Inflammation and cancer: back to Virchow?

Fran Balkwill, Alberto Mantovani

The response of the body to a cancer is not a unique mechanism but has many parallels with inflammation and wound healing. This article reviews the links between cancer and inflammation and discusses the implications of these links for cancer prevention and treatment. We suggest that the inflammatory cells and cytokines found in tumours are more likely to contribute to tumour growth, progression, and immunosuppression than they are to mount an effective host anti-tumour response. Moreover cancer susceptibility and severity may be associated with functional polymorphisms of inflammatory cytokine genes, and deletion or inhibition of inflammatory cytokines inhibits development of experimental cancer. If genetic damage is the “match that lights the fire” of cancer, some types of inflammation may provide the “fuel that feeds the flames”. Over the past ten years information about the cytokine and chemokine network has led to development of a range of cytokine/chemokine antagonists targeted at inflammatory and allergic diseases. The first of these to enter the clinic, tumour necrosis factor antagonists, have shown encouraging efficacy. In this article we have provided a rationale for the use of cytokine and chemokine blockade, and further investigation of non-steroidal anti-inflammatory drugs, in the chemoprevention and treatment of malignant diseases.

It was in 1863 that Rudolf Virchow noted leucocytes in neoplastic tissues and made a connection between inflammation and cancer. He suggested that the “lymphoreticular infiltrate” reflected the origin of cancer at sites of chronic inflammation. Over the past ten years our understanding of the inflammatory microenvironment of malignant tissues has supported Virchow’s hypothesis, and the links between cancer and inflammation are starting to have implications for prevention and treatment.

Panel 1 lists some cancers where the inflammatory process is a cofactor in carcinogenesis. About 15% of the global cancer burden is attributable to infectious agents, and inflammation is a major component of these chronic infections. Moreover, increased risk of malignancy is associated with the chronic inflammation caused by chemical and physical agents, and autoimmune and inflammatory reactions of uncertain aetiology.

Inflammatory cells in tumour microenvironment

The inflammatory microenvironment of tumours is characterised by the presence of host leucocytes both in the supporting stroma and in tumour areas. Tumour-infiltrating lymphocytes may contribute to cancer growth and spread, and to the immunosuppression associated with malignant disease.

Macrophages

Tumour-associated macrophages (TAM) are a major component of the infiltrate of most, if not all, tumours. TAM derive from circulating monocytic precursors, and are directed into the tumour by chemotactic cytokines called colony-stimulating factors that prolong survival of TAM. When appropriately activated, TAM can kill tumour cells or elicit tissue destructive reactions centred on the vascular endothelium. However, TAM also produce growth and angiogenic factors as well as protease enzymes which degrade the extracellular matrix. Hence, TAM can stimulate tumour-cell proliferation, promote angiogenesis, and favour invasion and metastasis. Direct evidence for the importance of protease production by TAM, neutrophils, and mast cells during experimental carcinogenesis has recently been reported. This dual potential of TAM is expressed in the “macrophage balance” hypothesis.

Dendritic cells

Dendritic cells have a crucial role in both the activation of antigen-specific immunity and the maintenance of tolerance, providing a link between innate and adaptive immunity. Tumour-associated dendritic cells (TADC) usually have an immature phenotype with defective ability to stimulate T cells. In breast cancer, immature TADC are interspersed in the tumour mass, whereas mature dendritic cells are confined to the peritumoral area. In papillary thyroid carcinoma TADC are also immature but they tend to localise at the invasive edge of the tumour. This distribution of TADC is clearly different from that of TAM, which are evenly scattered in tumour tissue. The immaturity of TADC may reflect lack of effective...
maturation signals, prompt migration of mature cells to lymph nodes, or the presence of maturation inhibitors. TADC are likely to be poor inducers of effective responses to tumour antigens.

