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Mechanism of resistance and therapeutic prospect of leukemia mediated by signaling pathway in bone marrow microenvironment

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Abstract. – Leukemia is a malignant disease of the blood system. Although the current research on the pathogenesis of leukemia is more and more in-depth and has an influential guiding significance for the ongoing clinical treatment of leukemia, its resistance and recurrence is still a challenging problem that needs to be solved. At present, several studies have indicated that the bone marrow microenvironment played an essential role in drug resistance of leukemia, forming a protective spot for them by interacting with leukemic cells, offering protective effects of leukemia cells from cytotoxic drugs. The bone marrow microenvironment can mediate the development of drug resistance in leukemia through many signal pathways, by affecting the growth, propagation, and apoptosis of leukemia cells. The microenvironment can promote cell survival, proliferation, and anti-apoptosis, and then mediate the drug resistance of leukemia. It is considered as a better guidance of clinical treatment by understanding the drug resistance mechanism of leukemia.

Key Words:
Leukemia, Bone marrow microenvironment, Drug resistance, Signaling pathway, Treatment.

Introduction

Leukemia is a malignant tumor of hematopoietic dysplasia. Although the accuracy of pathogenesis of the disease is evolving, the proportion of drug resistance and relapse is gradually progressing. In recent years, studies have shown that bone marrow microenvironment (BMM) and leukemia stem cells resistance were correlated. In 1978, the concept of bone marrow niche was proposed for the first time, which was a niche for the regulation of bone marrow microenvironment[1]. Bone marrow niche provides a "shelter" for leukemia cells, to make LSCs evade the killing effect of chemotherapy drugs, to obtain the resistance phenotype, and ultimately lead to acute myeloid leukemia (AML)[2]. The research found that bone marrow stromal cells (BMSCs) osteogenic differentiation and adipogenic differentiation regulate the hematopoietic stem cell (HSC) niche differently, which can promote osteoblast differentiation and proliferation of HSC[3]. However, adipogenic differentiation has the opposite effect on the regulation of HSC[4]. The BMSCs isolated from the bone marrow of AML patients showed a tendency to differentiate into adipocytes after 14 days of culture, but no significant difference was observed in the differentiation of osteoblasts[5]. It was suggested that the adipogenic differentiation of stromal cells in the bone marrow microenvironment of leukemia can hinder the normal hematopoiesis, and provide the living space for LSC, and then increase the drug resistance of leukemia cells. Besides, a large number of leukemia cells occupied the bone marrow microenvironment, increasing the bone marrow hypoxia. However, LSC can adapt to hypoxia and tend to be relatively static under hypoxic condition, being of particular significance for maintaining the survival of LSC. The bone marrow microenvironment in hypoxia promotes the synthesis of hypoxia-inducible factor-1 (HIF-1), as well as the expression of chemokine receptor -4 (CXR4) significantly.

It can then induce leukemia cells to migrate and adhere to the osteoblast niche, and finally enhance their drug resistance[6]. HIF-1 can promote angiogenesis in the microenvironment of leukemia. Through the up-regulation of vascular endothelial growth factor (VEGF) expression, LSC can better adapt to the hypoxic microenvironment of bone marrow and promote the occur-

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rence of drug resistance[7]. Therefore, bone marrow microenvironment plays a vital role in the drug resistance of leukemia cells. The following is a description of the mechanism of drug resistance mediated by the major signaling pathways in the bone marrow microenvironment.

Materials and Methods

Drug Resistance Mediated by CXCL12/CXCR4 Signaling Pathway

Chemokine CXCL12, also known as stromal cell-derived factor-1 (SDF-1), belongs to the chemokine protein family. It is mainly produced by BMSCs and endothelial cells and interacts with its specific receptor chemokine receptors (CXCR4) to deliver a series of pathophysiological changes. CXCL12 and CXCR4 can activate adhesion proteins by activating multiple signaling pathways, which can mediate cell migration, proliferation, and cell survival (Figure 1).

CXCR4 exists in a variety of cells, including lymphocytes, hematopoietic stem cells, endothelial cells, epithelial cells, cancer cells, etc.[8]. Studies have shown that it protects leukemic cells from spontaneous and chemotherapy-induced death by regulating the interaction of leukemic cells and bone marrow stromal cells[9]. Therefore, CXCR4 is considered to be a critical factor influencing the prognosis of leukemia drug resistance and leukemia survival. Liu et al[10] suggested that the expression of miR-146a was negatively correlated with CXCR4. Also, the resistance of K562 cells to Adriamycin (ADM) can be reduced significantly by reducing the resistance of CXCR4 to miR-146a by siRNA. This indicated that CXCR4 is the crucial factor of ADM resistance mediated by down-regulation of miR-146a.

