Inflammation and Cancer; An Introduction

Cancer and its Mechanisms

We are a society of cells that cooperate for the benefit of the whole, the self. Cancer breaks the rules of cooperation and takes over the organism without regard for the community of cells as a whole. The host, the self, may die due to the aberrant behaviour of a single cell and a pathological environment, which fosters its proliferation.

Cancer is the name for many diseases, however all cancers share common traits. Cancer cells differ from normal cells in two defining characteristics: they continue to divide in spite of natural constraints, which control healthy cells, and they leave their origins and invade distant tissues and establish new colonies or new tumours.

Cancer cells are unstable and by many accounts immortal. They can be killed, of course, but they have overcome a normal cell’s programming to only reproduce a set number of times. Normal cells may be programmed to divide 60 or so times and then enter senescence. We die of old age because our cells stop replicating.

Cancer is the price we pay for having cells that continually repair and renew themselves. Genes, which program the cell to exactly replicate itself, control the renewal process and when the program is wrong and the cell overcomes natural checks on reproduction the aberrant cell is created. In each cycle of replication the cells become increasingly unstable.

When this community of cancer cells grows it will need a blood supply. Tumours create an environment, which stimulates blood vessels to grow and feed the tumour. This is called angiogenesis.

The invasion by cancer cells from the primary tumour is called metastasis and it is
this activity that ultimately destroys the host. Although an original tumour may throw one million cells a day into the lymph and blood stream only .00015% take hold in a distant site. Almost all are killed by the body’s immune system and it is the defeat of the immune system, which concerns everyone with cancer.

There is considerable evidence that chronic inflammation plays a critical role in initiation, growth, angiogenesis and metastasis. Cancer is a wound that does not heal and cancer cells turn the immune system around to fuel its own growth.

Cancer is often a disease of old age as each time a cell replicates there is an opportunity to distort and to let the damaged DNA get passed on to the next generation. The environment that these aberrant cells find themselves in will determine their survival. Cancer cells do not take hold in a healthy environment. The environment is the somatic (physical), emotional (psychological) and the social; what we eat, what we do, how we relate, how we feel. It is the total sum of our life.

Cancer is complex and without a single cause. It takes many major insults to cells to produce a single aberrant cell and then to foster its survival.

SEVEN STOCHASTIC EVENTS OF CANCER

Cancer is one disease that fits the paradigm that “more we know, less we understand its intricacies” (Aggarwal & Gehlot 2009).

Pathological analyses of a number of organ sites reveal lesions that appear to represent the intermediate steps in a process through which cells evolve progressively from normalcy via a series of premalignant states into invasive cancers (Sarin & Prasad, 2005). Taken together, observations of human cancers and animal models argue that tumour development proceeds via a process formally analogous to Darwinian evolution, in which a succession of genetic changes, each conferring one or another type of growth advantage, leads to the progressive conversion of normal human cells into cancer cells (Corbellini & Preti, 2008).

There are essential alterations in cell physiology that collectively dictate malignant growth:

1. Induction of genetic instability; insensitivity to or suppression of growth-
inhibitory signals
2. Abnormal expression of genes and evasion of programmed cell death (apoptosis)
3. Abnormal signal transduction and failure of cell adhesion molecules (CAM); growth factor dysregulation
4. Abnormal cell-to-cell communication or gap junctional dysregulation
5. Sustained angiogenesis
6. Tissue invasion and metastasis
7. Immune evasion.

(Hanahan & Weinberg, 2000; Huston, 2006)

THE 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-κB, AP-1 and STAT3 and their gene products such as tumour necrosis factor, interleukin-1, interleukin-6, chemokines, cyclooxygenase-2, 5 lipooxygenase, matrix metalloproteases, and vascular endothelial growth factor, adhesion molecules and others have provided the molecular basis for the role of inflammation in cancer. These inflammatory pathways are activated by tobacco, stress, dietary agents, obesity, alcohol, infectious agents, irradiation, and environmental stimuli, which together account for as much as 95% of all cancers (Aggarwal & Gehlot 2009).

An important factor in malignancies is chronic inflammation (Macarthur, Hold, & El-Omar, 2004). Inflammation functions at all three stages of tumour development: initiation, progression and metastasis (Dalgliesh & O’Byrne, 2006). Inflammation contributes to initiation by inducing the release of a variety of cytokines and chemokines that alert the vasculature to release inflammatory cells and factors into the tissue milieu, thereby causing oxidative damage, DNA mutations, and other changes in the microenvironment, making it more conducive to cell transformation, increased survival and proliferation (NCI, 2009).
Chronic inflammation is associated with a high cancer risk. At the molecular level, free radicals and aldehydes, produced during chronic inflammation, can induce deleterious gene mutation and post-translational modifications of key cancer related proteins. Other products of inflammation, including cytokines, growth factors, and transcription factors such as nuclear factor kB, control the expression of cancer genes (e.g. suppressor genes and oncogenes) and key inflammatory enzymes such as inducible nitric oxide synthase and cyclooxygenase-2. These enzymes in turn directly influence reactive oxygen species and eicosanoid levels. The pro-cancerous outcome of chronic inflammation is increased DNA damage, increased DNA synthesis, cellular proliferation, disruption of DNA repair pathways and cellular milieu, inhibition of apoptosis, and promotion of angiogenesis and invasion. Chronic inflammation is also associated with immunosuppression, which is a risk factor for cancer (Hofseth & Wargovich, 2007).

