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The Role of Long Non-coding RNA in Acute Myeloid Leukemia: Mechanisms, Diagnostic Potential, and Therapeutic Implications

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Abstract

Context: Acute myeloid leukemia (AML) is a heterogeneous and aggressive form of leukemia characterized by the abnormal proliferation of immature myeloid cells. The identification of reliable biomarkers for early diagnosis and prognosis is essential for improving patient outcomes.

Evidence Acquisition: Emerging evidence suggests that long non-coding RNAs (lncRNAs), particularly tumor suppressor candidate 7 (TUSC7), play a significant role in cancer biology, including AML. Studies consistently show that TUSC7 is significantly downregulated in AML patients, suggesting its role as a tumor suppressor.

Results: The diagnostic potential of TUSC7 was highlighted in multiple studies, with receiver operating characteristic (ROC) curve analysis showing promising sensitivity and specificity in distinguishing AML patients from healthy individuals. While preliminary evidence suggests that lower TUSC7 expression may be linked to worse survival outcomes, further research is required to confirm its prognostic value. Long non-coding RNAs TUSC7 shows potential as a biomarker for AML, with its downregulation correlating with disease progression.

Conclusions: Although promising as a diagnostic tool, further studies are necessary to validate its use in prognosis and to explore therapeutic interventions targeting TUSC7. As research on TUSC7 advances, it may offer new avenues for personalized treatment strategies in AML.

Keywords: Acute Myeloid Leukemia (AML), lncRNA, TUSC7, Biomarkers

1. Context

Acute myeloid leukemia (AML) is a malignant and heterogeneous blood cancer caused by the clonal expansion of abnormal hematopoietic progenitor cells in the bone marrow (1). The AML is described as the infiltration of leukemic blasts that disturb normal hematopoiesis, resulting in various clinical features, including anemia, thrombocytopenia, neutropenia, and predisposition to infection. With an estimated incidence of approximately 20,000 new cases per year in the United States alone, AML is the most common acute leukemia of adults, with a median age at diagnosis of 68 years. Despite available aggressive treatments, including chemotherapy, targeted therapy, and hematopoietic stem cell transplantation, the outlook of AML is unfavorable. The overall survival rates have improved only slightly over the past few decades, especially in elderly patients or those carrying high-risk genetic mutations (2-5).

Acute myeloid leukemia pathogenesis is multistep, with the accumulation of genetic mutations and epigenetic alterations having a central role in leukemogenesis. The mutations have a tendency to affect vital transcription factors, signaling pathways, and regulatory molecules, causing disruption in normal hematopoietic differentiation and survival pathways. Acute myeloid leukemia is also notable for its cytogenetic heterogeneity, with recurring chromosomal translocations, inversions, and deletions serving as important diagnostic and prognostic markers. Mutations shared by AML are those in the FLT3, NPM1,

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and CEBPA genes, which dictate how the disease responds to treatment and outcome. Despite these developments in genetic characterization, the therapeutic landscape of AML still remains challenging due to the high relapse rate of the disease after initial remission and the development of resistance to conventional treatment. Therefore, new biomarkers for diagnosis, prognosis, and therapeutic monitoring are urgently required to enhance patient outcomes (3, 4, 6).

Recent advances in the molecular underpinnings of AML have underscored the central role of non-coding RNAs (ncRNAs) in the regulation of gene expression. While previously thought to represent "transcriptional noise", the current understanding is that non-coding RNAs, in particular long non-coding RNAs (lncRNAs), have fundamental roles in various cellular processes, including differentiation, apoptosis, and chromatin remodeling. These RNAs, typically longer than 200 nucleotides in length, do not code for protein but are involved in the regulation of gene expression at the transcriptional, post-transcriptional, and epigenetic modification levels. Emerging evidence has shown that lncRNAs are key players in the pathogenesis of a variety of cancers, including AML. These molecules are oncogenes and tumor suppressors, depending on the specific disease context, and have demonstrated their capacity to modulate cellular behavior through interactions with DNA, RNA, and proteins. In AML, a number of lncRNAs have been involved in the control of leukemogenesis, with the possibility of their utilization as new biomarkers for diagnosis, prognosis, and response to therapy (7, 8).