Moreover, the up-regulation of CXCR4 can promote the migration of CML cells to the bone marrow microenvironment, resulting in the arrest of CML cells in the G0/G1 phase. It is in a relatively quiescent state, to avoid the killing effect of drugs[11]. At the same time, by increasing the expression of CXCR4, CXCL12 up-regulates the downstream phosphatidylinositol-3 kinase/serine threonine kinase pathway (PI3K/Akt) and promotes the nuclear transcription factor Bκ (NF-κB) to the nucleus. It reduces the expression

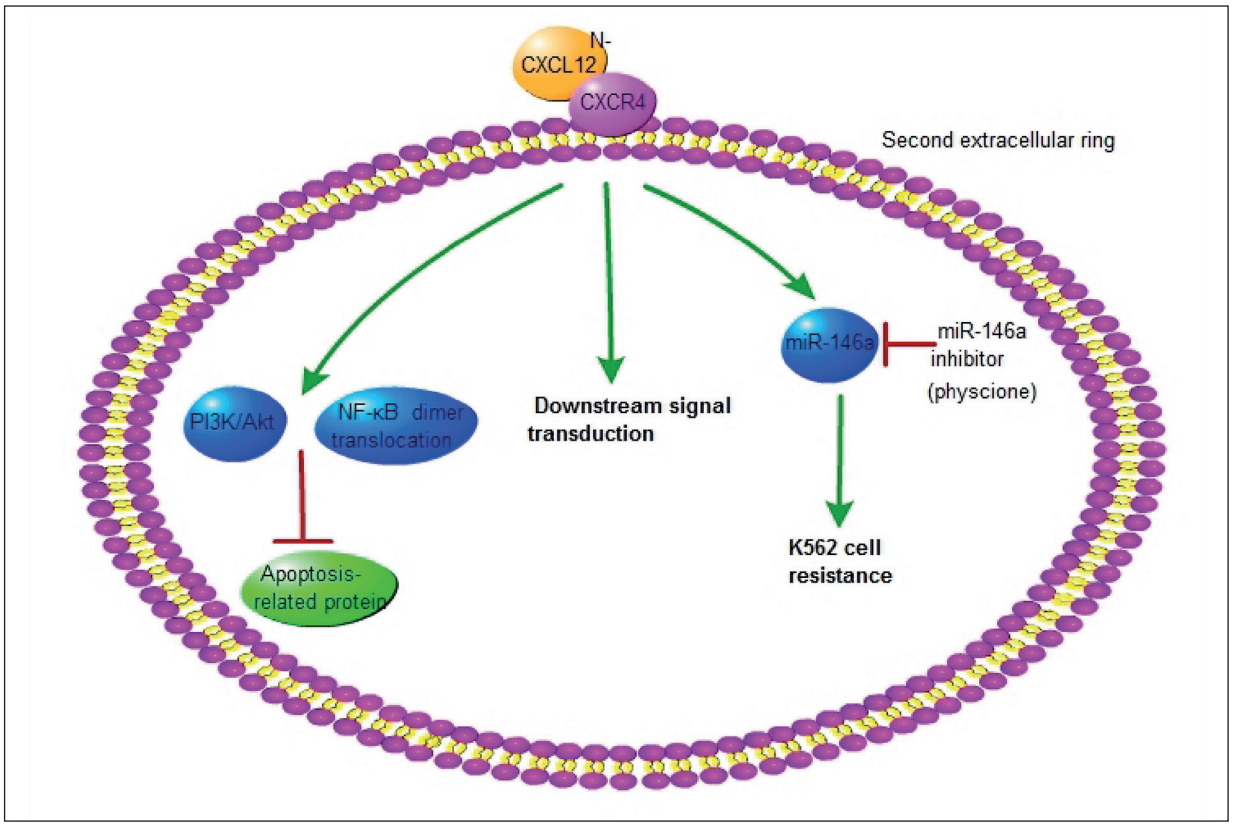

Figure 1. CXCL12/CXCR4 signaling pathway.

of apoptosis of related proteins and ultimately enhances the resistance of K562 cells to ADM[12]. It was reported[13,14] that CXCR4/SDF-1 signaling pathway also plays a role in the formation of mantle cell lymphoma (MCL) and autophagosome, promotes the survival of tumor cells in the bone marrow microenvironment, and also mediates cell resistance. *In vivo* experiments showed that CXCR4 antagonists could induce AML cells and progenitor cells into the blood circulation, or induce leukemia cell apoptosis, and then enhance the anti-leukemia effect of chemotherapy drugs[15]. PF-06747143, a novel CXCR 4 antagonist, can inhibit tumor growth and increase the survival rate by inhibiting signal pathway and cell migration induced by CXCL 12 and has significant survival benefits for disseminated AML[16]. Some results showed that down-regulation of miR-146a and up-regulation of CXCR4 might be correlated to the drug resistance of K562/ADM cells. Physcion can inhibit the CXCL12/CXCR4 signaling pathway by inducing the expression of miR-146a and reverse the drug resistance of K562/ADM cells to ADM. Therefore, given the low toxicity of emodin (physcion) on healthy cells, it may be considered as a potential adjuvant for the treatment of CML[10].

