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Research paper

Inhibition of glucose transporter 1 induces apoptosis and sensitizes multiple myeloma cells to conventional chemotherapeutic agents

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ABSTRACT

Despite the recent development of anti-myeloma drugs, the prognosis of high-risk multiple myeloma remains poor. Therefore, new effective treatment strategies for this disease are needed. It has been reported that high intensity of 18-fluorodeoxyglucose positron emission tomography is high-risk factor in myeloma, suggesting that glucose uptake can be therapeutic target in high-risk myeloma. In this study, we addressed the utility of glucose transporter 1 (GLUT1) as a therapeutic target for myeloma with increased glucose uptake. We found myeloma cell lines with elevated glucose uptake activity via GLUT1 up-regulation. STF-31, a selective GLUT1 inhibitor, completely suppressed the glucose uptake activity and induced apoptosis in GLUT1 expressing myeloma cells. On the other hand, this agent little shows the cytotoxicity in normal peripheral blood mononuclear cells. Moreover, STF-31 synergistically enhanced the cell death induced by melphalan, doxorubicin, and bortezomib. GLUT1 may be promising therapeutic target in myeloma with elevated glucose uptake.

1. Introduction

The median survival time of patients with multiple myeloma was less than a year during the 1970s; however, the development of new chemotherapeutic agents, including thalidomide, lenalidomide, and bortezomib, has improved the clinical outcome in the past decade. Currently, patients with standard-risk myeloma have a median overall survival of 6–7 years. However, patients with high-risk myeloma still have a median overall survival of less than 2–3 years [1]. Therefore, the development of new effective strategies for the treatment of high-risk myeloma is needed.

Recently, 18-fluorodeoxyglucose positron emission tomography (18-FDG/PET) has provided valuable prognostic information in multiple myeloma. For example, Zamagni et al. reported that 76% of PET-positive myeloma patients at an early initial diagnosis translated to a hypermetabolic state, and incomplete suppression of FDG uptake after treatment was strongly associated with low progression-free and overall survival rates [2]. Another study of 239 untreated myeloma patients found that prognostic implications linked to tumor FDG uptake activity: patients with bone lesions exhibiting maximum standardized uptake values greater than 3.9 demonstrated poor event-free survivals [3]. Because 18-FDG/PET utilizes increased glucose uptake in tumor cells, these clinical data suggest that increased glucose consumption is an attractive target for high-risk myeloma.

Glucose is incorporated into cells via the cell membrane glucose transporter (GLUT). The GLUT family is comprised of 14 GLUT subtypes [4]. It has been shown that, among those, increased GLUT1 expression is correlated with poor clinical outcome in different types of cancers. For example, Ramani et al. reported a significantly higher GLUT1 expression in malignant neuroblastomas than in benign counterparts. They have also shown that elevated GLUT1 expression was significantly associated with poor overall survival and event-free survival [5]. Another clinicopathological study revealed that GLUT1 expression was markedly higher in ductal carcinoma *in situ*, invasive ductal carcinoma, and lymph node metastasis than in normal tissue and ductal hyperplasia. The authors also demonstrated that high GLUT1 expression is correlated with high histological grade, and patients with high GLUT1 expression have poor overall survival and disease-free survival [6].

Given the association of GLUT1 and adverse prognosis in many kinds of cancer, in this study, we investigated the chemotherapeutic

Abbreviations: GLUT1, glucose transporter 1; 18-FDG/PET, 18-fluorodeoxyglucose positron emission tomography; PBMC, peripheral blood mononuclear cells.

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potential of GLUT1 inhibition in high-risk myeloma with increased glucose uptake by using myeloma-derived cultured cells in vitro. Our data suggests that inhibition of GLUT1 expression is a promising therapeutic approach for myeloma patients with high GLUT1 expression, not only as a monotherapy, but also as a combination therapy with standard anti-myeloma drugs.

