Inflammation and cancer: tumor initiation, progression and metastasis, and Chinese botanical medicines

Daniel Weber\textsuperscript{1, 2, 3}, Janelle M Wheat\textsuperscript{1, 4, 5}, Geoffrey M Currie\textsuperscript{1, 4, 5}
1. Faculty of Science, Charles Sturt University, Wagga Wagga, NSW 2678, Australia
2. Panaxea Medicine, Sydney, NSW 2015, Australia
3. World Federation of Chinese Medicine Societies, Beijing 100101, China
4. Centre for Research in Complex Systems, Charles Sturt University, Wagga Wagga, NSW 2678, Australia
5. Australian School of Advanced Medicine, Macquarie University, Sydney, NSW 2109, Australia

Abstract: Both historically and contemporarily, cancer is seen as an inflammatory process. Evidence has emerged in the last two decades that at the molecular level most chronic diseases, including cancer, are caused by a dysregulated inflammatory response. The identification of transcription factors such as nuclear factor-kappa B and signal transducer and activator of transcription 3 and their gene products such as tumor necrosis factor, interleukin-1, interleukin-6, chemokines, cyclooxygenase-2, and vascular endothelial growth factor, adhesion molecules and others has provided the molecular basis for the role of inflammation in cancer. Tumor initiation, its progression and metastasis and the failure of immune suppression of tumors all can be attributed in part to chronic and systemic inflammation. Chinese herbs have a long history in both treatment of cancer and suppression of inflammation. This paper looks at recent research on cancer and inflammation and Chinese herbs and compounds, which can be used in the treatment of cancer.

Keywords: neoplasms; inflammation; chemokine; cytokines; drugs; Chinese herbal

1 Introduction

In 1863, Rudolf Virchow (1821-1902) hypothesised that the origin of cancer was at sites of chronic inflammation. His hypothesis was that some classes of irritants, together with the tissue injury and the ensuing inflammation caused enhanced cell proliferation\textsuperscript{[1]}. In China, the 7th century CE, Chao Yuan-fang (550-630) reported, while working as an imperial physician: “Qi and water stagnation stays in the body, clustering as nodules (‘lumps’). Toxic heat fights healthy qi in the body, stagnating and steaming the body, causing hypochondriac pain and fullness.” This clinical observation in Zhu Bing Yuan Hou Lun (Treatise on Causes and Symptoms of Diseases, Vol. 12) was one of the first to mention toxic heat in regard to tumors (swellings) (China Culture n.d.). The term “toxic” in this context means all the things that may do severe harm to the body, externally or internally.

In more recent times, Kevin Chan\textsuperscript{[2]} reports that the source of toxic heat is tumor necrosis factor-alpha (TNF-\(
\alpha\)), interleukin-6 (IL-6) and other inflammatory cytokines, combined with blood stasis, hypoxia and a weakened cellular (helper T cells 1, Th1) immunity. The concept of toxic heat in traditional Chinese medicine (TCM) is central to cancer treatments. From a more orthodox position, Dalgleish and O’Byrne\textsuperscript{[3]} state, “It is recognised that cancer is a series of stochastic events involving permanent activation of oncogene pathways and deletion of tumor suppressor genes, and in the face of chronic inflammation, immune induction does not occur and the mutated cell survives to divide.”

TCM lists a number of heat-clearing herbs in its pharmacopoeia. Contemporary researches on traditional herbs have demonstrated efficacy in clearing toxic heat to stop angiogenesis, induce apoptosis and limit metastasis.

2 Chronic inflammation and cancer

The links between inflammation and cancer pathogenesis are well documented\textsuperscript{[4, 5]},

- Many inflammatory conditions predispose
the cell to cancer.

