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Regulation of Different Transcription Factors in EMT Transition in Acute Myeloid Leukemia (AML): A Comprehensive Analysis

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Abstract: Acute Myeloid Leukemia (AML) is a heterogeneous hematological malignancy characterized by uncontrolled proliferation and impaired differentiation of myeloid progenitor cells. Although epithelial–mesenchymal transition (EMT) is classically associated with solid tumors, emerging evidence suggests that EMT-like processes also play a critical role in hematological malignancies, including AML. These processes contribute to disease progression, drug resistance, stemness, and leukemic cell migration within the bone marrow niche. Central to EMT regulation are transcription factors such as SNAIL, SLUG, TWIST, ZEB1, and ZEB2, which orchestrate gene expression changes that promote mesenchymal phenotypes. This article explores the molecular mechanisms governing the regulation of these transcription factors in AML, the signaling pathways involved, and their implications in leukemogenesis and therapeutic resistance. Furthermore, it highlights the interplay between the bone marrow microenvironment and EMT-related transcriptional networks, offering insights into potential therapeutic targets.

Keywords: AML, EMT, transcription factors, SNAIL, TWIST, ZEB, leukemogenesis, drug resistance.

Introduction

Acute Myeloid Leukemia (AML) represents a group of aggressive hematopoietic malignancies marked by clonal expansion of immature myeloid blasts in the bone marrow, peripheral blood, and occasionally other tissues. Despite advances in chemotherapy, targeted therapy, and stem cell transplantation, AML continues to exhibit poor prognosis, particularly in elderly patients and those with relapsed or refractory disease.

Traditionally, epithelial–mesenchymal transition (EMT) has been studied in the context of solid tumors, where epithelial cells lose polarity and adhesion properties to acquire mesenchymal traits such as motility and invasiveness. However, recent studies have demonstrated that EMT-like transcriptional programs are also active in non-epithelial cancers, including AML. Although leukemic cells are not epithelial, they exhibit functional analogues of EMT, including enhanced migration, survival, immune evasion, and resistance to therapy.

The EMT program is largely governed by a set of transcription factors (TFs), often referred to as EMT-TFs, including SNAIL family proteins (SNAIL1, SNAIL2/SLUG), TWIST family members (TWIST1, TWIST2), and ZEB proteins (ZEB1, ZEB2). These TFs regulate a complex network of genes involved in cell adhesion, cytoskeletal remodeling, apoptosis resistance, and stemness. Understanding how these transcription factors are regulated in AML is crucial for identifying novel therapeutic strategies.

Objectives: This article explores the molecular mechanisms governing the regulation of these transcription factors in AML, the signaling pathways involved, and their implications in leukemogenesis and therapeutic resistance.

EMT-Like Phenomena in Acute Myeloid Leukemia (AML)

Although acute myeloid leukemia (AML) arises from hematopoietic rather than epithelial cells, accumulating evidence indicates that leukemic blasts undergo EMT-like changes, often referred to as *mesenchymal reprogramming*. Unlike classical epithelial–mesenchymal transition (EMT) observed in solid tumors, this process in AML does not involve a literal conversion of epithelial cells into mesenchymal cells. Instead, it represents a form of transcriptionally driven phenotypic plasticity, enabling leukemic cells to acquire features that enhance motility, survival, and resistance to therapy (Dongre & Weinberg, 2019; Shlush et al., 2017). This adaptive reprogramming allows AML cells to behave in ways functionally analogous to metastatic tumor cells, despite their non-epithelial origin.

A hallmark of EMT-like behavior in AML is the enhanced migratory and invasive capacity of leukemic blasts within the bone marrow microenvironment. This is largely mediated by alterations in adhesion molecules and chemokine receptors, particularly CXCR4, which plays a critical role in guiding leukemic cells toward stromal niches rich in its ligand CXCL12. These specialized niches provide a protective microenvironment that shields leukemic cells from chemotherapeutic agents and immune surveillance. Such niche-dependent survival closely mirrors the invasive and metastatic strategies driven by EMT in solid malignancies (Krause & Scadden, 2015).

