair, whilst elevated levels of this protein have been shown to lead to an inflammatory condition [79,80]. Circulating proinflammatory biomarkers, including IL-6 and TNF-α, have been shown to be involved in the pathophysiology of anxiety and depression in CRC patients [81,82]. Both psychopathological comorbidities can endure the following completion of cancer treatment and have been associated with unfavourable outcomes for CRC patients [82,83]. Miranda et al. (2018) also reported that depression and anxiety might be related to immunological changes caused by the tumour itself [82].

IL-8 is considered a proinflammatory cytokine with tumorigenic and proangiogenic properties. Consistent high levels of IL-8, among other proteins in CRC-derived serum, could afford potential biomarkers for the CRC initiation and progression [84]. The main functions of IL-8 are the promotion of neutrophil chemotaxis and angiogenic responses in endothelial cells. IL-8 has also been regarded as a prognostic biomarker for CRC [78]. Czajka-Francuz et al. (2020) developed a circulating cytokines-based model, combining IL-2, IL-8, IL-10 and IL-13, which could potentially exhibit the predictive value of fluorouracil (5-FU) treatment in Caucasian CRC patients. In their model, IL-8, IL-10 and IL-13 exhibit pro-tumour or immunosuppressive activity, whilst IL-2 demonstrated mainly anti-tumour action [85].

The only interleukin with potential anticancer properties is IL-2. IL-2 is a small monomeric glycoprotein (15.3 kDa) lymphokine, which binds with high affinity to its cell surface IL-2Rs. Overexpression of IL-2Rs is found mainly on the activated T cells [86]. IL-2 is secreted by T-helper type 1 cells and plays a key role in activating T cell mediated immune responses and stimulating the proliferation and differentiation of B cells and natural killer cells. It is also involved in the development of Tregs [85]. IL-2 has been used as an adjuvant in the treatment of patients with several types of cancer, including the CRC [87]. Of note, it was previously suggested that specific IL-2 polymorphisms had been associated with an elevated risk of developing CRC. More recently, it was reported that IL-2 could afford a marker of systemic antitumour activity [85].

IL-9 is a pleiotropic cytokine produced in different amounts by a wide variety of cells, including mast cells, natural killer cells, Th2, Th17, Treg, ILC2, and Th9 cells. Th9 cells are considered to be the main CD4 + T cells that produce IL-9 [88]. IL-9 has a potential dual role in tumour immunity since it has previously been shown to play tumorigenic roles in haematological malignancies [89–91] and antitumour roles in solid tumours [92–94]. Also, IL-9 can promote tumour progression in haematological tumours by promoting the proliferation and activation of lymphocytes, whilst in solid tumours, IL-9 can inhibit tumour development by activating innate or adaptive immune responses [95]. However, these roles are not absolute, given that previous reports have demonstrated that IL-9 can induce CRC cell proliferation and promote tumorigenesis in CRC cells and in other types of solid tumours, including pancreatic cancer and breast cancer [93,95,96].

The CXC family of chemokines CXCL1 to 17 are 8–10 kDa secreted proteins that attract neutrophils and lymphocytes and signal through chemokine receptors 1–8. Both the chemokines and their receptors have a role in either the promotion or inhibition of cancer and might be involved in CRC metastasis and resistance to treatment affording putative prognostic markers [97]. For instance, CXCL8 has been previously associated with neutrophil migration that promotes tumour growth, motility invasion and angiogenesis [98]. Specifically, overexpression of CXCL8 has been linked to inferior CRC overall survival, whilst CXCL12 and CXCR4 could potentially predict unfavourable CRC clinical outcomes and resistance to radiotherapy [99–102]. CXCR4 and its ligand CXCL12 afford the most thoroughly researched pair of proteins linked to metastasis in different types of cancers, including the CRC. Specifically, overexpression of CXCR4 has been linked to poor survival rates. This is because the CXCR4 has been shown to co-localize with CRC stem cell markers, including CD133 and CD44, and this co-localization has been associated with the epithelial mesenchymal transition process [97].

In addition, serum CXCL7 is another chemokine that might afford a putative poor prognostic biomarker of obstructive CRC when overexpressed in this type of malignancy [103]. The overexpression of CXCL7 has been linked to invasion and angiogenesis by activation of the PI3K/AKT/mTOR signalling pathways [103]. Overexpression of CXCR7 can also enhance the activity of Ras/Raf/mitogen-activated protein kinase (MAPK) by binding to the chemokine receptor CXCR1/CXCR2 [59]. A recent study proposed that CXCR7 could be used as a serum biomarker for the detection of CRC [59].

