

INTEGRATIVE ONCOLOGY NOTES/ number 1

📄 DANIEL WEBER PhD MSc

2009-11-14

Inflammation, Cell Cycle and Cancer; A Stochastic Event



The functional relationship between inflammation and cancer is not new. In 1863, Virchow hypothesized that the origin of cancer was at sites of chronic inflammation, in part based on his hypothesis that some classes of irritants, together with the tissue injury and ensuing inflammation they cause, enhance cell proliferation. Although it is now clear that proliferation of cells alone does not cause cancer, sustained cell proliferation in an environment rich in inflammatory cells, growth factors, activated stroma, and DNA-damage-promoting agents, certainly potentiates and/or promotes neoplastic risk (Coussens & Werb 2002).

This has been established by several sources, cancer can be promoted and/or exacerbated by inflammation and infections (Tan & Coussens 2007; Balkwill 2006; Dalglish & O'Byrne 2006). Indeed, chronic inflammation orchestrates a tumour-supporting microenvironment that is an indispensable participant in the neoplastic process. The mechanisms that link infection, innate immunity, inflammation, and cancer are essential to tumour progression and in addition, soluble mediators produced by cancer cells recruit and activate inflammatory cells (Lin and Karin 2007).

When it comes to cell division, cancer cells break just about all the rules. Cancer is a disease that originates in one's own cells. A change in the DNA causes an oncogene to be switched on. This leads to uncontrollable cell reproduction by mitosis (Pollack et al 1999). The development of cancer can

be viewed as an evolutionary process. Cells are constantly subject to mutations in their DNA, which are usually detrimental to the cell. But occasionally these changes produce cells that can escape the normal constraints and flourish as pathological tumours. There is also a growing recognition that changes in the microenvironment of cancer cells can promote their proliferation (Bissell & LaBarge 2005). Moreover, genomic instability caused by faulty cell division or defective DNA repair may increase the rate of potentially tumourigenic mutations and so contribute to cancer evolution (Marte 2004).

Cells also have tumour suppressor activities, which cause the cell to enter into quiescence. p53 gene, located human chromosome 17, is a gene with tumour suppressor activities. This protein contains 393 amino acids and a single amino acid substitution can lead to loss of function of the gene. Mutations at amino acids 175, 248, and 273 can lead to loss of function and changes at 273 (13%) are the most common (McBride et al 1986). These all act as recessive mutations. Dominant gain-of-function mutations have also been found that lead to uncontrolled cell division. Because these mutations can be expressed in heterozygous conditions, they are often associated with cancers. This genetic function of this gene is to prevent cell division of cells with damaged DNA (Lengauer et al 1998). Damaged DNA could contain genetic changes that promote uncontrolled cell growth. Therefore, preventing cell division until damaged DNA is repaired is one mechanism of preventing the onset of cancer (Murakami et al 1991). About 50% of human cancers can be associated with a p53 mutation including cancers of the bladder, breast, cervix, colon, lung, liver, prostate, and skin. p53 related cancers are also more aggressive and have a higher degree of fatalities (Levine 1998).