Another significant consequence of EMT-like reprogramming is the development of resistance to apoptosis and chemotherapy. AML cells undergoing this transition activate key survival pathways, including PI3K/AKT and NF-κB, which promote cell survival, inhibit apoptotic signaling, and enhance cellular adaptability under stress conditions. This survival advantage is further compounded by the acquisition of stem cell–like properties, such as self-renewal capacity, quiescence, and metabolic flexibility. These characteristics define leukemic stem cells (LSCs), which are capable of persisting after treatment and driving disease relapse and minimal residual disease (Testa & Riccioni, 2007; Thomas & Majeti, 2017).

EMT-like processes in AML are also associated with dynamic changes in cell adhesion and interaction with the microenvironment. Upregulation of adhesion molecules such as N-cadherin and various integrins strengthens the physical association between leukemic cells and bone marrow stromal cells. This close interaction not only facilitates retention within protective niches but also contributes to adhesion-mediated drug resistance (AMDR), a phenomenon in which cell–cell and cell–matrix interactions reduce the efficacy of chemotherapeutic agents (Gao et al., 2018).

The bone marrow microenvironment plays an active and indispensable role in reinforcing EMT-like characteristics. Stromal cells secrete a range of cytokines and growth factors, including TGF-β, IL-6, and CXCL12, which activate intracellular signaling cascades that promote survival, proliferation, and phenotypic plasticity. These signals create a feedback loop that sustains EMT-like reprogramming and enhances the adaptability of leukemic cells under therapeutic pressure (Meads et al., 2009).

At the molecular level, these phenotypic alterations are orchestrated by EMT-associated transcription factors, including SNAIL, TWIST, and ZEB. These TFs regulate the expression of genes involved in cell adhesion, cytoskeletal organization, apoptosis resistance, and stemness. By reshaping transcriptional networks, they enable leukemic cells to transition into more aggressive and therapy-resistant states. Importantly, the activation of these TFs in AML underscores the convergence between hematological malignancies and solid tumors in terms of underlying regulatory mechanisms (Lamouille et al., 2014).

Key Transcription Factors in EMT Regulation

The regulation of epithelial–mesenchymal transition (EMT) and EMT-like phenomena is orchestrated by a core set of transcription factors (TFs) that act as master regulators of cellular plasticity, migration, survival, and stemness. In acute myeloid leukemia (AML), although cells are non-epithelial in origin, these EMT-associated TFs drive a form of mesenchymal reprogramming, enabling leukemic cells to acquire aggressive, therapy-resistant phenotypes. Among the most prominent regulators are the SNAIL, TWIST, and ZEB families, each of which integrates signaling, epigenetic control, and microenvironmental cues to reshape transcriptional landscapes.

SNAIL Family (SNAIL1 and SLUG/SNAIL2): The SNAIL family, consisting of SNAIL1 and SLUG (SNAIL2), represents a group of zinc-finger transcriptional repressors that are pivotal in initiating EMT-like transcriptional programs. These proteins bind to E-box sequences within gene promoters, leading to the repression of adhesion-related genes and the activation of mesenchymal traits (Peinado et al., 2007). Their activity marks one of the earliest steps in cellular reprogramming toward a more invasive and survival-oriented phenotype.

In AML, aberrant upregulation of SNAIL proteins is strongly associated with enhanced leukemic cell survival and resistance to apoptosis. By repressing pro-apoptotic genes and modulating survival pathways, SNAIL enables leukemic blasts to persist even under chemotherapeutic stress (Zhang et al., 2012). Furthermore, SNAIL contributes to increased cellular motility and invasiveness, facilitating the migration of leukemic cells within the bone marrow and their interaction with protective stromal niches.

A defining feature of SNAIL function is its role in epigenetic reprogramming. SNAIL recruits chromatin-modifying complexes, including histone deacetylases (HDACs) and polycomb repressive complexes, leading to histone deacetylation and methylation at target loci. This results in stable and heritable transcriptional silencing of adhesion molecules, thereby sustaining the EMT-like phenotype over time (Batlle et al., 2000).

