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SOFT TISSUE TURMOURS AND THE STEROID HORMONE RECEPTORS

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INTRODUCTION

One hundred years ago, Georga Beatson laid the foundation for hormonal intervention in cancer by performing bilateral oophorectomy for advanced breast cancer and concluded: "We must look in the female to the ovaries as the seat of the exciting *cause of carcinoma*, certainly of the *mamma*, *in all probability of* the *female* generative organs generally, and possibly of the rest of body"[1]. It is known that, as with the female, the male reproductive system is also under strict steroid hormone control in both normal and disease states. Charles Huggins received the Nobel *Prize for* his great contribution to endocrine ablative surgery, *initially for prostate cancer* and later *on for breast cancer*[2]. These two *milestone in hormonal* tumour biology prompted further investigation into hormonal intervention *against cancer*. With subsequent scientific work, it is now evident that hormonal intervention can provide very effective therapy, not only for epithelial tumours, *but also for* non-epithelial soft tissue tumours.

SOFT TISSUE TUMOURS

Soft tissue tumours, *both benign and* malignant, arise from the mesodermally derived extraskeletal *tissues*. Consequently, *they develop in various anatomical sites even within visceral stroma* and neurovascular bundles. The malignant soft tissue tumours are more common in children, but relatively *uncommon* in adults, accounting for only 1% of all cancer. Soft tissue sarcomas represent 15% of all malignancies diagnosed in the paediatric population[3]. Soft tissue tumours are diverse in histology and *can arise anywhere* throughout the body including the extremities, the head and neck, the abdominal wall, the gastrointestinal tract and retroperitoneum, and the urogenital tract. Although the exact causal factor has not yet been established, the risk factors for soft tissue tumours may include post-radiation, post-chemical, *and post-drug* exposures, genetic predisposition, oncogene changes, and immunosuppression. Surgical resection with tumour-free margins is the treatment of choice in most cases of sarcoma with no evidence of metastasis. Elective regional lymphadenectomy is rarely indicated in patients with soft tissue sarcoma, and should be considered only in patients with epithelioid sarcomas. Although radiation therapy is sometimes required to increase the chance for local control, the role of adjuvant therapy in most soft tissue sarcomas remains controversial in terms of prolonging survival. The therapeutic outcome depends on various factors including the location, nature, and extent of the disease, and the adequacy of resection; the outcome

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and the adequacy of resection: the outcome varies from cure to fatality. Furthermore, the medical community is striving to find more effective methods of treatment for soft tissue tumours, especially sarcomas, because of the high incidence of distant metastases with high-grade lesions.

STEROID HORMONE RECEPTORS

In the body, all cells are exposed to steroid hormones, but their physiological actions are limited to those tissues which contain intracellular binding receptor proteins. These proteins specifically bind the individual classes of steroid hormones with high affinity and transmit the steroid signal to sensitive genes located throughout the chromatin. Steroid hormone receptors include oestrogen (ER), progestin (PR), androgen (AR), glucocorticoid (GR), mineralocorticoid, as well as the receptors for thyroid hormone, 1, 25-dihydroxy vitamin D3 (VDR), retinoids and so called 'orphan' receptors, which do not have recognized physiological ligands as yet.

With the advent of molecular biology, it became obvious that receptors for these hormones form a protein superfamily[4,5]. They are composed of comparable domains involved in ligand binding, DNA binding, dimerization, and transactivation. In each case the steroid receptors act as ligand inducible nuclear transcripton factors, with interactions between activated receptors and hormone response elements on the DNA directly modifying gene expression. The cloning of the steroid hormone receptors marks an important step forward in understanding the fundamental mechanisms of gene regulation and hormone action.

Because steroid sensitive tumours are relatively common, and because loss of their hormone sensitivity invariably worsens the prognosis for a patient, great attention has been paid to their study. Examination is the key to understanding the endocrine sensitivity of these tumours. The presence of steroid receptor proteins in histological specimens can often be assessed by means of either the conventional, commercially available steroid-binding assay (Dextran-Coated Charcoal), or immunohistochemistry by using a specific monoclonal antibody. By identifying receptors on individual cells, immunohistochemistry provides a valuable indication of the relative number of cells that do or do not contain receptor. The availability of the receptors can also be analysed by enzyme immunoassay, or Nothern blot analysis, or polymerase chain reaction.