- Cancers arise at sites of chronic inflammation.
- Functional polymorphisms of cytokine genes are associated with cancer susceptibility and severity.
- Distinct populations of inflammatory cells are found in many cancers.
- Extent of tumor-associated macrophage infiltrates correlates with prognosis.
- Inflammatory cytokines are detected in many cancers; high levels are associated with poor prognosis.
- Chemokines are detected in many cancers; they are associated with inflammatory infiltration and cell motility.
- Deletion of cytokines and chemokines protects against carcinogens, experimental metastasis and lympho-proliferative syndrome.
- Inflammatory cytokines are implicated in the action of non-genotoxic liver cancer.
- Inflammatory cytokine TNF is directly transforming in vitro.

The concept of inflammation in tumor initiation, progression and metastases is both contemporary and ancient.

Infection and chronic inflammation contribute to about 1 in 4 of all cancer cases\(^6\). Mediators of the inflammatory response (e.g., cytokines, free radicals, prostaglandins and growth factors) can induce genetic and epigenetic changes including point mutations in tumor suppressor genes, DNA methylation and posttranslational modifications, and this causes alterations in critical pathways responsible for maintaining the normal cellular homeostasis and leading to the development and progression of cancer\(^7\). Chronic inflammation induced by biological, chemical, and physical factors has been associated with increased risk of human cancer. Inflammation activates a variety of inflammatory cells, which induce and activate several oxidant-generating enzymes; they damage DNA, RNA, lipids, and proteins\(^8\). Furthermore, even tumors that are not epidemiologically linked to pathogens are characterised by the presence of an inflammatory component in their microenvironment. Hallmarks of cancer-associated inflammation include the presence of infiltrating leukocytes, cytokines, chemokines, growth factors, lipid messengers, and matrix-degrading enzymes\(^9\).

A substantial body of evidence supports the supposition that chronic inflammation can predispose an individual to cancer, as demonstrated by the association between chronic inflammatory bowel diseases and the increased risk of colon carcinoma\(^10\). Inflammatory mediators contribute to neoplasia by inducing preneoplastic mutations, adaptive responses, resistance to apoptosis, and environmental changes such as stimulation of angiogenesis\(^11\). Cytokines, free radicals, prostaglandins and growth factors, can induce genetic and epigenetic changes including point mutations in tumor suppressor genes, DNA methylation and posttranslational modifications, causing alterations in critical pathways responsible for maintaining the normal cellular homeostasis and leading to the development and progression of cancer. Inflammatory risk score (IRS) was associated with cancer-specific mortality\(^7\,\,12\).

2.1 Inflammation pathways There are two interrelated pathways that link inflammation and cancer. Firstly, there are genetic events leading to neoplastic transformation, which promote the construction of an inflammatory milieu. Secondly, tumor-infiltrating leukocytes, in particular macrophages, are prime regulators of cancer inflammation. Thus, the intrinsic pathway of inflammation driven by tumor cells, and the extrinsic pathway with tumor-infiltrating leukocytes both contribute to tumor progression\(^13\).

2.2 Tumor microenvironment The communication between the tumor cells and the surrounding cells — the microenvironment, helps drive the process of tumor progression. Two of the key hallmarks of cancer are dependent on the surrounding microenvironment. Angiogenesis creates the blood vessels and metastasis gives the tumor the ability to invade. If a cancer cell did not have these special characteristics, it would not be able to continue to grow\(^113\). Successive changes occurring at the tumor site during tumor progression resemble chronic inflammation. This chronic inflammatory reaction seems to be largely orchestrated by the tumor and it appears to promote tumor survival\(^114\). Aside from inflammation, hypoxia in the tumor microenvironment also contributes to the growth and spread of tumors\(^115\).

2.3 Cytokines Tumor development and growth are driven in many cases by inflammatory cells, which produce cytokines that subsequently stimulate the growth and survival of malignant cells\(^116\). The identification of such cytokines and their mechanisms of action are of importance because inhibition of protumorigenic cytokine action may offer therapeutic and preventive avenues of treatment\(^117\). The inflammatory conditions in some tissues increase the risk of cancer and cytokines and chemokines are components of an intensive dialogue promoting angiogenesis, metastasis, and subversion of adaptive immunity and changing response to hormones and to chemotherapeutic agents\(^118\).