The regulation of SNAIL itself is highly dynamic and controlled by multiple signaling pathways. TGF-β signaling acts as a chief inducer, activating SMAD-dependent transcription that enhances SNAIL expression (Xu et al., 2009). The NF-κB pathway further amplifies SNAIL activity by promoting both its transcription and protein stability, linking inflammatory signaling to leukemic progression (Julien et al., 2007). Additionally, the PI3K/AKT pathway stabilizes SNAIL by inhibiting GSK-3β-mediated phosphorylation and proteasomal degradation (Zhou et al., 2004). Together, these pathways ensure sustained SNAIL activation, driving leukemic cell plasticity, survival, and resistance.

TWIST Family (TWIST1 and TWIST2): The TWIST family, particularly TWIST1, comprises basic helix-loop-helix (bHLH) transcription factors that play a crucial role in mesenchymal differentiation and cellular adaptability. Depending on interacting partners and cellular context, TWIST proteins can function as either transcriptional activators or repressors, enabling them to regulate diverse gene networks (Yang et al., 2004).

In AML, **TWIST1** has emerged as a key regulator of leukemic stem cell (LSC) maintenance and chemoresistance. Elevated expression of TWIST1 is frequently observed in aggressive AML subtypes and is associated with poor prognosis. It promotes self-renewal while simultaneously inhibiting differentiation, thereby sustaining the pool of leukemic stem cells that drive disease progression and relapse (Wang et al., 2015).

A major contribution of TWIST1 to AML pathogenesis is its ability to modulate apoptotic pathways. It downregulates pro-apoptotic proteins such as BAX while upregulating anti-apoptotic factors like BCL-2, thereby enhancing cell survival under therapeutic stress. Additionally, TWIST1 interferes with p53-mediated apoptosis, allowing leukemic cells to evade programmed cell death and persist despite genomic damage (Vesuna et al., 2008).

The expression and activity of TWIST1 are tightly linked to environmental and intracellular signals. Hypoxia, a defining feature of the bone marrow microenvironment, induces hypoxia-inducible factor-1α (HIF-1α), which directly activates TWIST transcription (Yang et al., 2008). The Wnt/β-catenin pathway further enhances TWIST expression, linking EMT-like processes to stemness and self-renewal (Howe et al., 2003). Moreover, Notch signaling reinforces TWIST-driven transcriptional programs, promoting cellular plasticity and leukemic progression (Aster et al., 2017).

Thus, TWIST1 functions as a central integrator of microenvironmental cues and intracellular signaling, orchestrating EMT-like reprogramming, stem cell maintenance, and therapeutic resistance in AML.

ZEB Family (ZEB1 and ZEB2): The ZEB (Zinc finger E-box-binding homeobox) family, including ZEB1 and ZEB2, represents another critical group of EMT regulators. These transcription factors possess the unique ability to function as both repressors and activators, depending on the cellular context and interacting cofactors. They play a vital role in regulating gene networks associated with differentiation, adhesion, and cytoskeletal organization (Vandewalle et al., 2009).

In AML, ZEB1 is associated with increased cell proliferation, survival, and resistance to chemotherapy. Its overexpression leads to repression of differentiation-associated genes, thereby maintaining leukemic cells in an undifferentiated and proliferative state. ZEB2, while essential for normal hematopoiesis, becomes dysregulated in AML, contributing to leukemic transformation and disease progression (Goossens et al., 2011).

ZEB proteins promote cellular plasticity by repressing epithelial-like adhesion molecules and activating genes associated with mesenchymal characteristics. This dual regulatory capacity allows leukemic cells to dynamically adapt to environmental changes and therapeutic pressures, enhancing their survival and invasiveness.

