

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

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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 NF- κ B, AP-1 and STAT3 and their gene products such as tumour necrosis factor, interleukin-1 (IL-1), interleukin-6 (IL-6), chemokines, cyclooxygenase-2 (COX-2), and vascular endothelial growth factor (VEGF), adhesion molecules and others have 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: Cancer, Inflammation, Inflammatory markers, Cytokines, Chinese herbs (English words, which indicate a Chinese energetic property are capitalized. Chinese terms are in inverted commas.)

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^[1]. In China in 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 tumours (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^[2] reports that the source of toxic heat is tumour necrosis factor-alpha (TNF- α), 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, Dalglish and O'Byrne^[3] state: "It is recognised that cancer is a series of stochastic events involving permanent activation of oncogene pathways and deletion of tumour 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 pharmacopeia. Contemporary research 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^[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 tumour-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 infiltrate 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 tumour necrosis factor in directly transforming *in vitro*.

The concept of inflammation in tumour 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 tumour suppressor genes, DNA methylation and post-translational 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 tumours 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 pro-neoplastic 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 tumour suppressor genes, DNA methylation and post-translational 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, tumour-infiltrating leukocytes, in particular macrophages, are prime regulators of cancer inflammation. Thus, the intrinsic pathway of inflammation, driven by tumour cells and the extrinsic pathway with tumour-infiltrating leukocytes both contribute to tumour progression^[9].

2.2 Tumour microenvironment The communication between the tumour cells and the surrounding cells — the microenvironment, helps drive the process of tumour progression. Two of the key hallmarks of cancer are dependent on the surrounding microenvironment.

Angiogenesis creates the blood vessels and metastasis give the tumour the ability to invade. If a cancer cell did not have these special characteristics, it would not be able to continue to grow^[13]. Successive changes occurring at the tumour site during tumour progression resemble chronic inflammation. This chronic inflammatory reaction seems to be largely orchestrated by the tumour and it appears to promote tumour survival^[14]. Aside from inflammation, hypoxia in the tumour microenvironment also contributes to the growth and spread of tumours^[15].

2.3 Cytokines Tumour development and growth are driven in many cases by inflammatory cells, which produce cytokines that subsequently stimulate the growth and survival of malignant cells^[16]. 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^[17]. 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^[18].

IL-6 is a multifunctional cytokine that is critical to inflammatory, immunoregulatory, and hemopoietic responses^[19]. 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 in breast tumour mammospheres^[16]. IL-6 is able to promote tumour growth by upregulating antiapoptotic and angiogenic proteins in tumour cells. In murine models it has been demonstrated that antibodies against IL-6 diminish tumour growth^[22]. In a study by Salgado *et al*^[23], 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^[24].

Recombinant IL (rIL) -1 and rIL-6 both stimulate the liver synthesis of C-reactive protein (C-RP) 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 C-RP by the human liver cells^[25]. Elevation of both IL-6 and C-RP levels were 2.6 times more likely to die than those with low levels of both measurements^[26].

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^[27]. Persistently activated STAT3 increases tumour cell proliferation, survival and invasion while suppressing anti-tumour immunity^[28].

2.4 Inflammatory markers SAA & C-RP may be an important prognostic factor for breast cancer. In a multivariate analysis, C-RP showed significant associations with waist circumference, body mass index (BMI), age, history of heart failure, Tamoxifen use, and vitamin E supplementation^[29]. Elevated SAA and C-RP were associated with reduced overall survival, regardless of adjustment for age, tumour stage, race, and BMI^[30] and women in the highest third of C-RP levels had a two-fold increased risk of death^[30]. 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^[31].

Cyclooxygenase-2 (COX-2) is a key enzyme that catalyses 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^[32]. 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 malignancies and in their precursor lesions. Furthermore, genetic deletion or pharmacological inhibition of COX-2 suppresses tumour growth.

Elevated COX-2 expression is associated with poor prognosis in adenocarcinomas of the digestive tract and the breast^[33].

The presence of HER2/neu gene amplification is prognostically and therapeutically significant for patients with breast cancer. Lobular carcinomas are less likely than ductal carcinomas to have human epidermal growth factor receptor 2 (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%)^[34]. 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^[35]. The CXC 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, antiinflammatory drugs may provide a means of blocking these receptors, thereby targeting breast cancer stem cells^[36]. Evidence shows that many pathways that are classically associated with cancer may also regulate normal stem cell development^[37].