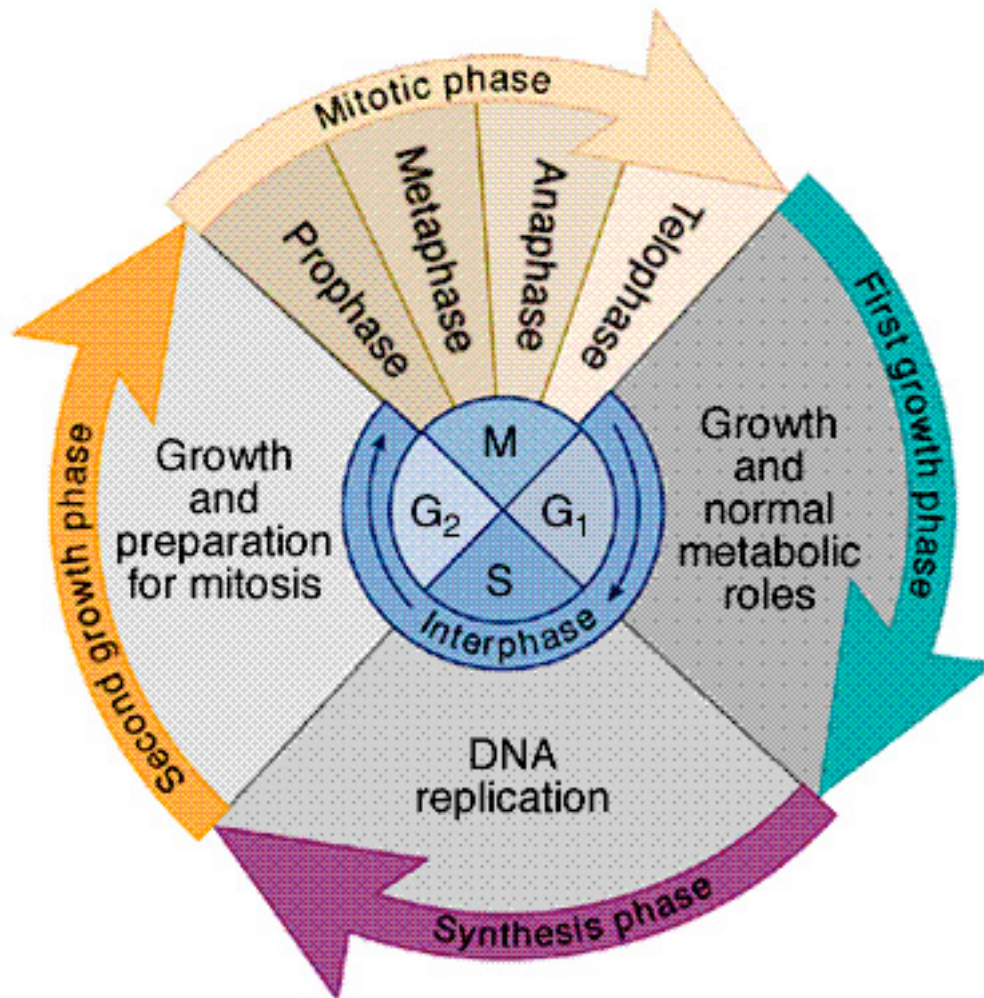
These two factors, uncontrolled growth and division, and a down-regulation of tumour suppressor function may be the first step cancer initiation. Clearly both factors must be present to turn a single aberrant cell into a tumour. Several factors seem to control this process; chronic inflammation, which includes down-regulation of cell mediated immunity and a corresponding up-regulation of humoral immunity. Secondly, the cellular inflammation involves changes in proto-oncogene to oncogene through growth factors acting upon various Kinases. A proto-oncogene is a gene whose protein product has the capacity to induce cellular transformation given it sustains some genetic insult. An oncogene is a gene that has sustained some genetic damage and, therefore, produces a protein capable of cellular transformation.

The process of activation of proto-oncogenes to oncogenes can include retroviral transduction or retroviral integration, point mutations, insertion mutations, gene amplification, chromosomal translocation and/or protein-protein interactions all of which involve growth factors initiated by cellular inflammation.

The initial flurry (1976–1985) in the discovery of oncogenes — mutated genes that allow unregulated cell growth — yielded a large number of proteins that are involved in cell signalling (Varmus 1987; Blume-Jensen & Hunter 2001). Signalling pathways begin with extracellular proteins — ligands, — which bind to specific cell-surface receptors that dimerise or oligomerise at the cell surface to begin the intracellular phase of signalling.

The cell cycle consists of four distinct phases: G1 phase, S phase (synthesis), G2 phase (collectively known as interphase) and M phase (mitosis). M phase is itself composed of two tightly coupled processes: mitosis, in which the cell's chromosomes are divided between the two daughter cells, and cytokinesis, in which the cell's cytoplasm divides forming distinct cells. Activation of each phase is dependent on the proper progression and completion of the previous one. Cells that have temporarily or reversibly stopped dividing are said to have entered a state of quiescence called G0 phase (Smith & Martin 1973).

