Somatostatin and Cancer

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The potential role of somatostatin (SRIF) in the diagnosis and treatment of nonendocrine human cancers is reviewed. There have been many reports of the growth-inhibitory activity of SRIF on normal and transformed cells in vitro. Many processes involved in malignant tumor growth depend on autocrine growth mechanisms, and somatostatin receptors (ssts) are present on many human cancers. It is possible that mutations in ssts result in a loss of check on proliferation in cancer cells. SRIF analogs may have a number of roles in clinical oncology. Use of radiolabeled tracers enables imaging of tumors bearing ssts; newer agents may enable positron emission tomography (PET) analyses or may be used to deliver lethal radiation doses to cells bearing a unique subset of sst. Although the ability of SRIF and its analogs to inhibit cellular proliferation has been shown in vitro, it has yet to be demonstrated in humans with cancer. Clinical improvements seen with SRIF or its analogs in cancer patients may be related to indirect effects, such as pain relief, reduction of gastrointestinal side effects of chemotherapeutic agents, effects on local production of growth factors, and inhibition of tumoral angiogenesis. Thus, with regard to their potential therapeutic role, SRIF analogs are likely to be used only in conjunction with other approaches, such as radiation, immunotherapy, chemotherapy, and growth factor modulation. Further research into the fundamental functions of each of the ssts and the intracellular actions of SRIF analogs will be needed to assess the potential usefulness of the latter in slowing the progression of human cancers.

CELLULAR SOMATOSTATIN (SRIF) receptors are present in many endocrine and neuroendocrine tumors (benign and malignant) and provide a basis for diagnosis and treatment of these neoplasms. This review will focus on the potential role that SRIF may play in the diagnosis and treatment of nonendocrine cancers, which affect larger numbers of patients worldwide.

HISTORICAL PERSPECTIVES ON THE USE OF SRIF TO REDUCE CELL PROLIFERATION

Soon after the initial description of SRIF in 1973,[1] reports that the peptide could inhibit the proliferation of normal[2] and transformed cells[3] began to appear. This growth-inhibitory activity has been attributed to several mechanisms, including inhibition of adenylate cyclase, changes in intracellular calcium levels,[4] alterations in membrane ionic conductances, and modulation of intracellular kinases and phosphatases. Seminal studies by Sussman et al[5] and Catalan et al[6] documented the ability of SRIF to reduce protein kinase activity and increase phosphoprotein phosphatase activity, respectively. The early report of Mascardo and Sheline,[3] demonstrating that centrosomal separation may be inhibited by SRIF, was provocative, but has yet to be verified.

CELLULAR MECHANISMS OF SRIF ACTION

Many of the processes involved in malignant tumor growth depend, in part, on autocrine mechanisms. This involves elaboration of a factor(s) that can bind to receptors on the cell of origin and stimulate growth. Factors that have been shown to be involved include epidermal growth factor (EGF), insulin-like growth factor-1 (IGF-1), and bombesin. Modulation of putative autocrine growth loops could be accomplished by the inhibition of growth factor secretion, by the downregulation of specific growth factor receptors, by suppression of intracellular signaling transcription systems, or by directly interfering with the transcription machinery necessary for generating growth proteins.

SRIF RECEPTORS

The utility of SRIF and it analogs in clinical oncology requires the presence of SRIF receptors (sst) on one of the following components: tumor cells, tumoral vascular endothelial cells, local cells that may produce growth factors, or distant cells producing endocrine growth signals. Analysis of many human cancers demonstrates that ssts are present, and furthermore, that multiple receptors may be present on a single cell type. The association of specific sst types with certain intracellular effectors is just beginning to be understood.[7] To date, five different mammalian ssts have been identified ($sst_{1\text{-}5}$), each encoded by a unique gene. It appears that transcripts for the receptors are present in many diverse tissues and in neoplastic cells. Inhibition of proliferation has been demonstrated by activation of sst_2 and sst_5, but does not appear to be mediated by sst_3 or sst_4.[7] Finally, following the pattern of oncogenes acting as surrogate components of growth factor signaling pathways, it is possible that mutations in ssts may result in loss of a check on proliferation, analogous to a p53 mutation, resulting in unchecked growth of a clone of cells. Such a possibility has recently been reported in a lung cancer cell line.[8]

CLINICAL APPLICATIONS

In addition to potential therapeutic applications of SRIF analogs in clinical oncology, the use of radiolabeled tracers has enabled investigators to image tumors, some of which appear to lack ssts. The human nonendocrine cancers that have been visualized in situ by SRF analog scanning are

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0026-0495/96/4508-1008$03.00/0

listed in Table 1. Efforts to increase the sensitivity and specificity of these imaging agents are ongoing. Newer agents may enable positron emission tomography (PET) analyses, while others may be constructed to deliver lethal radiation doses to a subset of cells expressing unique ssts. Pharmacological maneuvers, such as pretreatment with low-dose octreotide, may upregulate the levels of ssts in certain tumors. Creation of ligands that are highly specific for each sst will provide new insights into the biology of both the tumors and SRIF.

