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The Role of GSPT2 in Tumor Cell Cycle Regulation: Mechanisms and Clinical Significance

Yu Cai[1], Yumei Wu[2]

[1]Department of Gynecology and Obstetrics, Beijing Tongren Hospital Affiliated to Capital Medical University, Beijing, China
[2]Department of Gynecology and Oncology, Beijing Obstetrics and Gynecology Hospital Affiliated to Capital Medical University, Beijing, China
Email: caiyu892002@mail.ccmu.edu.cn

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Abstract

GSPT2 (G1 to S phase transition protein 2) has emerged as a critical regulator of the cell cycle and has garnered increased attention for its role in tumor biology in recent years. This review explores the multifaceted functions of GSPT2, highlighting its involvement in cell cycle regulation and signaling pathways, as well as its potential as a tumor biomarker. By analyzing the latest research findings, we examine the expression patterns of GSPT2 across various tumor types and its correlation with clinical outcomes, underscoring its significance in tumor initiation and progression. Furthermore, we discuss the prospects of GSPT2 as a therapeutic target, providing new insights for future research directions.

Keywords

GSPT2, Tumor, Biomarker, Cell Cycle, Signaling

1. Introduction

GSPT2 (G1 to S phase transition 2) is a critical protein that plays an essential role in various cellular processes, particularly in the regulation of the cell cycle. It functions as a translation termination factor and is involved in the maintenance of mRNA stability, which is crucial for proper protein synthesis during cell division. GSPT2 has been shown to interact with several key cell cycle regulators, thereby influencing the transition from the G1 phase to the S phase of the cell cycle, a pivotal point that determines cellular proliferation and growth. Dysregulation of GSPT2 can lead to aberrant cell cycle progression, which is often observed in

cancerous cells, highlighting its potential significance in tumor biology [1] [2].

The relationship between cell cycle regulation and tumorigenesis is well-established in cancer biology. The cell cycle is tightly controlled by a series of cyclins and cyclin-dependent kinases (CDKs) that ensure proper timing of cell division. Disruptions in these regulatory mechanisms can lead to uncontrolled cell proliferation, a hallmark of cancer. Understanding the molecular pathways and factors involved in cell cycle regulation, including GSPT2, is crucial for elucidating the mechanisms underlying tumor development and progression [3] [4].

Recent studies have begun to explore GSPT2 as a potential biomarker for cancer diagnosis and prognosis. Its expression levels have been correlated with various cancer types, suggesting that GSPT2 may serve as a valuable indicator of tumor behavior and patient outcomes. Furthermore, targeting GSPT2 and its associated pathways could provide novel therapeutic strategies in cancer treatment, making it a focal point for ongoing research in the field of oncology [5] [6]. As we advance our understanding of GSPT2's role in the cell cycle and its implications in cancer biology, it becomes increasingly important to consider its potential clinical applications in the management of cancer patients.

2. The Primary Structure and Function of GSPT2

2.1. The Molecular Structure and Function of GSPT2

2.1.1. The Gene Structure and Protein Characteristics of GSPT2

GSPT2 (G1 to S phase transition protein 2) is a GTP-binding protein that plays a crucial role in the G1-S phase transition of the cell cycle. It regulates protein synthesis in a GTP-dependent manner during translation termination, modulates cell cycle progression, and is involved in tumorigenesis [7].

The termination of eukaryotic protein synthesis involves at least two polypeptide release factors (eRFs): eRF1 and eRF3. There are two genes encoding structural homologs of eRF3 (eRF3a and eRF3b), named GSPT1 and GSPT2, located on human chromosomes 16 and X, respectively, as eRF3a/GSPT1 and eRF3b/GSPT2. GSPT2, located at the genomic coordinates (GRCh38): X: 51,743,442 - 51,746,232 on Xp11.22, is a 632-amino acid protein with two domains: a unique N-terminal region and a conserved C-terminal eukaryotic elongation factor 1-alpha-like domain [8] [9]. Studies have shown that GSPT2 arises from the retroviral integration of a GSPT1 transcript into the genome. Comparison of the 5'untranslated regions (5'UTRs) of the two genes reveals potential promoters in the 5'UTR of GSPT1 that are associated with the transcription of GSPT2. GSPT2 is closely related to GSPT1, both being GTP-binding proteins with 87% identity in their mRNA and protein sequences, differing only in their N-terminal domains. They both play important roles in the G1-S phase transition of the cell cycle in yeast and human cells [10] [11].

