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

Min Fei · Qinglei Hang · Sicong Hou · Songbin He · Changgeng Ruan

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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