Check for updates

ELSEVIER

Blood 142 (2023) 6611–6612

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Active STAT3 Prevents Selinexor-Induced Caspase-Independent Apoptosis in Multiple Myeloma

Ryan Michael Mack, BS[1], Mark Sellin, BS[2], Stephanie Berg, DO[3,4], Rohit Thalla, BS[5], Kanak Joshi, MS[6], Lei Zhang, PhD[7,8], Shanhui Liu, PhD[9], Peter Breslin, PhD[10,11,12], Kevin Barton, MD[13], Patrick Hagen, MD MPH[14], Jiwang Zhang, MD PhD[6,15,16]

[1] Department of Cancer Biology, Loyola University Chicago, Oak Park, IL
[2] Department of Cancer Biology, Maywood, IL
[3] Department of Medicine, Loyola University Chicago, Maywood
[4] Dana-Farber Cancer Institute, Brigham and Women's Hospital, Boston, MA
[5] Loyola University Chicago, Maywood, IL
[6] Department of Cancer Biology, Loyola University Medical Center, Maywood, IL
[7] Soochow University, Suzhou, China
[8] Department of Cancer Biology, Loyola University Chicago, Maywood
[9] Second Hospital of Lanzhou University, Lanzhou, China
[10] Department of Cancer, Loyola University Medical Center, Maywood, IL
[11] Department of Biology, Loyola University Chicago, Chicago
[12] Department of Molecular & Cellular Physiology, Loyola University Chicago, Chicago
[13] Department of Medicine, Loyola University-Chicago, Maywood, IL
[14] Division of Hematology and Oncology, Loyola University Medical Center, Maywood, IL
[15] Department of Pathology, Loyola University Medical Center, Maywood
[16] Department of Radiology, Loyola University Medical Center, Maywood

Multiple myeloma (MM) is an acquired malignant plasma cell disorder that typically develops late in life with a median age at diagnosis of 69 years and results in approximately 12,000 deaths per year. Currently, the standard treatment strategy for MM is a combination of 3 drugs with different mechanisms: dexamethasone, a proteasome inhibitor, and an immunomodulatory agent. Many MM patients acquire a "double-hit" of their *TP53* on Chromosome 17p region after multple rounds of treatment and become resistant to these conventional therapeutics. Thus, novel effective treatments for high-risk and relapsed and refractory (RR)-MM are urgently needed to overcome drug-resistance, especially in *TP53* null patients.

In many cancers, nuclear exporter protein XPO1 overexpression is induced by c-Myc and/or loss of p53. Previous studies have demonstrated that many RR-MM patients show increased expression/activity of XPO1, which is associated with aberrant cytosolic localization of its protein and RNA cargoes. Selective XPO1 inhibitor Selinexor (Sel) has been approved by FDA to treat relapsed and refractory multiple myeloma (RR-MM) in combination with a bortezomib + DEX regimen. Addition of Sel to this regiment significantly improves the overall response rate (˜75% vs. ˜60%) and progress free survival (13.9 months vs 9.5 months), regardless of risk factors including *TP53* status. However, only ˜50% of RR-MM patients benefit from Sel treatment. In addition, Sel has significant dose dependent side effects. It is important to determine the mechanism of Sel-resistance in order to identify biomarker(s) to predict Sel-resistance and develop novel effective combination therapies. .

In this study, we compared the response of 10 human MM cell lines to Sel treatment and identified Sel sensitive and resistant cell lines. Based on EC50, we divided the cell lines into Sel-sensitive group with EC_{50} values between 80.4 nM to 211.8 nM, and Sel-resistant groups with EC_{50} values >741.4 nM. We found that Sel sensitivity was notably independent of *TP53* mutation status, as well as other genetic mutations and chromosomal translocations. In resistant cells, high dose of Sel induces an off-target Caspase-mediated apoptosis because it could not be influenced by XPO1-knockdown but could be prevented using a pan-caspase inhibitor Z-VAD. In sensitive cell lines, low dose of Sel induces a Caspase-independent type of cell death because it could not prevented by pre-treated with Z-VAD. To investigate which programmed cell death pathways Sel works through, sensitive cells were treated using with Sel + inhibitors for necroptosis, ferroptosis, pyroptosis, and parthanatos. We found only parthanatos inhibitor could significantly prevent Sel-induced cell death. The parthanatos death pathway functions via DNA-damage/poly (ADP-ribose) polymerase-1 (PARP-1) activation. While proper PARP-1 levels are required for DNA damage repair, over-activation results in the release of apoptosis-inducing factor (AIF) from mitochondria to cytoplasm which then trans-

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/6611/2191262/blood-3207-main.pdf by guest on 02 June 2024

© 2023 by The American Society of Hematology

localize to the nucleus where it functions with macrophage migration inhibitory factor (MIF) to induce DNA fragmentation and cell death. We show via Western blotting and immunofluorescence imaging that upon Sel treatment, AIF shifts from the cytosol into the nucleus. Sel treatment was further assessed in combination with with Dex, where it showed a low synergistic effect with Dex in the sensitive cells but not in resistant cells, specifically when used sequentially. When assessing mechanisms of Sel resistance, phosphorylated STAT3 was uniquely observed in the resistant cell lines. To determine if STAT3 mediates resistance, resistant cell lines were pre-treated with a STAT3-PROTAC (SD36). Our study suggested that p-STAT3 predicts Sel-resistance, and Sel + STAT3 inhibitor combination is a novel effective regimen for MM, especially for these Sel-resistant cases.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-190030

Downloaded from http://ashpublications.net/blood/article-pdf/142/Supplement 1/6611/2191262/blood-3207-main.pdf by guest on 02 June 2024