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Cancer Signaling Pathways in Acute Myeloid Leukemia

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Abstract

Acute myeloid leukemia (AML) is a complex and heterogeneous hematological malignancy characterized by abnormal proliferation and impaired differentiation of myeloid precursor cells. The pathogenesis of AML is strongly associated with dysregulation of multiple cancer signaling pathways that control cellular proliferation, survival, apoptosis, metabolism, and stem cell maintenance. Key signaling cascades implicated in AML include FLT3, PI3K/Akt/mTOR, Ras/Raf/MEK/ERK, JAK/STAT, NF-κB, Wnt/β-catenin, Hedgehog, Notch, and p53 pathways. Aberrant activation or suppression of these pathways contributes to leukemogenesis, disease progression, therapeutic resistance, and relapse. FLT3 mutations represent one of the most common molecular abnormalities in AML and are closely linked with activation of downstream oncogenic signaling networks. Similarly, constitutive activation of PI3K/Akt/mTOR and MAPK pathways promotes leukemic cell growth and survival, while dysregulation of Wnt/β-catenin and Hedgehog pathways supports leukemic stem cell maintenance. In addition, alterations in JAK/STAT, NF-κB, and p53 signaling further contribute to AML pathophysiology and poor clinical outcomes. The extensive cross-talk among these pathways highlights the molecular complexity of AML and presents challenges for effective treatment. Understanding the mechanisms underlying signaling pathway dysregulation in AML remains essential for the development of targeted therapeutic strategies and improved patient management.

Keywords: *Acute myeloid leukemia, Cancer signaling pathways, Leukemogenesis, Therapeutic resistance*

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Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematological malignancy characterized by the uncontrolled proliferation and impaired differentiation of myeloid precursor cells in the bone marrow and peripheral blood. The disease arises from genetic and epigenetic abnormalities that disrupt normal hematopoiesis and activate oncogenic signaling pathways. These signaling networks regulate cell survival, proliferation, differentiation, metabolism, and apoptosis, thereby contributing to leukemogenesis, disease progression, therapeutic resistance, and relapse.

Understanding the dysregulated signaling pathways in AML has become essential for identifying molecular mechanisms underlying the disease and for developing targeted therapeutic strategies. Several signaling cascades have been implicated in AML pathogenesis, including FLT3 signaling, PI3K/Akt/mTOR, Ras/Raf/MEK/ERK, JAK/STAT, NF-κB, Wnt/β-catenin, Hedgehog, Notch, and p53 pathways.

FLT3 Signaling Pathway

FMS-like tyrosine kinase 3 (FLT3) is one of the most frequently mutated receptor tyrosine kinases in AML. FLT3 mutations, particularly internal tandem duplications (FLT3-ITD) and tyrosine kinase domain (FLT3-TKD) mutations, result in constitutive activation of downstream signaling pathways that promote leukemic cell proliferation and survival.

Activated FLT3 stimulates several downstream cascades, including PI3K/Akt/mTOR, Ras/MAPK, and JAK/STAT pathways. Persistent FLT3 signaling enhances cellular proliferation, inhibits apoptosis, and contributes to poor prognosis and increased relapse rates in AML patients. FLT3 mutations are therefore considered major drivers of leukemogenesis and important therapeutic targets.

PI3K/Akt/mTOR Signaling Pathway

The PI3K/Akt/mTOR pathway plays a central role in regulating cell growth, metabolism, proliferation, and survival. Aberrant activation of this pathway is commonly observed in AML and may result from receptor tyrosine kinase mutations, growth factor stimulation, or loss of negative regulators.

Activation of phosphoinositide 3-kinase (PI3K) leads to phosphorylation of Akt, which subsequently activates mammalian target of rapamycin (mTOR). mTOR regulates protein synthesis, cell cycle progression, and metabolic adaptation. Constitutive activation of the PI3K/Akt/mTOR pathway promotes leukemic cell survival, inhibits apoptosis, and contributes to chemoresistance in AML.

Cross-talk between PI3K/Akt/mTOR and other signaling pathways further enhances leukemic progression. Due to its significant role in AML biology, this pathway remains a major focus in targeted therapy research.

Ras/Raf/MEK/ERK (MAPK) Signaling Pathway

The mitogen-activated protein kinase (MAPK) pathway is another critical signaling cascade involved in AML development. This pathway transmits extracellular growth signals from membrane receptors to the nucleus through sequential activation of Ras, Raf, MEK, and ERK proteins.

Mutations in Ras genes, particularly NRAS and KRAS, are frequently detected in AML and lead to constitutive pathway activation. Persistent MAPK signaling promotes uncontrolled cell proliferation, survival, and impaired differentiation of hematopoietic progenitor cells.

The MAPK pathway also interacts with FLT3 and PI3K/Akt signaling networks, creating complex regulatory mechanisms that sustain leukemic cell growth and therapeutic resistance.

