Thiostrepton induces ferroptosis in pancreatic cancer cells through STAT3/GPX4 signalling

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Presenter: Tzu-Fan Chang
Commentator: Chu-An Wang, PhD

Date and Time: 2022.11.03, 15:00-16:00
Location: Room 601, Med College Building

Background:

Pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of pancreatic cancer, is a rapid progression cancer with less than 8% of 5-year survival rate. Unfortunately, most patients are not sensitive to chemotherapy, immunotherapy, and other treatment, making the treatment approach relatively deficient. Ferroptosis is an iron-dependent cell death caused by lipid peroxidation. Since KRAS and P53 mutation, the most two common mutations in PDAC, are associated with ferroptosis, understanding of ferroptosis may provide potential treatment option.
Thiostrepton (TST) is a translation inhibitor that has been used as anti-bacterial drug. TST has been reported to reduce the expression of FOXM1 in many cancers, but the characteristic of TST in pancreatic cancer remains unclear.

Objective:

The author uncovered a new role of TST in pancreatic cancer. They wanted to investigate whether TST can be used as a new clinical drug for pancreatic cancer.

Result:

Thiostrepton (TST) reduced the viability and colony formation of pancreatic cancer. TST promoted ferroptosis to a similar level as ferroptosis inducer RSL3. Next, the author found that TST reduced the expression of GPX4, but not SLC7A11, a cysteine transporter on mitochondria. Furthermore, TST reduced the expression of STAT3. After chromatin immunoprecipitation experiments, they found that STAT3 can bind to GPX4 and directly regulated its transcription. Therefore, TST-induced ferroptosis is dependent on the STAT3-GPX4 signaling pathway. To confirm whether TST had the same efficacy in vivo, the authors injected pancreatic cancer cells into immunodeficient mice and treated the tumors with TST. The results showed that TST was able to inhibit tumor malignancy in vivo and did not cause significant systemic toxicity.

Conclusion:

Thiostrpton (TST) can promote ferroptosis by inhibiting the expression of GPX4. The expression of GPX4 was regulated by STAT3, which can also be reduced by TST. Animal model revealed that TST had same efficacy in vivo and was well tolerated in mice.