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## Mini Review

# Tumor-Specific Growth Factor (TSGF): A Futuristic Tumor Biomarker in Early Diagnosis of Cancer

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## Abstract

Despite the significant improvement in the treatment modalities, cancer is one of the fastest-growing chronic disease conditions all over the world. Genetic and Epigenetic alterations in the normal physiology of the cell are the key factor for tumor development. These changes can trigger the production of abnormal protein expressions through stimulation of different signaling pathways and can deeply affect normal cell growth and proliferation. Any altered protein expression, genetic variation, micro-RNA or post-translational protein modifications that indicate tumorigenesis can act as an early signal termed as biomarker. Cancer, being a multistep process with accumulating genetic and epigenetic alterations, could be detected early with suitable biomarkers. There are several proteins such as AFP, CA-125, PSA Troponin, CEA, Osteoponin, CA-19.9 that act as biomarkers which help in early detection, prognosis, and monitoring of disease progression, a hunt for newer biomarkers with higher specificity and sensitivity is still ongoing. Tumor-specific growth factor (TSGF) is one such budding and prevailing tumor biomarker used for the early-stage detection of several types of carcinomas. TSGF is a gene that helps in tumor angiogenesis and gets released during the preliminary stages from cancer cells that ensure the vascular proliferation of the same. In this review, the clinical investigations of TSGF in different kinds of malignancy is discussed in detail and suggests the possibility of using TSGF as a biomarker in early diagnosis of cancer.

**Keywords:** Biomarker, Cancer, clinical implications, diagnosis, Tumor-Specific growth factor (TSGF)

**Running title:** *TSGF as a futuristic tumor biomarker*

## Introduction

Cancer is a significant public health concern that affects a wide range of populations globally. According to the reports published in the year 2021, about 1,898,160 new cancer cases and 608,570 cancer deaths were estimated worldwide[1]with lung, breast and prostate carcinomas as the most frequent types.[2] Carcinogenesis is the process of transformation of normal cells to neoplastic cells due to damage or alterations in the genetic apparatus. This could be due to accumulating mutations, alterations in genetic expression, activation of tumor promotor gene, or inactivation of tumor suppressor gene[3]. Tumor development is accompanied by several pathological processes, mainly inflammation, wherein there is a release of chronic inflammatory mediators and growth factors by the cancer cells that leads to disruption of the immune system due to alterations in the functions of various immune cells.[3-8] Advanced technologies like anti-sense therapy, anti-cancer vaccines, viral/von-viral gene delivery systems, anti-gene therapy, and tumor suppressor gene therapy are involved in abolishing the genetic damage. However, their clinical application is limited and thus is a matter of future perception.[3,9]

Regardless of the histological type, damage to genetic material and suppression of anti-tumor immunity are the common key factors that leads to cancer progression. Local tissue damage upon exposure to chemical, physical or biological carcinogens leads to temporary suppression of the anti-tumor immunity for tissue repair. However, due to damages caused by exogenous factors, imbalance in the sympathetic/hyper-sympathetic dominance, or tissue hypoxia[3,4] the normal physiological process of tissue repair becomes a pathophysiological resulting in formation of a cancer cell. Genetic and epigenetic variations cause altered protein expressions also leads to carcinogenesis. Alteration in the protein expressions badly affects the cell physiology and metabolism which produces and transmits signals to the neighbouring cells.[10,11]

A biomarker can be defined as a substance/ biomolecule that can be measured or as a structure or process that can be detected or predicted to analyze the outcome of several diseases.[12,13] Cancer biomarkers constitutes a wide range of biological entities such as nucleic acids, sugars, proteins, cytogenetic and cytokine entities as well as neoplastic cells in circulating body fluids.[14] These biochemical entities are produced by tumor cells that can be widely used for the patient assessment in numerous clinical settings like estimating the risk of developing cancer, screening of occult primary neoplasm, differential diagnosis between the benign and malignant tumors, predict the response or progression to therapy and monitoring the recurrence of disease condition.[15] Cancer biomarker discovery is continuing as an active and productive area of research wherein the clinicians and scientists are using the knowledge regarding tumors and advent of novel technologies for the development of a potential cancer biomarker. With the emergence of sophisticated and advanced genomic profiling techniques and molecular targeted therapies, identification and validation of tumor biomarker is now a part of cancer drug discovery process.[16]

Tumor-specific growth factor (TSGF) was first discovered by the scholars of the University of Toronto in the year 1989. TSGF is an internationally recognized term for certain carbohydrates and metabolites like lipoproteins, amino acids and enzymes that help in the growth and development of malignant cells.[17,19] Tumor specific growth factors are released by cancer cells during the early stages of tumor development and help in the proliferation of cells and peripheral blood capillaries. Thus, it promotes the angiogenesis of malignant cells which increases the blood supply to cancer tissue.[18,19] Scientific reports indicate that there is no

correlation between TSGF and non-malignant vascular proliferation and can be used as a potent indicator in distinguishing the normal cells from neoplastic cells[20] **(Figure 1).** Through this review, we aim to gather information on the studies conducted on association of TSGF and various types of cancers and discuss the possibility of using TSGF as a potential biomarker for prediction/ early diagnosis/ detection/ prognosis and treatment outcome of each type.

