Tumor-associated trypsin inhibitor (TATI) is a low-molecular-weight (6 kDa) trypsin inhibitor that has been used as a marker for ovarian cancer. It is also expressed together with tumor-associated trypsin by many other tumors, and increased serum concentrations of TATI occur in connection with these. TATI is a prognostic marker for ovarian, bladder, and kidney cancer, which may be associated with the participation of trypsin in protease cascades contributing to tumor invasiveness.

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Tumor-associated trypsin inhibitor (TATI)1 was initially isolated from the urine of a patient with ovarian cancer (1). TATI is a peptide produced at high concentrations by mucinous ovarian tumors, but it is expressed by several other tumors. TATI is identical to the earlier described pancreatic secretory trypsin inhibitor (PSTI) (2), which also is called the Kazal inhibitor (3). Clinically, TATI is most useful for monitoring of patients with mucinous ovarian cancer, but increased serum concentrations of TATI may occur in most types of cancer. In ovarian, bladder, and kidney cancer, TATI is a marker of adverse prognosis. This appears to be explained by the coexpression of TATI and tumor-associated trypsin, which is thought to participate in tumor-associated protease cascades mediating tumor invasion (4).

Structure, Expression, and Function
TATI is encoded by a gene comprising four exons located on chromosome 5. The promoter region of the gene contains an interleukin-6 (IL-6)-responsive element (5). TATI consists of 56 amino acids, has a molecular weight of 6242, and contains three disulfide bridges (2). TATI is a strong inhibitor of trypsin with a $K_i$ of 0.06 nmol/L. The interaction is reversible, TATI being gradually degraded by trypsin. The affinity for other serine proteases is low and probably not of physiologic importance (6).

TATI/PSTI is strongly expressed together with trypsinogen by pancreatic acinar cells. It is secreted into the pancreatic juice, where it constitutes 0.1–0.8% of the total protein (7). TATI is expressed at lower concentrations in several other healthy tissues, especially in the gastrointestinal and urogenital tracts, e.g., by Paneth cells in the small intestine (8), by mucous-producing cells in the intestine, and in the gall bladder, biliary tract, kidney, lung, liver, and breast (9, 10). Cancers originating from these tissues often produce TATI, e.g., pancreatic, colorectal, gastric, liver, lung, breast, and biliary tract cancers (4, 11–13). The strongest expression occurs in mucinous ovarian tumors, both benign and malignant (14). In hepatoma cells, the expression is induced by IL-6 (15), but secretion from the pancreas parallels that of trypsin (16). Thus expression appears to be regulated by different mechanisms in different tissues (15, 17).

In the pancreas, PSTI/TATI is thought to protect pancreatic cells from destruction induced by inadvertent activation of trypsinogen (7, 18). The fact that TATI is coexpressed with tumor-associated trypsin in cancer cells suggests that it may have the same function in extrapancreatic tissues (19). TATI may behave as an acute-phase reactant (20), but increased serum concentrations are observed only in connection with strong inflammatory reactions. Because TATI is expressed by the liver and the gene contains an IL-6-responsive element, it is likely that TATI derived from the liver increases the serum concentrations in inflammatory diseases (15, 17).

Clinical Use
The mean serum concentration of TATI in healthy individuals is 11 μg/L (reference interval, 3–21 μg/L) and that in urine is 25 μg/L (reference interval, 7–51 μg/L). Somewhat lower concentrations are obtained by an assay based on monoclonal antibodies (mean concentration, 6.9 μg/L; reference interval, 3.1–16 μg/L) (19). This change in reference values has to be considered when comparing results from various studies. The serum concentrations

1 Nonstandard abbreviations: TATI, tumor-associated trypsin inhibitor; PSTI, pancreatic secretory trypsin inhibitor; IL-6, interleukin-6; SCC, squamous cell carcinoma; CEA, carcinoembryonic antigen; and AFP, α-fetoprotein.
remain within this range after total pancreatectomy, suggesting that only part of TATI in the circulation of healthy individuals is derived from the pancreas (21), other potential sources being the liver and gastrointestinal mucosa. Because the results are dependent on the assay used, it is important to report the relevant reference values.

Because of its small molecular size, TATI is rapidly cleared from the circulation by renal excretion, with a half-life of 6 min (22). Therefore, renal failure causes increased concentrations of TATI in the serum (23). The increase correlates with the decrease in glomerular filtration rate, and serum TATI usually becomes increased when the glomerular filtration rate decreases to <40–60 mL/min (24). In dialysis patients, serum concentrations are strongly increased, reaching concentrations of 200–600 μg/L. Patients with concomitant cancer often have TATI concentrations exceeding 1000 μg/L (25).

**BENIGN DISEASE**

Pancreatitis invariably causes increases in TATI (or rather PSTI) in serum and urine, and the increase correlates with the severity of the disease (26). TATI concentrations >70 μg/L are associated with an adverse outcome (27). The increase can be explained by leakage of PSTI from the diseased pancreas. A variant of TATI in which asparagine-34 is replaced by serine is associated with chronic pancreatitis. The variant is thought to have reduced capacity to inhibit trypsin and thus to prevent inadvertent trypsin activation, which lowers the threshold to development of pancreatitis (28, 29).