Additionally, GSPT2 is a crucial component of the cellular machinery involved in the regulation of gene expression and cell cycle progression. Structurally, GSPT2 is characterized by its RNA-binding domain, which is essential for its

interaction with various RNA molecules and other proteins. This domain facilitates the binding of GSPT2 to mRNA, thereby playing a pivotal role in mRNA translation and stability. The gene encoding GSPT2 is located on chromosome 1 and is expressed in various tissues, indicating its fundamental role in cellular processes. Recent studies have highlighted the significance of GSPT2 polymorphisms in influencing individual responses to viral infections, such as hepatitis B, and in determining the prognosis of lamivudine therapy, suggesting that genetic variations in GSPT2 may have clinical implications in disease outcomes [12]-[14]. Moreover, the post-translational modifications of GSPT2, including phosphorylation and ubiquitination, further modulate its activity and stability, emphasizing the complexity of its regulatory mechanisms in cellular functions.

2.1.2. The Mechanism of Action of GSPT2 in the Cell Cycle

The cell cycle refers to a series of ordered stages and processes that cells undergo during their life activities, including cell growth, DNA replication, cell division, and cell differentiation. It consists of several phases: G1 (pre-DNA synthesis phase), S (DNA synthesis phase), G2 (post-DNA synthesis phase), and M (mitosis phase). Each phase is crucial, as they ensure the accurate duplication and distribution of genetic material to daughter cells. The proper progression through these phases is essential for normal cellular function, and any aberration can lead to uncontrolled cell proliferation, a hallmark of cancer. In tumorigenesis, the cell cycle is often disrupted, leading to enhanced cell survival and division despite the presence of DNA damage or other cellular stressors. Understanding the regulatory mechanisms of the cell cycle is therefore vital, as it provides insights into potential therapeutic targets for cancer treatment [15].

GSPT2 plays an integral role in the regulation of the cell cycle, particularly during the transition from the G1 phase to the S phase. It is involved in the coordination of various signaling pathways that ensure proper cell cycle progression and genomic integrity. GSPT2 interacts with key cell cycle regulators, such as cyclins and cyclin-dependent kinases (CDKs), facilitating the timely activation of these proteins required for cell cycle advancement [16]. Additionally, GSPT2 has been implicated in the response to cellular stress, where it aids in the maintenance of cell cycle checkpoints, ensuring that cells do not proceed to DNA replication when damaged [17] [18]. The dysregulation of GSPT2 expression or function can lead to aberrant cell cycle progression, contributing to oncogenesis and tumor progression. For instance, the role of GSPT2 in acute lymphoblastic leukemia has been highlighted, where its degradation leads to reduced cell viability, presenting a potential therapeutic target [19]. Overall, GSPT2 serves as a critical hub in the intricate network of cell cycle regulation, influencing both normal cellular functions and pathological conditions.

2.2. The Expression Pattern of GSPT2 in Tumors

2.2.1. The Expression of GSPT2 in Different Tumor Types

GSPT2, a member of the GSPT family, plays a crucial role in the regulation of gene

expression and cellular stress responses. Its expression varies significantly across different tumor types, suggesting a potential role in tumorigenesis and cancer progression. Recent studies have indicated that GSPT2 is overexpressed in various malignancies, including breast cancer and acute lymphoblastic leukemia (ALL) [17]-[19]. In breast cancer, for instance, high levels of GSPT2 expression are associated with poor prognosis, indicating that it may serve as a potential biomarker for disease severity and treatment response [16] [20]. Conversely, in gastrointestinal cancers, GSPT2 expression appears to correlate with the effectiveness of novel therapeutic agents targeting the cereblon E3 ligase complex, highlighting its role in mediating treatment responses [21]. These findings suggest that GSPT2 may have a multifaceted role in tumor biology, influencing both the development and progression of various cancer types.

2.2.2. The Relationship between GSPT2 and Tumor Stage and Grade

The relationship between GSPT2 expression and tumor staging and grading has garnered increasing attention in oncological research. Elevated levels of GSPT2 have been correlated with advanced tumor stages and higher grades in several cancers, indicating its potential utility as a prognostic marker. For instance, studies have shown that GSPT2 expression is significantly higher in late-stage breast cancer compared to early-stage disease, suggesting that it may play a role in the progression of the disease [16] [20]. Similarly, in acute lymphoblastic leukemia, increased GSPT2 levels have been associated with more aggressive disease phenotypes, further supporting its relevance in cancer progression [19]. The mechanisms by which GSPT2 influences tumor behavior may involve its role in regulating cellular responses to stress and apoptosis, which are critical in determining tumor aggressiveness and patient outcomes. Thus, GSPT2 not only serves as a marker for tumor staging and grading but also presents a potential therapeutic target, as modulating its activity could impact tumor progression and patient prognosis [9]. These insights underscore the importance of GSPT2 in cancer biology and its potential implications for patient management and treatment strategies.

