Rewiring of energy metabolism drives resistance to the proteasome inhibitor bortezomib

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1. Introduction

The proteasome inhibitor bortezomib (BTZ) is successfully applied in the treatment of multiple myeloma (MM), but its efficacy is restricted by the wide-spread occurrence of resistance. Metabolic alterations play an important role in cancer development and aid in the cellular adaptation to pharmacologically changed environments. Metabolic changes may therefore also play an essential role in the development of drug resistance. Interestingly, cells could become reliant on such drug-induced metabolic reprogramming, a vulnerability that could be exploited for therapy. However, specific metabolic pathways that can be targeted to improve the efficacy of bortezomib therapy remain unidentified.

2. Approach

In this study, the metabolic pathways involved in resistance to bortezomib were elucidated using a mass spectrometry-based metabolomics approach. To this end, bortezomib-sensitive and -resistant MM cell lines were profiled using a combination of steady-state metabolomics experiments and stable isotope labelling approaches. These metabolomics studies were complemented with a metabolism-oriented targeted proteomics approach, in which coverage of metabolic enzymes was optimized by fractionating cells into cytosolic and membrane fractions. Finally gene expression patterns of metabolic genes were investigated in genome-wide data of MM patient samples to link results in cell lines to BTZ response and outcome in patients.

3. Results

Our findings demonstrate that the metabolic profiles of bortezomib-sensitive and -resistant cells differ significantly. BTZ-resistant cells display an extensive rewiring of their mitochondrial energy metabolism on both the proteomics and metabolomics level. Mechanistically, metabolic rewiring results in increased activity of the mitochondrial tricarboxylic acid (TCA) cycle and electron transport chain (ETC). Surprisingly, BTZ-resistant cells use more glutamine to maintain their TCA cycle activity, but are less dependent on extracellular glutamine for survival as compared to sensitive cells, indicative of a high metabolic plasticity of BTZ-resistant cells. We identify metabolic drugs that can overcome bortezomib resistance, indicating that the increased ETC activity of resistant cells could be exploited to increase the efficacy of bortezomib therapy. Finally, we show that the observed rewiring of mitochondrial metabolism correlates to drug response in a cohort of MM patients.

4. Discussion

Collectively, our data provide novel mechanistic insights in the role of mitochondrial energy production in mediating bortezomib resistance. Our data indicate that metabolic rewiring of energy metabolism correlates to drug response in MM patients and provide rationale for combining bortezomib with metabolic drugs to increase treatment efficacy.