Lymphocytes

Natural killer cells are rare in the tumour microenvironment. The predominant T-cell population has a “memory” phenotype. The cytokine repertoire of these tumour-infiltrating T cells (TIL) has not been studied systematically but in some tumours (eg, Kaposi’s sarcoma, Hodgkin’s disease, bronchial carcinoma, and cervical carcinoma) they produce mainly interleukins (IL) 4 and 5 and not interferon-γ. IL 4 and 5 are cytokines associated with the T-helper type 2 (Th2) cells whereas interferon-γ is associated with Th1 responses. Polared Th2 responses are generally ineffective against tumours and viruses. Signalling via the T-cell receptor is also defective in TIL.10

Tumours: wounds that do not heal

Besides inflammatory cells, tumour stroma consists of new blood vessels, connective tissue, and a fibrin-gel matrix. In his 1986 review Dvorak showed how wound healing and tumour stroma formation share many important properties (“Tumors: wounds that do not heal”11). Wound healing is usually self-limiting whereas tumours secrete a vascular permeability factor, vascular endothelial growth factor (VEGF), that can lead to persistent extravasation of fibrin and fibronectin and continuous generation of extracellar matrix. Platelets in wounds are a critical source of cytokines, especially transforming growth factor β (TGF-β) and VEGF. Platelet release of such factors may also be important in tumour angiogenesis.12 In addition, malignant cells themselves secrete proinflammatory cytokines.13

Proinflammatory cytokines

The cytokine network of several common tumours is rich in inflammatory cytokines, growth factors, and chemokines but generally lacks cytokines involved in specific and sustained immune responses.14 There is now evidence that inflammatory cytokines and chemokines, which can be produced by the tumour cells and/or tumour-associated leucocytes and platelets, may contribute directly to malignant progression. Many cytokines and chemokines are inducible by hypoxia, which is a major physiological difference between tumour and normal tissue.15 Examples are tumour necrosis factor (TNF), IL 1 and 6, and chemokines.

Tumour necrosis factor

TNF is a major mediator of inflammation, with actions directed towards both tissue destruction and recovery. While inducing death of diseased cells at the site of inflammation, TNF stimulates fibroblast growth. It can destroy blood vessels but also induce angiogenic factors.15 Likewise, in malignant disease, high-dose local TNF selectively destroys tumour blood vessels,16 but when chronically produced this cytokine may act as an endogenous tumour promoter, contributing to the tissue remodelling and stromal development necessary for tumour growth and spread.

TNF can be detected in malignant and/or stromal cells in human ovarian, breast, prostate, bladder, and colorectal cancer, lymphomas, and leukaemias, often in association with ILs 1 and 6 and macrophage colony stimulating factor.17,18 In epithelial ovarian cancer, TNF mRNA is found in epithelial tumour islands, where there is a positive correlation with tumour grade.17 The p55 TNF receptor is found on tumour and stromal cells and the p75 receptor localises to the leucocyte infiltrate in ovarian cancer, suggesting possibilities for both paracrine and autocrine action.17 TNF is also implicated in the induction of a chemokine called monocyte chemotactic protein-1, which can regulate the macrophage and lymphocyte infiltrate,1 and of matrix metalloprotease-9, in the ovarian tumour microenvironment. In breast cancer, infiltrating macrophages are a major source of TNF, which may regulate thymidine phosphorylase, a key angiogenic enzyme in the tumour epithelium.19 In prostate cancer, tumour cell TNF production correlates with loss of androgen responsiveness. In non-Hodgkin lymphoma, myelogenus leukaemia, and chronic lymphocytic leukaemia, high

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**Glossary: Specialised leucocytes, cytokines, chemokines**

<table>
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<tr>
<th>Specialised leucocytes</th>
<th>Abbreviation</th>
<th>Group</th>
<th>New human nomenclature</th>
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<tbody>
<tr>
<td>Natural killer cells</td>
<td>NK</td>
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<td>Tumour-associated dendritic cells</td>
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<td>Tumour-associated macrophages</td>
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<td>Proinflammatory/Th1</td>
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<td>-</td>
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<td>Immune regulatory/Th2</td>
<td>-</td>
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<tr>
<td>Macrophage colony-stimulating factor</td>
<td>M-CSF</td>
<td>Growth factor</td>
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<td>Migration inhibitory factor</td>
<td>MIF</td>
<td>Proinflammatory</td>
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<td>Transforming growth factor β</td>
<td>TGFβ</td>
<td>Growth factor</td>
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<td>Tumour necrosis factor</td>
<td>TNF</td>
<td>Proinflammatory</td>
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<td>Vascular endothelial growth factor</td>
<td>VEGF</td>
<td>Angiogenic/vascular permeability</td>
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<td>CC</td>
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<td>Viral macrophage inhibitory protein</td>
<td>vMIP</td>
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circulating levels of TNF and its soluble receptors are associated with poor prognosis. There is also evidence for pro-cancer actions of TNF in animal models. For example, treatment of ascitic ovarian cancer xenografts with TNF promotes adhesion of free-floating tumour cells to the peritoneum and solid tumour formation, and overexpression of TNF confers invasive properties on some tumour cell lines.

