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The New Treatment Approaches of Myelodysplastic Syndrome

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Abstract

Background: Myelodysplastic syndrome (MDS) is a heteregenous group of bone marrow neoplasms characterized by dysplasia, intracellular apoptosis and high risk of transformation to acute leukemia [1]. Several treatment options have been developed for the management of MDS, however treatment outcomes are still not sufficient. Innate immune signaling system, epigenetic factors and nucleotide signaling pathway are proved to be significant pathogenetic mechanisms in MDS [2,7,11].

Aim: Is to evaluate different proved pathogenetic mechanisms as possible new targets of mds treatment with the purpose of increasing treatment efficacy and preventing disease progression to acute leukemia.

Methods: Literature, peer-reviewed articles on mds pathogenesis and clinical trial results have been searched in PubMed database.

Keywords: Myelodysplastic Syndrome; Nuclear Phosphoinositides; Phosphodiesterase E4; Chronic Innate Immune System Activation In MDS; Phospholipase-C1

Introduction

MDS is a heterogeneous group of bone marrow neoplasms characterized by dysplasia, intracellular apoptosis, with high risk of acute leukemia transformation. MDS has different subtypes and despite findings that have been made in understanding of MDS pathophysiology, the treatment results are still not sufficient. The current therapy for MDS patients is generally based on demethylating agents, aiming at inhibiting the activation of proliferation processes as well as inducing myeloid differentiation. Moreover, these treatments are often used alone or in combination with erythroid-stimulating agents, like erythropoietin, or immunomodulatory drugs with erythroid-specific effects, such as lenalidomide. Demethylating drugs act on a common modification that is detectable in most high-risk MDS, but they do not always completely eradicate the malignant clone and some patients can be refractory to the therapy. Moreover, azacitidine has to be administered until response is detectable, with the onset of possible collateral effects, and some patients can lose their positive response during the treatment95. On the other hand, the use of erythroid-stimulating agents is limited by iron overload and transfusion-dependence, whereas lenalidomide has many targets [17]. The stem cell transplantation remains the only curable option for many patient with high risk MDS, however the relevant population of patients are not eligible for ASCT due to poor performance status, older age and comorbidities. In this regard new therapeutic approaches are necessary for the management of MDS. Many studies were conducted to explore the nature of disease, pathogenesis mechanisms and new treatment options. Chronic inflammatory diseases associated with activated innate immune signaling pathways often precede MDS [1]. The role of molecular-genetic mutations, epigenetic factors are significant in MDS pathophysiology, however the definite pathogenesis of disorder mechanisms are still not fully understood. Overexpression of immune-related genes in HSPC is reported in over 50% of MDS patients [7]. In group of another pathogenetic factors are myeloid derived supressor cells (MDSC) that expresses immunosuppressive cytokines to reduce effector T cell proliferation. MDSC are increased in MDS BM.

Objective

The objective of this study is to investigate pathogenetic mechanisms of MDS in context of creating new treatment approaches.

Materials and Methods

Literature on mds pathogenesis were searched and reviewed in PubMed database. The systematic litreture review method have been choosed for conducting this study. Meta synthesis technique enable us to evaluate, intreprete finding of conducted multiple researchs on pathogenesis of mds.

Innate immune system activation in MDS

The role of innate immune system activation was investigated in different clinical studies. The innate immune system recognizes pathogens and host cellular by-products by pattern recognition receptors. Among the first receptors to be identified were Toll-like receptors. The chronic activation of TLR signaling pathway causes the impairment of normal hematopoiesis and alters the bone marrow microenvironment [1]. The best studied TLR in MDS is TLR4 and its ligands lipopolysaccharide (LPS) and S100A8/A9. In experimental studies administration of low concentration levels of LPS in mice, was meant to model chronic infection, results in myeloid-biased differentiation and loss of HSC fidelity [2]. Sustained activation of TLR4 correlates with ROS-mediated DNA damage, suggesting that chronic TLR4 signaling can directly result in accumulation of genotoxicity and contribute to malignant transformation [3]. Indeed, LPS was shown to induce MDS in mice with loss of the del (5q) gene mDia1, which corresponds with increased expression of the TLR4 cofactor, CD14 [4]. TLR2 is also implicated widely in MDS. Some preclinical studies demonstrates the potential of inhibiting IL1R/TLR-IRAK-TRAF6 signaling in MDS by targeting IRAK1 and/or IRAK4 with small molecules, or IL1RAP with antibodies. A phase I/II trial of low-risk MDS is underway testing the efficacy of an antagonistic monoclonal antibody to TLR2 [6].

The role of MDSC in MDS

Ongoing scientific researches are designed to explore the myeloid derived suppressor cells in pathogenesis of MDS. MDSC are activated by binding of CD33 to S100A9, a DAMP abundantly expressed by MDSC [9]. In support of a model in which MDSC-derived S100A9 expression contributes to MDS, S100A9 transgenic mice develop an MDS-like disease that coincides with increased activation of MDSC85. In contrast, blocking S100A9 signaling restored normal hematopoiesis, thus implicating MDSC as initiators of the MDS phenotype [10]. It is shown that activation of TLR2 leads to the proliferation of HSC in mice35, and increased apoptosis and impaired erythroid differentiation of human CD34+ BM cells.