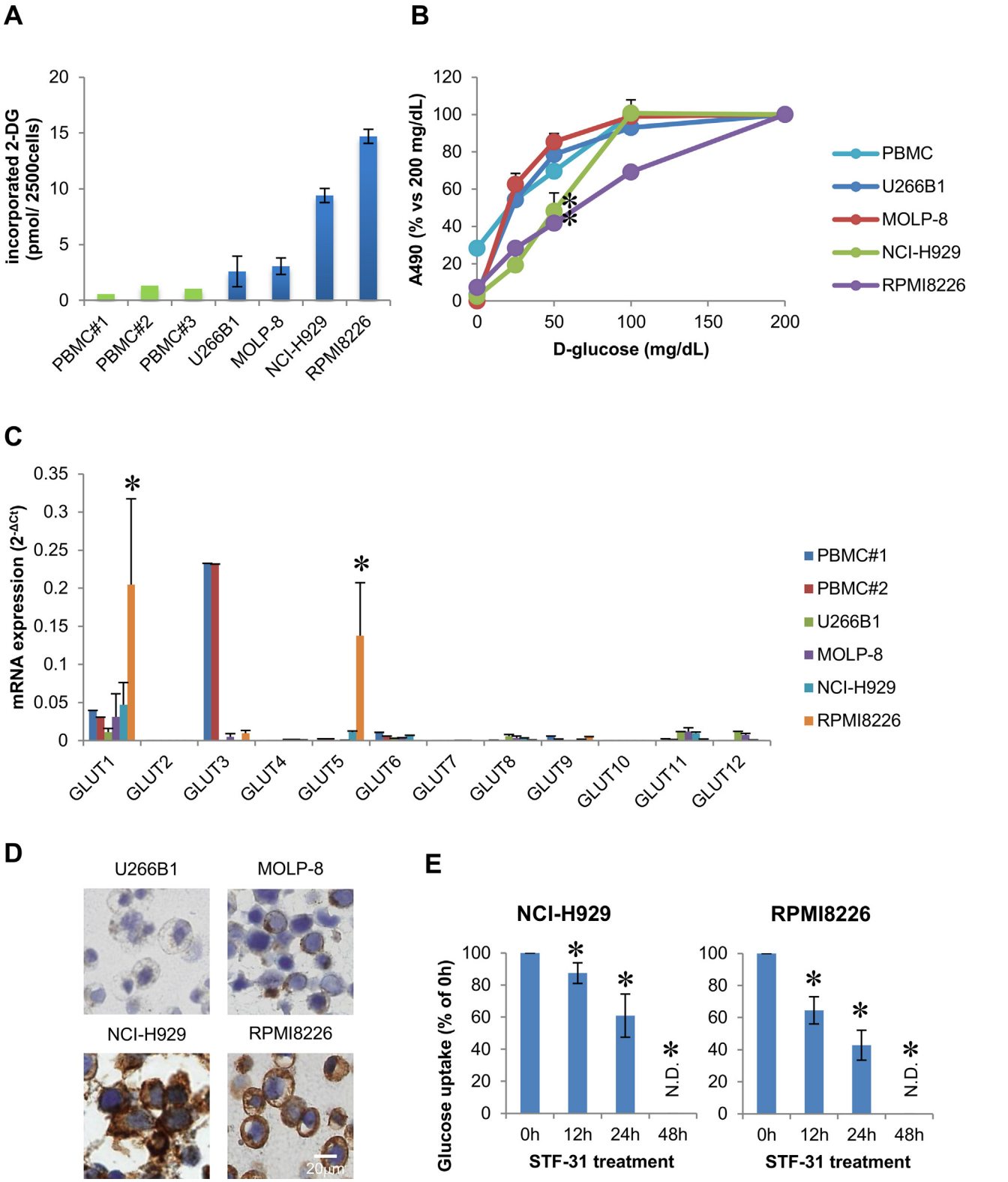

Fig. 1. The effect of GLUT1 expression on glucose uptake in myeloma cells. (A) The glucose uptake in four myeloma cell lines and PBMCs from three independent healthy donors. Data are mean ± SEM ($n = 3$ for myeloma cell lines; $n = 1$ for the PBMC sample). (B) The effect of changing extracellular glucose concentrations on four myeloma cell lines and PBMC. Data are mean ± SEM ($n = 3$). (C) The mRNA expression of GLUT1–12 in four myeloma cell lines and PBMCs. Data are mean ± SEM ($n = 3$). *$P < 0.05$ vs PBMC#1. (D) Immunohistochemistry of GLUT1 in myeloma cell lines. Nuclei were counterstained with Mayer's hematoxylin. (E) The time-dependent inhibitory effect of STF-31 on glucose uptake in NCI-H929 and RPMI8226 cells. Data are mean ± SEM ($n = 3$). *$P < 0.05$, N.D.: not detected.