One particular long non-coding RNA (lncRNA) that has received significant interest in the domain of cancer biology is tumor suppressor candidate 7 (TUSC7). Initially identified as a candidate tumor suppressor gene with potential involvement in a variety of malignancies, including colorectal cancer, osteosarcoma, and hepatocellular carcinoma, TUSC7 has more recently been implicated in AML. In various cancers, TUSC7 acts as a tumor suppressor by regulating critical genes involved in cell cycle regulation, apoptosis, and metastasis. The regulatory role is mostly attained through the modulation of different signaling pathways and interactions with important proteins and miRNAs. The TUSC7, for example, has been found to be able to suppress cancer cell growth and invasion and induce apoptosis in numerous tumor cells. Interestingly, TUSC7 expression levels are frequently reduced in these cancer types, which is consistent with its role as a tumor suppressor. In AML, TUSC7's role is still poorly described; however, recent studies show that it could have a role in the pathogenesis of the disease through similar mechanisms (9, 10).

Preliminary investigations of TUSC7 in AML revealed that this lncRNA can regulate the expression of genes implicated in hematopoietic differentiation and leukemic stem cell maintenance. These findings point to the potential of TUSC7 as a critical regulator of AML biology. Furthermore, studies show that reduced expression of TUSC7 can be associated with adverse clinical features in patients with AML, including resistance to chemotherapy and poor prognosis. Loss of TUSC7 expression may contribute to the pathogenesis of AML by disrupting normal cell cycle regulation, promoting the survival of aberrant cells, and enhancing the invasive potential of leukemic cells (11, 12).

While the exact molecular pathways by which TUSC7 functions in AML are under investigation, its involvement in the regulation of key oncogenes and tumor suppressors, such as p53 and miR-10b, suggests that it may exert broad effects on gene networks important for leukemogenesis. Tumor suppressor candidate 7 has also been found to associate with chromatin-modulating complexes, suggesting it may have a role in the epigenetic regulation of AML-related genes. The accumulating evidence for the involvement of TUSC7 in AML suggests that it might not just be a prognostic indicator but also a therapeutic target for intervention (12-14).

With its tumor-suppressive function and novel role in AML, TUSC7 is a promising candidate for ongoing investigation in hematologic malignancies. Our present understanding of TUSC7 in AML is the subject of this review, in which we will explore its molecular mechanisms of action, its promise in diagnosis, and its implications in therapy. Through the emphasis on recent findings concerning TUSC7, we aim to enhance the expanding repository of information related to the molecular framework of AML and the prospects for innovative therapeutic approaches based on lncRNAs in addressing this severe condition (15, 16).

2. The Role of Tumor Suppressor Candidate 7 in Cancer

The TUSC7, or LINC00902, is a long non-coding RNA (lncRNA) located on chromosome 3q13.31. Though first identified as a tumor suppressor in colorectal cancer, TUSC7 has subsequently been found to play a ubiquitous role in a wide range of cancers, such as non-small cell lung cancer (NSCLC), gastric cancer (GC), osteosarcoma, pancreatic carcinoma, and others. As a tumor suppressor, TUSC7 is most directly associated with the regulation of cellular proliferation, differentiation, and

apoptosis, which are all central processes in cancer biology. It accomplishes this by interacting with various molecular targets, including oncogenic microRNAs (oncomiRs), chromatin remodeling complexes, and major cell cycle regulators. The role of TUSC7 in cancer has made it a focal point for understanding the intricate web of gene regulation, as well as its potential application as a diagnostic and therapeutic target. Tumor suppressor candidate 7's tumor-suppressive function is mainly attributed to its role as a molecular sponge for oncomiRs, small non-coding RNAs that typically promote cancer development by suppressing the expression of tumor-suppressor genes. Through the sequestration of oncomiRs, TUSC7 inhibits their binding to target genes, and the expression of tumor-suppressor genes is thus restored. It is an important step in TUSC7's regulatory function in major cellular functions, including cell cycle control, apoptosis, migration, and invasion — processes whose deregulation plays an important role in cancer development and progression (17-22).

In CRC, TUSC7's tumor-suppressing function was reported earlier. The lncRNA functions by directly binding the oncogenic microRNA miR-211-3p, effectively sequestering it so that it is no longer able to target CDK6, a cyclin-dependent kinase that promotes cell cycle progression from G1 to S phase. Through the inhibition of miR-211-3p's capacity to suppress CDK6, TUSC7 triggers cell cycle arrest and represses excessive cell proliferation, a hallmark of cancer development. Consequently, TUSC7 downregulation in CRC has been linked with aggressive tumor behavior, increased proliferation, and lower patient survival rates. The molecular interaction of miR-211-3p with TUSC7 is a reflection of how lncRNAs play a role in regulating cancer progression through the modulation of oncomiRs and cell cycle regulators (23).

