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EDITORIAL

Receptors on Tumors Studied with Radionuclide Scintigraphy

In a word, vital phenomena are the result of contact between the organic units of the body and the inner physiologic environment.

Claude Bernard, circa 1865.

In the mid-1800s, a great debate raged among biologists about whether or not a kind of inner force animated and empowered living beings. It was argued that this vital force, the essence of life, existed outside of the natural physical laws governing inanimate objects. Ultimately, scientific evidence revealed something even more miraculous than this, namely that the phenomenon of "living' was based on a complex balance of multiple discrete influences from an inner physiologic environment on the organs, tissues, and cells of the body. In health, these influences result in a "reciprocal harmony" that endows living creatures with a spontaneity of action and a control over the external environment, which is not a property of inorganic objects.

Cancer amounts to a terrible disturbance of the reciprocal harmonies of this internal environment. Certain cells develop a destructive pattern of growth and the ability to metastasize from natural positions within the body to unnatural sites. The basic understanding of the complex derangements that result in a malignant tumor is still incompletely known. However, there is growing evidence for the major role of specific hormones and "growth factors" in promoting and sustaining the malignant state (*1*).

Tumor cell growth may be influenced by hormones and growth factors produced remotely in distant glands and tissues (endocrine effects); by adjacent cells and tissues (paracrine effects); or even by growth factors produced by the tumor cells themselves (autocrine effects) (*2*) (Fig. 1). Certain of these systems such as the effect of estrogen on breast cancer cells, or TGF-alpha, directly stimulate growth by acting at the level of the epidermal growth factor receptor (*3*). Several growth factors are actually inhibitory in action, including somatostatin, TGF-beta, and a 30-kilodalton molecular weight protein that has been recently described to bind to erb-b-2 receptor (*4*).

Such inhibitory substances may potentially have anti-tumor effects. Similarly, antibodies which block growth factor action are also of potential therapeutic importance (*5*).

Sometimes growth factors are previously well-characterized hormones, such as somatostatin, as in the case of the companion article to this editorial (*6*). Somatostatin, a hormone produced in the hypothalamus and the pancreas, has an inhibitory effect on the secretion of many important gastric hormones, including growth hormone, insulin, as well as the secretion of acid by the stomach. Many endocrine-related tumors, including carcinoid tumors, meningiomas, gastrinomas, pancreatic endocrine tumors, and paragangliomas have high affinity receptors for somatostatin (*7*). Direct action of somatostatin on these receptors may have therapeutic benefits by inhibiting tumor growth.

However, somatostatin itself does not have favorable properties as a therapeutic agent, since it is neutralized within a short time after intravenous injection. For this reason, analogues of somatostatin have been developed that have more favorable pharmacokinetics, including a longer duration of action. One of these is the somatostatin analogue octreotide (*8*).

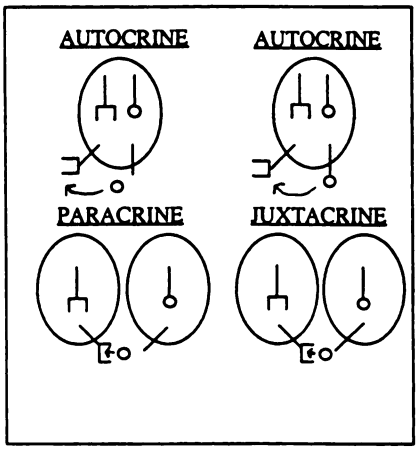

FIGURE 1. Hormonal effects and the "internal environment" in the region of the tumor cell. The cell secretes a growth hormone (O) that interacts with the receptor (U) to stimulate cell growth. Both receptor and hormone are shown with a straight protein tail (—) that represents a protein-connecting piece inserted in the membrane of the tumor cells after manufacture of the hormone or receptor complex by the cell. The hormone may be actively secreted into the external environment of the tumor cell (upper left) and stimulate the receptor directly. Alternatively, the receptor complex may interact with the hormone complex, while both hormone and receptor are fixed in the cell membrane of the tumor cell. These two modes are both "autocrine" effects, since the tumor cell produces a hormone that affects its own growth.

The paper by Bakker et al. (*6*) on the use of the iodinated somatostatin analogue, ^{123}I-tyr-3-octreotide, is representative of a new class of tumor imaging studies that are based on the binding and uptake of highly specific radiotracers that target functional components of the tumor cell, in this case the somatostatin receptor. Details of the biodistribution of the tracer in vivo, its metabolism and body clearance, as well as estimates of radiation absorbed dose, are presented.

The authors point out potentially important practical uses of such radiotracers (e.g., "apart from the detection of previously often unknown metastases or multiple tumor localizations with whole body scintigraphy, the visualization of somatostatin receptor-positive tumors may predict possible success of octreotide . . . therapy . . . .).