IL-6 is a multifunctional cytokine that is critical to inflammatory, immunoregulatory, and hemopoietic responses\(^119\). Two recent manuscripts\(^20,\,21\) outline the importance of autocrine IL-6 in lung and breast cancers, implicating IL-6 as an important activator of oncogenic signal transducer and activator of transcription 3 (STAT3) in lung adenocarcinomas and of Jagged-1/Notch signalling
breast tumor mammospheres. IL-6 is able to promote tumor growth by upregulating antiapoptotic and angiogenic proteins in tumor cells. In murine models it has been demonstrated that antibodies against IL-6 diminish tumor growth. In a study by Salgado et al., it was reported that there is a prognostic significance for serum IL-6 (sIL-6) measured at the time of diagnosis of metastasis. High serum levels of IL-6 correlate with poorer outcomes in breast cancer patients.

Recombinant IL-1 (rIL-1) and rIL-6 both stimulate the liver synthesis of C-reactive protein (CRP) and serum amyloid A (SAA), however, monospecific anti-rIL-6 antibodies reduce the stimulatory effect of rIL-1 on the synthesis of these proteins. These findings suggest that IL-6 plays a key role in the stimulation of synthesis of SAA and CRP by the human liver cells. Subjects with elevation of both IL-6 and CRP levels were 2.6 times more likely to die than those with low levels of both measurements.

IL-6 is a major mediator of inflammation and activator of STAT3 and serves to block apoptosis in cells during the inflammatory process, keeping them alive in very toxic environments. Unfortunately, these same pathways also serve to maintain cells progressing towards neoplastic growth, protecting them from cellular apoptotic deletion and chemotherapeutic drugs. Persistently activated STAT3 increases tumor cell proliferation, survival and invasion while suppressing antitumor immunity.

2.4 Inflammatory markers SAA and CRP may be important prognostic factors for breast cancer. In a multivariate analysis, CRP showed significant associations with waist circumference, body mass index (BMI), age, history of heart failure, tamoxifen use, and vitamin E supplementation. Elevated SAA and CRP were associated with reduced overall survival, regardless of adjustment for age, tumor stage, race, and BMI, and women in the highest third of CRP levels had a two-fold increased risk of death. Inflammatory mediators, which are demonstrated by these inflammatory markers, contribute to neoplasia by inducing proneoplastic mutations, adaptive responses, resistance to apoptosis, and environmental changes such as stimulation of angiogenesis. All these changes confer a survival advantage to a susceptible cancer cell.

Cyclooxygenase-2 (COX-2) is a key enzyme that catalyzes the biosynthesis of prostaglandins from arachidonic acid and plays a critical role in some pathologies including inflammation, neurodegenerative diseases and cancer. The expression of COX-2 is upregulated in many cancers. Furthermore, the product of COX-2 — prostaglandin H2 (PGH2) is converted by prostaglandin E2 (PGE2) synthase into PGE2, which in turn can stimulate cancer progression. COX-2 is an inducible, immediate-early gene, and its role has been related to inflammation, reproduction and carcinogenesis and its expression is elevated in a variety of human malignacies and in their precursor lesions. Furthermore, genetic deletion or pharmacological inhibition of COX-2 suppresses tumor growth.

Elevated COX-2 expression is associated with poor prognosis in adenocarcinomas of the digestive tract and the breast.

The presence of human epidermal growth factor receptor 2 (HER2/neu gene amplification is prognostically and therapeutically significant for patients with breast cancer. Lobular carcinomas are less likely than ductal carcinomas to have HER2/neu amplification while amplification is less frequent in Scarff-Bloom-Richardson (SBR) grade 1 ductal carcinomas than in grades 2 and 3. Metastatic carcinomas frequently displayed HER2/neu amplification (30%). HER2 is an indication of inflammation and is associated with elevated COX-2.

