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Survival Model of Intrahepatic Cholangiocarcinoma; Sex as a Biological Variable

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Cholangiocarcinoma is a primary liver cancer associated with high mortality (<10% 5-year survival rate) and limited treatment options. Moreover, the incidence of intrahepatic cholangiocarcinoma has risen by 165% since 1975; an escalation not from increased early detection. Thus, there is need for a reproducible tumor model and drug delivery approach. Nanoparticles offer an effective delivery system of regulatory nucleic acids. miR-210 antagonism enhanced tumor cell death upon gemcitabine and cisplatin treatment, and polymeric nanoparticles containing a CXCR4 inhibitor (PCX) targeted delivery to the liver tumor. To test anti-miR-210 in liver tumors, we injected human tumor cells directly into the lobe of a liver that had been cholestatically damaged via selective bile duct ligation. We used NOD-SCID mice and injected Mz-ChA-1 cells into the left lateral lobe. All mice to undergo this procedure developed tumors within their liver, as well as extensive peritoneal metastases. This model was used to test survival of mice in four treatment groups: Vehicle, gemcitabine/cisplatin, PCX with anti-miR-210 plus gem/cis, and PXC with anti-miR-210 without gem/cis. Results showed significantly increased survival of all treated groups in comparison to the vehicle group, however there was no significantly increased survival in anti-miR-210 treatment groups when compared to gem/cis alone. It should be noted that the survival benefit of all treatments was driven by responses in females, whereas males had no significant survival advantage for treated groups over control. Females also had significant survival in the specific treatment group PCX with anti-miR-210. This could suggest a possible role of sex as a biological variable for treatment responsiveness and warrants more exploration.