**Figure 1.** The above figure illustrates the role of Tumor-specific growth factor (TSGF) in the early stages of carcinogenesis. TSGF is a highly specific, extremely sensitive novel biomarker that helps in cancer cell proliferation and development. Mutation in the genetic apparatus of a cell triggers tumor development and TSGF gets released from the cancerous cells that promote tumor angiogenesis and vascular proliferation which further worsens the condition.

**A layout of clinical implication of tumor-specific growth factor in different types of cancer**

TSGF is produced by cancer cells and it is released into blood stream during the early stages of malignant tumor progression. The release TSGF promotes growth and proliferation of malignant cancer cells and peripheral capillaries. Increased proliferation of peripheral blood capillaries facilitates more supply of blood to tumor tissue which speeds up the tumor development[19,20] The promotion of angiogenesis of tumor cells is through the cloned T lymphocytes differentiation by inhibiting the lgM and IgG production.[17] The angiogenesis promoted with the help of TSGF produces high sensitivity and specificity with greater value in the diagnosis of malignant cells in the early stage.[17,21,22] Thus, serum levels of TSGF can manifest the existence of cancer.

Breast cancer is one of the most common malignant tumors among women population. Breast carcinoma badly influences women's life and health and is the second leading cause of cancer mortality among women population across the globe. A retrospective study was performed to evaluate the clinical significance of Color doppler ultrasound in combination with serum tumor biomarkers like TSGF, CEA, and CA15-3. Among 103 breast cancer patients, 50 patients were with benign breast lesions. Color Doppler Ultrasound revealed substantial difference in terms of tumor morphology, tumor boundary, internal echo, peak blood flow velocity (Vmax), resistance index (RI) and pulsatility index (PI). The ultrasound images showcased irregular tumor shape with unclear tumor boundaries and increased Vmax, RI and PI.[20]

Subsequently, the serum levels of TSGF was drastically higher in patients with breast cancer (157.69±46.72 U/ml) in comparison with benign lesion subjects (50.24±15.61 U/ml). Also, the serum TSGF level was found to be declined after breast cancer treatment (107.82±32.97 U/ml) than those before treatment. From the combined detection, ROC curve analysis conveyed the area under curve (AUC) of TSGF to be 0.843 while the Youden index to be 0.560. Also, the best cut-off value of TGSF was found to be 70.00 U/ml. Overall, the sensitivity and specificity of combined detection Color Doppler Ultrasound and serum TSGF marker was fund to be 88.89%. The study demonstrates that the combined use of Color Doppler Ultrasound and serum markers can improve the diagnosis of breast cancer rather than using it as a single detection method.[20]

A similar study was conducted using 70 breast cancer patients by *Chang-xiao et al,* to investigate the influence of neoadjuvant CAF chemotherapy on serum TSGF, CA15-3, and CA125 levels in breast cancer. All patients underwent surgery, but the observational group received neoadjuvant CAF chemotherapy (intravenous injection of cyclophosphamide, 5-

fluorouracil, and Adriamycin) were tested for serum levels of tumor markers before and after treatment. Serum levels of TSGF and other cancer antigen markers were subsequently reduced after the treatment as compared to that of pre-treatment. A positive correlation was also observed between TSGF and other cancer antigen markers namely, CA15-3 and CA125. From the study reports, the overall response rate (ORR) and disease control rate (DCR) of observational group was found to be 68.6% and 88.6% respectively when compared with control group (ORR- 42.6% and DCR- 72.3%). Overall study results reveal that TSGF can be used as an effective biomarker in the effective evaluation of neoadjuvant CAF chemotherapy in breast carcinoma.[28]

