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Various Signaling Pathways in Multiple Myeloma Cells and Effects of Treatment on These Pathways

Ali Dehghanifard,[1] Saeid Kaviani,[1] Saeid Abroun,[1] Mahshad Mehdizadeh,[2] Sajedeh Saiedi,[3] Amirhosein Maali,[4] Sasan Ghaffari,[5] Mehdi Azad[4]

Abstract

Multiple myeloma (MM) results from malignancy in plasma cells and occurs at ages > 50 years. MM is the second most common hematologic malignancy after non-Hodgkin lymphoma, which constitutes 1% of all malignancies. Despite the great advances in the discovery of useful drugs for this disease such as dexamethasone and bortezomib, it is still an incurable malignancy owing to the development of drug resistance. The tumor cells develop resistance to apoptosis, resulting in greater cell survival, and, ultimately, develop drug resistance by changing the various signaling pathways involved in cell proliferation, survival, differentiation, and apoptosis. We have reviewed the different signaling pathways in MM cells. We reached the conclusion that the most important factor in the drug resistance in MM patients is caused by the bone marrow microenvironment with production of adhesion molecules and cytokines. Binding of tumor cells to stromal cells prompts cytokine production of stromal cells and launches various signaling pathways such as Janus-activated kinase/signal transduction and activator of transcription, Ras/Raf/MEK/mitogen-activated protein kinase, phosphatidyl inositol 3-kinase/AKT, and NF-KB, which ultimately lead to the high survival rate and drug resistance in tumor cells. Thus, combining various drugs such as bortezomib, dexamethasone, lenalidomide, and melphalan with compounds that are not common, including CTY387, LLL-12, OPB31121, CNTO328, OSI-906, FTY720, triptolide, and AV-65, could be one of the most effective treatments for these patients.

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Introduction

Multiple myeloma (MM) is a plasma cell malignancy that develops in individuals aged ≥ 50 years.[1] MM is the second most common hematologic malignancy after non-Hodgkin lymphoma and constitutes 1% of all malignancies.[2] Despite the recent advances in the treatment of MM, it still remains largely incurable owing to the appearance of drug-resistant tumor cells.[3,4] To date, drug resistance has been the greatest problem in the treatment of MM. The average survival time for patients has been ∼9 months.[5] Interactions between MM cells and bone marrow (BM) stromal cells (BMSCs) play a critical role in the pathogenesis and drug resistance in MM patients. This contact, which induces cytokine production, including interleukin (IL)-6, is required for activation of NF-κB, which results in MM cell proliferation and protection against apoptosis.[6] NF-κB pathway inhibition is mostly achieved by proteasome inhibitors with enhancing IKβα. Ultimately, it leads to apoptosis by reducing the expression of antiapoptotic factors.[7] Various drugs have different pathways leading to apoptosis in MM cells, including NF-κB, IL-6/Janus-activated kinase (JAK)/signal transduction and activator of transcription (STAT), MEK/extracellular signal-regulated kinases (ERKs), caspase, mitogen-activated protein kinases (MAPKs), and phosphatidyl inositol 3-kinase (PI3K) signaling. Alkylating agents such as corticosteroids and bisphosphonates and drugs such as thalidomide, bortezomib (BTZ), and lenalidomide are common drugs that, with the help of autologous and allogenic BM transplantation, can improve the quality of life and prolong the survival of patients with MM.[8] Dexamethasone (DEX) as a glucocorticoid analog and BTZ (also called PS-341 or Velcade) as a proteasome-inhibiting agent are the

[1]Department of Hematology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
[2]Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran
[3]Health Research Institute, Research Center of Thalassemia and Hemoglobinopathy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4]Department of Medical Laboratory Sciences, Faculty of Allied Medicine, Qazvin University of Medical Sciences, Qazvin, Iran
[5]Department of Hematology, Faculty of Allied Medicine, Tehran University of Medical Sciences, Tehran, Iran

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Address for correspondence: Mehdi Azad, PhD, Department of Medical Laboratory Sciences, Faculty of Allied Medicine, Qazvin University of Medical Sciences, Qazvin 34197-59811, Iran
E-mail contact: haematologicca@gmail.com

