Link between inflammation and cancer

The link between inflammation and cancer was first proposed by Rudolph Virchow in 1863, when he observed leucocytes in neoplastic tissue. This hypothesis has been revisited and studied extensively in recent times, with the relationship between inflammation and cancer appearing increasingly likely. It appears chronic inflammation has a role in all phases of the tumorigenic process, as well as being a risk factor for the development of most cancers. However chronic inflammation can have both tumorigenic and antitumour actions, as well as affecting the immune system. Through a better understanding of the role of chronic inflammation in cancer, the treatment of other chronic inflammatory conditions such as diabetes, cardiovascular disease and rheumatic fever may also be revolutionised.

Chronic inflammation has been shown to have a causative role in the first stage of tumorigenesis, named tumour initiation. In this phase, normal cells are genetically altered to become malignant. The chronic inflammation which causes these changes may be a progression from acute inflammation if the injurious agent has persisted, however most of the time the response is chronic from the outset8. Causes of chronic inflammation include infection, alcohol abuse, acid reflux, asbestos and cigarette smoking. Prolonged inflammation has been shown to cause tumour initiation through multiple mechanisms, the key ones discussed here being free radical production and activation of the NF-κB transcription factor.

In chronically inflamed tissue there is increased production of free radicals such as reactive oxygen intermediates (ROI), hydroxyl radical (OHâˆ™) and superoxide (O2-âˆ™) and reactive nitrogen intermediates (RNI), nitric oxide (NOâˆ™)and peroxynitrite(ONOO-)3. These free radicals may be released

from leucocytes and other phagocytic cells infiltrating the inflamed tissue or could be induced from cytokines such as TNF3. These highly unstable molecules have been found to have oncogenic effects via multiple mechanisms such as direct DNA and protein damage, inhibition of apoptosis, mutation of DNA and cellular repair functions [such as p53, a tumour suppressor protein] and also through the promotion of angiogenesis. These mechanisms have also been proven clinically; for example, two weeks of exposure to TNF to nude mice in vitro was found to be sufficient to render cells cable of tumour formation. These effects were attributed to the induction of reactive oxygen. Another study focusing on the effects of chronic inflammation in colitis-associated cancer found that p53 mutations were found in both cancer cells and in inflamed, but nondysplastic epithelium. This suggested that the chronic inflammation associated with colitis was the cause of the genetic changes9. However whilst the free radicals released from leukocytes or induced from cytokines have an important role in tumour initiation, there are other factors contributing as well.

The activity of the NF-κB transcription factor also has a pivotal role in all phases of tumorigenesis, especially in tumour initiation. NF-κB is activated in response to stimulation by proinflammatory cytokines, and it regulates several genes whose products inhibit apoptosis and enhance cell cycle progression, angiogenesis and metastasis5, 10. Furthermore, a significant number of NF-κB target genes encode mediators of the innate immune response and inflammation, which includes cytokines, chemokines, proteases and COX-25, 10. NF-κB activation, like many inflammatory

cytokines, is also subject to a feed forward loop; activation of NF-κB in immune cells induces production of cytokines that activate NF-κB in cancer cells to induce chemokines that attract more inflammatory cells into the tumour. These effects combined mean that NF-κB is an important endogenous tumour promoter, whose effects can be produced via inflammation.

There are a number of important experiments highlighting the importance of inflammation-activated NF-κB activity. Firstly, NF-κB has been shown to be primarily activated by inflammation, represented in one study by cigarette smoke. In this study, when human histiocytic lymphoma cells were treated with cigarette smoke activation of NF-κB occurred in a dose and time dependent manner. The effects of NF-κB inhibition have also been experimentally explored; in a colitis associated model, deletion of IKKβ [inhibitor of nuclear factor kappa-B kinase subunit beta a kinase; leads to activation of NF-κB when stimulated] lead to a dramatic decrease in tumour incidence without affecting tumour size. Other studies have shown that when NF-κB activity is blocked; tumour activity is markedly diminished or abolished. These studies are representative of the evidence which shows that chronic inflammation activates NF-κB which in turn causes tumour initiation, regulation of the inflammatory environment and other pro-tumorigenic effects.

Cytokine polymorphisms have also been shown to have an effect on cancer risk. For example Helicobacter pylori induced gastric cancer was shown to be more likely to occur in the presence of certain proinflammatory IL-1 gene cluster polymorphisms. The bacteria H. pylori has also been shown to induce

gastric erosion and inflammation prior to mucosal associated lymphoid tumours. The fact that H. pylori is a prerequisite for the association of these polymorphisms with malignancy shows that inflammation is indeed needed for the development of gastric cancer in this setting.

Once the tumour has completed the first phase and become malignant it still requires a background of chronic inflammation to undergo tumour promotion. This is illustrated in the case of a rapidly growing tumour. When tumours grow rapidly they will at one point outstrip their blood supply and become oxygen and nutrient deprived. This results in necrotic cell death at the tumour's core and the release of proinflammatory mediators such as IL-1 and HMGB13. This inflammatory response promotes neoangiogenesis and provides surviving tumour cells with additional growth factors. Hence inflammatory has an ongoing role in providing nutrients to tumour cells.