Passage through the cell cycle requires the successive activation of different cyclin-dependent protein kinases (CDKs). Transient associations with cyclin regulatory subunits, binding of inhibitory polypeptides and reversible phosphorylation reactions, control these enzymes. To promote progression towards DNA replication, CDK/cyclin complexes phosphorylate proteins required for the activation of genes involved in DNA synthesis, as well as components of the DNA replication machinery (Elledge 1996). Subsequently, a different set of CDK/cyclin complexes triggers the phosphorylation of numerous proteins to promote the profound structural reorganisations that accompany the entry of cells into mitosis. At present, much research is focused on elucidating the links between CDK/cyclin complexes and signal transduction pathways controlling cell growth, differentiation and death (Nigg 2005).



During the multistep process of tumourigenesis, cells lose their normal ability to sense and repair DNA damage and to regulate cell cycle progression and apoptosis. In parallel, they acquire abnormal patterns of growth factor signalling, angiogenesis, and invasive growth. While the STATs are not known to contribute directly to cell cycle checkpoint regulation or DNA repair, they contribute to tumourigenesis through their intimate connection to growth factor signalling, apoptosis, and angiogenesis. In addition, because these molecules play key roles in immune responses, defective STAT signalling can favour tumour development by compromising immune surveillance (Bromberg & Darnell 2002).

The intercellular connections that characterise advanced forms of life would not be possible without a mechanism to remove individual cells that are no longer needed, or that function abnormally. Such physiological cell death, in the absence of inflammation, is achieved by apoptosis, a structurally distinct programmed cell death pathway. Defective regulation of programmed cell death may play a part in the aetiology of cancer, AIDS, autoimmune diseases,

and degenerative diseases of the central nervous system (Carson & Ribeiro 1993).

Commensurate with their roles in regulating cytokine-dependent inflammation and immunity, signal transducer and activator of transcription (STAT) proteins are central in determining whether immune responses in the tumour microenvironment promote or inhibit cancer. Persistently activated STAT3 increase tumour cell proliferation, survival and invasion while suppressing anti-tumour immunity (Yu & Jove 2004). The persistent activation of STAT3 also mediates tumour-promoting inflammation. STAT3 has this dual role in tumour inflammation and immunity by promoting pro-oncogenic inflammatory pathways, including nuclear factor- κ B (NF- κ B) and interleukin-6 (IL-6)–GP130–Janus kinase (JAK) pathways, and by opposing STAT1- and NF- κ B-mediated T helper 1 anti-tumour immune responses (Yu et al 2009).

Interleukin-6 [IL-6] is a pro-inflammatory cytokine secreted by T cells and macrophages to stimulate immune response to trauma, especially burns or other tissue damage leading to inflammation and with a well-documented role in cancer. (Rose-John et al 2007) IL-6 is an immune protein in the haematopoietins family and appears to be a growth factor of hybridomas and malignant cells. Its deregulation impacts numerous disease states, including many types of cancer. Consequently, modulating IL-6 may be an innovative therapeutic strategy in several diseases. (Hong et al 2007)

Members of the IL-6 cytokine family are involved in a variety of biological responses, including the immune response, inflammation, haematopoiesis, and oncogenesis by regulating cell growth, survival, and differentiation (Chung et al 1999). The binding of ligand to gp130 activates the JAK/STAT signal transduction pathway, where STAT3 plays a central role in transmitting the signals from the membrane to the nucleus (Hirano et al 2000).

BOTANICAL INTERVENTIONS

Scutellaria baicalensis:

A herbal preparation using *Scutellaria baicalensis* (huang qin, SB) was formulated to effectively protect cancer patients from inflammatory reactions. Although SB, is one of the most widely used herbs in oriental medicine for anti-inflammation, anti-cancer, anti-viral, anti-bacterial and tonifying the

immune response, the underlying mechanism(s) by which these effects are induced remains unclear. SB displays anti-inflammatory effects in a zymosan-induced mouse air-pouch model by reducing the expression of nitric oxide (NO), inducible NOS (iNOS), Cyclooxygenase2 (COX-2), Prostaglandin E2 (PGE2), Nuclear Factor-kappaB (NF-kappaB) and I kappa / B alpha as well as inflammatory cytokines, such as IL-1beta, IL-2, IL-6, IL-12 and TNF-alpha. In a similar manner, SB also reduced the production of nitric oxide, PGE2, IL-1beta, IL-2, IL-6, IL-12 and TNF-alpha. Additionally, SB interfered with the nuclear translocation of NF-kappaB p65 and p50, resulting in NF-kappaB-dependent transcriptional repression. It was further demonstrated that SB attenuated the activity of c-Raf-1/MEK1/2, Erk1/2, p38 and JNK phosphorylation in LPS-treated Raw 264.7 cells. The strong anti-inflammatory properties of SB occur by inhibition of iNOS, COX-2, PGE2, IL-1beta, IL-2, IL-6, IL-12 and TNF-alpha expression (Kim et al 2009).