In GC, TUSC7 serves a fundamental function in preserving a balance between pro-apoptotic and anti-apoptotic signaling. Research indicates that TUSC7 is linked to miR-23b, an oncomiR that targets and inhibits a number of pro-apoptotic genes. Through its binding to miR-23b, TUSC7 inhibits the inhibitory action of miR-23b on these pro-apoptotic genes, thus inducing apoptosis and inhibiting the growth and viability of cancer cells. In the case of TUSC7 loss or downregulation of expression, the inhibition of these pro-apoptotic genes leads to increased cell survival, resistance to apoptosis, and hence more aggressive cancer phenotypes. Loss of TUSC7 expression has been associated with poor prognosis in GC patients, highlighting the important function of this lncRNA in the maintenance of cellular homeostasis and the prevention of malignant transformation (24).

The regulatory role of TUSC7 extends beyond its miRNA interaction. In osteosarcoma, a highly malignant bone cancer common in children and young adults, TUSC7 has also been found to bind chromatin-modifying complexes, suggesting that its tumor suppressor function can also be through epigenetic regulation. Tumor suppressor candidate 7 thereby helps to regulate gene expression of the osteosarcoma cell proliferation, invasion, and metastasis genes. Downregulation of TUSC7 expression in osteosarcoma cells results in increased cellular motility and invasiveness, which is partly responsible for the poor prognosis and high metastatic rate of this particular malignancy (25, 26).

Further, in NSCLC, TUSC7 is demonstrated to be an important regulator of cell cycle progression and metastatic activity. In this carcinoma, TUSC7 functions as a potent suppressor of tumor growth by acting against several oncomiRs like miR-10b, which has been identified to regulate genes involved in cell migration and invasion. Non-small cell lung cancer overexpression of miR-10b has been linked with the promotion of metastatic potential, and TUSC7 suppresses this function by preventing miR-10b from downregulating its target genes. This dialogue reflects the complex role of TUSC7 in controlling the formation of tumors and their secondary spreading, an important prognostic determinant of cancer (27-29).

In pancreatic cancer, which is considered to be among the deadliest cancer types with high mortality rates, the levels of TUSC7 expression tend to be decreased, and the lack thereof has been linked with poor survival rates. The exact pathways by which TUSC7 regulates pancreatic cancer formation are under active research. However, as in other cancers, TUSC7's tumor suppressor role in pancreatic carcinoma is believed to be exerted through its binding of oncogenic miRNAs and its control of cell survival and apoptosis genes (30).

Despite the mounting body of evidence that supports the tumor-suppressive role of TUSC7 in many cancers, the exact molecular mechanisms through which it acts remain to be elucidated. However, it is clear that TUSC7 mediates its actions through a range of mechanisms, including the direct modulation of oncomiRs and binding with chromatin-modifying complexes, hence influencing gene expression at both transcriptional and post-transcriptional levels. Furthermore, reduction or downregulation of TUSC7 expression has been consistently associated with poorer clinical outcomes in a wide range of malignancies, thereby highlighting its function as a major tumor suppressor. These

observations imply that restoration or mimicry of TUSC7 function would be a useful treatment in those cancers where it is lost, such as colorectal cancer, GC, and osteosarcoma (31, 32).

However, the role of TUSC7 in AML, while promising, is yet to be determined. The genetic complexity and heterogeneity of AML may influence the manner in which TUSC7 functions in this hematologic cancer. Current evidence indicates that TUSC7 may play a comparable role in AML, regulating genes implicated in cell differentiation, apoptosis, and leukemogenesis. The study of TUSC7's role in AML is of the utmost importance as it can provide new insights into the molecular biology of the disease and open up therapeutic options.

3. Molecular Mechanisms of Tumor Suppressor Candidate 7 in Acute Myeloid Leukemia

The pathogenesis of AML is marked by a series of genetic and epigenetic changes that interfere with normal hematopoiesis, causing abnormal proliferation of immature myeloid cells. Although there have been considerable improvements in treatment approaches, AML is still an extremely heterogeneous condition, with a propensity to be resistant to standard therapies, particularly in the elderly or those with unfavorable genetic mutations. Elucidating molecular mechanisms that govern the trajectory of AML is essential to devise more effective and targeted therapeutic strategies. Recent reports have indicated that TUSC7, a long non-coding RNA (lncRNA), could be a significant player in the molecular profile of AML by demonstrating tumor-suppressive function with an influence on key pathways related to cell proliferation, apoptosis, and immune regulation (33, 34).