Wnt/β-Catenin Signaling Pathway Mediated Resistance

Wnt signaling pathway is a network of protein interactions, which has classical Wnt signaling pathway, namely Wnt/β-catenin signaling pathway and nonclassical Wnt signaling pathway, namely Wnt/Ca^{2+}/nuclear of activated T cells (NFAT) signal pathway. Both pathways regulate the growth of cells, but the Wnt /β-catenin signaling pathway plays an important role (Figure 2).

In the study of hematological malignancies, such as CML, ALL, and AML, it was found that the activation of the Wnt signaling pathway was detected. Hu et al[17] suggested that, in the acute phase of CML, BCR-ABL can activate PI3K/AKT signaling pathway and the expression of β-catenin, leading to the activation of Wnt/β-catenin signaling pathway. When inhibiting the kinase activity of BCR-ABL, PI3K or AKT, it can decrease the level of β-catenin in K562 cells and CML mice model. The activation of β-catenin was found to be increased in patients with recurrent ALL, and the Wnt target gene was significantly decreased with the Wnt inhibitor iCRT14[18]. Similarly, in AML cells, aberrant expression of β-catenin and ectopic nuclear participation in the maintenance of leukemic stem cells (LSC)

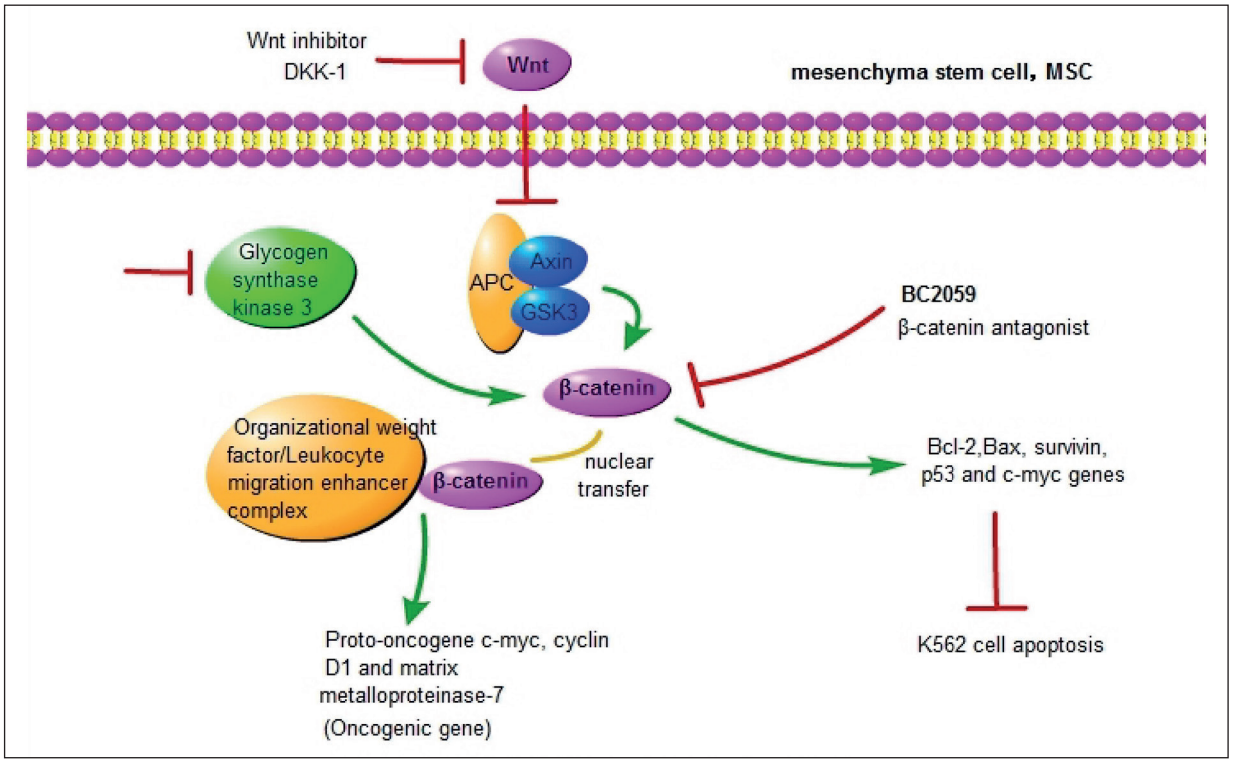

Figure 2. Wnt/β-catenin signaling pathway.

self-renewal[19]. Therefore, the Wnt/ β-catenin signaling pathway may play an essential role in the drug resistance of leukemia.