Direct evidence for the involvement of TNF in malignancy comes from the observation that mice lacking the gene for TNF are resistant to skin carcinogenesis. TNF may be involved in the early stages of skin tumour promotion in normal mice, being transiently but extensively induced in keratinocytes after application of tumour promoter. Pentoxifylline (an inhibitor of inflammatory cytokine production) inhibits papilloma development in skin carcinogenesis models, and intraperitoneal injection of TNF enhances papilloma development and vascularisation of tumours.

**Interleukins 1 and 6**

In mouse models of metastasis, treatment with an IL-1 receptor antagonist (which inhibits the action of IL-1) significantly decreased tumour development, suggesting that local production of this cytokine aids development of metastases. Moreover, mice deficient in IL-1β were resistant to the development of experimental metastases. In human multiple myeloma the malignant cells home to the bone marrow where they stimulate stromal cells to secrete the inflammatory cytokines IL-1, IL-6, and TNF. The cytokines stimulate myeloma cell growth and promote resistance to therapy. Intraperitoneal injection of mineral oil in mice induces chronic inflammation followed by

**Chemokines**

Inflammatory cytokines are major inducers of a family of chemoattractant cytokines called chemokines that play a central role in leucocyte recruitment to sites of inflammation. Most tumours produce chemokines of the two major groups (or CXC) and (or CC). Typically CXC chemokines are active on neutrophils and lymphocytes whereas CC chemokines act on several leucocyte subsets including monocytes, eosinophils, dendritic cells, lymphocytes, and natural killer cells but not neutrophils. Evidence from murine models and human tumours suggests that CC

**Figure 1: Chronic inflammation, tissue damage, and chronic infection may stimulate cytokines and chemokines that contribute to development of malignant disease**

**Panel 2: Actions of cytokines and chemokines which may facilitate cancer growth, invasion and metastasis**

- DNA damage via reactive oxygen
- Inhibition of DNA repair via reactive oxygen
- Functional inactivation of tumour suppressor genes
- Autocrine/paracrine growth and survival factors for malignant cells
- Induction of vascular permeability and extravasation of fibrin/fibronectin
- Tissue remodelling via induction/activation of matrix metalloproteinases
- Control of tumour-cell migration, direct and indirect
- Control of leucocyte infiltrate
- Modulation of cell:cell adhesion molecules
- Subversion of host immune responses
- Stimulation of angiogenesis and angiogenic factor production
- Resistance to cytotoxic drugs
- Loss of androgen responsiveness

myeloma. IL-6-deficient mice resist these changes, showing defective recruitment of macrophages to the peritoneum and a reduced incidence of myeloma.
Chemokines are major determinants of macrophage and lymphocyte infiltration in melanoma, carcinoma of the ovary, breast, and cervix, and in sarcomas and gliomas. In Hodgkin’s disease the malignant Reed-Sternberg cells express two chemokines, the macrophage-derived chemokine and thymus and activation-regulated chemokine, that attract Th2 lymphocytes. Production of the chemokine eotaxin correlates with eosinophil infiltration in Hodgkin’s lymphoma. Eosinophils are frequently present in tumours such as colorectal cancer.