2.5 Cancer stem cells Observations have led to the hypothesis that only a few cancer cells are actually tumorigenic and that the tumorigenic cells could be considered as cancer stem cells. The CXCR chemokine receptor 1 (CXCR1) is found on the cancer stem cells and triggers growth of stem cells in response to inflammation and tissue damage. Investigation has suggested an important link between inflammation, tissue damage and breast cancer, which may be mediated by cancer stem cells. Furthermore, anti-inflammatory drugs may provide a means of blocking these receptors, thereby targeting breast cancer stem cells. Evidence shows that many pathways that are classically associated with cancer may also regulate normal stem cell development.

Clearly, inflammation due to immune dysregulation plays a critical role in tumor initiation, progression and metastases. There is a need for pharmaceutical agents to block receptors sites, and to diminish production of inflammatory cytokines and transcription activators. Fortunately, there are a significant number of botanicals and their compounds that have already been shown to reduce inflammatory markers, reduce tumor size, reduce angiogenesis and induce apoptosis.

3 Herbs and compound interventions

Chinese herbs have been used in the treatment of cancer since the time of Huangdi Neijing (Yellow Emperor’s Canon of Internal Medicine; Plain Conversation) written in the final centuries B.C. E and today PubMed lists over 1,000 peer-reviewed articles on cancer and Chinese herbs (accessed June 2010). Traditional Chinese herbal medicines that for centuries have been used in disease prevention and treatment are finding use as alternatives to Western cancer therapies.

Sumu (Lignum Sappan, 赤木) was first mentioned in Xin Xiu Ben Cao (Newly Revised Materia
Medica) by Su Jing in 657-659 CE and its action is said to “activate blood”, “open channels and relieve pain”. The aqueous extract of Lignum Sappan (AELS) may markedly decrease the levels of TNF and IL-6[42], and it has also been shown it can kill cancer cell lines of HL-60, K562, L929 and Yac-1 at the concentration of 2 μL/mL in vitro. The survival time of mice treated with AELS is increased by 185% (P < 0.01) by ip 0.2 mL/mouse×7 d[41].

Use of Baitowong (Radix Pulsatillae, 白头翁) goes back to the Shennon Ben Cao Jing (Shennong’s Classic of Materia Medica, 2nd century CE) and is said to “clear heat” and “eliminate toxin”. It strongly inhibits the secretion of TNF, IL-1 and IL-6 from Kupfer cells stimulated by lipopolysaccharide (LPS)[42]. Xian and Qian[43] state that Baitowong is an “innovative antitumor drug of high effect and low toxin”. Triferpenoid saponins isolated from Baitowong appear to be an important promoiety for the enhancement of anticancer activity of their aglycones[46].

Machixian (Herba Portulacae Oleracea, 马齿苋) may act on adipose cells damaged by the high-lipid serum to increase cell viability and lower the levels of TNF-α and IL-6 secreted by adipose cells[43]. Its use is first mentioned in Xin Xiu Ben Cao and is said to “clear heat” and “eliminate toxin” and also “cool blood” and stop bleeding.

Supernatant TNF-α and IL-6 decrease significantly after Shanglu (Radix Phytolaccae, 商陆) decoction culture[42] while Yehuhua (Flores Dendranthematitis Indici, 野菊花) has an inhibitory effect on sIL-2R, IL-6 and TNF-α[47]. Yehuhua “clears heat and eliminates toxins” and Shanglu is said to “eliminate water accumulation” and were both first mentioned in Shennon Ben Cao Jing.