Endometrial cancer is the most common gynecological malignancy observed in perimenopausal and postmenopausal women with high incidence of mortality rate. Patients are more likely to be cured if endometrial cancer is diagnosed at early stages. Thus, proper diagnosis is very important. A study conducted by *Yu B et al.* estimated the clinical value of TSGF and CA-125. Blood samples from peripheral veins were collected from all patients through simple needle aspiration technique. Blood samples from uterine veins were collected from the patients with endometrial cancer. The serum levels of TGSF and CA-125 from the blood samples collected through peripheral and uterine veins of endometrial cancer subjects were compared with those in uterine fibroids (uterine myoma) patients (non-tumor controls) and normal women subjects.[21]

The specificity and sensitivity of serum TSGF level were found to be 62.5% and 64.9% respectively in the disease group. Subsequently, the sensitivity of TSGF was gradually increased to 75.7% during combined detection of TSGF and CA-125. From the study data, the serum TSGF level was found to be 72.2±13.3 U/ml in endometrial cancer patients than those with non-tumor patients (55.5±14.6 U/ml) and normal subjects (46.1±10.2 U/ml). It was found that the TSGF level was gradually increasing with the progression of endometrial carcinoma and thus detection of serum TSGF biomarker in the blood can be valuable in the early diagnosis of endometrial malignancy.[21]

An alternative study performed by *Chen HH eta l.,* in 106 patients with endometrial carcinoma, the patients were divided into observation and control groups. 57 patients in the observational group had undergone laparoscopic surgery along with two doses of TC chemotherapy (paclitaxel + carboplatin). The serum TSGF levels before treatment were not significantly different between observational and control group. But *Chen HH et al.*, and team reported changes in the level of serum TSGF after TC chemotherapy along with surgical treatment. From the study results, a drastic increase in the serum TSGF levels was observed in control (88.72±12.67 U/L) and observational (89.66±13.18 U/L) groups before treatment. Whereas, after treatment, the level of serum TSGF was significantly reduced in control (57.42±8.17 U/L) and observation (44.45±4.62 U/L) groups. Thus, the authors suggest TSGF molecule can be used to analyze the efficacy of adjuvant chemotherapy and related surgical treatment modalities.[25]

Oral Squamous cell carcinoma (OSCC) is most common but most fatal type of Oral malignancy characterized by invasive growth and frequent regional metastasis. A case-controlled study was designed using 80 OSCC patients to investigate the use of three potential tumor biomarkers namely, long non-coding RNAs, TSGF and SCCA. From the study results, *Shaoe T et al.,* and his team showed that the serum TSGF levels was significantly high in different stages of tumor development with or without lymphatic metastasis. Also, the serum TSGF levels can distinguish between the oral squamous cell carcinoma and control subjects with AUC of 0.648, sensitivity of 63.3% and specificity of 66.7%.[24]

Another study reported by *Jie Z et al.,* analyzed the therapeutic effect of different doses of $^{125}$I radioactive particle brachytherapy using serum TSGF and other tumor biomarkers in oral carcinoma. Out of the 78 oral carcinoma patients, one group received a high dose of $^{125}$I radioactive particle brachytherapy while the other group received a low dose of $^{125}$I radioactive particle brachytherapy. It was found that a high dose of particle brachytherapy was efficient in decreasing the serum levels of TSGF (59.73±6.12 µg/ml) than those of low dose (68.53±7.12 µg/ml) group. The study demonstrates that high dose particle brachytherapy with radioactive $^{125}$I is a safe and effective treatment in comparison with low dose particle brachytherapy.[29]

Pancreatic malignancy is referred as the most common digestive malignancy with very high incidence of mortality rate, rapid proliferation and diagnostic difficulties. A study was conducted to evaluate the efficacy of Cryoablation. A study was performed to in 31 patients with pancreatic malignancy to evaluate the clinical significance of CA242, CA199, CA125 (carbohydrate antigens), CEA (carcinoembryonic antigen) and TSGF before and after the cryoablation in pancreatic carcinoma. The serum levels of TSGF and other cancer antigens were measured before and one-month post-treatment. Serum levels of TSGF (17.0± 1.0 U/ml) were found to be higher in the pancreatic cancer group as compared to that of control group, pre-treatment. But one-month post-treatment, the serum TSGF level (14.1± 0.9 U/ml) and other cancer antigen biomarkers were significantly reduced thus making TSGF an important index for the early detection and prognosis of pancreatic carcinoma.[26]