Human and murine tumours also frequently secrete CXC chemokines such as interleukin-8. These chemokines are potent neutrophil attractants yet neutrophils are rare in tumours. However, both IL-8 and a related chemokine called “gro” induce proliferation and migration of melanoma cells. When the gro gene was overexpressed in a non-malignant melanocyte cell line, the cells could form tumours in mice. This effect probably involved both direct growth stimulation and promotion of an inflammatory response. Inflammation and wound healing have indeed been implicated in the initial steps of melanocyte oncogenesis. IL-8 production is also associated with the tumorigenic and metastatic potential of pancreatic cancer cells and this chemokine is strongly inducible by hypoxia.

Helicobacter pylori induced gastritis is associated with gastric carcinoma and mucosa-associated lymphoid tissue B-cell lymphoma. BCA-1 is one of the chemokines induced by H pylori, and it is thought that BCA-1 attracts B-cells to the mucosa where they become targets for the carcinogenic process that occurs during inflammation.

Receptors for chemokines (CCR and CXCR) are expressed both by infiltrating leukocytes and by cancer cells. The leukocytes may lose receptor expression once they are exposed to inflammatory chemokines in the tumour microenvironment, as shown for CCR2 on TAM in ovarian cancer. Downregulation of CCR2 is likely to act as a signal for the retention of macrophages at the tumour site. Melanoma cells express the CXC receptors CXCR 1 and 2, and the ligand for these receptors (IL-8) will stimulate migration and proliferation of these tumour cells. An ovarian cancer cell line also expressed a functional form of CXCR2. These observations raise the interesting possibility that tumour cells may use chemokine gradients to spread around the body.

Mechanisms of action of inflammatory cytokines in tumour microenvironment

An inflammatory cytokine network may influence survival, growth, mutation, proliferation, differentiation, and movement of both tumour and stromal cells. Moreover, these cytokines can regulate communication between tumour and stromal cells, and tumour interactions with the extracellular matrix. We will now look in more detail at the mechanisms by which cytokines and chemokines might act to promote tumours (panel 2, figure 1).

DNA damage

TNF is a transforming agent for carcinogen-treated fibroblasts. Two weeks of exposure to the cytokine in vitro is sufficient to render cells capable of tumour formation in nude mice. The molecular basis may involve induction of reactive oxygen. Reactive oxygen in the form of NO is often generated by inflammatory cytokine induction of NO synthase. NO can directly oxidise DNA, resulting in mutagenic changes, and may damage some DNA repair proteins. Furthermore, inducible NO synthase has been detected in gynaecological carcinomas. Inflammatory cytokines may also affect genome integrity via inhibition of cytochrome p450 or glutathione S-transferase isoenzymes.

Figure 2: Kaposi’s sarcoma virus human herpesvirus 8 encodes three chemokines that recognise receptors preferentially expressed on polarised Th2 cells

These cells are ineffective viral and antitumour effectors and produce cytokines which block differentiation of Th1 cells and activation of macrophages.

Bypassing p53

Another link between inflammatory cytokines and DNA damage comes from recent studies of the regulation of the tumour-suppressor protein p53. In tumours, p53 is often functionally inactivated even though the p53 gene remains intact. A search for negative regulators of p53 activity highlighted an inflammatory cytokine known as migration inhibitory factor. Treatment of cells with this factor overcame p53 activity. It is not clear whether other cytokines can also inactivate p53 but chronic bypass of p53 function could enhance the proliferation of initiated cells, extend lifespan, and create a deficient response to genetic damage. Migration is also strongly induced by hypoxia.

Actions as growth and survival factors

Cytokines and chemokines have the potential to stimulate tumour-cell proliferation and survival and some of them may also act as autocrine growth and survival factors for malignant cells. IL-6 is a growth factor for haematological malignancies; IL-1 has growth stimulating activity for gastric carcinoma that may be related to genetic predisposition and for myeloid leukaemias; and growth of melanomas is promoted by IL-8 and related chemokines.

Angiogenesis

Angiogenesis is important in the evolution of both cancer and inflammatory diseases that may predispose to cancer. Once a tumour is established it may attain further characteristics, via mutations or hypoxia, which stimulate new blood vessels.