A distinctive feature of ZEB regulation is its tight control by microRNAs, particularly the miR-200 family. These miRNAs bind to the 3′ untranslated regions (UTRs) of ZEB mRNAs, leading to their degradation or inhibition of translation. In AML, downregulation of miR-200 results in increased ZEB expression, thereby promoting EMT-like characteristics and disease aggressiveness (Gregory et al., 2008).

The disruption of the miR-200–ZEB regulatory axis represents a critical mechanism underlying leukemic progression. This imbalance not only enhances migration and survival but also reinforces stemness and resistance to therapy, making it a promising target for novel therapeutic interventions.

Signaling Pathways Regulating EMT Transcription Factors in AML

The regulation of EMT-associated transcription factors (TFs) in acute myeloid leukemia (AML) is governed by a highly interconnected network of intracellular signaling pathways. These pathways integrate extracellular cues from the bone marrow microenvironment with intracellular molecular machinery, ultimately controlling the expression, stability, and activity of EMT regulators such as SNAIL, TWIST, and ZEB. Through dynamic crosstalk and feedback loops, these signaling cascades orchestrate EMT-like reprogramming, promoting leukemic cell survival, plasticity, and resistance to therapy.

TGF-β Signaling Pathway: The Transforming Growth Factor-beta (TGF-β) pathway is one of the most potent and well-characterized inducers of EMT and EMT-like processes across cancer types, including AML. Upon binding of TGF-β ligands to their receptors, receptor serine/threonine kinases are activated, leading to phosphorylation of SMAD2 and SMAD3. These phosphorylated SMADs associate with SMAD4, forming transcriptionally active complexes that translocate into the nucleus to regulate EMT-related gene expression (Xu et al., 2009; Lamouille et al., 2014).

In AML, TGF-β signaling exerts multifaceted effects on leukemic cells. It induces the expression of EMT transcription factors such as SNAIL, TWIST, and ZEB, thereby promoting phenotypic plasticity and transcriptional reprogramming. One of its main roles is the induction of cellular quiescence, allowing leukemic stem cells to enter a dormant state that is less susceptible to chemotherapeutic agents. This quiescent phenotype contributes significantly to minimal residual disease and relapse.

Beyond its direct effects on leukemic cells, TGF-β also plays a crucial role in immune modulation. It suppresses anti-tumor immune responses by inhibiting cytotoxic T-cell activity and enhancing immune checkpoint signaling, thereby facilitating immune evasion. Additionally, TGF-β activates survival pathways and supports the maintenance of leukemic stem cells, further enhancing drug resistance and disease persistence (Batlle & Massagué, 2019). Thus, TGF-β serves as a central hub linking EMT-like programming with immune escape and therapeutic failure in AML.

Wnt/β-Catenin Signaling Pathway: The Wnt/β-catenin pathway is essential for normal hematopoietic stem cell function but becomes aberrantly activated in AML. In its active state, β-catenin escapes proteasomal degradation, accumulates in the cytoplasm, and translocates to the nucleus, where it interacts with TCF/LEF transcription factors to regulate gene expression (Clevers & Nusse, 2012).

In leukemic cells, dysregulated Wnt signaling enhances the expression of EMT-related TFs such as TWIST and ZEB, thereby promoting cellular plasticity, migration, and survival. A critical function of this pathway is the maintenance of leukemic stem cell (LSC) self-renewal, which underlies disease initiation, persistence, and relapse (Wang et al., 2010). By sustaining stemness-associated transcriptional programs, Wnt signaling enables leukemic cells to resist differentiation cues and remain in a primitive, therapy-resistant state.

Moreover, Wnt/β-catenin signaling contributes to chemoresistance by activating downstream survival genes and protecting cells from apoptosis. Its interaction with EMT transcription factors further amplifies its effects, creating a reinforcing loop that stabilizes the leukemic phenotype. This makes the Wnt pathway a critical therapeutic target, particularly in strategies aimed at eradicating leukemic stem cells.