JAK/STAT Signaling Pathway

The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway mediates cytokine and growth factor signaling involved in hematopoiesis and immune regulation. Dysregulation of this pathway contributes to AML pathogenesis through abnormal activation of STAT transcription factors, especially STAT3 and STAT5.

Constitutive JAK/STAT signaling enhances leukemic cell proliferation, survival, and self-renewal while suppressing apoptosis. FLT3-ITD mutations can activate STAT5 directly, thereby linking FLT3 abnormalities with JAK/STAT dysregulation in AML.

Abnormal STAT activation has also been associated with poor clinical outcomes and resistance to chemotherapy, highlighting the importance of this pathway in AML progression.

NF-κB Signaling Pathway

Nuclear factor kappa B (NF-κB) is a transcription factor involved in inflammation, immune responses, cell survival, and apoptosis regulation. In AML, constitutive NF-κB activation supports leukemic cell survival and resistance to apoptosis.

Activation of NF-κB induces the expression of anti-apoptotic genes, cytokines, and survival proteins that enhance leukemic cell persistence within the bone marrow microenvironment. NF-κB signaling also contributes to inflammatory responses that promote AML progression.

Interactions between NF-κB and other pathways, including PI3K/Akt and MAPK signaling, further strengthen pro-survival mechanisms in AML cells.

Wnt/β-Catenin Signaling Pathway

The Wnt/β-catenin pathway is essential for stem cell maintenance, self-renewal, and hematopoietic development. Aberrant activation of β-catenin signaling has been implicated in leukemic stem cell survival and AML progression.

Under normal conditions, β-catenin levels are tightly regulated by degradation complexes. However, dysregulation of Wnt signaling results in β-catenin accumulation and nuclear translocation, where it activates transcription of genes involved in proliferation and stemness.

Enhanced Wnt/β-catenin signaling contributes to maintenance of leukemic stem cells, disease relapse, and resistance to conventional therapies in AML.

Hedgehog Signaling Pathway

The Hedgehog signaling pathway regulates embryonic development, stem cell maintenance, and tissue regeneration. In AML, abnormal Hedgehog activation has been associated with leukemic stem cell survival and disease progression.

Binding of Hedgehog ligands activates Smoothened (SMO), leading to activation of GLI transcription factors that regulate genes involved in proliferation and survival. Persistent Hedgehog signaling supports leukemic cell maintenance and contributes to therapeutic resistance.

The pathway is particularly important in preserving leukemic stem cell populations, which are often responsible for relapse following treatment.

Notch Signaling Pathway

The Notch signaling pathway plays a complex role in hematological malignancies. In AML, Notch signaling may function either as a tumor suppressor or oncogenic pathway depending on the cellular context and molecular environment.

Notch receptors interact with ligands on neighboring cells, leading to cleavage and release of the Notch intracellular domain, which regulates gene transcription. Dysregulation of Notch signaling can affect differentiation, proliferation, and apoptosis in AML cells.

Although the precise role of Notch signaling in AML remains incompletely understood, evidence suggests that altered Notch activity contributes to leukemogenesis and disease heterogeneity.

p53 Signaling Pathway

The p53 pathway is a major tumor suppressor network responsible for regulating DNA repair, cell cycle arrest, senescence, and apoptosis. Mutations or functional inactivation of p53 are associated with aggressive AML and poor prognosis.

Loss of p53 function allows leukemic cells to evade apoptosis and accumulate additional genetic abnormalities. Abnormal p53 signaling also contributes to genomic instability and resistance to chemotherapy.

Interactions between p53 and other oncogenic pathways influence AML progression and therapeutic response, making this pathway highly relevant in AML research.

Cross-Talk Among Signaling Pathways in AML

AML progression is not driven by a single signaling pathway but rather by complex interactions among multiple interconnected networks. Cross-talk between FLT3, PI3K/Akt/mTOR, MAPK, JAK/STAT, NF-κB, and Wnt signaling pathways creates an integrated oncogenic environment that promotes leukemic cell survival and resistance to treatment.

This signaling complexity contributes to disease heterogeneity and presents challenges in achieving durable therapeutic responses. Simultaneous dysregulation of multiple pathways often enables leukemic cells to bypass targeted inhibition, leading to relapse and treatment failure.

Conclusion

Cancer signaling pathways play central roles in the initiation, progression, and therapeutic resistance of AML. Dysregulation of FLT3, PI3K/Akt/mTOR, MAPK, JAK/STAT, NF-κB, Wnt/β-catenin, Hedgehog, Notch, and p53 signaling pathways contributes significantly to leukemogenesis and maintenance of leukemic stem cells. The extensive cross-talk among these pathways further complicates AML biology and influences disease outcome. Improved understanding of these molecular signaling networks remains essential for advancing targeted therapeutic approaches and improving prognosis in AML patients.

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