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Editorial

The idea that cancer and inflammation are linked is not new, but has become more prominent in the past ten years. During this time, a number of seminal papers have changed our ideas about the role of the inflammatory mediators and infiltrating host cells of the innate immune system in the cancer microenvironment. These papers are supported by definition of the cytokine and chemokine network and identification of leucocyte subsets that contribute to chronic inflammation. A study of inflammation and cancer also provides an intellectual context for understanding a fact that has been largely ignored during dissection of the genetic basis of cancer, i.e., that cancers are not only composed of genetically altered malignant cells.

The major tenets that have led us to study the role of the innate immune system in the initiation, promotion and progression of cancer are all discussed in this special issue of the *European Journal of Cancer*. The first evidence comes from large population-based studies either on cancer incidence and NSAID use or on development of cancers at sites of chronic inflammation. In this issue of *EJC* two papers strengthen this argument, one on endometriosis as a model for inflammation-hormone interactions in ovarian and breast cancers, and the other a prospective cohort study of circulating C-reactive protein and subsequent cancer outcomes. Epidemiologic studies have also shown that the chronic infections of hepatitis and gastritis predispose to cancer development. The paper by Matysiak-Budnik and Megraud discusses the biological basis for the involvement of chronic *Helicobacter pylori* infection in the aetiology of gastric cancer.

The second major area of evidence linking cancer and inflammation is that the host cells infiltrating cancers are more likely to be involved in promoting tumour growth and spread than in initiating a host anti-tumour response. Pioneering work by Alberto Mantovani and his colleagues in Milan has defined tumour-infiltrating macrophages as key players in tumour promotion. A paper from his group (Sica et al.) discusses their recent data on M2 polarised macrophages in this context. The role of tumour infiltrating cells and the proteases they produce are also discussed in the context of skin cancer models both by van Kempen et al. and Margareta Mueller. Although the models are quite different, and there are differences in the detail, very similar conclusions can be drawn concerning the role of innate host responses in cancer development. Van Kempen et al. have highlighted proteases as important mediators of inflammation-promoted cancers but these and many other contributors have discussed inflammatory cytokines and chemokines.

This leads to the third major area of evidence that links cancer and inflammation – presence of a complex cytokine and chemokine network in cancers. It is therefore not surprising that two major inflammatory mediators, TNF-α and IL-1β, can act as tumour promoters in a range of different experimental cancer models and in vitro systems. Szlosarek et al. and Apte et al. describe the sometimes paradoxical ways in which these powerful cytokines influence malignancy. Cytokines such as TNF-α and IL-1β are major inducers of chemotactic chemokines. Cancers possess a complex network of chemokines and their receptors which appear to determine the extent and phenotype of the leucocyte infiltrate, tumour cell survival and spread as well as influence angiogenesis. These aspects of cancer chemokine biology are covered by two comprehensive reviews from Barrett Rollins and Strieter et al.

A major advance in our understanding of inflammatory processes in malignancy has come from identification of NF-κB as a critical molecular link. Its role in the induction of inflammatory cytokines and in inhibiting apoptosis has been defined in a number of experimental models as described by Pikarsky and Ben-Neriah, and Assenat et al. As in the case of the NF-κB-induced cytokines TNF-α and IL-1β, the effects of NF-κB pathways in malignancy can be paradoxical. Eli Pikarsky and Yinon Ben-Neriah propose a model which is relevant to many of the issues discussed in this special issue of *EJC*.

The fourth major tenet of cancer inflammation research is inhibition/deletion of some inflammatory mediators delays or inhibits the development of experimental cancers. Many of the chapters in this issue give examples of this. An important question for readers of *EJC* is the relevance of these new data to cancer prevention and treatment in humans. Many of the chapters address this is some detail but we have also commissioned a chapter on the potential of one class of biological therapy, antagonists of cytokines and chemokines. Antagonists of TNF-α, IL-1 and IL-6 have already shown clinical efficacy in chronic inflammatory diseases and Yan et al. discuss their potential in cancer therapy. Targeting cancer inflammation is an attractive approach that may complement existing therapies. However, it is also important to acknowledge that the inflammatory environment of cancer may also alter the response to, and toxic effects of, cancer chemotherapy, as discussed by Assenat et al.

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Due to time and space restrictions we have not been able to cover all aspects of this important area of cancer research. For instance, inflammatory mediators such as free radicals and cyclo-oxygenases are also important, and macrophages are certainly not the only host cells that can promote cancer development. We have also focused on the role of the innate immune system. The inflammatory response is not only tumour-promoting but also immunosuppressive. Targeting cancer inflammation may also remove these suppressive influences and encourage anti-tumour immune responses. But adequate discussion of this equally important area would require another special issue of *European Journal of Cancer*.

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