The serum levels of TNF-α, IL-6 and IL-10 decrease following baicalin treatment[48]. The flavonoid baicalin, isolated from the dried root of Huangqin (Radix Scutellariae Baicalensis, 黄芩) is widely used in traditional Chinese herbal medicine for its anti-inflammatory, antipyretic and anti-hypersensitivity effects. The in vitro effects of baicalin on the growth, viability, and induction of apoptosis in several human prostate cancer cell lines, including DU145, PC-3, LNCaP and CA-HPV-10 indicate that baicalin has direct antitumor effects on human prostate cancer cells[49]. Franke et al.[50] combined baicalin with scutellarin (also from Huangqin), and two extracts purified from Danshen (Radix Salviae Miltiorrhizae, 丹参) (SM-470, circulatory stimulant) and Chaye (Camelliae sinensis, 茶叶) (Cam-300, antipyretic), and examined their antiproliferation effects on human breast cancer cell lines MCF-7 and T-47D. All four compounds inhibited MCF-7 and T-47D cell proliferation, SM-470, Cam-300, scutellarin and baicalin inhibited the proliferation of human breast cancer cells as well as CAL-27 and FaDu cells. Furthermore, baicalein significantly inhibits LPS-induced PGE2 production and COX-2 enzyme activity and inhibits inflammatory reaction[50]. Scutellarin may elicit its therapeutic effect by inhibiting the production of serum TNF-α, IL-6 and IL-8 while decreasing the expressions of B-cell lymphoma-2 (Bcl-2) and intercellular adhesion molecule-1 (ICAM-1), and enhancing the activity of natural killer cells[51].

Qianhu (Radix Peucedani, 前胡), which literally means “before barbarian” was first mentioned in Leigong Pao Zhi Lun (Lei’s Treatise on Processing of Drugs) by Lei Xiao in 500 CE. It may reduce the extent of infarct scope, the excitable neural virulence and the depolarization around the infarct spot after cerebral ischemia, prevent and treat ischemic apoplexy, and this may relate to calcium antagonism and prevention of the cytokines such as IL-6 and IL-8[52]. Its therapeutic action is said to “redirect qi downwards” and “dispel phlegm”. The phenols, flavonoids and coumarins in Qianhu have an important anti-oxidant effect and the pyranocoumarins extract could be a potential multidrug resistance (MDR) reversing agent in cancer cells[53].

Cryptotanshionine (CTSO) is a major constituent of tanshinones, which are extracted from the medicinal herb Danshen and have well-documented anti-oxidative and anti-inflammatory effects. CTSO can reduce PGE2 synthesis and reactive oxygen species generation catalysed by COX-2, without influencing COX-1, and is directed against enzymatic activity of COX-2[54].

The anti-inflammatory properties of neoandrographolide might result from the inhibition of inducible nitric oxide synthase (iNOS) and COX-2 expression through inhibiting p38 mitogen-activated protein kinases (MAPKs) activation[55]. Denglongguo (Physalis peruviana, 灯笼果) is widely used in folk medicine and can inhibit LPS-induced NO release and PGE2 formation and COX-2 expression in a dose-dependent pattern[56]. Dingxiang (Flos Syzygii Aromatici, 丁香) extract has been reported to reduce tumor size and neoangiogenesis in a xenograft model of human ductal carcinoma in situ (DCIS). Aqueous leaf extract Luole (Herba Ocimi Basilici, 罗勒) inhibits proliferation, migration, anchorage independent growth, 3D growth, morphogenesis and induction of COX-2 protein in breast cancer cells[57].

STAT3 is constitutively activated in most human solid tumors and is involved in the proliferation, angiogenesis, immune evasion, and anti-apoptosis of cancer cells and CTSO was identified as a potent STAT3 inhibitor. The inhibition of STAT3 phosphorylation is caused by a Janus kinase 2 (JAK2)-independent mechanism, in which suppression of JAK2 phosphorylation was a secondary effect of CTSO treatment[58]. The constitutive activation of STAT3 is frequently detected in human breast cancer cell lines as well as clinical breast cancer
specimens and may play an important role in the oncogenesis of breast carcinoma. Activated STAT3 may participate in oncogenesis by stimulating cell proliferation, promoting tumor angiogenesis, and resisting apoptosis\(^{[59]}\).