Pulsatilla chinensis

Bai tou weng (BTW) affected the secretion of TNF, IL-1 and IL-6 from Kupffer cells (KC) stimulated by Lipopolysaccharide (LPS). BTW strongly inhibited the secretion of TNF, IL-1 and IL-6 from KC stimulated by LPS, and the effect increased with time and concentration of the drug. Conclusion: One of the anti-inflammatory mechanisms of BTW may possibly be that it could suppress the secretion of TNF, IL-1 and IL-6 from KC stimulated by LPS (Kun 2004).

Indirubin (Indigo Naturalis)

An Indirubin derivative inhibits STAT3 signalling and induces apoptosis in human cancer cells and was found to display marked antitumour properties and relatively low toxicity in animal model studies (Hoessel et al 1999). Hoessel demonstrated that indirubins inhibit CDKs, resulting in cell cycle arrest and inhibition of tumour cell proliferation. Findings suggest that the E804 fraction blocks Stat3 signalling in breast cancer cells by inhibiting upstream c-Src kinase activity. This result is similar to the finding that PD180970, a selective Src kinase inhibitor, blocks Stat3 activation and induces apoptosis of breast cancer cells (Garcia et al 2001).

STAT3 protein has an important role in oncogenesis and is a promising anticancer target. Indirubin, the active component of a traditional Chinese herbal medicine, has been shown previously to inhibit cyclin-dependent kinases, resulting in cell cycle arrest. Indirubin derivatives block constitutive STAT3 signalling in human breast and prostate cancer cells. In addition, E804

derivative directly inhibits Src kinase activity. Levels of tyrosyl phosphorylation of c-Src are also reduced in cultured cells 30 min after E804 treatment. Tyrosyl phosphorylation of STAT3 known to be phosphorylated by c-Src, was decreased, and constitutive STAT3 DNA binding-activity was suppressed in cells 30 min after E804 treatment. The anti-apoptotic proteins Mcl-1 and Survivin, which are encoded in target genes of Stat3, were down regulated by indirubin derivatives, followed by induction of apoptosis. These results demonstrate that E804 directly blocks the Src-STAT3 signalling pathway, suggesting that the anti-tumour activity of indirubin compounds is at least partially due to inhibition of this pathway (Yu & Jove 2004).

Signal transducer and activator of transcription (STAT) proteins have been shown to play an important role in tumour cell survival and proliferation (Buettner et al 2002; Bromberg et al 1999). One STAT family member, STAT3, is often constitutively activated in many human cancer cells and tumour tissues and has been shown to induce expression of genes involved in cell proliferation and survival (Bromberg & Darnell 2000). Recently, STAT3 has been implicated as a promising target for cancer therapy (Darnell 2002; Turkson & Jove 2000). Tyrosine kinases that phosphorylate STAT3, particularly JAK and Src kinases, also have been investigated as potential targets for cancer treatment (Luo et al 2004; Yu et al 1995).

Rheum palmatum

Flow cytometric analysis of breast cancer cells exposed to Rheum palmatum (da huang) suggested that it arrests cells in the G2/M phase of the cell cycle. Results indicate that many of the herbs used in traditional Chinese medicine for the treatment of cancer have significant growth inhibitory effects on breast cancer cells in vitro (Campbell et al 2002).

Tetrandrine

Tetrandrine (a major component of *Stephania tetrandrae* / fen fang ji), the herbal alkaloid blocks voltage-gated Ca²⁺ channels, intracellular Ca²⁺ pumps and large-conductance Ca²⁺-activated K⁺ (BK) channels. The signalling pathways that underlie tetrandrine-mediated inhibition of tumour cell proliferation and cytotoxicity are the K⁺ channels, which play an important role in the regulation of cell cycle progression, apoptosis and immunoreactions (Wang et al 2004).