Notch Signaling Pathway: The Notch signaling pathway is a highly conserved regulator of cell fate decisions, proliferation, and differentiation. In AML, aberrant Notch activation contributes to leukemic progression and the maintenance of undifferentiated cell states. Activation occurs through ligand binding, followed by proteolytic cleavage of the Notch receptor and release of the Notch intracellular domain (NICD), which translocates to the nucleus to regulate transcription (Aster et al., 2017).

Notch signaling influences EMT-like processes by modulating the expression of TFs such as SNAIL and TWIST. Through these downstream effectors, it promotes cell survival, proliferation, and resistance to apoptosis, thereby enhancing leukemic cell fitness under stress conditions. Notch also plays a role in maintaining stem cell–like properties, further contributing to disease persistence.

Importantly, Notch signaling does not act in isolation. It engages in extensive crosstalk with other pathways, particularly TGF-β and Wnt/β-catenin, forming a complex regulatory network that amplifies EMT-like phenotypes and leukemic progression (Takebe et al., 2015). This integrative function highlights its role as a key coordinator of multiple oncogenic signals in AML.

PI3K/AKT/mTOR Signaling Pathway: The PI3K/AKT/mTOR pathway is one of the most frequently activated signaling cascades in AML and serves as a central regulator of cell growth, metabolism, and survival. Activation of PI3K leads to phosphorylation of AKT, which

subsequently activates mTOR and other downstream targets that drive protein synthesis and cellular proliferation (Testa & Riccioni, 2007).

This pathway plays a critical role in EMT-like regulation by stabilizing EMT transcription factors, particularly SNAIL and TWIST. It achieves this by inhibiting GSK-3β, a kinase responsible for phosphorylating these TFs and targeting them for proteasomal degradation. As a result, EMT TFs accumulate and sustain transcriptional reprogramming associated with plasticity and survival.

In addition, PI3K/AKT signaling suppresses apoptotic pathways and enhances resistance to chemotherapeutic agents. Its persistent activation is strongly associated with poor clinical prognosis, aggressive disease behavior, and therapeutic resistance (Martelli et al., 2010). The pathway also influences metabolic reprogramming, enabling leukemic cells to adapt to nutrient-limited and hypoxic conditions within the bone marrow microenvironment.

NF-κB Signaling Pathway: The NF-κB signaling pathway is a master regulator of inflammation, immune responses, and cell survival. In AML, constitutive activation of NF-κB is a common feature that significantly contributes to disease progression and resistance to therapy.

NF-κB promotes EMT-like phenotypes by inducing the expression of transcription factors such as SNAIL and ZEB, thereby enhancing cellular plasticity and invasive potential (Julien et al., 2007). It also activates a broad range of pro-survival genes, including anti-apoptotic proteins, which protect leukemic cells from programmed cell death and cytotoxic stress.

Furthermore, NF-κB plays a crucial role in mediating interactions between leukemic cells and the bone marrow microenvironment. By regulating the production of cytokines and the expression of adhesion molecules, it strengthens the supportive niche that sustains leukemic growth and survival (Karin, 2006). This microenvironmental reinforcement not only enhances disease progression but also contributes to adhesion-mediated drug resistance.

Role of the Bone Marrow Microenvironment

The bone marrow microenvironment (BMM) serves as a highly specialized and dynamic niche that profoundly influences the behavior of leukemic cells in acute myeloid leukemia (AML). Far from being a passive structural scaffold, it is a complex and interactive ecosystem composed of stromal cells, endothelial cells, mesenchymal stem cells, immune components, extracellular matrix (ECM) proteins, soluble cytokines, and hypoxic niches. Through continuous bidirectional communication with leukemic blasts, this microenvironment actively regulates EMT-like transitions, cellular plasticity, survival, and therapeutic resistance (Meads et al., 2009).

A defining feature of the bone marrow niche is its hypoxic microenvironment, which plays a crucial role in shaping leukemic cell behavior. Low oxygen tension leads to stabilization of hypoxia-inducible factor-1 alpha (HIF-1α), a master regulator of cellular adaptation to hypoxia. HIF-1α drives the transcription of EMT-associated factors such as TWIST, thereby promoting stemness, metabolic adaptation, and survival under stress conditions (Semenza, 2012). This hypoxia-driven reprogramming enables leukemic cells to persist in a quiescent, therapy-resistant state, particularly within protected niches.