Indirubin derivatives have been found to block STAT3 signalling in human breast cancer, which results in apoptosis\(^{[60,61]}\).

Lastly, the level of SAA was decreased in mice after treatment of triptolide extracted from Leigongteng (Radix et Rhizoma Tripterygii, 乳公藤) and this related to lower production of TNF-\(\alpha\), interferon-\(\gamma\) and IL-4\(^{[62]}\).

There are also a number of more obscure herbs that have been reported to reduce C-RP and SAA. Further evaluation of these herbs is recommended\(^{[63]}\):

- **Fructus Vaccinii Vitis-idaeae** — Yuejuyu (越橘果)
- **Quercus Pedunculata** — Lishupu (栋树皮)
- **Rhizoma Acori Tatarinowii** — Shichangpu (石菖蒲)
- **Herba Origani Vulgaris** — Niuzhi (牛至) or Tuxiangru (土香薷) or Baihuayinchen (白花茵陈)
- **Semen Plantaginis** — Cheqianzi (赤前子)

4 Conclusion

Although the role of inflammation in promoting carcinogenesis has generated much interest in the last 10 to 15 years, the Greek physician Claudius Galenus already observed almost 2 000 years ago some similarities among cancer and inflammation. Inflammation promotes carcinogenesis as well as angiogenesis and metastasis and a recent discovery of an interaction between microRNAs and innate immunity during inflammation has further strengthened the association between inflammation and cancer\(^{[21]}\). Researches on the molecular mechanisms that link inflammation and cancer have significantly increased in recent years. Bolhath and Greten\(^{[64]}\) analysed genetic evidence indicating that the transcription factors nuclear factor-kappa B (NF-\(\kappa\)B) and STAT3 have a central role in this context by regulating distinct functions in cancer cells and surrounding non-tumorigenic cells.

Herbs and compounds in combination can reduce "toxic heat" or inflammation by downregulating cytokine expression, and transcription factors NF-\(\kappa\)B and STAT3 to induce apoptotic activities in tumor cells. While many of these herbs and compounds have some evidence of efficacy against chronic inflammation, further studies are needed to evaluate their effects on tumors.

REFERENCES


Daniel Weber\(1, 2, 3\), Janelle M Wheat\(4, 5\), Geoffrey M Currie\(4, 5\)
1. Faculty of Science, Charles Sturt University, Wagga Wagga, NSW 2678, Australia
2. Panacea Medicine, PO BOX 289 Alexandria, Sydney, NSW 2015, Australia
3. 世界中医药学会联合会，北京 100101
4. Centre for Research in Complex Systems, Charles Sturt University, Wagga Wagga, NSW 2678, Australia
5. Australian School of Advanced Medicine, Macquarie University, Sydney, NSW 2109, Australia

摘要: 古往今来, 癌症都被视为一个炎症过程。过去 20 多年的研究已经从分子水平证实大部分慢性疾病包括癌症都是由炎症反应失调所引起的。转录因子如核因子-κB 与信号转导和转录激活因子 3 以及它们的基因产物如肿瘤坏死因子、白细胞介素 1、白细胞介素 6、趋化因子、环氧合酶 2、血管内皮生长因子、黏附分子等的发现为阐释炎症在癌症过程中的作用提供了分子基础。肿瘤的发生、发展和转移以及机体无法对其产生免疫抑制都可以部分地用慢性全身炎症反应来解释。中药用于治疗癌症及炎症具有悠久的历史。本文介绍了近期有关癌症与炎症的研究进展以及用于治疗癌症的中药和中药复方。

关键词: 肿瘤；炎症；炎症趋化因子类；细胞因子类；中草药