Magnolol

Magnolol (Mag), an active constituent isolated from the Chinese herb hou po (*Magnolia officinalis*) has long been used to suppress inflammatory processes. Chronic inflammation is well known to be involved in vascular injuries such as atherosclerosis in which interleukin (IL)-6 may participate. Signal transducer and activator of transcription protein 3 (STAT3), a transcription factor involved in inflammation and the cell cycle, is activated by IL-6 (Alas & Bonavida 2001). The effects of Mag on IL-6-induced STAT3 activation and downstream target gene induction in endothelial cells (ECs) inhibited IL-6-induced Tyr705 and Ser727 phosphorylation in STAT3 without affecting the phosphorylation of JAK1, JAK2, and ERK1/2. Mag pre-treatment of these ECs dose dependently suppressed IL-6-induced promoter activity of intracellular cell adhesion molecule (ICAM)-1 that contains functional IL-6 response elements (IREs). Mag treatment markedly inhibited ICAM-1 expression on the endothelial surface. As a result, reduced monocyte adhesion to IL-6-activated ECs was observed. Furthermore, Mag suppressed IL-6-induced promoter activity of cyclin D1 and monocyte chemotactic protein (MCP)-1 for which STAT3 activation plays a role. Mag inhibits IL-6-induced STAT3 activation and subsequently results in the suppression of downstream target gene expression in ECs (Chen et al 2006).

Paeoniae Radix

Paeoniae Radix (PR) is the root of traditional Chinese Herb named *Paeonia lactiflora*, which is commonly used to treat liver diseases in China for centuries. Several earlier studies have indicated that PR has anticancer growth activities, however the mechanism underlying these activities was unclear and remained to be elucidated. The molecular mechanism of the effect of PR on human hepatoma cell lines, HepG2 and Hep3B show that the water-extract of Paeoniae Radix (PRE) had inhibitory effect on the growth of both HepG2 and Hep3B cell lines. The induction of internucleosomal DNA fragmentation and chromatin condensation appearance, and accumulation of sub-G1 phase of cell cycle profile in PRE treated hepatoma cells evidenced that the cytotoxicity of PRE to the hepatoma cells is through activation of the cell death program, apoptosis. The activation of apoptosis by PRE is independent of the p53 pathway as Hep3B cell is p53-deficient. In addition, the differential gene expression of PRE treated HepG2 was examined by cDNA microarray technology and RT-PCR analysis. The gene expression of BNIP3 was up regulated while ZK1, RAD23B, and HSPD1 were down regulated during early apoptosis of the hepatoma cell mediated by PRE (Lee et al 2002).

Daniel's Comment

Chronic inflammation, from whatever cause; bacterial, viral, oxidative, dietary, autoimmune or environmental factors have a considerable impact on the initiation, progression and metastasis of cancer. Age, obesity and Type II Diabetes, alcohol, smoking, lack of exercise, glycation and methylation are all involved in cancer initiation and are pro-inflammatory in nature.

Most of these herbs here described are defined in Traditional Chinese Medicine (TCM) as cold and bitter, dispersing and act by suppressing chronic inflammation. Bai shao is the exception in this list and it acts by up-regulating p53 tumour suppressor gene as does *Astragalus membranaceus* (huang qi) and *Ganoderma lucidum* (ling zhi), both cell mediated immune up-regulators. The uses of botanicals in TCM often involve the dual activation of the Heat Clearing and the cell tonifying principles. There is a dynamic relationship between pro-inflammatory cytokines, IL-1, IL-6 and IL-10 with STAT3 protein, which are the 'yang' and is opposed by the anti-inflammatory cytokines, IL-2 and IL-12, and IFNY, which is the 'yin'. Botanicals used in cancer both disperse the 'Heat Toxin' and tonify the cellular yin.

In later 'Integrative Oncology Notes' I will examine other events, which are involved in cancer development including apoptosis, angiogenesis, metastasis and immune evasion.