The role of GSPT2 in tumor cell proliferation is multifaceted and involves various molecular mechanisms. GSPT2 is known to interact with several key proteins involved in cell cycle regulation, including cyclins and cyclin-dependent kinases (CDKs). These interactions are essential for the proper progression of the cell cycle, particularly during the G1 to S phase transition. Elevated levels of GSPT2 have been observed in various cancer types, suggesting that its overexpression may drive tumor cell proliferation. Moreover, GSPT2 has been shown to influence the stability of mRNA transcripts that encode for proteins critical for cell cycle progression, thereby enhancing the expression of oncogenes while suppressing tumor suppressor genes. This imbalance can lead to enhanced cell division and tumor growth. Additionally, GSPT2 may also play a role in the DNA damage response, where it helps maintain genomic stability. Disruption of GSPT2 function can result in increased susceptibility to DNA damage, further promoting tumorigenesis.

Thus, targeting GSPT2 or its downstream signaling pathways may represent a promising approach for inhibiting tumor cell proliferation and improving cancer treatment outcomes [3] [4].

2.2.3. The Relationship between GSPT2 Expression and Clinical Prognosis

The relationship between GSPT2 expression and clinical prognosis has garnered attention in recent cancer research. Elevated levels of GSPT2 have been associated with poor prognosis in several cancer types, including breast and gastrointestinal cancers. In breast cancer, high GSPT2 expression is linked to advanced disease stages and reduced overall survival rates, suggesting that it may serve as an independent prognostic factor [15] [19] [20]. This is corroborated by findings in gastrointestinal cancers, where GSPT2 expression levels correlate with tumor progression and patient outcomes, indicating its potential utility in stratifying patients based on risk [20]. These findings collectively suggest that GSPT2 is a marker of tumor, making it a valuable target for future therapeutic strategies aimed at improving patient prognosis in various malignancies.

The ability of cancer cells to invade surrounding tissues and establish secondary tumors is a complex process that involves multiple steps, including epithelial-mesenchymal transition (EMT), migration, and invasion. GSPT2 is not only implicated in tumor cell proliferation but also plays a significant role in the metastatic process. Research has indicated that GSPT2 may facilitate these processes by modulating the expression of genes associated with cell motility and invasion. For instance, GSPT2 has been linked to the regulation of matrix metalloproteinases (MMPs), which are enzymes that degrade extracellular matrix components, allowing cancer cells to invade adjacent tissues. Furthermore, GSPT2's involvement in signaling pathways, such as the PI3K/Akt and MAPK pathways, can enhance the migratory and invasive capabilities of tumor cells. The expression of GSPT2 has been correlated with increased metastatic potential in various cancer types, suggesting that it may serve as a prognostic marker for metastasis. Inhibiting GSPT2 function could potentially reduce the metastatic spread of tumors, making it a target of interest for therapeutic intervention in advanced cancer stages. Understanding the precise mechanisms by which GSPT2 contributes to metastasis will be crucial for developing effective strategies to combat cancer spread [22].

2.3. The Relationship between GSPT2 and Cell Cycle Regulation

2.3.1. The Role of GSPT2 in the G1/S Transition

GSPT2, a member of the GSPT family, has been implicated in the regulation of the cell cycle, particularly during the G1 to S phase transition. This transition is crucial for cell proliferation, as it marks the point where the cell commits to DNA replication. Studies have shown that GSPT2 interacts with various cell cycle regulators, suggesting its role in modulating the activity of proteins involved in this transition. For instance, GSPT2 can influence the stability and activity of cyclins and cyclin-dependent kinases (CDKs), which are essential for the progression

through the cell cycle. The degradation of certain proteins, facilitated by GSPT2, may also play a role in ensuring that the cell cycle progresses in a timely manner. Dysregulation of GSPT2 has been linked to various cancers, indicating that its proper function is critical for maintaining normal cell cycle dynamics. Furthermore, the use of GSPT1/2 degraders, such as SJ6986, has demonstrated efficacy in preclinical models, highlighting the therapeutic potential of targeting GSPT2 in malignancies characterized by aberrant cell cycle regulation [23].

2.3.2. The Relationship between GSPT2 and Cell Proliferation and Apoptosis

GSPT2 plays a significant role in the balance between cell proliferation and apoptosis. The expression levels of GSPT2 have been shown to correlate with cell proliferation rates; higher levels of GSPT2 are often associated with increased cell growth and division. This is likely due to its involvement in mRNA translation and stabilization, which are critical for the synthesis of proteins that promote cell cycle progression and inhibit apoptosis. Conversely, when GSPT2 expression is downregulated, cells may exhibit increased sensitivity to apoptotic signals, leading to enhanced cell death. This dual role of GSPT2 suggests that it is a key player in determining cell fate, particularly under stress conditions or in response to chemotherapeutic agents. The modulation of GSPT2 levels could therefore serve as a potential therapeutic strategy to manipulate cell survival in cancer treatments, where apoptosis resistance is a common challenge. The ongoing research into the mechanisms by which GSPT2 influences these pathways continues to shed light on its importance in cancer biology and the potential for targeted therapies [10] [11] [23].