One of the major mechanisms by which TUSC7 exerts its tumor-suppressive effects in AML is through its role as a competing endogenous RNA (ceRNA). A ceRNA acts as a molecular sponge to bind microRNAs (miRNAs) so that they cannot bind to their target messenger RNAs (mRNAs). In this manner, TUSC7 is able to counteract the repressive activity of oncomiRs — miRNAs that promote tumorigenesis via repression of tumor suppressors (35). One of the more well-characterized oncomiRs in AML is miR-23b, which has been shown to promote leukemic cell survival by directly repressing PTEN, a significant tumor suppressor. PTEN functions to repress the PI3K/AKT pathway, which has the role of controlling cell growth, survival, and apoptosis. Downregulation of PTEN by miR-23b initiates the activation of the PTEN/Nrf2 pathway, thereby increasing the cell's resistance to oxidative stress. This is frequent in leukemic cells, where oxidative stress is the cause of survival and chemoresistance. The TUSC7 reverses the effect by binding to miR-23b, thereby deactivating its function and reactivating PTEN expression. This re-establishes the regular regulation of the PI3K/AKT signaling pathway, which in turn diminishes the survival of leukemic cells and renders them more vulnerable to chemotherapeutic drugs (14, 26).

Apart from its function in the regulation of microRNA (miRNA), TUSC7 also plays a pivotal role in regulating inflammatory signaling pathways in AML. Among the key targets of TUSC7 is the NOD-like receptor protein 3 (NLRP3) inflammasome, which has a central function in the initiation of pyroptosis, a type of programmed inflammatory cell death. Pyroptosis is an inflammatory form of cell death induced by infection or cell stress and is an important mechanism for immune response. In AML, TUSC7 activation of NLRP3 induces pyroptotic cell death, which limits the survival and development of leukemic cells. This process is interesting in that it suggests TUSC7 not only has the potential to directly regulate leukemia cell survival but also influence the inflammatory tumor microenvironment, which is a key driver of AML pathogenesis (18, 31).

Apart from its immediate effect on cell viability, TUSC7 also affects the immune microenvironment of AML. Leukemic cells may evade immune surveillance, and this allows them to survive and expand despite the presence of an immune system. The TUSC7 controls the polarization of macrophages, which are immune cells that can either promote or inhibit tumor growth depending on their activation status. Studies have shown that TUSC7 engages with key signaling pathways such as STAT3, SHP2, and STAT6, which are core to macrophage function regulation. By influencing these pathways, TUSC7 can shape macrophage polarization into an immune-suppressive phenotype that would favor leukemic cell survival and immune evasion. In this context, TUSC7 may act not just by increasing the malignant phenotypes of AML cells, but also by modeling the broader immune milieu to favor a tumor microenvironment for leukemia growth (32, 33).

Taken together, these findings suggest that TUSC7 is a multifaceted regulator of AML, affecting cell viability, programmed cell death, immune regulation, and inflammatory pathways. Through miRNA regulation, inflammasomes, and immune pathways, TUSC7 assists in coordinating a molecular event network that dictates AML development. At a more fundamental level, exploration of these mechanisms is crucial to identifying novel therapeutic strategies that would

target TUSC7's pathways and revive tumor-suppressive function in AML.

4. Diagnostic Potential of Tumor Suppressor Candidate 7 in Acute Myeloid Leukemia

The determination of effective biomarkers for the diagnosis and prognosis of AML remains the most critical task in hematology. The conventional diagnostic methods now include bone marrow biopsy and genetic analysis, which are invasive and time-consuming tests. However, TUSC7 has been shown to be a very strong candidate for a non-invasive AML biomarker with potential utility in diagnosis and even prognosis. In AML, TUSC7 is commonly downregulated in cancer cells, and this is correlated with poor clinical outcomes, including increased relapse risk and reduced survival. Several studies have demonstrated that the expression of TUSC7 is significantly lower in AML patients compared with normal controls, suggesting that the loss of TUSC7 expression may be an early event in the disease process. Here, TUSC7 can serve as a highly effective biomarker for the diagnosis of AML, allowing physicians to detect the disease earlier and potentially treat the disease before its progression (34-36).