Nuclear inositide signaling pathway in MDS

Phosphoinositides regulates cellular functions, such as cell proliferation, differentiation and apoptosis. The secretion of interleukin 8 is controlled by cyclin adenosine monophosphate family, such is PDE4. The nuclear inositide signaling pathways have also been investigated in MDS. Italian group of scientists from Bologna have demonstrated the role of nuclear signaling pathway in MDS. Inositides are cellular secondary messengers that regulates the balance between cell apoptosis and cell cycle progression of normal and damaged cells. Phosphoinosities cycle enzyme phospholipase C B-1 hydrolysis generates diacylglycerol inositol 1, 4,5-tryphosphate a second messengers which plays fundamental role in G1 of the cell cycle, mainly targeting cyclin D, as well as in G2/M [11,17]. It is shown that nucleus contains phosphoinositol 3 kinase enzymes PIK/AKT signaling pathway, the activation of PIK/AKT results in altering control of cell proliferation and apoptosis. It is known that PIK/AKT activation involved in many cellular processes such as cell proliferation, differentiation and apoptosis. It has been demonstrated that PIK3 is involved in hematopoietic cell differentiation, suggesting that this enzyme could affect the generation of MDS blast cells. FISH analyses disclosed the presence of mono allelic deletion of PI-PLCB1 in about 30% of MDS patients. It was revealed that MDS patients bearing mono-allelic mutation both at high and low risk of evolution into AML, rapidly evolved to AML. The PI-PLB1 mutation is not only associated with evolution to AML but also has prognostic role, thus the presence of PCB1 in subgroup of low risk MDS patients indicates poor prognosis. Interestingly along with PIK3 level, the reduction of AKT is observed. This factor indicates the opposite role of PIK3 and AKT. Quantification of the expression of PLCB and levels of activated AKT are attractive predicting factors for the responsiveness of demethylating factors. Phosphoinositide phospholipase C gamma1 (PI PLC-gamma) Indeed, the lack of PI-PLCgamma1 is correlated with an impaired erythropoiesis in mouse models, whilst the same enzyme is associated with granulocyte maturation in zebrafish. It is demonstrated that nuclear PI-PLCbeta1 and PI-PLCgamma1 have been both implicated in MDS pathogenesis, although they play different roles. Interestingly, the amount of nuclear PI-PLCbeta1 can be used also to monitor the loss of response to the epigenetic treatment during the drug administration, therefore predicting not only positive outcomes, but also negative responses to the therapy. In MDS, and specifically in low-risk patients treated with erythropoietin, PI-PLCgamma1 is upregulated in those subjects that show both a favourable response to the treatment and an improvement of anemia36. That is why the modulation of PI-PLCgamma1 in low-risk MDS could be essential to promote a correct erythropoiesis [17].

The role of cAMP in MDS

Another group of investigators have been examined cyclic nucleotide phosphodiesterase (PDE) isoforms expression in MDS and evaluate its role as an prognostic factor. Cyclic adenosine monophosphate (cAMP) family, such as PDE4 regulates pro-inflammatory cellular functions, such as proliferation, cytokine secretion, and chemotaxis. The expression of IL8 and other inflammatory cytokines controlled by PDE4, Inhibitors of PDE4 can increase intracel-

lular cAMP levels, which causes a broad spectrum of anti-inflammatory effects in almost all cells of immune system. Study analysis showed that PDE4A and PDE4C expression were significantly up-regulated and that PDE4B and PDE4C were significantly not up-regulated in patients with MDS. Also it was revealed that PDE4 and IL8 are interconnected and that their higher expression might be needed in pathogenesis of MDS. The inhibition of PDE4 inhibitors could be considered as theurapeuthic option for MDS treatment.

Results

Conducted studies indicates that chronic innate immune signaling in MDS HSC and the microenvironment provides a rationale for the development of therapies that targets oncogenic innate immune pathways. Targeting of the S100A9-CD33—TLR4 axis restores hematopoiesis in MDS-like mouse model, in part by dampening the activity of MDSC. As, such monoclonal antibodies to CD33 are being investigated in low risk MDS patients. Latest studies have shown that hypomethylating agents targets PIK3 signaling pathway. The study of the Italian group of scientists showed that the levels of PIK could predict the degree of Azacitidine effectiveness. Patients with high level of PIK3 demonstrate good responsiveness to Azacitidine and improvement of clinical status [12]. Expansion of MDSC indicate poor prognosis in MDS [8]. Hence, PDE4 might be active therapeutic agents for MDS by modulating both inflammatory and apoptotic pathways in MDS [16]. Other clinical study findings indicates that lipid signal pathway can become therapeutic target in MDS. Certainly, future therapies are being designed to counter this situation, particularly in terms of blocking the common lipid signaling pathway of phosphatidic acid→diacylglycerol. Agents that block this pathway include pentoxifylline, lisophylline, and ciprofloxacin [13-15].

Conclusion

Evaluation of conducted study results on MDS proved that multiple identified components involved in development of MDS pathogenesis, such as chronic innate immune system activation, phosphoinositide signal pathway (messengers and phosphoinositide genesis enzymes) could be considered as targets for developing new treatment agents, treatment protocols and become prognostic factors of MDS treatment efficacy.

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