Gastric carcinoma is yet another commonly observed malignancy were no obvious symptoms are observed. But most of the patients clinically diagnosed by gastric malignancy will be already in the middle or advanced stage of tumor development thus making susceptible to delay the best treatment regimen. A study conducted by *Yin LK et al.* among gastric cancer patients (Group 1) and gastric benign disease (Group 2) along with a normal control group, estimated serum levels of TSGF and other tumor biomarkers. The study involved 40 patients with gastric carcinoma (GC) and the serum levels of the aforementioned tumor biomarkers were compared with the serum samples of 30 normal healthy volunteers and 40 patients with gastric benign diseases (GBD). From the study results, the serum levels of TSGF molecule in GC group (76.19±11.84 U/ml) was found to be more than the GBD (62.27±11.45 U/ml) and healthy group (5.94±10.66 U/ml). Thus, TSGF molecule can be used as an important molecule for the early diagnosis and detection of gastric carcinoma.[27]

Colon cancer is the most common alimentary canal malignancy which has a higher incidence of mortality rate. To explore the expression and significance of TSGF along with CEA and AFP, a study was conducted by *Hu Y et al.,* in 43 colon cancer patients with radical operation. The study reported that the expression of TSGF, CEA, and AFP to be significantly high before radical surgery. One-month post-surgery, the expression rates of TSGF, CEA, and AFP were drastically declined, thus suggesting the possibility of using TSGF as a biomarker to evaluate the effect of radical operation for colon cancer. The results indicate the elevated levels of serum TSGF in subjects before radical surgery (77.33±7.02 U/ml) in comparison with post-radical operation (72.14±6.13 U/ml). Thus, the authors' states, TSGF molecule can be used as an effective tumor biomarker in the evaluation of Radical operation in colon cancer, tumor differentiation and early diagnosis.[23]

The mortality rate of rectal carcinoma is exponentially increasing due to accelerated pace of life, eating disorders and environmental related factors. TSGF and many other tumor biomarkers are widely explored in different types of malignancy. A study conducted in 100 patients with rectal carcinoma *Ji WB et al.,* analyzed specificity and sensitivity of serum TSGF using ELISA. The specificity of CEA, CA153, TSGF, and CA125 in control and observation groups had significant difference. Also, the sensitivity of CEA, CA153, TSGF, and CA125

between the control and observation groups depicted significant difference. The study. Results indicate that the sensitivity and specificity of TSGF was found to be 44.7% and 63.6% respectively. Subsequently, the sensitivity of combined detection of serum biomarkers was found to be 85.7%. Thus, the authors convey, combined detection of tumor biomarkers was found to be more sensitive rather than single detection of different tumor biomarkers. The authors commenced that TSGF can be used for the early diagnosis of rectal cancer if validated properly and can be used as a promising tumor biomarker in rectal malignancy diagnosis clinically.[18]

Osteocarcinoma, a progressive primary bone malignancy that commences from the immature stromal spindle cells. A retrospective study published in the year 2020 by *Zhang Q et al.*, reported that TSGF as a relatively specific serum marker for osteocarcinoma. 75 osteocarcinoma patients were provided with neoadjuvant chemotherapy with three different courses of treatment. Blood samples were collected before and after chemotherapy treatment and tested for serum markers like COX-2 (Cyclooxygenase-2), VEGF (Vascular endothelial growth factor), TGF-β (Transforming growth factor-beta), TSGF (Tumor-specific growth factor) and b-FGF (basic fibroblast growth factor). Serum levels of TSGF and other related tumor biomarkers were significantly decreased after chemotherapy treatment but were still higher than the normal control group indicating that chemotherapy treatment can decrease the proliferation of osteosarcoma cells. The data obtained from the retrospective study depicts the mean serum levels of TSGF decreased significantly after chemotherapy. The serum TSGF levels of patients in observational group before and after chemotherapy was found to be 86.23±12.19 U/L and 52.86±8.41 U/L respectively than that of control group (25.5±4.95 U/L).[17]

The role of TSGF as a tumor biomarker in early detection and diagnosis has been explored in non-small cell lung carcinoma (NSCLC) as well. A retrospective analysis was conducted to determine the significance of TSGF along with other cancer antigen biomarkers like CEA (Carcinoembryonic antigen), CYFRA – (Cytokeratin fragment antigens 21-1), and Neuron-specific enolases (NSE). The study demonstrated that the positive rate of each selected biomarker was observed at low levels during the NSCLC diagnosis. A significant level of serum TSGF was useful for the primary diagnosis of NSCLC. From the study, the median and positive rate of TSGF was found to be 56–67μ/ml and 10.14% respectively. Even though the positive rate was lower, TSGF can be used as a budding tumor marker in the diagnosis of NSCLC. Depending on limited biomarker development, further validation is required for the determination of specificity and sensitivity of TSGF in NSCLC patients.[30]

Several reports suggest TSGF as an efficient diagnostic marker in the detection of hepatocellular carcinoma since its sensitivity can reach up to 82% at the cut-off value of 62U/L.[13,32,33] A simultaneous determination of serum TSGF level along with other tumor biomarkers namely, AFP, CEA, TSA, and ferritin showcased sensitivity and specificity of 98.4% and 99% respectively at the cut-off value of 65U/L.[32] **(Table 1)**.

