The Oncogenic Role of Mucin 1 (MUC1) and Its Therapeutic Potential in Acute Myeloid Leukemia

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Abstract

Mucin 1 (MUC1), a transmembrane glycoprotein with critical roles in cell signaling and immune regulation, has been increasingly recognized as a key player in the pathogenesis of Acute Myeloid Leukemia (AML). Aberrant overexpression of MUC1 on leukemic blasts contributes to disease progression by promoting oncogenic signaling, enhancing resistance to apoptosis, and fostering immune evasion. Its hypoglycosylated form, predominantly observed in AML, disrupts normal cell-cell interactions, facilitates leukemic cell adhesion to the bone marrow niche, and contributes to chemoresistance. This review highlights the multifaceted role of MUC1 in AML pathophysiology, focusing on its involvement in the activation of critical pathways such as PI3K/Akt, NF-κB, and β-catenin, which promote leukemic cell survival, proliferation, and therapeutic resistance. Clinically, high MUC1 expression is correlated with adverse outcomes, including disease aggressiveness, relapse risk, and reduced survival, making it a promising biomarker for risk stratification. Emerging therapeutic strategies targeting MUC1 include monoclonal antibodies, peptide-based vaccines, small molecule inhibitors, and antibody-drug conjugates, many of which have demonstrated preclinical efficacy and are progressing to clinical evaluation. Novel immunotherapeutic approaches, such as MUC1-targeted chimeric antigen receptor (CAR) T-cell therapies, offer exciting potential to overcome chemoresistance and improve patient outcomes.

By synthesizing the latest research, this review underscores the clinical significance of MUC1 in AML and the transformative potential of MUC1-targeted therapies. Further investigation into the molecular mechanisms underlying MUC1's oncogenic functions and the optimization of therapeutic strategies will be crucial for translating these insights into effective treatments for AML, ultimately improving survival and quality of life for affected patients.

Keywords: Mucin 1, Acute Myeloid Leukemia

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Introduction

Acute Myeloid Leukemia (AML) is a heterogeneous clonal disorder characterized by the uncontrolled proliferation of myeloid precursor cells, leading to bone marrow failure and systemic manifestations. AML primarily affects adults, with a median age of diagnosis around 68 years. Risk factors include exposure to ionizing radiation, benzene, prior chemotherapy, and genetic predispositions such as inherited bone marrow failure syndromes [1].

The pathophysiology of AML involves a combination of genetic and epigenetic alterations. Recurrent chromosomal translocations, such as t(8;21), inv(16), and t(15;17), and mutations in genes such as FLT3, NPM1, and DNMT3A drive leukemogenesis. These alterations disrupt normal hematopoiesis, leading to the accumulation of immature myeloid blasts and suppression of normal hematopoietic function [2].

The clinical presentation of AML is variable and often includes symptoms of bone marrow failure, such as fatigue, recurrent infections, and bleeding. Extramedullary disease, such as myeloid sarcomas, may also occur. Diagnosis typically requires integration of clinical, morphological, immunophenotypic, cytogenetic, and molecular findings [3].

A bone marrow biopsy and aspirate are central to diagnosing AML. Morphologically, AML is defined by the presence of ≥20% blasts in the bone marrow or peripheral blood, except in cases with specific genetic abnormalities. The blasts are evaluated for morphological features such as Auer rods and cytoplasmic granules, which provide clues to the subtype of AML [4].

Immunophenotyping by flow cytometry is a critical diagnostic tool in AML. It allows for the identification of leukemic cells based on the expression of specific surface and cytoplasmic markers, such as CD13, CD33, CD34, and HLA-DR. Lineage-specific markers help differentiate AML from other hematologic malignancies and are essential for subclassification [5].

Cytogenetic analysis provides vital prognostic and therapeutic information. Karyotyping identifies chromosomal abnormalities that stratify patients into favorable, intermediate, or adverse risk groups. For instance, core-binding factor (CBF) abnormalities, including t(8;21) and inv(16), are associated with a favorable prognosis, while complex karyotypes and monosomal karyotypes predict poor outcomes [6].

Molecular diagnostics have revolutionized AML classification and management. Next-generation sequencing (NGS) panels are widely used to identify mutations in genes such as FLT3, NPM1, and CEBPA. FLT3 internal tandem duplications (FLT3-ITD) are associated with an adverse prognosis, while NPM1 mutations confer a favorable prognosis when FLT3-ITD is absent [7].

Minimal residual disease (MRD) assessment has emerged as an essential tool for monitoring treatment response and predicting relapse. Techniques such as multiparameter flow cytometry (MFC) and quantitative polymerase chain reaction (qPCR) detect MRD with high sensitivity,

guiding post-remission therapy. MRD negativity is associated with improved survival outcomes [8].

Advanced imaging techniques, such as positron emission tomography-computed tomography (PET-CT), have limited but expanding roles in AML. PET-CT is particularly useful in identifying extramedullary disease, such as myeloid sarcomas, and evaluating treatment response in these cases. However, its routine use is not currently recommended [9].

