Ribonucleotide reductase is an effective target to overcome gemcitabine resistance in gemcitabine-resistant pancreatic cancer cells.
Ribonucleotide reductase is an effective target to overcome gemcitabine resistance in gemcitabine-resistant pancreatic cancer cells with dual resistant factors

Abstract

Gemcitabine is widely used for pancreatic, lung, and bladder cancer. However, drug resistance against gemcitabine is a large obstacle to effective chemotherapy. Nucleoside transporters, nucleoside and nucleotide metabolic enzymes, and efflux transporters have been reported to be involved in gemcitabine resistance. Although most of the resistant factors are supposed to be related to each other, it is unclear how one factor can affect the other one. In this study, we established gemcitabine-resistant pancreatic cancer cell lines. Gemcitabine resistance in these cells is caused by two major processes: a decrease in gemcitabine uptake and overexpression of ribonucleotide reductase large subunit (RRM1). Knockdown of RRM1, but not the overexpression of concentrative nucleoside transporter 1 (CNT1), could completely overcome the gemcitabine resistance. RRM1 knockdown in gemcitabine-resistant cells could increase the intracellular accumulation of gemcitabine by increasing the nucleoside transporter expression. Furthermore, a synergistic effect was observed between hydroxyurea, a ribonucleotide reductase (RR) inhibitor, and gemcitabine on the gemcitabine-resistant cells. Here we indicate that RR is one of the most promising targets to overcome gemcitabine resistance in gemcitabine-resistant cells with dual resistant factors.

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