**Table 1.** The table elucidates the summary of clinical studies performed on Tumor-specific growth factor (TSGF) with their published results.

| Sr.no. | Type of Cancer | No. of patients | Outcome of the study | Reference |
|---|---|---|---|---|
| 1 | Breast Carcinoma | 103 breast cancer patients<br>50 patients benign lesions | Combined use of Color Doppler Ultrasound with the detection of serum TSGF and other markers was found to be effective tool in early diagnosis of breast cancer | 20 |
| | | 70 patients | Neoadjuvant CAF therapy was found to be effective in breast cancer patients | 28 |

| | | | | |
|---|---|---|---|---|
| 2 | Endometrial Cancer | 37 patients | Combined detection of serum TSGF and CA125 could be effective approach for the early diagnosis of endometrial cancer. | 21 |
| | | 106 patients | TC chemotherapy significantly improved serum TSGF and other inflammatory markers in endometrial cancer patients | 25 |
| 3 | Oral Carcinoma | 80 patients with OSCC<br>70 healthy subjects | TSGF if validated through large scale prospective study can be a novel circulating biomarker for the detection of OSCC. | 24 |
| | | 78 patients | High dose brachytherapy with radioactive $^{125}I$ exerted safe and effective treatment with clinical values more beneficial than the lower dose treatment. | 29 |
| 4 | Gastric cancer | 45 patients with gastric cancer<br>40 patients with gastric benign disease<br>30 healthy subjects | Combined detection of TSGF and other serum biomarkers depicted better sensitivity and accuracy rather than single detection. | 27 |
| 5 | Pancreatic Cancer | 31 pancreatic cancer patients | Combined detection of TSGF and other serum biomarkers was found to be effective for the early detection of pancreatic cancer and predicting the efficacy after cryoablation. | 26 |
| 6 | Colon Cancer | 43 patients | Serum TSGF can be used to evaluate the effect of radical surgery for colon carcinoma | 23 |
| 7 | Rectal Cancer | 100 patients with rectal carcinoma | Joint detection of serum TSGF and other biomarkers could improve the early diagnostic yield of rectal carcinoma | 18 |
| 8 | Osteocarcinoma | 75 patients with osteocarcinoma<br>55 healthy patients | Serum level of TSGF was lowered after successful chemotherapeutic regimen | 17 |
| 9 | Non-small cell lung carcinoma | 276 patients with Non-small cell lung carcinoma | Considerable amount of TSGF was found in the serum samples of NSCLC patients with significant positive rate of 10.14% | 30 |
| 10 | Hepatocellular Carcinoma | 170 patients with HCC | Tumor marker determination with TSGF improved the positive rate of tumor diagnosis in Hepatocellular carcinoma | 32 |

## Conclusion

With tremendous knowledge of comprehensive genomic profiling and rapid changes in various molecular targeted therapies, a significant progress has been observed in cancer biology research. This ensures a good impact for the early detection, prognosis, diagnosis, and prevention of cancer. Despite such progression, cancer remains a deadly chronic disease with never-ending questions in the treatment modalities and screening methods. According to National Cancer Institute (NCI), a biomarker is a molecule that can be found in blood, body fluids, or tissue which can be used as a significant indication to detect any kind of disease ailment. Tumor-specific growth factor or TSGF is a tumor antigen marker that helps in the vascular proliferation of tumor cells, thereby promoting tumor angiogenesis. The correlation between TSGF and hyperplasia of neoplastic cells is reported in several studies, but no association was found between TSGF and non-cancerous cells. The release of highly sensitive TSGF molecule from malignant cells is triggered with increased blood flow during the early stage of cancer development which boosts tumor cell proliferation. Several studies demonstrate TSGF as a potential tumor biomarker in the early detection and diagnosis of malignancy in various cancer. All these studies established a positive correlation of TSGF molecule with other tumor-related cancer antigen biomarkers which is helpful in the prognosis and screening of

cancer. To conclude, TSGF is a highly specific and sensitive tumor antigen marker that may be used alone or in combination for the early detection and diagnosis of several types of cancer. Proper validation through large-scale prospective research is required to ensure the more appropriate utility of serum TSGF as a biomarker molecule in the early cancer diagnosis.

**Conflict of interest**

The authors declare no conflict of interest.

**Ethical issues**

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