Apart from its diagnostic utility, TUSC7 has also been found to be useful as a prognostic marker. Early reports have shown that low levels of TUSC7 expression correlated with advanced stages of the disease and poor survival in patients with AML. Thus, TUSC7 can potentially be used to stratify patients based on their risk for disease progression and plan treatment strategies appropriately. In addition, because TUSC7 expression is closely associated with key tumor-suppressive mechanisms in AML, it could potentially provide insight into the underlying molecular mechanisms driving disease progression (30, 37).

One of the most encouraging characteristics of TUSC7 as a biomarker is that it is stable and expressed in circulating exosomes. Exosomes are small vesicles released by cells into the blood and can carry molecular signatures, such as RNA, proteins, and lipids, that reflect the state of the tumor. Tumor suppressor candidate 7 can be detected in the exosomes of many AML patients, which makes it an excellent candidate for liquid biopsy technologies. Liquid biopsies enable the minimally invasive tracking of disease progression, recurrence, and response to treatment by measuring molecular markers in peripheral blood samples. It is much less invasive than conventional biopsy methods and can potentially offer real-time monitoring of a patient's disease status. By incorporating TUSC7 within a panel of lncRNA biomarkers, physicians could increase the sensitivity and specificity of the diagnosis of AML, enabling more precise and earlier treatment interventions (29, 30).

Furthermore, the incorporation of TUSC7 into liquid biopsy panels would also facilitate real-time treatment response monitoring. Since AML has high rates of relapse, particularly in those carrying high-risk genetic mutations, monitoring TUSC7 levels would allow the determination of whether the leukemia is responding to therapy or if the patient is likely to suffer relapse. This consideration could be of particular significance in the era of targeted therapies and immunotherapies, as these interventions need continuous monitoring to ensure the effectiveness of the treatment.

5. Therapeutic Implications of Tumor Suppressor Candidate 7 in Acute Myeloid Leukemia

The therapeutic potential of TUSC7 in AML is another area of active research. Through its tumor suppressor function, strategies to restore TUSC7 expression or to recapitulate its function can yield novel therapeutic approaches. One such approach is the use of RNA-based therapies, including antisense oligonucleotides, siRNAs, and CRISPR-mediated gene activation, to enhance TUSC7 expression in leukemic cells (34-38).

One strategy would be the development of synthetic miRNA sponges that mimic TUSC7's ability to sequester oncogenic microRNAs such as miR-23b. Such RNA decoys could be specifically delivered to AML cells to inhibit the oncogenic activity of miR-23b and other oncomiRs. Exosome-mediated delivery systems have the additional advantage that they can be engineered to deliver TUSC7 mimics directly to the bone marrow microenvironment, enabling targeted and efficient delivery of therapy with minimal systemic side effects (35, 36).

Immunotherapeutic interventions can be augmented by TUSC7 reconstitution. Through the promotion of the activation of the NLRP3 inflammasome and induction of pyroptotic cell death, TUSC7 might streamline the immune system to identify and eliminate leukemic cells. The regulation of macrophage polarization may also transform the immunosuppressive microenvironment of AML into one that favors immune-mediated tumor elimination (37, 38).

6. Challenges and Future Directions

Although the prospects of TUSC7 in AML are promising, several challenges have to be overcome. The genetic and epigenetic heterogeneity of AML renders the interpretation of TUSC7 expression patterns

difficult. Elucidating the context-dependent roles of TUSC7 in different AML subtypes will be instrumental in developing successful targeted therapies.

Additionally, the complete molecular mechanisms through which TUSC7 regulates AML progression are not well understood. Further studies using multi-omics approaches, including genomics, transcriptomics, and proteomics, are required to map out the regulatory pathways involving TUSC7.

Lastly, the clinical validation of TUSC7 as a biomarker and potential therapeutic target will necessitate large-scale studies and clinical trials. Standardized assays for the detection and measurement of TUSC7 in clinical specimens are essential to provide reproducibility and accuracy. Clinical trials of TUSC7-based therapies, either alone or in combination with current drugs, will be required to establish their safety, efficacy, and long-term effects.

7. Conclusions

Tumor suppressor candidate 7 is emerging as a critical player in the pathogenesis of AML, with its tumor-suppressive role in modulating microRNAs, epigenetic regulation, and immune responses. As a potential diagnostic and prognostic biomarker, TUSC7 holds promise for improving the early detection and risk stratification of AML. Furthermore, its therapeutic potential, through the restoration of its expression or the mimicry of its function, offers exciting avenues for novel treatments. However, further research is needed to fully understand the molecular mechanisms of TUSC7 in AML and to translate these findings into clinical practice.

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