In addition to hypoxia, cytokine signaling within the BMM is a major determinant of EMT-like behavior. Stromal cells secrete a wide range of soluble factors, including TGF-β, interleukin-6 (IL-6), and CXCL12, which activate multiple intracellular signaling cascades such as PI3K/AKT, JAK/STAT, and MAPK pathways. These signals converge on EMT-related transcription factors, reinforcing transcriptional programs that enhance proliferation, inhibit apoptosis, and promote drug resistance (Meads et al., 2009). The CXCL12–CXCR4 axis, in particular, facilitates the homing and retention of leukemic cells within protective niches, further strengthening their resistance to therapy.

Equally important are direct cell–cell and cell–matrix interactions, which contribute to the phenomenon of adhesion-mediated drug resistance (AMDR). Leukemic cells express adhesion molecules such as integrins and cadherins (e.g., N-cadherin) that enable tight binding to stromal cells and ECM components. These physical interactions activate intracellular survival pathways and shield leukemic blasts from the cytotoxic effects of chemotherapy (Gao et al., 2018). The resulting protective niche not only enhances survival but also facilitates the maintenance of leukemic stem cells.

Moreover, the BMM fosters metabolic reprogramming and immune modulation, further supporting leukemic persistence. Stromal-derived signals can shift leukemic metabolism toward glycolysis and oxidative stress resistance, while also suppressing anti-tumor immune responses. This integrated support system ensures that leukemic cells can adapt to environmental and therapeutic pressures with remarkable efficiency.

In summary, the bone marrow microenvironment acts as a central regulator of EMT-like processes in AML, orchestrating signaling pathways, transcriptional programs, and cellular interactions that collectively promote leukemic cell survival, plasticity, and resistance. Its critical role in disease progression makes it an essential target for the development of microenvironment-directed therapeutic strategies.

EMT Transcription Factors and Drug Resistance in AML

EMT-like reprogramming in AML is a key driver of therapeutic resistance, which remains one of the most significant challenges in achieving long-term remission. Leukemic cells that undergo EMT-like transitions acquire a range of adaptive features that enable them to survive, evade treatment, and eventually contribute to disease relapse.

A major mechanism underlying this resistance is the activation of anti-apoptotic pathways. EMT-associated transcription factors such as TWIST and SNAIL upregulate members of the BCL-2 family, tipping the balance toward cell survival and allowing leukemic cells to evade programmed cell death even under intense chemotherapeutic stress (Vesuna et al., 2008). This resistance to apoptosis is a hallmark of aggressive and refractory AML.

Another important factor is the alteration of drug transport mechanisms. EMT-like leukemic cells often exhibit increased expression of efflux transporters, such as ATP-binding cassette (ABC) transporters, which actively pump chemotherapeutic agents out of the cell. This reduces intracellular drug accumulation and significantly diminishes treatment efficacy (Zhang et al., 2012).

EMT-like processes also sustain a population of leukemic stem cells (LSCs), which are intrinsically resistant to therapy. These cells remain in a quiescent state, making them less susceptible to drugs that target rapidly dividing cells. Their ability to self-renew and repopulate the leukemic clone is a major cause of minimal residual disease and relapse.

In addition, EMT-like reprogramming induces metabolic adaptations that support survival under therapeutic stress. Leukemic cells often shift toward aerobic glycolysis (the Warburg effect) and enhance antioxidant defenses, enabling them to withstand oxidative damage and energy deprivation (Wang et al., 2015). These metabolic changes further reinforce resistance to treatment.

At the molecular level, transcription factors such as TWIST and SNAIL act as central regulators of these drug-resistant phenotypes. TWIST promotes stemness and anti-apoptotic gene expression while interfering with tumor suppressor pathways, including p53-mediated apoptosis. SNAIL, on the other hand, represses pro-apoptotic and adhesion-related genes, facilitating survival within protective niches and enhancing cellular adaptability (Lamouille et al., 2014).

