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The synergistic tumor growth-inhibitory effect of probiotic *Lactobacillus* on transgenic mouse model of pancreatic cancer treated with gemcitabine

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Pancreatic cancer is one of the most lethal and chemo-resistant cancers worldwide. Growing evidence supports the theory that the gut microbiota plays an essential role in modulating the host response to anti-cancer therapy. The present study aimed to explore the effect of probiotics as an adjuvant during chemotherapy for pancreatic cancer. An *LSL-Kras^{G12D/-}-Pdx-1-Cre* mouse model of pancreatic ductal adenocarcinoma (PDAC) was created to study the effects of using four-week multi-strain probiotics (*Lactobacillus paracasei* GMNL-133 and *Lactobacillus reuteri* GMNL-89) as an adjuvant therapy for controlling cancer progression. At 12 weeks of age, pancreatitis was induced in the mice by two intraperitoneal injection with caerulein (25 µg/kg 2 days apart). Over the next 4 weeks the mice were treated with intraperitoneal injections of gemcitabine in combination with the oral administration of probiotics. The pancreas was then harvested for analysis. Following caerulein treatment, the pancreases of the *LSL-Kras^{G12D/-}-Pdx-1-Cre* transgenic mice exhibited more extensive pancreatic intraepithelial neoplasia (PanIN) formation. Combined treatment with gemcitabine and probiotics revealed a lower grade of PanIN formation and a decrease in the expression of vimentin and Ki-67. Mice that received gemcitabine in combination with probiotics had lower aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels. Notably, the use of high-dose probiotics alone without gemcitabine also had an inhibitory effect on PanIN changes and serum liver enzyme elevation. These findings suggest that probiotics are able to make standard chemotherapy more effective and could help improve the patient's tolerance of chemotherapy.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
EMT	Epithelial to mesenchymal transition
GEMMs	Genetically engineered mouse models
HCAs	Heterocyclic amines
H&E	Hematoxylin and eosin

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