Liquid biopsies are an emerging diagnostic modality in AML. They involve the analysis of circulating tumor DNA (ctDNA) in peripheral blood to detect genetic abnormalities. Liquid biopsies offer a minimally invasive approach for disease monitoring and may complement bone marrow biopsies in assessing MRD and tracking clonal evolution during therapy [10].

The integration of these diagnostic modalities into clinical practice has transformed the landscape of AML management. Combining traditional techniques, such as morphology and cytogenetics, with advanced molecular and imaging tools enables precise risk stratification, personalized therapy, and improved outcomes. Future research should focus on standardizing and validating emerging diagnostic approaches to further enhance their utility in AML care [11].

Mucin 1 (MUC1) Expression in Acute Myeloid Leukemia

Overview of MUC1

Mucin 1 (MUC1) is a high-molecular-weight transmembrane glycoprotein primarily expressed on the apical surface of epithelial cells. It plays critical roles in cellular signaling, adhesion, and immune modulation. Structurally, MUC1 consists of an extracellular domain with tandem repeat sequences heavily glycosylated with O-linked glycans, a transmembrane domain, and a cytoplasmic tail that mediates intracellular signaling. Aberrant expression and hypoglycosylation of MUC1 are commonly observed in malignancies, contributing to tumor progression, immune evasion, and resistance to therapy [11].

MUC1 in Hematologic Malignancies

While MUC1 is traditionally associated with epithelial cancers, its expression in hematologic malignancies, including Acute Myeloid Leukemia (AML), has garnered significant attention. Unlike its polarized expression in normal epithelial cells, MUC1 is overexpressed and distributed across the entire surface of leukemic blasts in AML. This aberrant expression facilitates leukemogenesis by promoting cell proliferation, survival, and chemoresistance [12].

Role of MUC1 in Leukemogenesis

In AML, MUC1 contributes to leukemogenesis by activating oncogenic signaling pathways such as PI3K/Akt, NF-κB, and β-catenin. The MUC1-C subunit, generated by proteolytic cleavage, translocates to the nucleus and interacts with transcription factors to promote the expression of genes involved in cell cycle progression and anti-apoptotic mechanisms. These activities drive the proliferation and survival of leukemic cells [13].

Impact on the Bone Marrow Microenvironment

The hypoglycosylated form of MUC1 expressed in AML alters cell adhesion and migration. It disrupts interactions between leukemic blasts and the bone marrow stromal niche, facilitating the egress of blasts into the peripheral blood and contributing to disease dissemination. Additionally, MUC1 modulates the secretion of cytokines and chemokines, creating an immunosuppressive microenvironment that supports leukemic progression [14].

Immune Evasion and MUC1

MUC1 aids immune evasion in AML by impairing the recognition and elimination of leukemic blasts by immune cells. It inhibits natural killer (NK) cell cytotoxicity and downregulates activating receptors such as NKG2D. MUC1 also promotes the recruitment and expansion of regulatory T cells (Tregs), which suppress anti-leukemic immune responses, further contributing to immune escape [15].

Prognostic Implications of MUC1 Expression in AML

High levels of MUC1 expression in AML are associated with poor prognosis. Studies have demonstrated a correlation between MUC1 overexpression and increased disease aggressiveness, chemoresistance, and reduced overall survival. As a result, MUC1 is being investigated as a potential biomarker for risk stratification and prognostic evaluation in AML patients [16].

Therapeutic Targeting of MUC1 in AML

Given its role in AML pathogenesis, MUC1 has emerged as a promising therapeutic target. Various strategies, including monoclonal antibodies, small molecule inhibitors, and peptide vaccines, are under development to inhibit MUC1 signaling and enhance anti-leukemic immune responses. These approaches aim to overcome chemoresistance and improve treatment outcomes in AML [17].

Monoclonal Antibodies Against MUC1

Monoclonal antibodies targeting MUC1 have shown promise in preclinical models and early-phase clinical trials. Antibodies such as GO-203 and TAB004 selectively bind to the hypoglycosylated form of MUC1, blocking its interaction with oncogenic signaling pathways and inducing apoptosis in leukemic cells. These agents are also being investigated in combination with standard chemotherapy to enhance therapeutic efficacy [18].

Peptide Vaccines Targeting MUC1

Peptide-based vaccines targeting MUC1 aim to elicit robust T-cell-mediated immune responses against leukemic blasts. For example, the MUC1-derived peptide vaccine Tecemotide has demonstrated immunogenicity in preclinical studies, with ongoing trials evaluating its potential in AML. Combining these vaccines with immune checkpoint inhibitors may further enhance their efficacy [19].

MUC1-Targeted Immunotherapies

Innovative immunotherapeutic approaches targeting MUC1, such as chimeric antigen receptor (CAR) T-cell therapy, are under investigation. CAR T cells engineered to recognize MUC1 selectively target leukemic blasts, sparing normal cells. Preclinical studies have shown encouraging results, with significant tumor regression observed in AML models [20].

Small Molecule Inhibitors

Small molecule inhibitors targeting the MUC1-C subunit represent another promising strategy. These agents disrupt the dimerization and nuclear translocation of MUC1-C, thereby inhibiting oncogenic signaling. Compounds such as GO-203 have demonstrated preclinical efficacy in inducing apoptosis and sensitizing leukemic cells to chemotherapy [21].

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