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Perspectives and Commentaries

Hormone Receptors and Cancer

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(A COMMENT ON: Hanauske AR, Osborne CK, Chamness G *et al.* Alteration of EGF-receptor binding in human breast cancer cells by antincoplastic agents. *Eur J Cancer Clin Oncol* **23**, 545–552, 1987.)

THE HORMONES through systemic secretion, the growth factors which are secreted near or by the target cell, can be viewed as regulators of biochemical processes which lead eventually to cell differentiation and cell division. Binding to receptors initiates the cascade of events which characterize the hormone biological activities. The receptors are specific for target cells and provide specific recognition of the hormone. They are complex proteins which appear to contain a full program of activation whereas the ligand, which may be a very simple and stable molecule, like the steroid hormones, acts only to get the information expressed by the receptor. Indeed, the steroid hormone receptors [1] are molecular adaptors with sufficient chemical complexity to interpret the complex code that specifies the genetic changes comprising the hormone response, and each steroid regulates the expression of different genes in different target cells. As a rule, the maximal biological response is achieved before all the receptors are occupied: hormone concentrations are thus limiting relative to number of receptors.

Two general patterns of hormone–receptor interaction have been recognized. Water-soluble hormones, like polypeptides or catecholamines, interact with cell surface receptors and, through cAMP or other soluble intracellular messengers, activate protein kinases and phosphatases which regulate cellular processes by phosphorylation and dephosphorylation mechanisms. Lipid soluble hormones, like steroids [2] and the thyroid hormones bind to specific nuclear receptors and increase their affinity for specific DNA regulatory elements; this hormone–receptor complex appears to associate with promoter/enhancer elements of specific target genes resulting in activation of transcription [1]. The same receptor molecule contains both recognition and activation regions, like the epidermal growth factor receptor which has an extracellular domain, a transmembrane domain and an intracellular kinase domain. The recognition and activation regions have been especially well defined recently for steroid hormone receptors [3]. Indeed, sequence comparisons together with mutation analysis have defined two conserved regions that correspond to important functional domains: the hormone-binding domain (region E) located in the C-terminal half of each of the receptors and a domain which determines the specificity of the receptor for the transcription of target genes (region C).

In normal cells the receptor concentrations are regulated. The homologous hormone regulates its own receptors in various ways, including internalization of cell surface receptors with or without accelerated destruction (down-regulation), reversible inactivation, translocation and insertion into membranes, biosynthesis or processing of nuclear receptors. Moreover, the pattern of gene regulation by a given steroid hormone is often strongly affected by the concerted action of other hormones with synergistic and permissive effects [1]; permissive effects reflect in some cases the induction by one hormone of functional receptors for another hormone, like estradiol which appears to permit the synthesis of the progesterone receptors.

A fundamental trait of tumor cells is a decreased dependence on growth factors for the promotion

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of their growth [4]. However, some tumors, like breast carcinoma, are still regulated by a variety of steroid and protein hormones. This is an important property since it allows, clinically, through the use of anti-estrogens for instance, one to control cell growth by chemical means and with minimal toxicity [5, 6]. Moreover, measurement of estrogen and progesterone receptor (ER, PR) concentrations are not only useful as predictors of a patient's response to endocrine manipulations but also as a prognostic index of the course of the disease and even of the pattern of relapse [6–8]: in primary disease the presence of ER has been shown indeed to correlate with favorable histologic and cell kinetic features. Although the evidence must still be considered inconclusive, breast tumors may be heterogeneous and contain cells with a mixture of various receptor positivities as well as completely autonomous cell types, a situation that profoundly influences the effectiveness of hormone therapy [8]. Moreover, some women with an ER-positive tumor fail to respond to hormonotherapy because of a defect in the intracellular cascade of events that normally controls the biological responsiveness to an endocrine stimulus. On the other hand, the natural history of estrogen-responsive breast cancer often involves a phenotypic change to an estrogen-unresponsive, more aggressive tumor. This is also found after hormonotherapy which, unlike chemotherapy, favors the selective proliferation of progesterone receptor-negative, more malignant clones [8].

How do tumors acquire partial or complete autonomy? In this regard, it should be recalled that the mechanisms of action of the proto-oncogene-encoded proteins are few. In the cytoplasm these proteins may regulate levels of critical second messenger molecules along the pathway that determines the cell response to growth stimulatory factors; in the nucleus, these proteins may modulate the activity of the cell transcriptional machinery. The evidence suggests that the activities of these cytoplasmic and nuclear oncogenes products are complementary rather than additive [4]. In view of their mechanisms of action, the hormone receptors play an obvious role in oncogene activation and can even assume the role of oncogene-encoded proteins when constitutively activated in the cytoplasm or deregulated in the nucleus [4]. Moreover, their structure has been found to be homologous to that of the products of known viral oncogenes [3, 4], the epidermal growth factor (EGF) and insulin receptors being similar to the product of avian erythroblastosis v-erb B, steroid and thyroid hormone receptors being similar to the product of v-erb A, whereas the macrophage colony-stimulating factor receptor is closely related to the transforming gene of the feline sarcoma virus, v-fms. In this regard, various abnormalities of receptor structure and function have been described in tumor cells including amplification of EGF receptor gene in epidermoid carcinoma cells [9], constitutive activation of insulin receptor by translocation in leukemia [10], development of ectopic receptors in pituitary tumors allowing cells to respond to hormonal signals to which they are normally unresponsive, mutation of glucocorticoid receptors becoming constitutive activators of transcriptional enhancement [11]. Concerning breast cancer, the HER-2/neu oncogene, which is related to but distinct from the EGF receptor, has been shown recently to be amplified in 30% of primary tumors, this amplification being a significant predictor of both overall survival and time to relapse in the node-positive patients [12]. In addition, excessive expression of receptor function in tumor cells may result from an abnormal upstream activation due to autocrine secretion of growth factors: for instance, transforming growth factors (TGF-α) which are EGF related and potent mitogens have been found to be constitutively secreted at high levels by some estrogen-independent human breast cancer cell lines; moreover, the secretion of TGF-α can be stimulated by estradiol in estrogen-responsive cells, which may account in part for the tumorigenic activity of estradiol in human breast cancer [13].

It is therefore reasonable, as described by Hanauske *et al.* in a recent issue of this Journal [14], to look for cytotoxic drugs which by their effects on cell membranes might interfere with growth factor–receptor interactions. The authors show that cisplatin and vinblastine at high concentration can inhibit the binding of EGF to human cancer breast cells. Obviously, one major disadvantage of chemotherapy in this regard is its lack of specificity. Unlike tamoxifen for instance, which is a specific antagonist of estrogens, these cytotoxic drugs are not expected to distinguish receptors for EGF from receptors to other protein hormones, including negative growth factors, like TGF-β, which can be released by cells to control their own growth. Nevertheless, a therapeutic effect by this mechanism is quite possible. For that matter, it may be relevant that vinblastine therapy has recently been shown to be effective in idiopathic thrombocytopenic purpura, this effect being associated with a decrease in the number of available F_c (IgG) receptors on phagocytic cells [15].

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