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Adhesion to fibronectin induces p27^{Kip1} nuclear accumulation through down-regulation of Jab1 and contributes to cell adhesion-mediated drug resistance (CAM-DR) in RPMI 8,226 cells

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Abstract Mounting evidence has been shown that integrin-mediated cellular adhesion confers resistance to chemotherapy of multiple myeloma. The molecular mechanism underlying cell adhesion-mediated drug resistance (CAM-DR) is, however, poorly understood. In this report, we demonstrated that RPMI 8,226 cells accumulated p27^{Kip1} in the nucleus when they were adhered to fibronectin (FN). The adhesion-mediated p27^{Kip1} nuclear recruitment was regulated via the down-regulation of Jab1, a negative regulator of cell cycle. Overexpression of Jab1 reversed the elevated p27^{Kip1} in the nucleus, which needed phosphorylation of p27^{Kip1} on Serine 10, whereas inhibition of Jab1 by siRNA further increased the elevated p27^{Kip1}. Furthermore, we found overexpression of Jab1 did not affect 8,226 cells adhesion to FN, but reversed doxorubicin or mitoxantrone-induced CAM-DR phenotype. In conclusion, our data suggest that Jab1 plays an important role in CAM-DR, which depends on pSer10-p27^{Kip1}-mediated subcellular localization of p27^{Kip1}. The understanding of this novel molecular mechanism may prove valuable in designing new therapeutic approaches for CAM-DR in Multiple myeloma.

Keywords Jab1 · p27^{Kip1} · pSer10-p27^{Kip1} · Multiple myeloma · Cell adhesion-mediated drug resistance

Abbreviations

MM	Multiple myeloma
BM	Bone marrow
Jab1	Jun activation domain-binding protein 1
MRD	Eliminate minimal residual disease
ECM	Extracellular matrix
FN	Fibronectin
CAM-DR	Cell adhesion-mediated drug resistance
CDKI	Cyclin-dependent kinase inhibitor

Introduction

Multiple myeloma (MM), one of the most common hematological diseases, is characterized by the homing and uncontrolled proliferation of malignant plasma cells localized within its local bone marrow (BM) microenvironment [1–4]. Despite the advent of several novel

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