The inflammatory cell infiltrate, particularly TAM, may contribute to tumour angiogenesis, and there are many reports of associations between macrophage infiltration, vascularity, and prognosis. Moreover TNF, IL-1, and IL-6 can stimulate production of angiogenic factors such as VEGF. Inflammatory macrophages also produce TGF-β1 that is itself angiogenic and induces production of VEGF.

Chemokines also have a role. Some CXC chemokines (eg, IL-8) are proangiogenic whereas others such as IP-10 have antiangiogenic activity. Chemokines have direct
actions on microvascular endothelial cells. In addition, CC chemokines may inhibit or stimulate angiogenesis indirectly, via their influence on TAM. In many tumours (eg, non-small-cell lung cancer and pancreatic carcinoma) it is the balance between proangiogenic and antiangiogenic cytokines and chemokines, rather than absolute amounts, that regulates tumour angiogenesis.

Invasion and metastasis

Cytokines and chemokines affect various stages in the process of metastasis. TNF and CC chemokines can induce production of proteases important for invasion in both tumour cells and macrophages. Indeed, monocytes infiltrating the tumour tissue may provide cancer cells with a ready-made path for invasion (the “countercurrent invasion theory”). In one skin tumour model, paracrine matrix metalloproteinase-9 production by inflammatory cells was implicated in epithelial hyperproliferation, angiogenesis and increased malignant potential, and skin tumour development was reduced in mice genetically “knocked out” for this protein. Chimaeric mice expressing this metalloproteinase only in cells of bone marrow origin developed skin tumours at the same rate as control mice, highlighting the importance of stromal inflammatory cells in epithelial carcinogenesis. TNF and IL-1 augment expression of adhesion molecules on endothelial cells. IL-18 derived from the endothelium may be the ultimate mediator of one tumour cytokine-induced adhesion molecule. Certain tumour cells have receptors for adhesion molecules and use these molecular tools, typical of migrating leucocytes, to seed at distant anatomical sites. Furthermore, chemokine agonists induce migration or proliferation of some tumour cells. Receptors that are essential for lymphocyte and dendritic cell homing to lymph nodes, could play a role in lymphatic dissemination of certain carcinomas. Direct evidence for chemokines guiding the secondary localisation of cancer has been obtained in one mouse model. Mice deficient in Fas detected in many cancers, associated with inflammatory infiltrate and cell motility

Deletion of cytokines and chemokines protects against carcinogens, experimental metastases and lymphoproliferative syndrome

Inflammatory cytokines implicated in action of non-genotoxic liver carcinogens

The inflammatory cytokine TNF is directly transforming in vitro

Interfering with chemotherapy

Another similarity between inflammation and cancer is raised plasma concentrations of acute-phase proteins (such as C-reactive protein and α,-acid glycoprotein). The latter binds with high affinity to, and blocks activity of, the experimental cancer drug STI571 which normally has activity against chronic myelogenous leukaemia in mice. If acute-phase proteins do bind to and inactivate anticancer drugs there would be obvious implications for therapy.

Local inflammation and systemic anti-inflammation: a paradox

In terms of inflammatory reactions, neoplastic disorders constitute a paradox. Tumours produce inflammatory cytokines and chemokines and are infiltrated by leucocytes. However, neoplastic disorders are associated with a defective capacity to mount inflammatory reactions at sites other than the tumour, and circulating monocytes from cancer patients are defective in their capacity to respond to chemoattractants.

Various factors originating in the tumour microenvironment may contribute to the systemic anti-inflammation associated with cancer. Chemokines leaking into the systemic circulation are likely to desensitise circulating leucocytes; increased concentrations of TNF receptors and the type II decoy IL-1 receptor may buffer inflammatory cytokines; and tumours also produce anti-inflammatory cytokines. Thus a defective capacity to mount a systemic inflammatory response in cancer patients could coexist with continuous leucocyte recruitment at the tumour site.