The activation of the pathway can increase the expression level of β-catenin in the cytoplasm by inhibiting the activity of glycogen synthetase kinase-3 (GSK-3). Next, the β-catenin binds with tissue-coding factor/leuko-kinesis-enhancing factor (TCF/LEF), to up-regulate the downstream oncogenes, such as the expression of c-myc, cyclin D1, matrix metalloproteinase-7 (MMP-7). Research showed that the microenvironment of bone marrow mesenchymal stem cells (MSC) could activate the Wnt/β-catenin signal pathway, regulation of Bcl-2, Bax, survivin, p53, and c-myc genes, and then inhibit the apoptosis signaling pathway and protect K562 cells from apoptosis. The Wnt inhibitor DKK (dickkopf)-1 can down-regulate the expression of β-catenin, and activate the increase of K562 apoptosis[20]. Fiskus et al[21] showed a joint application of the β-catenin antagonist BC2059 and Panobinostat, which can induce the apoptosis in acute myeloid leukemia stem/progenitor cells. It discovered that the inhibition of Wnt/β-catenin signaling pathway may be a new molecular mechanism for the lateral branch sensitivity of Multidrug resistance (MDR) cells. Therefore, the Wnt/β-catenin signaling pathway is a potential therapeutic target for the selective killing of multidrug resistance mediated by MDR P-glycoprotein (Pgp)[22]. Therefore, it is of great clinical significance to explore the mechanism of Wnt/β-catenin signaling pathway in the treatment of leukemia

NF-κB Signaling Mediated Resistance

NF-κB signaling pathway exists in many leukemia cells, especially in LSC, and shows persistent activation (Figure 3). It is involved in the occurrence, development, and recurrence of leukemia. Research has shown[23] that in CML blastic K562 cells and human acute mononuclear leukemia, THP-1 cells and acute promyelocytic leukemia (APL) in HL-60 cells, the transcription activity of NF- KB was significantly higher than the control group. Besides, the continuous activation can change the expression levels of apoptosis-related proteins Bax and Bcl-2 and then hinder the apoptosis of leukemia cells, ultimately affecting their survival. In recent years, it was reported that NF- kB pathway activation could promote the proliferation of leukemia cells and inhibit the cell apoptosis, thus weakening the killing effect of chemotherapy drugs on it, also involving leukemia prognosis and resistance[24]. For example, the NF-kB signaling pathway by