Previous studies by this same group have documented that in comparison to somatostatin the ^{123}I-tyrosine octreotide: (a) competes in the nanomolar range for binding at the somatostatin receptor; (b) has comparable biologic activity in inhibiting secretion of growth hormone by cultured rat pituitary cells (*9*); (c) is an excellent diagnostic imaging agent for patient studies of endocrine tumors (*10*). In previous studies by Lamberts et al. (*11*), there was a relationship between the ability to take up the ^{123}I-octreotide and the responsiveness to somatostatin analogues, in terms of growth suppression of these malignancies. Thus, the investigators have shown that this compound is highly interesting for diagnostic imaging and also has important potential for biologically characterizing tumors.

It is possible that quantification of receptors may play a role in the future of tumor-receptor scintigraphy, perhaps in order to determine optimal treatment schedules for a compound like octreotide. To date, the studies of receptors on tumors have been largely qualitative, and gamma camera and even SPECT methodologies are difficult to adapt to a more rigorous quantification technique. However, positron emission tomography is inherently quantitative, and methods have already been developed to assess the concentration of specific cell-associated receptors based on external imaging (*12,13*) and even to apply such methods therapeutically to determine more optimal treatment strategies (*14*) (e.g., occupancy of dopamine receptors during therapy of schizophrenia with dopamine antagonists). By extension, it may become important in the future to determine the presence and approximate concentration of tumor-associated receptors against which therapy is planned; to determine the level of occupancy of such receptors during the course of therapy; and if possible, to monitor a metabolic response parameter of tumors (such as the assimilation of ^{11}C-methionine) by pituitary tumors that respond to bromocryptine, a dopamine receptor antagonist (*15*).

If positron labels can be found for ligands such as octreotide (^{124}I-124, half-life 4 days, could be used) or if SPECT methods can be made truly quantitative, it is possible that quantitative somatostatin receptor measurements could be made with radioiodinated octreotide. Before such a goal becomes a reality, however, it will be necessary to do much more detailed pharmacokinetics and analysis of metabolites than are reported in the paper by Bakker et al. For a review of some of the considerations in developing a method for receptor quantification based on external imaging methods, please refer to a paper by Sawada et al. (*16*). Sawada et al. discuss the presence of labeled metabolites in tissue after intravenous injection; the amount of ligand in blood as a function of time and its protein bound fraction; the rates of tissue transport; and the amount of "nonspecific" binding in tissues.

New knowledge in this field of growth factors and tumor-associated receptors is being added rapidly. A listing of some of the more common growth factor systems of relevance to nuclear medicine is shown in Table 1 (*6,9–11,17–25*). Antibodies may be potentially useful as probes to detect receptors and also to quantify receptor number. However, much work needs to be done to develop formal quantitative methods based on antibody binding to receptors. Still, in a semiquantitative sense, the studies of anti-epidermal growth factor anti-

TABLE 1
Tumor-Associated Receptors Imaged by Radioisotopic Scintigraphy

Receptor	Tumor type	Radiopharmaceutical
Transferrin	Lymphoma, Lung	^{67}Ga-citrate (*20, 21*)
Estrogen	Breast	^{18}F-estradiol (*23*)
Somatostatin	Endocrine-related	^{123}I-somatostatin-like (*6, 9–11*)
EGF	Lung, glioma, breast	Monoclonal antibodies, labeled with ^{131}I (*18*), ^{111}In (*19*), ^{125}I (*22*)
EGF	Cervical cancer	^{123}I-epidermal growth factor (*17*)
Dopamine	Pituitary tumors (prolactinomas)	^{11}C-(N)-methylspiperone (*24*)
Bombesin	SCLC	^{111}In-labeled anti-bombesin monoclonal antibody (*25*)

bodies are encouraging because the highest uptake was seen after injection into nude mice bearing human tumors expressing high receptor concentration; medium uptake in tumors with medium receptor concentration; and low uptake in tumors receiving low uptake (*26*). Based on animal studies, other tumor-associated receptors that seem to show promise in regard to potential for imaging include peripheral benzodiazepine receptors (*27*).

George de Hevesy stated that "by adding a radioactive isotope to atoms or molecules, we can label these and follow their path. That the labeling device was bound to find a very extended field of applications was clear already in 1913 when it was first applied . . ." (*28*).

Knowledge about tumor cell-associated receptors, particularly in relationship to the growth of cancer cells, owes much to the tracer principle as applied to in-vitro systems. Now, with modern nuclear medicine imaging methods, we see this new knowledge about cancer cells put to use in studies that actually characterize biologic features of tumors in situ in the host. Current methodology allows for both detection of the presence of tumors as well as detection of the presence of specific receptors on tumors. Such methods are useful for both diagnosis and staging of tumors and also for predicting response of these same tumors to receptor-mediated anti-tumor strategies. In the future, more quantitative methods for determining receptor number should be developed in order to derive more precise biologic and clinical inferences from the in vivo expression of tumor-associated growth factor and hormonal receptors.

ACKNOWLEDGMENTS

The author wishes to acknowledge the valuable suggestions of Dr. John Mendelsohn, who provided Figure 1.

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