Molecular Cancer Therapeutics

Cancer Biology and Signal Transduction

Expression of GRP78, Master Regulator of the Unfolded Protein Response, Increases Chemoresistance in Pancreatic Ductal Adenocarcinoma

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Abstract

The prognosis for patients with pancreatic ductal adenocarcinoma (PDAC) is dismal. Although gemcitabine (GEM) is the standard chemotherapeutic agent for adjuvant therapy of resectable PDAC, recurrent disease is observed in an alarming number of GEM-treated patients. Regardless of the adjuvant therapy, the vast majority of patients treated with chemotherapy after surgical resection show tumor recurrence. A better understanding of the molecular mechanisms that contribute to chemoresistance would aid the development of more effective treatment strategies. GRP78 is an endoplasmic reticulum (ER) chaperone protein that primarily resides in the lumen of the ER and is the master regulator of the unfolded protein response (UPR). Here, we report that expression of GRP78 is significantly higher in GEM-resistant PDAC compared to GEM-sensitive PDAC patient samples. We show that GRP78 induces chemoresistance in PDAC cells. Our results also show that knockdown of GRP78 reduces chemoresistance in PDAC. Finally, we found that IT-139, a ruthenium-based anticancer drug, can overcome GRP78-mediated chemoresistance. *In vitro*, IT-139 restores sensitivity to cytotoxic drugs in drug-resistant PDAC cells and induces twice as much cell death in combination treatment compared with GEM alone. *In vivo*, a single weekly IT-139 treatment in combination with GEM caused a 35% increase in median survival and a 25% increase in overall survival compared to GEM alone. Collectively, our data show that GRP78 expression promotes chemoresistance in PDAC and therapeutic strategies, blocking the activity of GRP78 increases the efficacy of currently available therapies. *Mol Cancer Ther; 15(5); 1043–52. ©2016 AACR.*

Footnotes

- **Note:** Supplementary data for this article are available at Molecular Cancer Therapeutics Online (http://mct.aacrjournals.org/).

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