Inflammatory cytokines as cancer-modifier genes

Cytokine genes are highly polymorphic and since polymorphisms are frequently in regions of DNA that regulate transcription or posttranscriptional events, they may be functionality significant. Four studies of such polymorphisms and cancer susceptibility and severity suggest that some cytokines may be cancer-modifier genes. Systemic release of TNF and lymphotxin contributes to the severity of non-Hodgkin lymphoma. In a study of 273 lymphoma patients, the TNF-308 polymorphism was associated with high plasma levels of the cytokine at presentation of disease.
Associations have also been found between genotype changes in the promoter regions of TNF and prostate cancer. The relative risk of incidence for prostate cancer was 14-fold higher in men with the TNF-308 G allele (G/G) at 488 base pair of TNF-308. Patients with extensive corpus gastritis, hypochlorhydria, and gastric atrophy as a result of H pylori infection have the greatest risk of gastric malignancy. IL-1β is upregulated during H pylori infection, is important in the inflammatory response of the gastric mucosa, and is a potent inhibitor of gastric acid secretion. A decreased flow of gastric secretions may increase damage by allowing accumulation of bacterial toxins and inflammatory mediators. IL-1 gene cluster is a marker of gastric acid secretion. Adecreased flow of gastric secretions response of the gastric mucosa, and is a potent inhibitor of during

Nonsteroidal anti-inflammatory agents

People who have taken non-steroidal anti-inflammatory drugs (NSAIDs), are at reduced risk of colon cancer. This may also be true for cancers of the oesophagus, stomach, and rectum, and in rodents experimental bladder, breast, and colon cancer is reduced when NSAIDs are administered concurrently with carcinogens. NSAIDs inhibit cyclooxygenase enzymes and angiogenesis. Cyclooxygenase-2 is induced by cytokines and expressed in both inflammatory disease and cancer. When the cyclooxygenase-2 inhibitor celecoxib was tested on familial adenomatous polyposis patients in a double-blind placebo-controlled study, six months of twice daily treatment with 400 mg led to a significant reduction in the colorectal polyph burden.

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IL-6 is a major growth factor for myeloma cells. In advanced disease there is an excess of IL-6 production and raised serum concentrations are associated with plasmablastic proliferative activity and short survival. When a mouse monoclonal antibody to IL-6 was given to ten patients with myeloma there was evidence of a biological effect, with decreased C-reactive protein, lower IL-6 production, and resolution of low-grade fever in six patients. However, host response to the murine antibody complicated this study.

Implications for prevention and treatment

TNF blockade

Two TNF antagonists (etanercept, Enbrel [Immunex]) and infliximab, Remicade [Centocor]) have been licensed for clinical trial in the treatment of rheumatoid arthritis and Crohn’s disease, with over 70 000 patients now treated. There is clinical evidence for five actions of the anti-TNF antibody in rheumatoid arthritis joint tissue—namely, inhibition of cytokine/chemokine production, reduced angiogenesis, prevention of leucocyte infiltration, inhibition of matrix metalloproteases, and improvement of bone marrow function—and all these actions would be useful in a biological therapy for cancer.

Apart from the data on TNF and cancer growth and spread, some experiments suggest a role for TNF in the development of cancer cachexia, and this might be another benefit of TNF antagonist therapy. Thalidomide inhibits the processing of mRNA for TNF (and VEGF), and continuous low-dose thalidomide has shown activity in patients with advanced myeloma. Several clinical studies are underway using etanercept to assess the role of anti-TNF therapy as a single agent or in combination with other therapies in malignancy. The role of etanercept in ameliorating the adverse effects of other cancer therapies is also being evaluated. There are also ongoing and planned clinical trials with infliximab. As with other "biological" approaches to cancer treatment, anti-TNF therapy may be optimal in an adjuvant setting with minimal disease. Careful recording of the incidence of malignant disease in patients receiving TNF antagonists for inflammatory disease could give some indication of the potential of these agents in the chemoprevention of cancer.

Chemokine antagonism

The chemokine system is part of the strategy used by tumours to recruit pro-tumour inflammatory responses and to seed at distinct anatomical sites. Chemokine receptors belong to a family of receptors (7 transmembrane G-protein coupled receptors) which is already a target of pharmacological interest. Tumours driven by chemokines and those where chemokines are implicated in metastasis (eg, seeding to lymph nodes) may be an appropriate target for chemokine antagonists now under development. This approach is supported by data from mouse experiments.


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