The enzyme cyclooxygenase-2 (COX-2) has also been found to play an important part in tumour promotion. The COX-2 enzyme is an inducible carcinogenic found in inflamed and malignant tissue. It is inducible by inflammatory mediators such as IL-1β and NF-κB14. This enzyme is believed to cause inhibition of apoptosis, modulation of cellular adhesion and motility, promotion of angiogenesis and immunosuppression. Epidemiological evidence also implicates COX-2 in many cancers; COX-2 has been found to be enhanced in colorectal cancer, invasive breast tumours and ovarian tumours. Trials have shown that pharmacological inhibition of this enzyme is associated with a reduction of 40-50% in the morbidity and mortality of colorectal cancer. However NSAIDS have been shown to be ineffective in tumours with low or absent COX-2 activity, pointing to COX-2 as its

mechanism of action. Hence by blocking the inflammatory stimulation and subsequent tumorigenic actions of COX-2 positive tumours the prevalence of colorectal cancer has been proved to be reduced.

There are many mediators induced by inflammation which assist in tumour promotion, including TNF-alpha and the following interleukins: IL-1, IL-6, IL-8 and IL-182. However there is also considerable overlap between tumour promotion and progression, with many of these mediators also contributing towards the latter. The effects of inflammatory mediators can be broadly classified; firstly, inflammatory cytokines have been shown to cause DNA damage and p53 bypass. These actions have been considered previously with the example of TNF8. Cytokines have also been shown to have actions as growth and survival factors, particularly IL-1 and IL-68. Furthermore they have a role in angiogenesis, with cytokines and chemokines such as TNF, IL-1, IL-6 and IL-8 able to induce the production of angiogenic factors such as VEGF8. Lastly, inflammatory cell production of matrix metalloproteinases (MMPs) has been shown to assist in local tissue invasion by cancer2, 8. Transgenic mice lacking MMP were shown to have reduced cellular hyperproliferation and a decreased incidence of invasive tumours. MMPs have been shown to promote cancer invasion by proteolytic cleavage of the extracellular matrix substrates and activate other MMPs to facilitate tumour invasion. Certain chemokines may also induce the migration of tumour cells. It can be seen from the diverse actions of these inflammatory mediators that they do not only act in one dimension; there is overlap between all the phases of tumorigenesis.

Although there are many tumorigenic effects of chronic inflammation, the presence of inflammation may at times be inhibitory to cancer10. A review article examining inflammation concluded that production of an optimal amount of inflammation appeared to be most favourable to cancer growth. Too little inflammation and the tumour showed limited vascularisation and growth, whereas too much inflammation accompanied by a strong monocyte infiltration was associated with cytotoxicity and cancer elimination. This higher inflammation levels have been thought to be associated with enhancement of the cross-presentation of tumour antigens and induction of an antitumour immune response. This enhancement of the antitumour response can be seen in a subset of breast and pancreatic tumours. In these tumours there is a tendency to develop excessive inflammatory infiltration of TAM which is associated with a better prognosis. This has been attributed to the ability of these TAMs to destroy tumour cells, as opposed to contributing to the inflammation and development of the cancer. Further experiments showed that NF-κB was important in determining this balance between the protumour and antitumour properties of macrophages8. However blockage of inflammation may also be delirious. It has been found that administration of TNF blockers in patients with rheumatoid arthritis increases their risk of developing lymphomas16. Therefore care must be taken before altering the balance of inflammation in the body.

The inflammation associated with tumorigenesis also has the potential to alter the activity of the immune system, which in turn may affect tumour severity. Many immune cells can be found in the tumour environment, such as macrophages, dendritic cells (DC), T cells and NK cells. However among

these tumour-associated macrophages (TAM) and T cells are frequently the most common leukocytes found in tumours.

TAM is the major inflammatory component of the stroma of many tumours, being capable of promoting angiogenesis, matrix remodelling through MMP production and suppression of adaptive immunity. TAM are especially important in hypoxic regions of tumours, where they increase angiogenesis through the secretion of angiogenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF)16. The other major pro-tumoral function of TAM is through the suppression of adaptive anti-tumour immune responses. This occurs though blockage of DC maturation and expanded levels of immature myeloid cells. The importance of TAM has been supported by many clinical studies which have found a general correlation between high macrophage tumour content and poor patient prognosis.

T cell responses are ineffective and blunted in the majority of tumours. The suppression of a T cell response occurs through the effects of TAM, as well as the result of defective T cell receptor signalling and increased levels of IL-4 and IL-516. Increased levels of these two interleukins is associated with the T-helper type 2 cell (Th2), which is generally ineffective against tumours. Tumours such as bronchial carcinoma and cervical carcinoma produce mainly IL-4 and IL-5 as opposed to interferon-γ, which is associated with Th1 responses and a better prognosis16. Hence the immune system itself may contribute towards the development of certain tumours, as well as causing an ineffective defence against others.

Chronic inflammation appears to have an integral part in tumorigenesis, having a role in all three stages of tumour development. In tumour initiation chronic inflammation causes an increased production of free radicals resulting in the conversion of normal cells to malignant cells. NF-κB is also vital in this stage, as well as having tumorigenic effects in the other phases of tumorigenesis. After this point, increased inflammation as a result of polymorphisms, COX-2 activity, cytokines and immune system function appear to drive tumour development. However inflammation may also be regulated in tumours as a high inflammatory response has been associated with tumour regression. This concept is supported by the pathogenesis of diseases such as psoriasis, which is a chronic inflammatory disease that does not lead to an increase in cancer risk, and may even reduce it. The relationship between inflammation and cancer appears quite complex and intertwined; however when fully elicited will provide breakthroughs in the treatment of all chronic inflammatory conditions.