The Role of CCK in Tumor Growth

T.E. Solomon

Cancers of the gastrointestinal tract, particularly those of colonic, pancreatic, and gastric origin, are major causes of disability and death in the Western world. There has been little progress in our understanding of the causes and progression of these diseases in spite of remarkable advances in the area of tumor biology. One such advance is the realization that "growth factors" may modulate the proliferative rates of malignant neoplasms. Peptides such as epidermal growth factor, the transforming growth factors, and several others may affect tumor growth through direct actions on tumor cell receptors, receptors may be "overexpressed" in tumor cells, and these factors may even be synthesized and released by tumor cells to initiate autocrine growth stimulation. It is also possible that other substances, such as gastrointestinal hormones, may modulate cancer cell growth rates. This idea comes from the well-known trophic effects of gastrointestinal peptide hormones on various target tissues, and the possibility that malignant cells originating from these tissues may retain specific hormonal receptors that still influence proliferation. CCK is a potent growth stimulant of the normal exocrine pancreas [1], and many studies have used this background as an impetus to determine whether CCK also affects pancreatic cancer growth. Several reviews are available on the topic of gastrointestinal hormones and their potential role in pancreatic and other gastrointestinal cancers [2–6].

Pancreatic cancer in humans occurs more commonly in men than women and shows a progressive increase with age; its incidence has increased dramatically in the past 70 years [7]. There are rather vague suggestions that, among several risk factors, diets high in meat and fat increase the incidence of pancreatic cancer [8]. This suggests that the protein and fat components of such diets may elevate plasma CCK levels and predispose subjects to growth promotion of cancer cell clones. Overall, there is no convincing data to support any connection between risk factors and development or course of pancreatic cancer, however. It would be useful to determine whether subjects at risk of developing pancreatic cancer

1 Kansas City, VA Medical Center, 4801 Linwood Blvd., Kansas City, MO 64068 USA
have elevated plasma CCK levels over long periods of time and whether patients with pancreatic cancer have altered plasma CCK levels. Whatever the results of such studies, it is still possible that growth rates of pancreatic malignancies may be modulated by normal levels of circulating CCK. It would also be of interest to determine the presence of CCK receptors on primary pancreatic cancers and the presence of CCK gene expression products in such tissue.

Experimental studies on the effects of CCK on pancreatic cancer growth can be broadly divided into those using various animal-derived tumors and those using tumors of human origin. Considerable information can be gained about the general properties of pancreatic cancer growth regulation in experiments with animal-derived neoplasms, but human cancers must ultimately be studied to define potential growth regulatory and therapeutic effects associated with CCK. Thus, most of the work discussed here will involve studies on human pancreatic cancer cell lines grown in vitro or as xenografts in the immunodeprived nude mouse. These two systems each have advantages: in vitro studies allow careful control of the hormonal medium, fairly rapid characterization of growth effects, and the ability to perform many experiments under similar conditions; in vivo studies provide a system in which to determine the effects of dietary manipulation, sex, age, and other host factors.

In the few available studies with xenografts of human pancreatic cancer in nude mice, results suggest that endogenous CCK can modulate tumor growth. Hudd et al. [9] administered an extremely large dose of CCK-8 (50 μg/kg twice per day for 2 weeks) to groups of mice bearing either early passages of four different primary nonpancreatic tumors or two different established pancreatic cancer cell lines. In two of the groups bearing non-pancreatic cancers, tumor growth was suppressed. No effects were seen in the groups bearing pancreatic cancers. The lack of data on lower doses of CCK makes these results difficult to interpret. Smith et al. have examined the effects of CCK, a high fat diet, and the CCK receptor antagonist L-364 718 on growth of the established human pancreatic cancer cell line SW-1990 in nude mice [10,11]. Large doses (5, 15 or 25 μg/kg twice per day s.c. in gelatin for 4 weeks) of a synthetic CCK analog increased several measurements of tumor growth after 4 weeks of treatment [10]. In other studies, it was found that tumor xenografts in mice fed a high fat diet grew more rapidly than those in mice fed a normal diet [11]. The CCK receptor antagonist L-364 718 reversed the effects of the high fat diet and also slowed the growth of the tumors in mice on a regular diet. Although these findings are suggestive of a growth effect of endogenous CCK, further data on plasma CCK levels would be helpful, as would studies with a greater number of cancer cell lines. In a related study, Alexander et al. [12] found that bombesin, a releaser of CCK in some species, inhibited the growth of a human pancreatic cancer xenograft but stimulated pancreatic growth in the host animals. Again, measurements of plasma CCK in response to bombesin