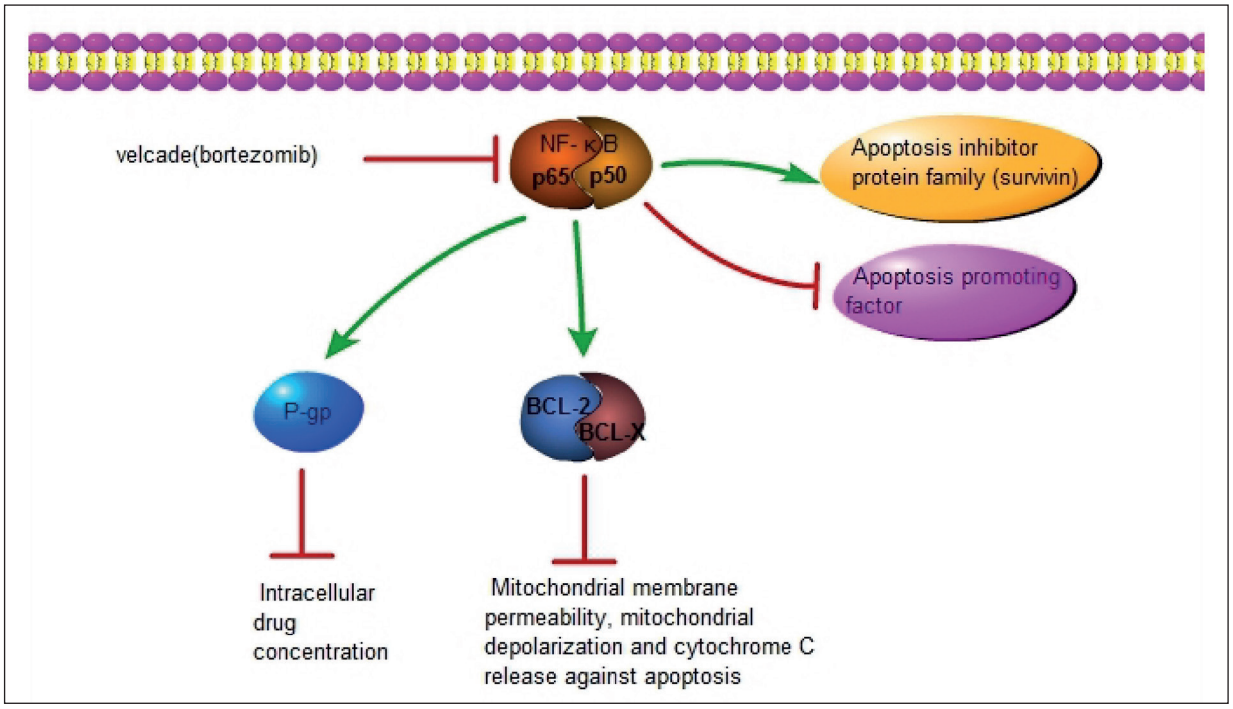

Figure 3. NF-κB signaling pathway.

enhancing the transcription of the anti-apoptotic protein genes BCL-2 and BCL-X, increases its expression, especially BCL-XL. Thereby, it reduces the permeability of the mitochondrial membrane, the inhibition of mitochondrial depolarization, and cytochrome C release, to play the anti-apoptosis effect[25]. Besides, it can inhibit cell apoptosis by upregulating the inhibitor expression of the apoptosis protein (IAP) family such as survivin[26], and by down-regulating the expression of proapoptotic factors[27].

Moreover, NF-kB signaling pathway can induce the abnormal nuclear factor E2 and the related factor 2 (Nrf2) in the AML cell continuous activation. The inducing process protects the cells from oxidative stress damage, promotes the survival of leukemia cells, and even produces resistance to cytotoxic chemotherapy drug resistance[28]. The activation of the signaling pathway may also upregulate the expression of P-glycoprotein (P-gp) in the cell membrane, pump the drug into the extracellular region, and decrease the concentration of intracellular drugs, thereby mediating multidrug resistance in leukemic cells[29]. The use of bortezomib to the nuclei of NF-kB plays an inhibitory effect on the translocation, leading to multidrug resistance protein 1 (MDR1) decreased expression and down-regulation of P-gp, thereby increasing the intracellular drug concentration, drug-induced cell killing effect[29].

Drug Resistance Mediated by PI3K/AKT Signaling Pathway

In recent years, PI3K/AKT is widely expressed in cells and is one of the most important signaling pathways in cells. It plays a role in inhibiting apoptosis and promoting cell proliferation (Figure 4). PI3K activates itself by phosphorylation of serine/threonine in Akt (Protein Kinase B) molecules. The effect of Akt on the activation of its downstream target molecules, including pro-apoptotic protein Bad and Caspase-9, NF-kB and Foxo, cyclin-dependent kinase inhibitor P21 and glycogen synthase kinase 3 β (GSK3 β), inhibits apoptosis and promotes cell cycle process[30]. In the study of leukemia pathogenesis, the persistent activation of PI3K/AKT signaling pathway plays an important role. The Akt kinase in primary AML cells was continuously activated, and PI3K inhibitors significantly reduced the survival rate of AML cells[31]. Recent studies have shown that the PI3K/AKT signaling pathway is closely related to drug resistance in leukemic cells. Abnormal activation of the PI3K/AKT

