of the efficacy of the prostate-specific antigen test in finding lesions that were then biopsied and reported as cancer but have not (at least, not yet) displayed the morbidity and mortality characteristic of prostate cancer. A 1974 spike in the reported incidence of cancer of the breast came at a time when the wives of the U.S. president and vice-president had breast cancer and coincided with the first broad public attention to mammography. That spike was not followed by any change in mortality detectable at the national level. Similarly, there is evidence that lung cancer screening programs lead to the detection and treatment as cancer of many lesions with prognoses far better than the usual forms of lung cancer. There are parallel chains of evidence for cancer of the thyroid and ovary.

Whether these newly detected lesions should even be called ‘‘cancer’’ is not always clear. Microscopic appearance may be the best surrogate yet found for the future biologic behavior of a lesion, but ‘‘best’’ in this context does not necessarily mean good enough. There is little point in argument about whether the new approach to the diagnosis of cancer leads to over-diagnosis, or the old one to under-diagnosis; the important thing is that they lead to incomparable results, and the broadening definition of cancer can create an impression of an alarming rise in incidence with little change in the biologic situation.

What is needed is a new way to define a ‘‘gold standard,’’ suitable for routine use in the practice of oncology, that is a better predictor of future biologic behavior than is microscopic appearance. This is likely to be a difficult task, but the time to start is now.

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References


Note

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Re: Expression of Somatostatin Receptor Subtype 1–5 Genes in Human Pancreatic Cancer

Recently, Fisher et al. (1) examined messenger RNA (mRNA) expression of the somatostatin receptor subtypes (sst1–5) in 11 specimens of pancreatic adenocarcinoma tissues and nine human pancreatic cancer cell lines. Several tumors and cell lines expressed multiple subtypes, including sst1, sst2, and sst5. However, only one cell line (MIA PaCa-2) displayed high-affinity binding sites for somatostatin-14. Fisher et al. concluded that a defect of receptor protein expression at the cell surface in pancreatic cancers could provide an explanation for the failure of somatostatin analogues to delay tumor progression as observed in clinical trials.

We previously demonstrated that the receptor sst2 mediated the antiproliferative effect of somatostatin analogues in vitro, through the activation of the tyrosine phosphatase SHP1 (2,3). It is interesting that we and Fisher et al. found that the sst2 subtype was expressed in MIA PaCa-2 cells grown in vitro (4) or in vivo (by xenograft into athymic mice) (5). Expression of sst2 in MIA PaCa-2 cells correlates well with 1) the high affinity of RC-160 (a somatostatin analogue) for somatostatin receptors described in these cells (6) and 2) the antiproliferative effect of the treatment with this analogue for both in vitro cell culture and in vivo in the xenograft model (6). We previously evaluated the sst1–5 mRNA expression on both primary and metastatic pancreatic adenocarcinoma specimens and human pancreatic cell lines by use of reverse transcription and polymerase chain reaction (4). We also detected the presence of multiple sst mRNAs but, in comparison with normal pancreatic tissue specimens, we observed a specific loss of sst2 subtype expression in tumor tissues and in most of the cell lines tested. We thus concluded that the loss of sst2 expression in pancreatic cancer could confer a growth advantage for these tumors and could provide one of the explanations for the frequent lack of therapeutic effect of somatostatin analogues adminis-

tered in such adenocarcinomas. We confirmed this hypothesis after stable transfection of human sst2 in the two pancreatic cell lines BxPC-3 and CaPan-1 (both did not express sst2 normally), resulting in the decrease or suppression of both in vitro and in vivo tumorigenicity (7).

Besides sst2, we also demonstrated that sst1 and sst5 mediated the antiproliferative effect of the stable somatostatin analogues (2). These subtypes are also expressed in human pancreatic cancers but, until now, no data were available about their expression at the protein level as well as their functional properties in human pancreatic cancer cells. Moreover, as Fisher et al. (1) discussed, expression of sst mRNAs in human tissues does not necessarily imply a relevant expression of sst at the protein level. This fact was demonstrated by negative ligand-binding experiments and the absence of an antiproliferative effect in several cell lines after treatment with somatostatin.

In conclusion, all existing data (including those from clinical studies evaluating somatostatin analogue scintigraphy in patients with pancreatic cancer) argue in favor of a frequent defect of somatostatin receptor subtype expression at the mRNA or protein levels. Immunocytochemical studies are required to advance the knowledge of sst expression in pancreatic cancers. Moreover, specific and sensitive immunocytochemical tools would allow selection of sst-positive tumors that could respond to somatostatin analogue adjuvant therapy.

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References

(3) Lopez F, Esteve JP, Buscail L, Delesque N, Saint-Laurent N, Theveniau M, et al. The ty-
rosine phosphatase SHP-1 associates with the sst2 somatostatin receptor and is an essential component of sst2-mediated inhibitory growth signaling. J Biol Chem 1997;272:24448–54.


Note

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