Although many studies using transformed cell lines, cell lines derived from human tumors, and animal models[9] have demonstrated that SRIF or its analogs can inhibit cellular proliferation (see other reports in this supplement), this promise has not yet been realized in humans with cancer. Clinical research efforts that have investigated the potential usefulness of SRIF analogs in nonendocrine cancer patients are listed in Table 2.

Some of the clinical improvements in cancer patients may be related to indirect effects of SRIF. For instance, SRIF has notable pain-relieving effects, occurring possibly via interactions with subsets of opioid receptors.[7] SRIF is also helpful in reducing the gastrointestinal side effects, such as diarrhea and hypermotility, of chemotherapeutic agents. Additional indirect effects of SRIF analogs may be mediated by the effects of the peptides on local production of growth factors, which keep the tumor cells progressing through the cell cycle. This effect has been demonstrated in vitro with fibroblasts derived from breast cancer tumors.[10] Another potential effect of SRIF analogs is the inhibition of tumoral angiogenesis[11,12] by reducing production of angiogenic factors or their receptors or by altering tumoral blood flow.

Table 1. In Vivo Imaging of Human Cancers

Tumor Type	Imaging Agent	% Positive	Reference
Renal cancer	^{111}In-pentetreotide	72	13
Breast cancer	^{111}In-pentetreotide	75	14
Lung cancer	^{123}I tyr^3-octreotide	84	15
Lung cancer	^{111}In-pentetreotide	100	16
Lung cancer	^{111}In-pentetreotide	100	17
Lung cancer	^{111}In-pentetreotide	90	18
Meningioma	^{111}In-pentetreotide	100	19
Meningioma	^{111}In-pentetreotide	100	20
Lymphoma	^{111}In-pentetreotide	86	21
Thyroid cancer	^{111}In-pentetreotide	75	22
Hodgkin's disease	^{111}In-pentetreotide	91	23
Lymphoma	^{111}In-pentetreotide	62	24
Neuroblastoma	^{111}In-pentetreotide	75	25
Paraganglioma	^{123}I tyr^3-octreotide	100	26
Paraganglioma	^{111}In-pentetreotide	95	27
Melanoma	^{111}In-pentetreotide	75	28
Glioma	^{111}In-pentetreotide	57	29
Astrocytoma	^{111}In-pentetreotide	80	30

Table 2. Activity of SRIF Analogs in Human Cancers

Type of Cancer	Analog	Response	Reference
Prostate	BIM 32014	Minimal benefit	31
Prostate	BIM 32014	40% increased PS 20% lower PSA	32
Colon	Octreotide	No change in survival	33
Colon	Octreotide	Decreased proliferation index	34
Breast	Octreotide	No clear benefit	35
Breast	Octreotide	No clear benefit	36
Breast	Octreotide	No clear benefit	37
GI cancers	Octreotide	No clear benefit	38
SC lung cancer	Octreotide	No clear benefit	39

Abbreviations: GI, gastrointestinal; SC, subcutaneous; PS, performance status; PSA, prostate-specific antigen.

FUTURE CONSIDERATIONS

It is unlikely that an SRIF analog by itself will be able to stop the cell cycle or induce apoptosis in malignant cancers, such as those arising in the lung or breast. Further research into these two events may identify potential intracellular activities, such as phosphorylations, that may be blocked by highly selective SRIF analogs. It is more likely that SRIF analogs will play a contributory role in conjunction with other approaches, such as radiation, immunotherapy, chemotherapy, or growth factor modulation.[40,41] Further research into the fundamental actions that are linked to each of the newly discovered ssts will be critical for the field to progress. At this point, it seems premature to continue with any clinical studies other than safety and dose-tolerance trials using SRIF analogs. Their usefulness in slowing the progression of human cancer will require a more complete understanding of their intracellular actions and interactions.

The principal challenges for the future are therefore as follows: (1) to encourage more research into the biology of sst subtypes in specific human cancers; (2) to develop highly selective analogs for imaging and therapy; (3) to combine the use of SRIF analogs and conventional chemotherapy or radiotherapy in selected tumors; (4) to explore the use of analogs to deliver radiotherapy or toxins to cells expressing one class of sst; and (5) to further define the mechanisms that upregulate tumor-specific ssts.

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