Finally, it was reported that elevated expression of CXCL1 is predictive of lung metastasis in patients with CRC, confirming that colon cancer cells have a tendency to target the lung in order to establish secondary tumours [104].

1.13. Current and potential; therapies targeting chemokines

Targeting the immune system with clinically validated therapeutic strategies, such as monotherapies or immuno-mediated therapies provides potential avenues for discovering new effective drugs aiding in the suppression of cancer cell proliferation and metastasis. Chemokines and chemokine receptors have been solely investigated as potential cancer therapeutic targets due to their aberrant presence in the tumour inflammatory microenvironment. The controversial role of the chemokine CCR5 still remains to be elucidated regarding its pro- or anti-tumoral role when expressed in different cell types. During the tumorigenesis of CRC, the CCR5 chemokine, along with its three ligands, enhances tumour cell proliferation and tumour growth, and thus provides a potential therapeutic axis that could be targeted in order to cease these processes. The negative allosteric inhibitor Maraviroc is a FDA approved antagonist that has been used to reduce tumour growth in CRC by blocking the binding of CCR5 to its ligand CCL5 [105]. A recent study targeted CCR5 receptors via RNAi and by Maraviroc and demonstrated that inhibition of CCR5 induced significant antineoplastic effects, including inhibition of proliferation, migration, colony formation and interference with cell cycle-related signalling cascades. Their findings also highlighted CCR5 is an attractive therapeutic target, which could be incorporated into the treatment regimens of CRC patients with an early-stage liver metastasis as they might be more responsive to this treatment approach [106]. Phase 1 clinical trials during which a combination of Maraviroc and chemotherapy has been incorporated (clinicaltrials.gov identifier: NCT01736813) and confirmed the therapeutic efficacy of CCR5 blockade in CRC metastasis in three out of five patients bymitigating a pro-tumour inflammatory microenvironment by targeting both tumour cells and tumour-associated macrophages [107]. Furthermore, additional clinical trials and other studies have suggested a potential synergy between CCR5 inhibitors and immune checkpoint inhibitors. For instance, a phase 2 clinical trial (clinicaltrials.gov identifier: NCT03631407) completed in June 2021 investigatedthe safety and efficacy of vicriviroc (MK-7690) in combination with pembrolizumab (MK-3475) in participants with advanced/metastatic microsatellite stable (MSS) CRC (MK-7690–046). However, there are no posted results from this clinical trial to this date. Haag et al., (2020) studied theeffects of Maraviroc in the innate immune system by CCR5 blockade alongside the effects of pembrolizumab on the adaptive immune system by PD-1 inhibition in the treatment of mismatch repair proficient CRC. The results demonstrated that therapy with a combination of pembrolizumab and maraviroc prolonged disease stabilizations and increased the overall survival in patients [108].

Another important candidate target for therapy is the chemokine CXCL12. The CXCL12–CXCR4/CXCR7 axis has been shown to be involved in the survival, tumour growth, angiogenesis, metastasis, TME, and drug resistance of CRC. The aforementioned tumorigenic activities of the chemokine make it a potentially valuable therapeutic target in CRC patients [18]. The Noxxon Pharma AG, MERCK Sharp and Dohme Corp clinical trial (clinicaltrials.gov identifier: NCT03168139) studied

the inactivation of CXCL12 by Olaptesed pegol as a monotherapy. Olaptesed pegol was used to directly target CXCL12 and check whether the inactivation of CXCL12 could lead to changes in the tumour microenvironment. The study was completed in May 2020 and was shown to be safe for the participants involved in the trial. Thus, introducing this type of monotherapy might render the tumours more susceptible to immuno-oncological approaches such as checkpoint inhibition.

