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Glutamine-dependent SLC6A14 In Pancreatic Cancer Mediates Glutamine Production In Tumor Microenvironment To Support Gemcitabine Chemoresistance.

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Background : Pancreatic Ductal Adenocarcinoma (PDAC) is known as one of the fatal cancers that have a high mortality worldwide. Gemcitabine is one of well-known drugs to treat pancreatic cancer patients. However, as a limit of mono-therapy, gemcitabine tends to cause drug resistance in pancreatic cancer. Therefore, it is significant to discover novel therapeutic agents for gemcitabine resistance therapy. The present study represents the first study evaluating the relationship between gemcitabine resistant cancer cells and tumor micro-environment in PDAC.

Methods : Here, we found that regulation of SLC6A14 disrupts glutamine production from surrounding tumor microenvironment to weaken drug resistance in PDAC cells. In addition, blockade of SLC6A14 dysregulated cell proliferation as determined by WST assay and induced high levels of ROS as determined by DCF-DA staining via FACS and evidenced by down-regulation of NRF2 and GPX4 expression. Moreover, inhibition of SLC6A14 showed anti-tumor effect as proved by inactivated mTOR and NF-κB expression. Further, our findings showed that suppression of SLC6A14 effectively decreases tumor size and growth in gemcitabine-resistant pancreatic cancer in vivo.

Results : Altogether, our results indicate that SLC6A14 is involved in oncogenic effect in PDAC by inducing glutamine production from tumor micro-environment.

Conclusions : SLC6A14 could be a novel potential candidate to improve weakness of gemcitabine monotherapy in drug resistance in PDAC.

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