Cytokines in the Genesis and Treatment of Cancer

Caligiuri M, Lotze M (Eds)
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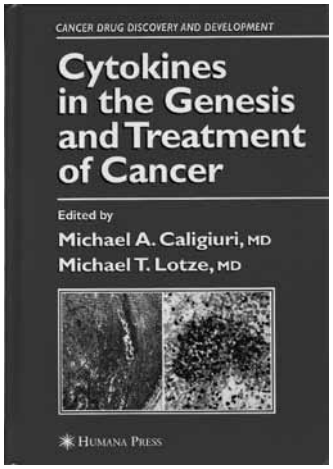
This useful volume, one of the *Cancer Drug Discovery and Development* series by Humana Press, offers an overview of a complex area at the intersection of immunology, growth factors and cancer. Although the editors are authorities in the roles of natural killer cells and dendritic cells in cancer immunology, they have chosen a wide range of experts to survey cytokines and cancer in 24 contributions. The book is divided into four sections: infectious agents, cytokines and cancer; cytokines and carcinogenesis; cytokines and tumour stroma/metastasis; and cytokines in the treatment of cancer.

The first section emphasises the role of cytokines released by the inflammatory process in the promotion of cancers, be it gastric carcinoma induced by H.pylores infection, adult T-cell leukaemia (ATLL) induced by HTLV-1 viral infection or Hodgkins disease associated with EBV infection. It is clear that cytokines can contribute to the oncogenic nature of certain viruses by influencing the proliferation of infected cells, suppressing cellular antiviral tactics and inhibiting apoptosis. The inflammatory process also generates mutagenic free radicals with assistance from cytokines. Disappointingly for Australian readers, the role of HPV-induced cytokines in generation of cervical cancer is not addressed, nor is inflammation from UV exposure and skin cancers considered here.

The section on cytokines and carcinogenesis is the main part of the book and reviews the involvement of key immune-related cytokines such as TNFa, TGFb and ILs-1/4/6 and 10. Murine models are also dealt with in a wide ranging chapter by Mark Smythe from the Peter McCallum Cancer Centre. The paradoxical ability of several of these to act both as tumour regressors and tumour progressors is dealt with in relation to local concentration (therapeutic doses or paracrine/angiogenic levels) and cell context. For example, while TNFa at high doses is vasculotoxic and useful for sarcoma treatment, anti-TNFa treatments appear useful as an adjunct to chemotherapy. The role of altered TGFb signalling via smads in overcoming the tumour suppressive actions of this chameleon cytokine is analysed in detail, explaining how it acts as a tumour promoter for many established cancers such as colon, head and neck cancers and lymphoma.



Priming of natural killer and dendritic cells for tumour attack by interleukin variants is addressed in the chapter by Michael Lotze. The anti-tumour affects of IL-4 and 13, together with their ability to suppress inflammatory cytokines and chemokines appeared promising, but the clinical ineffectiveness of IL-4 and Il-13 treatments generally has rather led to the use of these cytokines to target cytotoxins to a number of solid tumours, with evident success in glioblastoma, for example. The importance of IL-6 in driving multicentric Castlemans disease (lymph node hyperplasia), and the use of humanised MAbs to IL-6 provide a good example of a disorder where monotherapy is highly effective.

One major omission is the lack of a chapter on IGF-1 (there is one paragraph in the section on multiple myeloma), despite recent strong evidence that IGF-1 deficient rats, mice and humans are resistant to the initiation and progression of a wide variety of cancers (Waters & Barclay (2007) Endocrinology 148, 4533).

The section on stromal interactions contains an excellent chapter on macrophage/tumour cell interactions and stromal cell interactions involving fibroblast TGFb. It is complimented by chapters on tumour-induced angiogenesis and the role of tumour chemokines in promoting neoplastic growth, inflammation and angiogenesis. The angiotoxic actions of TNFa and IFNa are also examined.

The final section deals with successes in treating human cancer with cytokine-based therapies. It is evident that even with accepted treatments such as the use of IL-2 or IFNa in renal cancer and melanoma, and IFNa for CML and Kaposi sarcoma, the percentage of complete remission is generally <20%, albeit in resistant tumours. In some cases, such as IL-12, toxicity was a major issue, and effectiveness unimpressive. For others, the promising results with small scale trials were not evident with large phase III trials. Likewise, combinations of cytokines (many have been trialled) have not provided clear benefit in larger trials over monotherapy with chemotherapeutics or the clinically accepted cytokines referred to above. However, adenoviral infection of dendritic cells with key cytokines does offer improved prospects for tumour vaccines. Similarly, while the prospects for anti-cytokine treatment appear promising, apart from TNFa antagonism there are few clinical results, which need rectification. Finally, the signal benefit of adjunct therapy after chemotherapy, particularly with cytokines G-CSF and GM-CSF, and EPO for fatigue/anaemia, is emphasised in the last chapter.

Overall this book makes a credible effort to cover a very diverse field and is a useful contribution to our understanding of the intersection between immune cytokines and cancer.

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