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Metformin reverses multidrug resistance and epithelial–mesenchymal transition (EMT) via activating AMP-activated protein kinase (AMPK) in human breast cancer cells

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Abstract Breast cancer is the most frequently diagnosed tumor type and the primary leading cause of cancer deaths in women worldwide and multidrug resistance is the major obstacle for breast cancer treatment improvement. Emerging evidence suggests that metformin, the most widely used antidiabetic drug, resensitizes and cooperates with some anticancer drugs to exert anticancer effect. However, there are no data regarding the reversal effect of metformin on chemoresistance in breast cancer. In the present study, we investigated the resistance reversal effect of metformin on acquired multidrug-resistant breast cancer cells MCF-7/5-Fu derived from MCF-7 breast cancer cells and innate multidrug-resistant MDA-MB-231 breast cancer cells, and we found that metformin resensitized MCF7/5-FU and MDA-MB-231 to 5-fluorouracil (5-FU), adriamycin, and paclitaxel. We also observed that metformin reversed epithelial–mesenchymal transition (EMT) phenotype and decreased the invasive capacity of MCF7/5-FU and MDA-MB-231 cells. However, there were no significant changes upon metformin-treated MCF7 cells. Moreover, we found metformin treatment activated AMPK signal pathway in MCF7/5-FU and MDA-MB-231 cells and compound C, the AMPK inhibitor, could partly abolish the resensitization and EMT reversal effect of metformin. To the best of our knowledge, we are the first to report that metformin can resensitize multidrug-resistant breast cancer cells due to activating AMPK signal pathway. Our study will help elucidate the mechanism of chemoresistance and establish new strategies of chemotherapy for human breast cancer.

Keywords Breast cancer · Multidrug resistance · Metformin · EMT

Introduction

Breast cancer is the most frequently diagnosed tumor type and the primary leading cause of cancer deaths in women worldwide. Breast cancer accounted for 23 % (1.38 million) of all new cancer cases and 14 % (458,400) of the total cancer deaths in 2008 [1]. Chemotherapy is an important therapeutic method for breast cancer patients. However, the development of multidrug resistance usually results in the failure of chemotherapy, even after combination chemotherapy, which leads to tumor recurrence and further progression. Although a number of factors, including overexpression of the ATP-binding cassette (ABC) membrane transporter family, have been shown to contribute to multidrug resistance [2], the mechanism of multidrug resistance is still not completely understood. Therefore, it is necessary to investigate the mechanisms of multidrug resistance and develop new strategies for chemotherapy.

In our previous study, we had established a multidrug-resistant breast cancer cell line (MCF7/5-FU) to investigate the mechanism of multidrug resistance. MCF7/5-FU was derived from a well-characterized human breast cancer cell

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