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Book Review

Growth Regulation by Nuclear Hormone Receptors

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THE TERM nuclear hormone receptors did not exist when the last issue of Cancer Surveys devoted to "Hormones and Cancer" was published in 1986 and so, in view of the expansion of this field, now seems a good time to produce a volume dedicated to growth regulation by nuclear receptors. To date, progress in analysing the structure and function of nuclear hormone receptors as transcription factors has been far more rapid than our understanding of their role in growth control and this is reflected in the contributions to this volume of Cancer Surveys. It continues to emphasise the importance of oestrogen and androgen receptors but also includes articles on thyroid hormone and retinoic acid receptors and other related receptor proteins.

It has been almost a century since oestrogens were first implicated in breast cancer following the use of oophorectomy by Sir George Beatson for the treatment of metastatic breast cancer [1]. Subsequently, orchiectomy was found to be effective in the treatment of prostate cancer by Huggins and his co-workers [2]. A major breakthrough in our understanding of steroid hormone action came about with the discovery of receptors for oestrogens in the 1960s by Gorski and Jensen and their colleagues; their work led to models for the mechanism by which steroid hormones regulate gene expression in target tissues [3, 4]. More recently, with the isolation of recombinant DNA clones for the individual steroid receptors, it has become clear that they represent members of a much larger family of proteins referred to as nuclear hormone receptors [5–7]. In addition to steroid receptors, the family of proteins includes the receptors for thyroid hormone and retinoic acid and also many novel receptors whose hormonal ligand and target genes have not yet been identified. These so-called "orphan receptors", which currently number in excess of thirty, are likely to be involved in new signalling pathways completely unsuspected until now.

In view of the structural similarities between the receptors it has been thought that the mechanisms by which they regulate gene expression will be conserved [5–7]. While this is true to some extent, it is becoming apparent that the receptors do exhibit a number of interesting differences which contribute to variations in their overall transcriptional activity. The most obvious difference in the action of nuclear receptors is that the binding of a hormonal ligand is required to promote the DNA binding of all steroid hormone receptors but not for the thyroid hormone and retinoic acid receptors [8, 9]. This difference is probably a consequence of an interaction between steroid hormone receptors and heat shock proteins that appears to block receptor dimerisation and thereby inhibit DNA binding activity [10]. In the case of the glucocorticoid receptor the heat shock proteins may also mask nuclear localisation signals that are presumably only exposed or activated upon hormone binding [11]. It has now been shown that even those receptors which are usually located in the cell nucleus undergo a process of shuttling between the cytoplasm and the nucleus [12]. In this issue of Cancer Surveys, the subcellular localisation of receptors and the process of nucleocytoplasmic shuttling is discussed by E. Milgrom and his colleagues. Steroid hormone binding is required not only to promote specific DNA binding but also to induce full transcriptional activity of the receptor [6]. The primary role of thyroid hormone and retinoids appears to be on transcriptional activation since their receptors are capable of binding to responsive genes, even in the absence of hormone [8, 9]. Another major difference amongst nuclear hormone receptors is that steroid receptors bind to DNA as homodimers [6, 13], whereas it is beginning to emerge that a number of others, including those for thyroid hormone and retinoic acid, are more likely to bind as heterodimers [14–16]. Since many of these receptors exist in more than one form, even in a single cell-type, it is not yet clear which combinations actually exist in target cells and how this affects the regulation of hormone responsive genes.

Obviously ligands that compete with the hormone for binding to the receptor and which interfere with DNA binding or inhibit transcriptional activity will function as hormone antagonists. Perhaps the best characterised antagonist is the non-steroidal anti-oestrogen, tamoxifen, used as adjuvant therapy for post-menopausal women with breast cancer. However, it has been known for some time that despite the efficacy of treating breast cancer with tamoxifen, especially when the primary tumour is oestrogen receptor-positive, therapeutic failure often results from the development of drug resistance. Potential mechanisms for the development of breast cancer cells that are insensitive to hormone are discussed by R. King and K. B. Horwitz while tamoxifen resistance itself is discussed by S.-Y. Jiang and V. C. Jordan. Alternative anti-oestrogens to tamoxifen have now been developed that are reported to be devoid of any agonist activity and these are described by A. Wakeling. Mutations in the oestrogen receptor are predicted to be one means for generating either tamoxifen resistance or hormone insensitivity; examples of these, together with their potential consequences, are reviewed by K. B. Horwitz and W. L. McGuire and his colleagues. The occurrence of mutations in the androgen receptors found in prostate tumours has yet to be reported but a growing number of inherited mutations have been identified that cause defective development and growth of sex accessory tissues as discussed by A. O. Brinkman and J. Trapman. The importance and potential role of androgens in prostate cancer is reviewed by G. Wilding.

There are now two examples of receptors which when mutated are associated with leukemia. One involves the viral protein v-*erb*A, a mutant version of the thyroid hormone receptor α, which in combination with v-*erb*B, a truncated version of the EGF/TGFα receptor, induce erthroleukemias and sarcomas in

chickens. The possibility that v-*erb*A is acting as a dominant negative version of the normal ligand-dependent thyroid hormone receptor is discussed by J. Ghysdael and H. Beug. The second example is associated with a specific t(15,17) reciprocal translocation which disrupts the gene for retinoic acid receptor α and results in the formation of a fusion protein named PML-RAR. H. de The and A. Dejean discuss the possibility that it too is acting as a dominant negative oncogene. Both thyroid hormone and retinoic acid have extremely diverse actions in probably every tissue in the body: their role in normal growth and development is reviewed by V. K. K. Chatterjee, J. R. Tata and by G. Morriss-Kay, respectively. A. B. Roberts and M. B. Sporn discuss the intriguing possibility that TGF-β might act as key regulators of retinoids and steroid hormones in the control of cell growth. Finally, a number of chemicals that act as carcinogens in the liver stimulate the proliferation of organelles called peroxisomes. It has now been shown that members of the nuclear receptor family mediate the action of peroxisome proliferators and S. Green discusses a model for receptor-mediated carcinogenesis.

The reviews in this volume clearly demonstrate the progress that has been made in identifying and characterising many members of the nuclear receptor family. Much of this work has been facilitated by the use of artificial model systems and this type of work has certainly told us a great deal about what receptors are capable of doing. More now needs to be done to extend this work to more natural genes in target cells, particularly those encoding rate limiting factors involved in the process of cell growth.

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