2.4. The Prospect of GSPT2 as a Tumor Biomarker

2.4.1. The Clinical Application Potential of GSPT2

GSPT2 is increasingly recognized as a potential biomarker in various malignancies. Its expression levels have been correlated with tumor progression and patient prognosis, suggesting that GSPT2 could serve as a valuable indicator for clinical outcomes. Recent studies indicate that elevated GSPT2 expression is associated with poor prognosis in breast cancer, highlighting its potential utility in stratifying patients based on risk [24]. Furthermore, the role of GSPT2 in regulating cellular stress responses, particularly in the context of ferroptosis, positions it as a critical player in tumor biology. The ability to monitor GSPT2 levels in clinical settings could provide oncologists with a tool for better predicting treatment responses and tailoring therapeutic strategies to individual patients. Additionally, the integration of GSPT2 expression analysis into existing diagnostic frameworks may enhance the precision of cancer management, ultimately leading to improved patient outcomes.

2.4.2. Research Progress on GSPT2 as a Therapeutic Target

Research into GSPT2 as a therapeutic target has gained momentum, particularly

due to its involvement in key cellular processes such as apoptosis and stress response pathways. Investigations have demonstrated that targeting GSPT2 can sensitize cancer cells to chemotherapeutic agents, suggesting that modulation of its activity could enhance treatment efficacy. For instance, studies have shown that inhibiting GSPT2 expression leads to increased susceptibility of tumor cells to ferroptosis, a form of regulated cell death that is being explored as a novel therapeutic strategy in oncology [24] [25]. Furthermore, the development of small molecules or RNA-based therapies aimed at downregulating GSPT2 expression is currently under investigation, with preliminary results indicating promising outcomes in preclinical models. These findings underscore the potential of GSPT2 not only as a biomarker for cancer prognosis but also as a viable target for therapeutic intervention, paving the way for future clinical trials that could validate its role in cancer treatment. As research progresses, the therapeutic implications of GSPT2 may lead to innovative approaches in combating various malignancies, ultimately enhancing patient care and survival rates.

3. Conclusions

In summary, GSPT2 plays a pivotal role in tumor biology, particularly in the regulation of the cell cycle and signal transduction pathways. Its involvement in these critical processes underscores the importance of GSPT2 as a molecular player that can influence tumor growth and progression. The current body of research highlights the potential of GSPT2 as a biomarker in cancer diagnostics and prognostics, indicating its ability to provide insights into tumor behavior and patient outcomes.

As we look to the future, the exploration of GSPT2 as a biomarker offers exciting avenues for personalized treatment strategies. By understanding the differential expression and functional implications of GSPT2 in various cancer types, we can better tailor therapeutic interventions to individual patients. This could lead to improved efficacy of existing treatments and the development of novel therapies that specifically target GSPT2-related pathways.

Looking ahead, future research should focus on several key areas to fully harness the potential of GSPT2 in clinical applications. Firstly, there is a need for comprehensive studies that delve deeper into the molecular interactions and pathways associated with GSPT2, particularly in different cancer contexts. Understanding how GSPT2 integrates with existing oncogenic pathways will be essential for developing targeted therapies. Secondly, large-scale clinical trials are necessary to validate GSPT2 as a reliable biomarker and to assess its utility in predicting treatment response and patient outcomes.

Additionally, the development of GSPT2 inhibitors and the exploration of combination therapies that include GSPT2 modulation could pave the way for innovative treatment strategies. As we balance the diverse research perspectives on GSPT2, it becomes imperative to integrate findings from basic research with clinical insights, ensuring that future advancements in GSPT2-related cancer

therapies are both scientifically sound and clinically relevant.

In conclusion, GSPT2 holds significant promise as both a biomarker and a therapeutic target in oncology. The ongoing exploration of its roles and mechanisms will undoubtedly provide valuable insights that could lead to improved diagnostic and treatment strategies, ultimately enhancing patient care in cancer management.

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Declaration Section

Publication Consent

The publication of all data, figures, and conclusions in this study has been approved by all participants, collaborators, and relevant institutions. There are no disputes regarding copyright or publication rights.

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Author Contributions

Yu Cai was primarily responsible for Subject design, Implementation, Yumei Wu made significant contributions in Writing-review & editing.

Conflicts of Interest

All authors of this study declare that there are no conflicts of interest that may affect the impartiality of the study results. We commit to maintaining an objective and impartial attitude in writing the research report and publishing the research findings, without being influenced by any external factors.

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