REFERENCES

- Alas S & Bonavida B. Rituximab Inactivates Signal Transducer and Activation of Transcription 3 (STAT3) Activity in B-Non-Hodgkin's Lymphoma through Inhibition of the Interleukin 10 Autocrine/Paracrine Loop and Results in Down-Regulation of Bcl-2 and Sensitisation to Cytotoxic Drugs. *Cancer Research* 61, 5137-5144, July 1, 2001
- Balkwill F. TNF- α in promotion and progression of cancer. *Cancer and Metastasis Reviews*. Volume 25, Number 3 / September, 2006. DOI: 10.1007/s10555-006-9005-3
- Bissell MJ & LaBarge MA. Context, tissue plasticity, and cancer: Are tumour stem cells also regulated by the microenvironment? *Cancer Cell*. Volume 7, Issue 1, January 2005, Pages 17-23. doi:10.1016/j.ccr.2004.12.013
- Blume-Jensen P & Hunter T. Oncogenic kinase signalling. *Nature* 2001 411, 355-365.
- Bromberg JF, Wrzeszczynska MH, Devgan G, Zhao Y, Pestell RG, Albanese C. & Darnell JE, Jr. Stat3 as an oncogene. *Cell*. 1999 Aug 6;98(3):295-303.
- Bromberg J F & Darnell J E, Jr. Stat proteins and oncogenesis. 2000 *Oncogene* 19, 2468-2473. doi:10.1172/JCI15617.
- Buettner R, Mora L B & Jove R. Activated STAT Signalling in Human Tumours Provides Novel Molecular Targets for Therapeutic Intervention. 2002 *Clinical Cancer Research*. 8, 945-954.
- Campbell MJ, Hamilton B, Shoemaker M, Tagliaferri M, Cohen I & Tripathy D. Antiproliferative activity of Chinese medicinal herbs on breast cancer cells in vitro. *Anticancer research* ISSN 0250-7005 2002, vol. 22, no6C, pp. 3843-3852
- Carson DA & Ribeiro JM. Apoptosis and disease. *The Lancet*. Volume 341, Issue 8855, 15 May 1993, Pages 1251-1254. doi:10.1016/0140-6736(93)91154-E
- Chen S-C, Chang Y-L, Wang DL & Cheng J-J. Herbal remedy magnolol suppresses IL-6-induced STAT3 activation and gene expression in endothelial cells. *Br J Pharmacol*. 2006 May; 148(2): 226-232.
Published online 2006 March 6. doi: 10.1038/sj.bjp.0706647.
- Chung TDK, Yu JJ, Spiotto MT, Bartkowski M & Simons JW. Characterisation of the role of IL-6 in the progression of prostate cancer. *The Prostate* 1999. Volume 38 Issue 3, Pages 199 - 207

Coussens LM & Werb Z. Inflammation and cancer. *Nature* 420, 860-867(19 December 2002). doi:10.1038/nature01322

Dalgliesh AG & O'Byrne KO. Inflammation and Cancer: The Role of the Immune Response and Angiogenesis. Dalgliesh AG & Haefner B Eds. In *The Link Between Inflammation and Cancer*. Springer Publishing. 2006

Darnell J E Jr. TRANSCRIPTION FACTORS AS TARGETS FOR CANCER THERAPY. 2002 *Nature Reviews. Cancer* 2, 740-749.

Elledge SJ. Cell Cycle Checkpoints: Preventing an Identity Crisis. *Science* 6 December 1996: Vol. 274. no. 5293, pp. 1664 - 1672 DOI: 10.1126/science.274.5293.1664

Garcia R, Bowman TL, Niu G, Yu H, Minton S, Muro-Cacho CA, Cox CE, Falcone R, Fairclough R, Parsons S, et al. Constitutive activation of Stat3 by the Src and JAK tyrosine kinases participates in growth regulation of human breast carcinoma cells. 2001 *Oncogene* 20 (20), 2499-2513

Hirano T, Ishihara K and Hibi M. Roles of STAT3 in mediating the cell growth, differentiation and survival signals relayed through the IL-6 family of cytokine receptors. *Oncogene*. 2000, vol. 19, no 21 (193 p.) (2 p.3/4), pp. 2548-2556

Hoessel R, Leclerc S, Endicott JA, Nobel ME, Lawrie A, Tunnah P, Leost M, Damiens E, Marie D, Marko D, et al. Indirubin, the active constituent of a Chinese antileukaemia medicine, inhibits cyclin-dependent kinases. 1999 *Nature Cell Biology*. 1, 60-67. pmid:10559866

