16th World Congress on
Gastroenterology- Therapeutics & Hepatology
November 21, 2022 | Webinar

Cancer-associated fibroblasts suppress ferroptosis and induce gemcitabine resistance in pancreatic cancer cells through exosome-derived ACSL4-targeting miRNAs

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Pancreatic cancer remains one of the deadliest cancer types in the world. Severe chemotherapy resistance leads to poor prognosis in patients with advanced pancreatic cancer, highlighting the need to investigate mechanisms and develop therapies to overcome chemo resistance.

Primary NFs and CAFs were collected from PDAC patient tumour samples and Para cancerous pancreatic tissues. Exosomes were isolated by ultra-centrifugation and identified via western blotting, nanoparticle tracking analysis, and transmission electron microscopy. CAF-derived miRNAs were analysed by RT-qPCR and high-throughput sequencing. GEM was used to induce ferroptosis, and ferroptosis levels were evaluated via measuring lipid ROS, cell viability, and intracellular Fe2+ levels. A xenograft tumour model was used to evaluate in vivo tumour response.

Exosomes derived from CAFs in PDAC did not exhibit innate GEM resistance. CAFs promoted chemo resistance in PDAC cells following GEM treatment by secreting exosomes, potentially through maintaining signalling communication with cancer cells. Mechanistically, miR-3173-5p derived from CAF exosomes sponged ACSL4 and inhibited ferroptosis after uptake by cancer cells.

The present study reveals a new mechanism of acquired chemo-resistance in PDAC and suggests this miR-3173-5p/ACSL4 pathway as a possible therapeutic target in Gem-resistant pancreatic cancer

Biography

Ran Qi has his passion in improving the treatment of pancreatic cancer. After years of clinical work experience accumulation and summary, he highlights the importance of elucidating the mechanisms of ferroptosis in chemotherapy resistance. His research provides new ideas for the improvement of chemotherapy sensitivity in cancer by blocking specific miRNA packaging into exosomes.

Received: November 6, 2022; **Accepted**: November 7, 2022; **Published**: November 30, 2022