ROLE OF HORMONE RECEPTORS IN TUMOURS

It is apparent that steroid hormone receptors are of great importance in the control of growth and development of steroid hormone sensitive tissues in their normal and disease states. This has been well controlled therapeutically with antihormonal drugs, which bind to these receptors, thereby competing with endogenous steroid hormones. Other mechanisms of action include inhibition of the epithelial growth factor, transforming growth factor-alpha (TGF-α), and stimulation of the epithelial inhibitory factory TGF- ß. Such hormone depletion is also achieved by surgical ablation of steroidogenic glands. The presence of steroid receptors in carcinoma of the breat and the prostate provides useful information concerning the likelihood of response to ablative or manipulative hormonal therapy. It also provides effective palliative treatment for those patients whose metastatic tumours are of the hormone-dependent type. Steroid receptors have also been identified in tumours not traditionally considered hormonally sensitive. These include carcinoma of the colon, kidney, lung, pancreas, and malignant melanoma. Moreover, there is accumulating evidence of the presence of steroid hormone receptors in mesenchymal tissues and in their malignant counterparts. The clinical significance of steroid receptors in these tumours has yet to be determined.

LITERATURE REVIEW

There are many clinical observations which suggest an endocrine correlation to the natural history of soft tissue toumours. Most histological types of sarcomas have better prognosis in younger patients of both sexes, with improved survival rates particularly evident in female. However, better survival in females appears to be inversely proportional to their menopausal status. There is apreponderance of juvenile nasopharyngeal angiofibroma in adolescent males, some of whom have been empirically treated with oestrogen[6]. However, data from these trials are minimal and allow no definitive conclusions to be drawn. Aggressive fibromatoses (desmoids) usually observed in young women appear to be stimulated by pregnancy, particularly those located in the anterior abdominal wall[7]. Similar observations have been found with a number of intracranial tumours, which could explain the frequency of meningiomas in women relative to men, their increased growth rate during pregnancy, and their association with breast cancer[8]. In contrast, fibroleiomyomatous hamartomas and benign metastasizing leiomyomas present in the lung undergo regression during pregnancy and the postpartum period[9].

The demonstration of sex steroid receptors in diverse human tumours including meningiomas, lung cancer, thymomas and lymphomas suggests the hormonal dependency of these tumours[10]. Therefore, a potential role for therapeutic hormonal manipulation in those meningiomas not responding to other therapy has been advocated. Recently, Carroll et al[11] found steroid receptors in astrocytic neoplasms, which suggests possible adjunct hormonal therapy for the treatment of astrocytom as may be useful. Moreover, lymphangioleiomyomatosis occurs exclusively in women, usually during child-bearing years and is characterized by proliferation of smooth muscle along the lymphatic vessels of the abdomen, thorax, and lung, resulting in interstitial and obstructive lung disease, recurrent pneumothoraxes, and chylous pleural and ascitic effusions. Banner et al.[12] have shown the efficacy of oophorectomy in this disease because of its hormonal dependency. This evidence is further supported by the immunohistochemical detection of steroid receptors in a case of pulmonary lymphangioleiomyomatosis[13,14].

It has been well established that the clinical response is correlated to hormonal therapy in breast and prostate carcinomas with specific steroid hormone receptors. Other than carcinomas, mammary soft tissue sarcomas, such as angiosarcoma, show sex hormone preponderance. Also angiosarcoma of the breast mostly affects the females of reproductive age group. Recently, specific steroid hormone receptors have been demonstrated in a case of angiosarcoma, which could indicate the possible role of hormonal manipulation in the treatment of the fatal disease of the breast[15]. On the other hand, steroid receptor expression was not demonstrated in stromal cells of phyllodes tumour of the breast; and the receptors were restricted to the luminal epithelial cells[16]. Therefore, the absence of steroid receptor expression suggests the ineffectiveness of hormonal therapy for phyllodes tumour of the breast. These findings also imply heterogeneity of expression between patients and within an individual tumour.

The presence of specific high-affinity, saturable cytoplasmic receptors for all cases of steroid hormones in a histologically diverse series of sarcomas clearly suggests that human soft tissue sarcomas located outside the reproductive tract may be hormonally responsive. Chaudhuri et al.[17] have indicated that receptor distribution in soft tissue sarcoma may be influenced by sex, the anatomical location of the lesion, and its histologic origin. Weiss et al.[18] have also demonstrated the steroid hormone receptors in soft tissue tumours of diverse histologic type. Recently,

Nielsen et al.[19] have demonstrated a high frequency of steroid hormone receptors in smooth-muscle tumours of the vulva and their frequent enlargement during pregnancy. Their findings suggest that steroid hormones may affect the growth of these tumours and that hormonal manipulation, especially in leiomyosarcomas, may have a role in their treatment.

CONCLUSION

Various clinical and laboratory observation suggesting hormonal dependency of some soft tissue tumours indicate that investigation of a larger group of patients amenable to statistical analysis is warranted. In conclusion, the presence of a specific steroid hormone receptor in soft tissue tumours raises the possibility of singling out those patients with hormone receptors for subsequent endocrine therapy. These findings may give rise to a new approach to the rational therapy of soft tissue tumours.

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