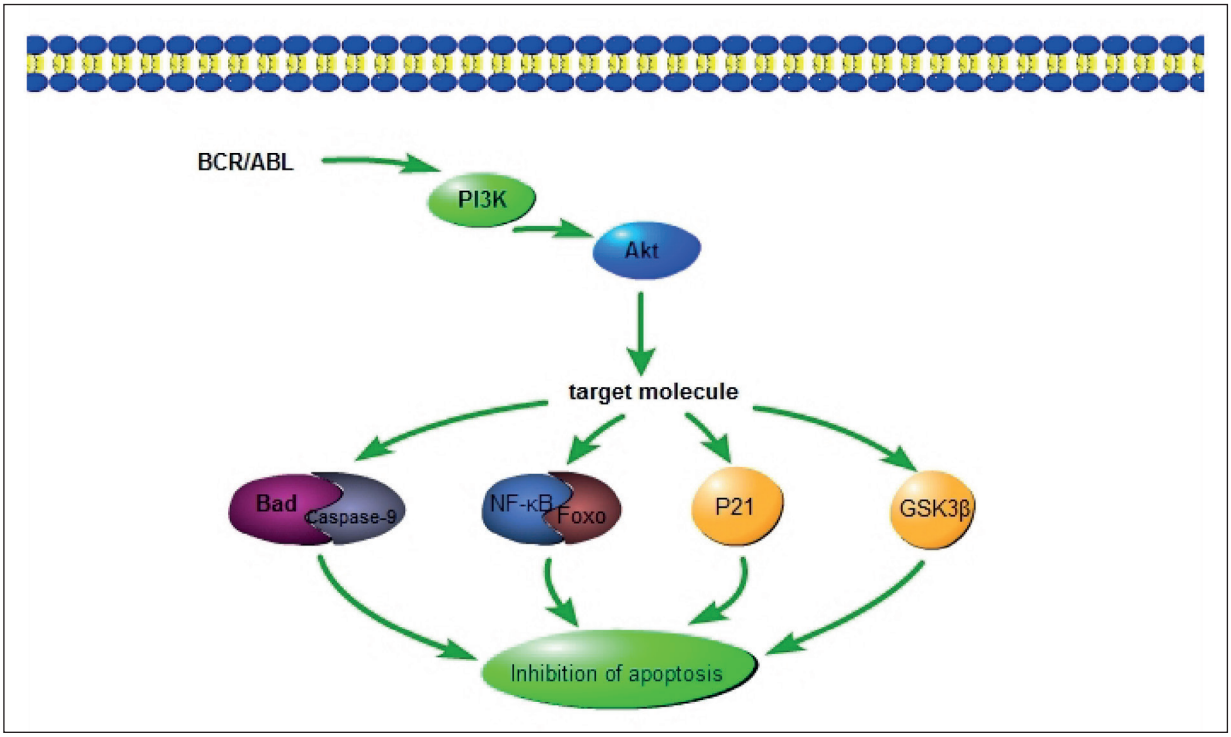

Figure 4. PI3K/AKT signaling pathway.

signaling pathway can cause leukemia cells to resist doxorubicin (ADM), and the leukemic doxorubicin resistant cell K562/ADM can enhance its sensitivity to ADM by using the PI3K inhibitor LY294002[32]. Tazzari et al[33] suggested that the expression of PI3K/Akt and multidrug resistance-related protein 1 (MRP1) levels were positively related to AML cells, which induced leukemia resistance by enhancing the expression of MRP1. The activation of PI3K can also lead to a survival advantage in vivo by improving the glycolysis of tumor cells. For example, BCR/ABL accelerates the glucose transport by activating PI3K by activating CML, and ultimately promotes the survival of CML cells. Mungamuri et al[34] showed that PI3K/Akt is also involved in Notch1 signaling pathway. The process inhibits the apoptosis and the phosphorylation of PI3K/Akt, and activates the Notch1 pathway through the inhibition of the mammalian target of rapamycin (mTOR). Thereby, p53 induced apoptosis of the tumor cells decreases, resulting in the occurrence of drug resistance. However, Notch1 can also inhibit apoptosis in other systems via the PI3K/Akt signaling pathway[35]. At the same time, PI3K/AKT signaling pathway can mediate the resistance of K562/ADM cells by affecting the expression of P-gp, and the reversal of the cell resistance by inhibiting the PI3K/AKT signaling pathway[36]. Therefore, the inhibition of the PI3K/AKT signaling pathway can reduce the resistance of leukemia cells and provide a target for the treatment of leukemia.

Drug Resistance Mediated by Notch Signaling Pathway

A notch-signaling pathway is composed of three parts, such as Notch receptor, Notch ligand (DSL protein) and intracellular effector molecule (CSL-DNA binding protein). Notch receptors are expressed in HSC. Notch ligands are derived from BMSCs (Figure 5). In bone marrow microenvironment, cell proliferation and differentiation can be mediated by the interactions. Osteoblasts are known to act as regulatory elements of the HSC niche and affect the function of LSC *in vivo* via the activation of the Notch signaling pathway[37].