Clearly, inflammation due to immune dysregulation plays a critical role in tumour 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 tumour 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 Interior Medicine: Plain Conversation*) written in the final centuries B.C.E^[38] 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^[39].

Sumu (*Lignum Sappan*, 苏木) was first mentioned in *Xin Xiu Ben Cao* (*Newly Revised Materia Medica*) by Su Jing in 657-659 CE and its action are said to “activate blood”, “open channels and relieve pain”. The aqueous extract of *Lignum Sappan* (AELS) may markedly decrease the level of TNF and IL-6^[40], it has also been shown it can kill cancer cell lines of HL-60, K562, L929 and Yac-1 at the concentration of 2 μ L/mL *in vitro*. The survival time of mice treated with AELS is increased by 185% (P0.01) by ip 0.2mL/mouse \times 7 d^[41].

Baitouwong's (*Radix Pulsatillae*, 白头翁) use goes back to the *Shennong Ben Cao Jing* (*Shennong's Classic of Materia Medica*, 2nd CE) and is said to “clear heat” and “eliminate toxin”. It strongly inhibits the secretion of TNF, IL-1 and IL-6 from Kupffer cells stimulated by lipopolysaccharide (LPS)^[42] Xian and Qian^[43] state that Baitouwong is an “innovative antitumour drug of high effect and low toxin”. Triterpenoid saponins isolated from Baitouwong appear to be an important moiety for the enhancement of anticancer activity of their aglycones^[44].

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 cell^[45]. 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^[46] while Yejuhua (*Flos Dendranthematis Indici*, 野菊花) has an inhibitory effect on sIL-2R, IL-6 and TNF- α ^[47]. Yejuhua “clears heat and eliminates toxins” and s Shanglu is said to “eliminate water accumulation” and were both first mentioned in *Shennong 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 antiinflammatory, antipyretic and antihypersensitivity 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 antitumour effects on human prostate cancer cells^[49]. Franek *et al*^[39] 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 anti-proliferation effects on the 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, baicalin significantly inhibited 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 expression of B-cell lymphoma 2 (Bcl-2) and intercellular adhesion molecule-1 (ICAM-1), and enhancing the activity of nature kill cell^[51].

Qianhu (*Radix Peucedani*, 前胡), which literally means “before barbarian” was first mentioned in *Lei Gong Pao Zhi Lun* 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, 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 antioxidant effect and the pyranocoumarins extract could be a potential multidrug resistance (MDR) reversing agent in cancer cells^[53].

Cryptotanshinone (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 antiinflammatory 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 tumour size and neoangiogenesis in a xenograft model of human ductal carcinoma in situ (DCIS). Aqueous leaf extract 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 tumours 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; with 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 tumour 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 serum amyloid A was decreased in mice after triptolide treatment (extracted from Leigongteng (*Radix et Rhizoma Tripterygii*, 雷公藤)) and this related to lower production of TNF- α , interferon- γ 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:

- Yuejuguo (*Fructus Vaccinii Vitis — idaeae*, 越橘)
- Lishupi (*Quercus Pedunculata*, 栎树皮)
- Shichangpu (*Rhizoma Acori Tatarinowii*, 石菖蒲)
- Niuzhi (*Herba Origani Vulgaris*, 牛至 or Tuxiangru, 土香薷 or Baihuayinchen, 白花茵)
- Cheqianzi (*Semen Plantaginis*, 车前子)^[63]

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 similarity 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^[7]. Research on the molecular mechanisms that link inflammation and cancer have significantly increased in recent years. Bollrath and Greten^[64] analyse genetic evidence indicating that the transcription factors NF- κ B and STAT3 have a central role in this context by regulating distinct functions in cancer cells and surrounding non-tumourigenic cells.

Herbs and compounds in combination can reduce “toxic heat” or inflammation by downregulating cytokine expression, and transcription factors NF- κ B and STAT3 to induce apoptotic activities in tumour cells. While many of these herbs and compounds have some evidence of efficacy against chronic inflammation, further studies are needed to evaluate their effect on tumours.

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