Kim EH, Shim B, Kang S, Jeong G, Lee JS, Yu YB, Chun M. Anti-inflammatory effects of *Scutellaria baicalensis* extract via suppression of immune modulators and MAP kinase signalling molecules. *J Ethnopharmacol*. 2009 Aug 21. [Epub ahead of print] PMID: 19699788

Kun Y. In vitro effects of Bai Tou Weng on TNF, IL-1 and IL-6. *Tian Jin Yi Ke Da Xue Xue Bao*. 2004; 10(1): 59-61

Lee SMY, Li MLY, Tse YC, Leung SCL, Lee MMS, Tsui SKW, Fung KP, Lee CY & Waye MMY. *Paeoniae Radix*, a Chinese herbal extract, inhibit hepatoma cells growth by inducing apoptosis in a p53 independent pathway. *Life Sciences* Volume 71, Issue 19, 27 September 2002, Pages 2267-2277. doi:10.1016/S0024-3205(02)01962-8

Lengauer C, Kinzler KW & Vogelstein B. Genetic instabilities in human cancers. *Nature* 1998; 396(6712):643-649

Levine A. p53, the Cellular Gatekeeper for Growth and Division. *Cell*, 1998 Volume 88, Issue 3, Pages 323-331

Lin W-W and Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer. *J. Clin. Invest.* 117:1175–1183 (2007). doi:10.1172/JCI31537.

Luo C & Laaja P. Inhibitors of JAKs/STATs and the kinases: a possible new cluster of drugs. 2004 *Drug Discovery Today* 15;9(6):268-75.

Marte B. Cell division and cancer. *Nature Insight*. Vol 432 No 7015 pp293-341 18 November 2004

McBride OW, Merry D & Givolt D. The gene for human p53 cellular tumour antigen is located on chromosome 17 short arm. *Proc. Nati. Acad. Sci. USA*. Vol. 83, pp. 130-134, January 1986. *Genetics*

Murakami Y, Hayashi K, Hirohashi S & Sekiya T. Aberrations of the Tumour Suppressor p53 and Retinoblastoma Genes in Human Hepatocellular Carcinomas. *Cancer Research* 51, 5520-5525, October 15, 1991

Nigg EA. Cyclin-dependent protein kinases: Key regulators of the eukaryotic cell cycle. *BioEssays* 2005. Volume 17 Issue 6, Pages 471 - 480. DOI: 10.1002/bies.950170603

Pollack JR, Perou CM, Alizadeh AA, Eisen MB et al. Genome-wide analysis of DNA copy-number changes using cDNA microarrays. *nature genetics* • volume 23 • september 1999

Rose-John S, Waetzig GH, Scheller J, Grötzinger J, Seegert D. The IL-6/sIL-6R complex as a novel target for therapeutic approaches. *Expert Opinion on Therapeutic Targets*. 2007 May;11(5):613-24.

Smith JA and Martin L. "Do cells cycle?". *Proc. Natl. Acad. Sci* 1973. U.S.A. 70 (4): 1263–7. PMID 4515625

Tan T-T & Coussens LM. Humoural immunity, inflammation and cancer. *Current Opinion in Immunology*. Volume 19, Issue 2, April 2007, Pages 209-216

Turkson J & Jove R. STAT proteins: novel molecular targets for cancer drug discovery. 2000 *Oncogene* 19, 6613-6626.

Varmus HE. Oncogenes and transcriptional control. *Science* 1987 238, 1337–1339.

Wang G, José R. Lemos JR & Iadecola C. Herbal alkaloid tetrandrine: from an ion channel blocker to inhibitor of tumor proliferation. *Trends in Pharmacological Sciences*. Volume 25, Issue 3, March 2004, Pages 120-123. doi:10.1016/j.tips.2004.01.009

Yu CL, Meyer DJ, Campbell GS, Lerner AC, Carter-Su C, Schwartz J. & Jove R. Enhanced DNA-binding activity of a Stat3-related protein in cells transformed by the Src oncoprotein 1995 *Science* 269, 81-83. DOI: 10.1126/science.7541555

Yu H & Jove R. The STATs of cancer — new molecular targets come of age. *Nature Reviews Cancer* 4, 97-105 (February 2004) | doi:10.1038/nrc1275

Yu H, Pardoll D and Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. *Nature reviews/cancer* November 2009; vol. 9