Inflammation is a complex process that requires distinct cell types and factors, which act in a coordinated manner to control tissue damage against pathogenic, traumatic, or toxic injury. The inflammatory process is highly coordinated by pro- and anti-inflammatory molecules that regulate cell chemotaxis, migration, and proliferation (Benelli, Lorusso, Albini, & Noonan, 2006; Charo & Ransohoff, 2006). Generally, inflammation ends up as a healing process. However, if this process is not properly ordered, the result is persistent inflammation. Chronic inflammatory conditions have been found to mediate a wide variety of diseases including psoriasis, rheumatoid arthritis, osteoarthritis, metabolic syndrome-associated disorders, ocular disorders, Crohn’s disease and cancer (Coussens & Werb, 2002; Tan & Coussens, 2007).

Cancer is a multistep process during which cells acquire genetic alterations that drive the progressive transformation of normal cells into highly malignant cells. Cancer cells are characterised by uncontrolled growth, escape from apoptosis, sustained angiogenesis, tissue invasion, and metastasis (Hanahan & Weinberg, 2000). Chronic inflammation has also been implicated in cancer development and may influence many of the aforementioned processes that contribute to the multistage development of tumours (Coussens & Werb, 2002; Balkwill, Charles, & Mantovani, 2005).
In 1863, Rudolph Virchow first discovered leukocytes in neoplastic tissues, suggesting a link between inflammation and cancer (Costa, Incio, & Soares, 2007, p. 156). It has been demonstrated that the tumour microenvironment highly resembles an inflammatory site. These environmental changes favour tumour progression by the secretion of cytokines and chemokines by leukocytes, generating reactive oxygen and nitrogen species that can directly damage cell cycle controlling genes (Blankenstein, 2004). 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 (Burke, Relf, Negus, & Balkwill, 1996). 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 (Koong et al., 2000).

Epidemiological studies and molecular analyses of mouse models, have highlighted a strong contribution of chronic inflammation to tumour development in which the tumour microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, survival and migration. (Coussens & Werb, 2002).

The generation of the pro-tumourigenic microenvironment strongly depends on the activation of several transcription factors, mainly nuclear factor-κB (NF-κB), signal transducer and activator of transcription 3 (Stat3) and hypoxia-inducible factor-1α (HIF-1α) (Mantovani, Allavena, & Sica, 2008). These transcription factors regulate the expression of important cytokines, such as tumour necrosis factor α (TNFα), interleukin-1 and -6 (IL-1, IL-6) that are critically involved in the crosstalk between cancer cells and cells of the tumour stroma (Germano, Allavena, & Mantovani, 2008). Soluble mediators produced by cancer cells recruit and activate inflammatory cells, which further stimulate tumour progression (Lin & Karin, 2007).

Local cell mediated immunity (CMI) is attenuated and angiogenesis is increased along with other growth factors (Whiteside, 2006, p. 104). 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 (Dalgleish & O’Byrne, 2006, p. 5).

**Links Between Inflammation and Cancer Pathogenesis**

1. Many inflammatory conditions predispose the cell to cancer
2. Cancers arise at sites of chronic inflammation
3. Functional polymorphisms of cytokine genes are associated with cancer susceptibility and severity
4. Distinct populations of inflammatory cells are found in many cancers
5. Extent of tumour-associated macrophage infiltrate correlates with prognosis
6. Inflammatory cytokines are detected in many cancers; high levels are associated with poor prognosis
7. Chemokines are detected in many cancers; they are associated with inflammatory infiltrate and cell motility
8. Deletion of cytokines and chemokines protects against carcinogens, experimental metastasis and lympho-proliferative syndrome
9. Inflammatory cytokines are implicated in the action of non-genotoxic liver cancer
10. Inflammatory cytokine tumour necrosis factor in directly transforming cells *in vitro* (Balkwill & Mantovani, 2001)

**Conclusion**

Aggarwal & Gehlot (2009) in their recent study provided nearly 300 references to the link between cancer and inflammation and claimed conclusive proof that inflammation is a critical mediator of cancer. They go on to say, “anti-inflammatory agents should be explored for both prevention and treatment of cancer. Although numerous cell culture and animal studies have identified several natural anti-inflammatory agents, their true potential will be recognised only through well-controlled clinical trials.”
Many studies have also been done in China examining this link (Yuan & Lin 2000) and the Chinese pharmacopeia offers many hundreds of herbs and compounds, which are useful in all of the seven stochastic events of cancer. Further ‘Integrative Oncology Notes’ will explore in greater detail this process as well as looking at ‘scientific’ testing of blood, saliva and urine to determine inflammation levels and then looking at which herbs and/or compounds are capable of reducing these inflammatory markers.

References


Germano G, Allavena P and Mantovani A: Cytokines as a key component of cancer-related