Several additional therapeutic targets in CRC have been proposed, but have not been tested in clinical trials yet. In 2017,it was demonstrated that the expression of CXCL1 facilitates cell seeding and outgrowth of metastases at distant sites. The researchers proposed the potential incorporation of CXCL1 as a therapeutic target; however, its role in human CRC needed to be further elucidated [104]. Three years later, Łukaszewicz-Zając (2020) reported that CXCL1/CXCR2 targeting might afford a potentially useful new strategy in the treatment of CRC patients. Due to the limited number of studies regarding this new therapy axis CRC, its potential must be further evaluated[109]. More recently, it was proposed that CXCL1 could act as a molecular therapeutic target for the metastasis of advanced CRC. The researchers demonstrated that CXCL1 could promote cell proliferation, migration, invasion and inhibit apoptosis in CRC [110]. Even though, it appears as if more experiments are necessitated to confirm the role of CXCL1 in CRC patients, the chemokine might be a promising therapeutic target for a new therapeutic strategy for CRC, based on our current knowledge of its oncogenic properties.

Multiple clinical trials have been designed to investigate potentially effective drug combinations against CRC. One such, clinicaltrials.gov identifier: NCT03403634, is a phase IIA clinical trial, which started in April 2018 and was completed in August 2019. This study investigated how celecoxib, recombinant interferon alfa-2b, and rintatolimod work together in treating colorectal cancer that has metastasised to the liver. The drugs have distinct modes of action, where celecoxib might act as an tumour cell growth suppressor, recombinant interferon alfa-2b is thought to potentially improve the body's natural immune response, whereas rintatolimod is primarily used as a stimulator to the immune system. Combined oral administration of celecoxib, alongside an intravenous administration of recombinant interferon alfa-2b and rintatolimod has demonstrated promising outcomes at treating CRC that has spread to the liver. The clinical trial has been completed and revealed that this combination was clinically safe for patients with metastasised CRC; however, complete analysis and interpretation of the results are pending and to be posted.

1.14. Potential treatment methods – the use of microRNAs in CRC

The miRNAs are small non-coding single stranded RNAs ranging from 20 to 25 nucleotides in size that fine-tune gene expression by binding to the 3′-UTR of the mRNA targets post-transcriptionally, leading to gene silencing [111]. According to a recent study, miRNA functions contribute to both immune homeostasis and the control of immune tolerance. Deregulation of miRNAs is frequently reported in various types of tumours leading to immune disorders and immune evasion [112]. Inflammatory mediators, chemokines and cytokines can regulate miRNA expression, which in turn can contribute to the regulation of a plethora of genes associated with inflammation and tumorigenesis [79]. MiRNAs can control diverse processes, including cell proliferation, differentiation, apoptosis, angiogenesis, epithelial mesenchymal transition (EMT), metastasis and metabolic pathways in cancer and subsequently, through their expression profiles, they could serve as diagnostic or prognostic biomarkers or as potential therapeutic interventions [113].

More specifically, miRNAs are considered attractive therapeutic strategies due to their low toxicity and their multi-targeting properties [114]. Regulation of miRNA expression can be achieved either by miRNA mimics or miRNA replacement and miRNA inhibition therapies. The miRNA mimics or replacement therapy aims to restore the function of tumour suppressor miRNAs. This can be achieved using synthetic dsRNA molecules with the identical sequence as the natural miRNAs that will be able to bind effectively on their mRNA target and exert their tumour suppressor functions. Alternative methods would be to reactivate the transcription, restore a deleted genomic locus or inhibit miRNA sponges. Regarding the miRNA inhibition therapy, this aims to prevent the expression of miRNAs that have been found to exert oncogenic properties. To succeed in this, antisense oligonucleotides, miRNA masks, antagomirs, locked nucleic acid anti-miRNAs, or small miRNA inhibitors can be used. Nevertheless, the controlled in vivo delivery of miRNAs remains challenging. The nanotechnology assisted miRNA delivery is being exploited as a potential solution to this issue. Current delivery systems are designed with great focus on the tumoral characteristics, including the acidic extra- and intra-cellular environment, the enhanced thermal sensitivity, the redox imbalances of cancer tissues and the pH imprint, in order to aid in targeting the therapies to a specific site or site of action [115]. Nanocarriers have attracted attention mainly due to their structural ability, biocompatibility, and biodegradability [116].

In CRC, several miRNAs have been shown to participate in cellular processes such as angiogenesis, EMT and interaction with the microenvironment [117]. According to Huang et al. (2015), miR-19a played a significant role in lymph metastasis and mediated the TNF-α induced EMT in CRC cells, making it a potential marker of lymph node metastasis [118]. This is in agreement with the findings in which it was found that miR-19a can promote CRC tumorigenesis via targeting TIA1 [119] and later of it was demonstrated that miR-19a enhanced cell proliferation and metastatic processes in CRC by targeting thrombospondin-1 [120].

