The serine protease inhibitor Kazal type 1 (SPINK1) was initially isolated from bovine pancreas by Kazal and colleagues. A similar protease inhibitor was later identified in human pancreatic juice and called “pancreatic secretory trypsin inhibitor.” By means of immunologic techniques, SPINK1 was later identified as a tumor-associated peptide and isolated from the urine of a patient with ovarian cancer. Hence, it was called “tumor-associated trypsin inhibitor” (TATI) (1). This name has been used in most studies of its use as a tumor marker [reviewed in (2)]. TATI was shown to be a serum and urine marker for many types of cancer, but it was not found to be superior to earlier known markers that had been identified for diagnostic use. It was an independent prognostic marker for several types of cancer, however. Tumors producing SPINK1 have been shown to also produce trypsin, and because trypsin activates matrix metalloproteinases, which have been shown to mediate cancer invasion, an association between SPINK1 production and an adverse prognosis in cancer was ascribed to its coproduction with trypsin. SPINK1 was thought to have a role in cancer similar to the one it has in the pancreas, where it protects the pancreas by inhibiting prematurely activated trypsin (2).

Mechanisms by which SPINK1 could exert alternative functions were suggested by its structural similarities with epidermal growth factor (EGF): a 50% sequence homology, a molecular size of approximately 6 kDa, and the presence of 3 intrachain disulfide bridges (2). This similarity with EGF prompted studies on the ability of SPINK1 to act as a growth factor. In 1985, SPINK1 was shown to bind to surface receptors and to stimulate DNA synthesis in fibroblasts, but EGF and several other growth factors did not compete with SPINK1 for binding. Results supporting the role of SPINK1 as a growth factor have been obtained in several recent studies. SPINK1 has been identified as a tumor-promoting factor in studies of altered gene expression in prostate and breast cancer and by proteomic analysis of the spent medium of colon cancer cell lines (3–5). SPINK1 has been shown to be the major proinvasive factor produced by colon cancer cells. The long-term prognostic value of SPINK1 has further been demonstrated by findings of its production in tissues in studies of archival samples of prostate, hepatocellular, colon, and breast cancers (2–5).

The role of SPINK1 in tumor growth has also been confirmed experimentally in tissue culture studies and by studies of tumor xenografts in immune-deficient mice. Recombinant SPINK1 increases the invasion in collagen gel by several colon cancer cell lines, but a SPINK1 mutant, SPINK1 K18Y, which does not inhibit trypsin, has no effect on invasion. Furthermore, an antibody to SPINK1 inhibits the invasiveness of HT29 5M21 cells (4). In patients with colorectal cancer, high serum concentrations of SPINK1 have been shown to indicate an adverse prognosis (2).

A recent study by Ateeq et al. has focused attention on the role of SPINK1 and, potentially, its use as a target in the treatment of prostate cancer (3). SPINK1 is known to be produced in the prostate and in prostate cancer, and its production increases with a higher tumor grade (2). Strongly increased SPINK1 production is found in about 10% of all prostate cancers, and this feature is associated with an adverse prognosis. In surgically resected patients, increased SPINK1 production is inversely related to E26 transformation–specific (ETS) rearrangements, but that is not the case in endocrine-treated patients (2). Ateeq et al. investigated the mechanisms by which SPINK1 is associated with an adverse prognosis in prostate cancer (3). They showed that SPINK1 induces an aggressive phenotype of the prostate cancer cell line 22RV1. Knock-down of SPINK1 production reduced these effects, whereas forced production increased cell proliferation and invasiveness. Administration of a monoclonal antibody to SPINK1 reduced cell proliferation and the invasion and growth of SPINK1-producing 22RV1 tumor xenografts in mice. This inhibitory effect was enhanced by coadministration of EGF receptor (EGFR) antibodies (3). SPINK1 has been shown to exert its effect by binding to EGFRs, but other mechanisms could also be in-
volved. There are 4 EGFRs, which are activated by several growth factors, and these factors have been classified on the basis of which receptors they activate. SPINK1 is now classified as an EGFR ligand, but thus far, it is not known which receptor or receptors it activates and which are produced in the prostate. The fact that EGF does not compete with SPINK1 for binding to cell surface receptor suggests that SPINK1 binds to different EGFRs (2).

SPINK1 may be secreted by the same cell that it stimulates, and thus it can be classified as an autocrine growth factor. Xenograft experiments have confirmed it to be druggable, and because of the effect of SPINK1 antibodies on prostate, colon, and breast cancer xenografts, it has been suggested that humanized monoclonal antibodies to SPINK1 should be developed for cancer therapy (3–5). Although this approach is analogous to the use of EGFR antibodies, it might carry adverse side effects. SPINK1 protects the pancreas from premature activation of trypsinogen, and in humans, interference with this mechanism may increase the risk of pancreatitis.

A few studies on the use of EGFR inhibitors to treat prostate cancer have been performed, and a response has been observed in about 10% of the cases. Interestingly, this is the proportion of prostate cancers that show increased SPINK1 production; however, it is not known whether the response is associated with SPINK1 production and whether combined use of EGFR inhibitors and SPINK1 antibodies would improve the response (2).

An interesting question is whether increased circulating concentrations of SPINK1 contribute to cancer development. The SPINK1 (serine peptidase inhibitor, Kazal type 1) gene contains an interleukin-6–responsive element, and in hepatoma cells, the production of SPINK1 is induced by interleukin-6 and interleukin-1. Thus, it is not surprising that SPINK1 also behaves as an acute-phase reactant in patients with severe injury and infections. There is a strong association between infections and cancer, and it is therefore tempting to speculate that infections causing increases in inflammatory cytokines cause increased SPINK1 production, thereby contributing to increased cancer risk (2).

Although SPINK1 is primarily thought to act as an autocrine growth factor, the addition of SPINK1 to culture medium also increases the invasiveness of tumor cells that do not produce it (3). Therefore, conditions with increased plasma concentrations of SPINK1 may provide information on its role in cancer development. Patients on hemodialysis have highly increased plasma concentrations of SPINK1, and they also are at increased risk of cancers of the kidney, bladder, and endocrine organs, but not of other cancers that have been associated with increased SPINK1 production. The mechanisms behind the increased cancer risk in dialysis patients are not known, however, and this increased risk of cancers may also be explained by increased concentrations of other factors.

Interestingly, SPINK1 production is not associated with an adverse prognosis in all tumors. In ventricular and bladder cancer, loss of SPINK1 production in tumor tissue has been shown to be associated with an adverse prognosis. In these cancers, SPINK1 may protect against tumor invasion by inhibiting trypsin, which is involved in the protease cascades mediating invasion (2).

It is likely that humanized SPINK1 antibodies to be used for treatment of human tumors are under development. Patients suitable for such treatment need to be selected on the basis of SPINK1 production in tumor tissue. Many patients with advanced prostate cancer have clearly increased serum concentrations of SPINK1. Thus, measurement of SPINK1 in serum may also be useful for identifying patients suitable for antibody therapy and for monitoring the response to treatment (2).

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