Patients with severe injury and inflammatory disease may have clearly increased TATI concentrations (20, 23). However, in patients with pelvic inflammatory disease, TATI concentrations start increasing only when serum C-reactive protein is clearly increased (>90 mg/L). Thus, only a strong acute-phase reaction appears to trigger TATI expression. Although the increase in inflammatory disease is a limiting factor, it does not invalidate the use of TATI as a tumor marker (30).

Adult-onset type II citrullinemia is associated with increased expression of TATI/PSTI in the liver and clearly increased serum concentrations. The disease is caused by a deficiency of argininosuccinate synthetase, but the mechanism causing increased TATI expression is not known (31).

**MALIGNANT DISEASE**

Various types of cancer may cause increases in TATI in the serum and urine. In most cancers, this increase is caused by production by the tumor, but an acute-phase reaction induced by tissue destruction associated with cancer invasion most likely contributes to the increased TATI concentration seen in advanced disease (4). The concentrations in serum and urine correlate strongly (32), but there is more variation in urine concentrations; therefore, serum measurements are to be preferred.

**Gynecologic cancers.** Increased serum and urine concentrations of TATI are common in ovarian cancer. In patients with mucinous cancers, which constitute 10–15% of all ovarian cancers, ~45% of the cases have increased TATI already in stage I and 90–100% in stage IV disease. TATI can be used for monitoring of these patients and is therefore a complement to CA 125, which is the most sensitive marker for other types of ovarian cancer. The combined use of TATI and CA 125 improves differentiation between malignant and benign ovarian masses (33, 34). In nonmucinous cancers, TATI expression is associated with high-grade tumors. Increased serum concentrations occur in 50–60% of the patients with stage III-IV disease, and in these patients, an increased value before therapy is an independent prognostic factor for adverse outcome (35, 36).

Endometrial cancer is associated with increased TATI in 55–60% of the patients with advanced disease but in only 20% of those with early disease (11, 19, 37). TATI is equally often increased in cervical cancer (11), but the sensitivity of TATI is inferior to that of squamous cell carcinoma (SCC) antigen and carcinoembryonic antigen (CEA); TATI is therefore of limited utility in this disease (38).

**Gastrointestinal cancers.** TATI is sensitive marker for pancreatic cancer, being increased in 75–95% of patients. Specificity is limited by the frequent increased concentrations in patients with pancreatitis and benign hepatobiliary disease (32).

In gastric cancer, 40–65% of patients have increased TATI. This finding is most common in patients with anaplastic tumors, which is contrary to the behavior of CEA. TATI is therefore a useful complement to CA 19-9 and CEA. Strongly increased preoperative serum concentrations indicate poor prognosis [reviewed in Refs. (39, 40)].

Approximately 60–80% of patients with hepatocellular and 75–100% of those with biliary tract cancer have increased TATI. In hepatocellular cancer, the sensitivity and specificity are similar to those of a-fetoprotein (AFP). TATI is therefore a useful marker in AFP-negative patients (19, 41). High TATI concentrations occur in the bile of hepatoma patients (42), and the tumor cells express TATI (5).

Increased TATI concentrations occur in 34–74% of patients with colorectal cancer (19), but TATI is inferior to CEA, and the combined use of TATI and CEA does not substantially improve the diagnostic accuracy (43).

**Urologic cancers.** In bladder cancer, TATI has been found to be more useful than other commonly used serum markers, i.e., tissue polypeptide antigen, CEA, AFP, human chorionic antigen subunit β, prostate-specific antigen, SCC antigen, and CA 19-9. Depending on stage, increased concentrations occur in 22–70% of the cases, and TATI can be used for monitoring of this disease (44).
Preliminary studies suggest that TATI is a strong prognostic factor for adverse outcome in bladder cancer (Keltoniemi et al., submitted for publication).

In renal cell cancer, TATI is a more sensitive marker (69%) than CEA, CA 15-3, CA 125, and CA 19-9 and has been found to be suitable for monitoring of disease progression after surgery. However, increased concentrations are associated mainly with advanced disease, and TATI is not useful for early diagnosis (45). TATI has recently been found to be an independent prognostic factor in renal cell carcinoma (46).

Other cancers. Increased TATI concentrations occur in 20–50% of patients with lung cancer, but TATI is clearly inferior to CEA. In a comparative study of TATI, CEA, CA 50, and neuron-specific enolase as markers for lung cancer screening, the combination of TATI and CEA gave the highest sensitivity (74%) at a specificity of 90%. However, none of the markers appeared to be useful for early detection of this disease (47).

In breast cancer, TATI is increased in 65% of the cases with advanced disease. Thus, TATI is less sensitive than CA 15-3, and the combination of TATI with other markers is not useful (48).

Increased TATI concentrations occur in ~30–60% of patients with head and neck cancer, and TATI can be used to monitor the course of the disease. In a comparative study, TATI was found to be superior to Cyfra 21-1 (49).

Conclusions

Clinically, TATI is most useful for monitoring of mucinous ovarian cancer, but its use as a prognostic marker may be the most important application in the future. The prognostic value appears to be associated with the coexpression of TATI and trypsin in many tumors. Thus, an increase in TATI may reflect expression of trypsin in the tumor. Because trypsin activates some proteases associated with tumor invasion, e.g., prourokinase (50) and matrix metalloproteinase-2 and -9 (51), which often occur in the same tumors as trypsin, it is likely that trypsin participates in protease cascades associated with tumor invasion. The prognostic value of TATI can probably be explained by this mechanism.

References