Another miRNA with potential oncogenic properties and candidate for miRNA inhibition therapy in CRC is miR-21. A recent study hypothesized that miR-21 might protect both fibroblasts and cancer cells from cell death directed by TNF-α paracrine and autocrine activity in CRC [121]. The same year, it was reported that miR-21 was highly expressed in CRC tissues, positively associated with the degree of malignancy of patients and negatively associated with survival [122]. The elevated expression of miR-21 in the tumour tissues of CRC has shown to serve as an independent prognostic and predictive biomarker as well as a putative therapeutic target [123,124]. In general, miR-21 has been shown to play a critical role in regulating many target genes and pathways mainly implicated in tumour proliferation, invasion, apoptosis and metastasis [124]. Specifically, miR-21 has been shown to modulate the expression of multiple cancer-related target genes such as *PTEN, TPM1*, and *PDCD* [123]. In another study, all these three miR-21 target genes were down-regulated by exosomes from colon cancer cells, and, further, silencing of *PDCD4* mimicked miR-21 functional effects. This evidence suggested that targeted inhibition of miR-21 exosomes may represent a novel approach for the treatment of CRC [125].

On the contrary, it was demonstrated that low miR-302c levels were correlated with deeper tumour invasion, lymph node metastasis and advanced tumour, nodes and metastasis (TNM) stage in CRC, whilst overexpression of miR-302c repressed processes like migration and invasion [126]. Subsequently, this evidence proposes that miR-302c might exhibit tumour suppressor properties and could afford a biomarker associated with an unfavourable prognosis when miR-302c is downregulated in CRC. Their findings are in line with another study which also indicated that miR-302c inhibited migration and invasion by promoting apoptosis through the Wnt/b-catenin signalling pathway by binding to CARF protein [127]. Interestingly, it was also suggested that CXCL1 exerted its oncogenic role in CRC via inhibiting the JAK-STAT signalling pathway, when miR-302e was downregulated, implying its putative tumour suppressor role. Notably, miR-302e belongs to the same miR-302 family, which impedes angiogenesis and cell invasion of CRC, as the miR-302a [128].

In microsatellite-unstable colorectal cancer, CXCL8 production and cell proliferation has been shown to enhance by the loss of miR-484, indicating a potential regulatory role for CXCL8 and miRNAs [129].

Table 1
The list of clinical trials on CRC using chemokines and chemokine receptors and their current status.