Notch signaling pathway is closely related to the occurrence and development of leukemia, such as in study of chronic lymphocytic leukemia (CLL). It was found that Notch molecules are highly expressed or mutated in CLL cells, and these Notch molecules are related to the prognosis, anti-apoptosis and drug resistance of CLL[38]. Nwabo et al[39] showed that bone marrow MSCs could protect CLL cells from apoptosis induced by spontaneous and subsequent variety of drugs, including fludarabine, cyclophosphamide, bendamustine, prednisone, and hydrocortisone. Moreover, using a combination of Notch-1, Notch-2,

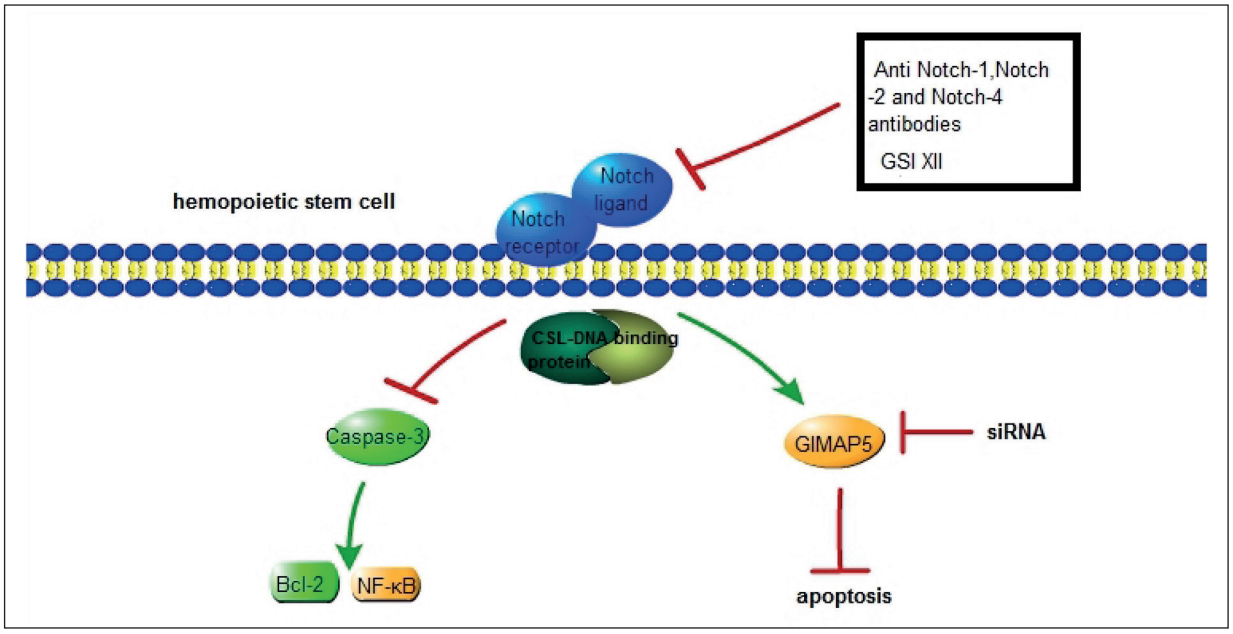

Figure 5. Notch signaling pathway.

and anti-Notch-4 antibody or a γ-secretase inhibitor XII (GSI XII) can reverse this protective effect, showing that Notch-1, Notch-2, and Notch-4 signaling play an essential role in BMSCs mediated survival and drug resistance of CLL cells. In addition, Zhang et al[40] found that the mRNA expression levels of Notch-1, Notch-2, Bcl-2 and NF-κB genes in CLL cells were significantly higher than that in healthy controls, but there was no significant difference between Notch-3 and Notch-4 genes. The expression of Notch1 protein was down-regulated when L1210 cells were inhibited by cytosine arabinoside (Ara-C) and dexamethasone. Therefore, it was proved that the Notch signaling pathway mediates the anti-apoptotic and drug resistance of leukemia cells, but the specific mechanism of action of various Notch molecules remains unclear. Nwabo et al[39] detected the Notch signaling pathway of CLL cell could promote the drug resistance by reducing the activity of Caspase-3 and improving overexpression of Bcl-2 and NF-κ B. Chadwick et al[41] suggested that in acute T-lymphoblastic leukemia (T-ALL) cell lines, the Notch signaling pathway can protect cells from apoptosis by up-regulating the expression of Anti-apoptotic intracellular protein gene GIMAP5. When siRNA was used to knock down the expression of the GIMAP5 gene, it can promote apoptosis induced by Glucocorticoid. Also, in the multiple myeloma (MM) study, we found that the Notch signaling pathway can increase the expression of integrin (αvβ5) in myeloma cells and then enhance its adherence to vitronectin. It is known that the adhesion mediated by MM can protect myeloma cells from drug-induced apoptosis and ultimately mediate the resistance of MDR cells[42]. The notch1 inhibitor can also enhance the sensitivity of human gastric cancer cell line SGC 7901/DDP to chemotherapeutic drugs[43]. Therefore, the Notch signaling pathway is a valuable direction for the study of leukemia therapy.