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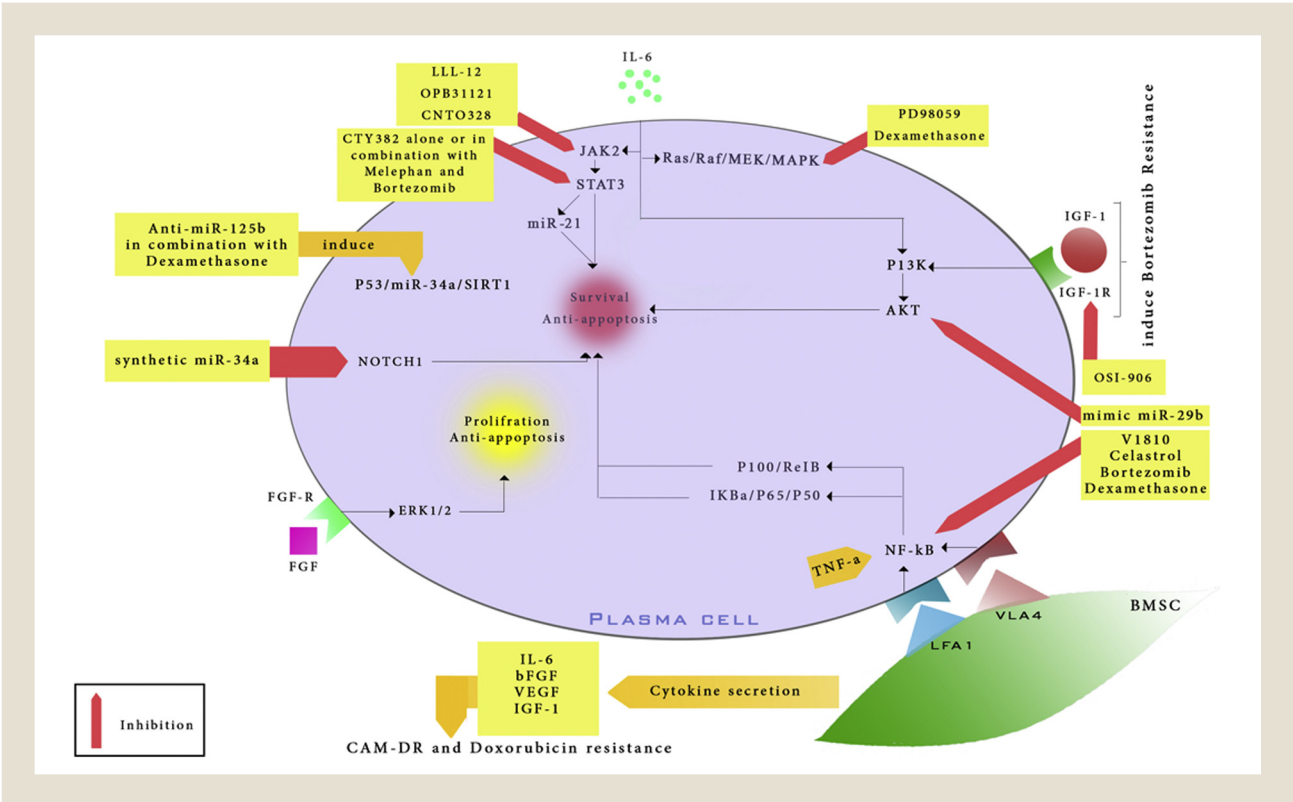
most effective and widely used drugs for the treatment of MM.[9,10] Proteasome inhibitors such as BTZ and carfilzomib (Kyprolis) are anticancer agents that can induce apoptosis in various cancer cells.[7] The combined application of new drugs has led to a paradigm shift in the treatment of patients with MM, improved outcomes.[11]

In the present report, we describe the various signaling pathways involved in cell growth, survival, and apoptosis in MM and the effects of various drugs on these pathways that induce apoptosis and overcome drug resistance.

BM Microenvironment in MM and Drug Resistance

An intricate relationship exists between MM cells and the BM microenvironment that increases the survival rate of MM cells during disease. This phenomenon occurs with the production of cytokines and growth factors and by direct contact with the cells during the physical interaction between stromal cells and extracellular matrix molecules.[12] The adhesion of MM cells to extracellular matrix proteins and BMSCs produces cytokines that induce the growth and survival rate of MM cells and protects them against the effects of drug-induced apoptosis through induction of PI3K/AKT and/or JAK2/STAT3 signaling (Figure 1).[13-15] The level of cytokines is related to the severity and progression of the disease and also participates in drug resistance.[16] MM patients have increased levels of vascular endothelial growth factor, basic fibroblast growth factor (bFGF), and IL-6 in BM plasma, which are produced by MM cells and BMSCs.[17,18] The reaction between BMSCs and MM cells occurs by 2 different mechanisms. The first one results in partial inhibition of MM cell proliferation and arrest in the G_0/G_1 phase, which could be the first target of treatment for apoptotic drugs. The second indirectly leads to the production of soluble factors and inhibition of mitochondrial apoptosis in MM cells.[15] Cell adhesion is the main reason for the primary drug resistance in MM and many malignant diseases. Adhesion

Figure 1 **Intracellular Signaling Pathways and Effects of Various Drugs on These Pathways in Multiple Myeloma (MM) cells. Different Signaling Pathways Such as NF-κB, Phosphatidyl Inositol 3-Kinase (PI3K)/AKT, Janus-Activated Kinase (JAK)/Signal Transduction and Activator of Transcription (STAT), Ras/Raf/MEK/Mitogen-Activated Protein Kinase (MAPK) Lead to Cell Proliferation and Survival. NF-κB Signaling Is Activated by Binding of MM Cells to Bone Marrow Stromal Cells (BMSCs) and Subsequent Cytokines, Such as Tumor Necrosis Factor (TNF)-α Production and Is Inhibited by V1810, Celastrol, Bortezomib (BTZ), and Dexamethasone (DEX) Drugs. Inhibition of JAK/STAT Signaling, Which Is Activated by Cytokine Secretion, in Particular, Interleukin (IL)-6, Occurs by LLL-12, OPB31121, CNTO32, and CTY387, Alone or Combined With Melphalan and BTZ. Insulin-like Growth Factor-1 (IGF-1) and IGF-1 Receptor (IGF-1R) Both Increase Cell Survival in MM by Activating PI3K/AKT Signaling. OSI-906 Precipitates Apoptosis in MM Cells by Inhibiting IGF-1R. Proliferation of MM Cells Is Realized by Ras/Raf/MEK/MAPK Signaling; However, These Pathways Can Be Terminated by PD98059 and DEX Drugs. Additionally, Mimic Micro-RNA (miR)-29b Inhibits the AKT Pathway. Synthetic miR-34a Inhibits the NOTCH/Delta Pathway Causing Cell Survival. Anti—miR-125b Induces Apoptotic Proteins in Combination With DEX**



Abbreviations: bFGF = basic fibroblast growth factor; CAM-DR = cell adhesion-mediated drug resistance; FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor; VEGF = vascular endothelial growth factor.