Clinical Trials					
	Study Title	NCT Number	Study Conditions	Phase	Status
1	A study of Type-1 Polarized Dendritic cell (αDC1) vaccine in combination with Tumour-selective Chemokine modulation (Interferon-α2b, Rintatolimod, and Celecoxib) in subjects with Chemo-Refractory Metastatic Colorectal cancer	NCT02615574	• Metastatic Colorectal Cancer	II	Withdrawn
2	Chemokine-Modulatory Regimen for Recurrent Resectable Colorectal Cancer	NCT01545141	• Colorectal Cancer • Colorectal Carcinoma • Colorectal Tumours • Neoplasms, Colorectal	I/II	Terminated
3	Celecoxib, Recombinant Interferon Alpha-2b, and Rintatolimod in Treating Patients with Colorectal Cancer Metastatic to the liver	NCT03403634	• Recurrent Colorectal Carcinoma • Stage IV Colorectal Cancer AJCC v7 • Stage IVA Colorectal Cancer AJCC v7 • Stage IVB Colorectal Cancer AJCC v7	II	Completed
4	Pembrolizumab and Olaparib in Homologous-recombination Deficient (HRD) Advanced Colorectal Cancer (CRC)	NCT05201612	• Metastatic Colorectal Cancer	II	Not yet recruiting
5	Afilbercept or Bevacizumab as Second-line Treatment of RAS Mutated Metastatic Colorectal Cancer	NCT04397601	• Metastatic Colorectal Cancer	I	Recruiting
6	Dendritic Cell Vaccination in Patients with Lynch Syndrome or Colorectal Cancer with MSI	NCT01885702	• Colorectal Cancer	I/II	Active, not recruiting
7	Changes in Inflammatory Response After Immuno-Nutrition Compared to Standard Nutrition in Colorecta Cancer Tissue	NCT04732442	• Colon Cancer	N/A	Completed
8	CCR5-blockade in Metastatic Colorectal Cancer	NCT01736813	• Colorectal Cancer • Neoplasm Metastasis	I	Completed
9	Safety and Efficacy of Vicriviroc (MK-7690) in Combination with Pembrolizumab (MK-3475) in Participants with Advanced/Metastatic Microsatellite Stable (MSS) Colorectal Cancer (CRC) (MK-7690–046)	NCT03631407	• Colorectal Neoplasms	II	Completed
10	Prebiotic Effect of Eicosapentaenoic Acid in Treatment for Colorectal Cancer Liver Metastases	NCT04682665	• Colon Cancer	II/III	Recruiting
11	Olaptesed (NOX-A12) Alone and in Combination with Pembrolizumab in Colorectal and Pancreatic Cancer	NCT03168139	• Metastatic Colorectal Cancer	I/II	Completed
12	Impact of Aerobic Exercise on Immune Response and Side Effects of Cancer Treatments	NCT04715061	• Colorectal Cancer Stage IV	N/A	Recruiting
13	Prevention using EPA Against Colorectal Cancer	NCT04216251	• Colorectal Adenoma • Colorectal Cancer	I/II	Recruiting
14	Effect of Transversus Abdominis Plane Block with Compound Lidocaine and Esketamine on Pain After Surgery	NCT05122338	• Postoperative Pain	N/A	Not yet recruiting
15	Vandetanib-eluting Radiopaque Embolic Beads in Patients with Resectable Liver Malignancies	NCT03291379	• Metastatic Colorectal Cancer	Early I	Completed
16	Omega-3 Fatty Acid for the Immune Modulation of Colorectal Cancer	NCT03661047	• Colon Cancer	II	Withdrawn
17	A Study of KF-0210 in Advanced Solid Tumours Patients	NCT04713891	• Advanced Solid Tumour • Colorectal Cancer	I	Recruiting

The same study also revealed that miR-484 could inhibit the expression of CD137L and IL-8, which in turn prevented the activity of microsatellite unstable CRC cells suggesting its use as a potential therapeutic target. The same year, Lu and Lu (2015) demonstrated that serum miR-484 expression levels were significantly lower in patients with early-stage CRC, whilst the serum miR-484 was overexpressed in patients with advanced CRC. Consequently, the detection of miR-484 may afford a useful biomarker for the early diagnosis and accurate prognosis of CRC [130]. The different genes and pathways can affect stages of CRC development from early adenoma to CRC development. This ultimately can also lead to tumour heterogeneity and drug resistance by the release of chemokines such as CCL20, CXCL12, CXCL13. (Fig. 3).Table. 1.

2. Conclusion

CRC is a type of cancer that is highly prevalent and deadly. The chemokines associated with CRC are instrumental in shaping the immune microenvironment and clinical outcomes. The overlapping functions of many chemokine-chemokine receptor axes make it difficult to fully understand their exact roles. For instance, the chemokine CXCL12, plays an important role in CRC metastasis, whereas CCL2, is strongly associated with the accumulation of macrophages within the hypoxic microenvironment of CRC. Furthermore, the chemokines CXCR4 and CXCR7 are examples of tumour growth regulators as their expression in CRC increases with tumour stages. They enhance tumour growth and thus lead to a poor prognosis and decreased overall survival rates within CRC patients. Moreover, the intracellular pathways that are regulated by many of these chemokines-chemokine receptors are also common. It is noteworthy that the overall effects of chemokines are dependent on the types of cells on which the receptor is present and the overall stage and grade of cancer. A major failure of the current therapy in CRC is due to drug resistance and heterogeneity of this cancer type. Both of these aspects of the CRC are regulated by chemokines and their receptors. Therefore, it is very important to understand the intricate details of the different immune cell populations and other cells of the tumour microenvironment that are regulated by the chemokines. In the future, further investigation is warranted to pinpoint the molecular mechanisms of the chemokines and their receptors to find prognostic biomarkers and novel individualised therapeutic targets.

Conflict of Interest

There is no conflict of interest with the content of the manuscript.

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Fig. 1, Fig. 2 and Fig. 3 were created using BioRender.com. The chemical structures of the drugs were made with ChemDraw.

Conflict of Interest

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