Drug Resistance Mediated by Hedgehog Signaling Pathway

The Hedgehog signal, also known as the Hh signal, is regulated by two receptors on the target cell membrane, Patched (Ptc) and Smoothened (Smo), among which the receptor Ptc plays a negative regulatory role in Hh signaling, and the receptor Smo is the essential receptor for the Hh signaling pathway. Typically, the Hh signaling pathway regulates the growth and differentiation of embryonic tissue cells. However, when it is abnormally activated, it can enhance the expression of downstream target genes such as c-myc and VEGF, leading to tumor development. Hh ligands binding with the receptor Patched1 (PTCH1) on the cell surface release the inhibition of Smo.

Then, the activation of Smo by inhibiting kinase activities such as Glycogen synthase kinase 3β (GSK3 β) regulates protein degradation and Gli protein (Gli1, Gli2, and Gli3) subcellular localization, and finally, regulates Hedgehog response genes to promote cell survival and proliferation.

The Hh signaling pathway may be critical for LSC maintenance and proliferation.

In the bone marrow microenvironment, the Hh signal pathway can induce Chronic B lymphocytic leukemia (B-CLL) cell survival and reduce apoptosis, which makes leukemia cells resistant to chemotherapy. This effect may be reversed by cyclopamine, which is a specific inhibitor of the Hh pathway[44]. Babashah et al[45] showed that the upregulation of Hh Smo signaling proteins in CD34+ cells from patients with confirmed CML was associated with reduced expression of miR-326. It was also found that the overexpression of miR-326 could lead to downregulation of SMO, thereby inhibiting cell proliferation and increasing apoptosis rate. Thus, downregulation of miR-326 may be a possible mechanism for the unrestricted activation of SMO in the Hh signaling pathway, and the upregulation of miR-326 may benefit the elimination of CML stem/progenitor cells. In addition, through the regulation of downstream target gene transcription factor Gli1, Hh signaling pathway can regulate the cell cycle protein B (Cyclin B) activity. By adjusting the P21 (a protein inhibitor of cyclin-dependent protein kinase), Hh signaling pathway can block cell dormancy, affect cell proliferation and eventually mediated multidrug resistance[46]. Therefore, the targeting therapy for Hh signaling pathway may provide a favorable basis for overcoming leukemia resistance. Kobune et al[47] found that cyclopamine can induce apoptosis in drug-resistant CD34+ AML cells by increasing Bcl-2 and increase its sensitivity to Ara-C. However, because cyclopamine has significant toxicity, it has not been adequately applied in the clinic. An active oral agent, GDC-0449, has substantial clinical efficacy in the treatment of malignancies occurring in Hh signaling pathways (> 50% effective)[48]. Hh inhibitor Vismodegib or Smo small interfering RNA (siRNA) can also reduce the viability of CML cells by blocking the Hh signaling pathway[49]. Oroxyloside A can overcome the resistance

of CML mediated by bone marrow microenvironment to imatinib by inhibiting Hedgehog pathway[50]. Therefore, this signal pathway can be used as another focus in the study of targeted therapy for clinical leukemia.

Conclusions

This review summarized several major signaling pathways mediated by bone marrow microenvironment in the pathogenesis of leukemic cell resistance. These signaling pathways in leukemia cell proliferation, differentiation, apoptosis, migration and drug resistance play a pivotal role in several different ways of interaction between them, the formation of more complex regulatory networks, drug resistance mediated by leukemia cells. There are other signaling pathways, such as HIF-1α/VEGF, vascular cell adhesion molecule-1/very late antigen-4 (VCAM-1/VLA-4), vascular endothelial growth factor-A/vascular endothelial growth factor receptor 2 (VEGF-A/VEGFR2), extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK)[51-52], etc. involved in the survival and resistance of leukemia cells, which constitute a complex regulatory mechanism. Fully understanding the mechanism of drug resistance signaling pathway can provide practical guidance for the clinical treatment of leukemia. Most of these signaling pathways are mediated by cell adhesion molecule (CAMS), which can reduce chemotherapeutic defense by modulating or blocking adhesion interaction, thus providing a new target for the treatment of leukemia[53]. It has been found that the combination of the two inhibitors can also increase the number of affected proteins in the target pathway and multiple parallel signal pathways, and can be converted to promote cell death. Therefore, the combination of inhibitors can lead to the selection of clinical drugs, the formulation of treatment plans, and the elimination of drug resistance induced by the microenvironment in AML[54].

Conflict of Interest

The Authors declare that they have no conflict of interests.

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