Together, these transcription factors establish a coordinated transcriptional program that integrates survival signaling, stemness, metabolic adaptation, and microenvironmental

interactions. This program not only drives resistance to chemotherapy but also enables leukemic cells to dynamically adapt to changing conditions.

Therapeutic Implications

Targeting EMT-like reprogramming in acute myeloid leukemia (AML) represents a promising and evolving therapeutic frontier, particularly in overcoming drug resistance and preventing disease relapse. Although direct inhibition of EMT transcription factors (EMT-TFs) such as SNAIL, TWIST, and ZEB remains technically challenging due to their nuclear localization and lack of well-defined binding pockets, indirect targeting strategies aimed at upstream regulators and downstream effectors have shown considerable potential.

One of the most effective approaches involves the use of small molecule inhibitors that disrupt key signaling pathways sustaining EMT-like phenotypes. In particular, inhibitors of the PI3K/AKT/mTOR pathway play a crucial role in destabilizing EMT-TFs by reactivating GSK-3β–mediated degradation mechanisms. This leads to reduced expression of survival genes and increased sensitivity to apoptosis (Martelli et al., 2010). Similarly, targeting pathways such as TGF-β, Wnt/β-catenin, and NF-κB can suppress EMT-associated transcriptional programs, thereby limiting leukemic cell plasticity, invasion, and resistance.

Another powerful strategy lies in epigenetic therapy, which addresses the reversible nature of EMT-driven transcriptional changes. Agents such as histone deacetylase (HDAC) inhibitors and DNA methyltransferase inhibitors can reverse gene silencing mediated by EMT-TFs like SNAIL and ZEB. By restoring the expression of tumor suppressor genes and pro-apoptotic pathways, these therapies promote cellular differentiation and apoptosis, counteracting the stem-like and resistant phenotype of leukemic cells (Peinado et al., 2007). This reprogramming approach is particularly valuable in targeting leukemic stem cells (LSCs), which are often refractory to conventional treatments.

Emerging evidence also highlights the therapeutic potential of microRNA (miRNA)-based interventions. MicroRNAs are critical post-transcriptional regulators of gene expression, and their dysregulation is closely associated with EMT-like processes. For instance, restoration of the miR-200 family can suppress ZEB-mediated transcription, thereby reversing mesenchymal traits and reducing chemoresistance (Gregory et al., 2008). These small non-coding RNAs act as molecular switches that can re-establish epithelial-like characteristics and sensitize leukemic cells to therapy.

Importantly, combination therapeutic strategies are gaining increasing attention. Integrating EMT-targeting agents with conventional chemotherapy or targeted therapies offers a synergistic approach that addresses both the rapidly proliferating leukemic bulk and the quiescent, therapy-resistant stem cell population. Such combinations can disrupt protective signaling networks within the bone marrow microenvironment while simultaneously enhancing drug efficacy.

Furthermore, targeting the bone marrow niche itself—including cytokine signaling (e.g., CXCL12–CXCR4 axis) and adhesion-mediated interactions—can weaken the supportive environment that sustains EMT-like phenotypes and drug resistance. This dual targeting of both leukemic cells and their microenvironment provides a more comprehensive therapeutic strategy.

Conclusion

The regulation of transcription factors involved in EMT-like processes plays a crucial role in the pathogenesis, progression, and treatment resistance of AML. Transcription factors such as SNAIL, TWIST, and ZEB orchestrate complex gene expression programs that enhance leukemic cell survival, plasticity, and interaction with the bone marrow microenvironment. Their activity is tightly regulated by multiple signaling pathways, including TGF-β, Wnt, Notch, and PI3K/AKT. Understanding these regulatory networks provides valuable insights into AML biology and opens new avenues for therapeutic intervention. Targeting EMT-related

transcriptional programs may significantly improve treatment outcomes and reduce relapse rates in AML patients.

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