The inhibition of pancreatic cancer progression by PI3K-activated MSC proteomes

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Background and Hypothesis:
Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer with a very poor survival rate. The PI3K pathway has been studied extensively in cancer cells which has led to the creation of PI3K inhibitor drugs. To explore an uncharted and counterintuitive use of the PI3K pathway, PI3K was activated in mesenchymal stem cells (MSCs) and the action of their conditioned medium (CM) on PDAC was examined. We hypothesized that PI3K-activated MSC-derived CM is capable of suppressing tumor growth and migration.

Project Methods:
To generate the treatment conditioned media, we first isolated and grew MSCs in DMEM + 10% serum and added 50 μM of PI3K activator (YS49) and incubated for 24 hours. Afterwards, we exchanged the media with fresh DMEM + 10% serum and incubated for another 24 hours. Next, we hyper-centrifuged the media to extract the conditioned media and used the media to treat PANC-1, PA03C, ASPC-1, PANC10.05, and PANC198 pancreatic cancer cell lines. *In vitro* viability and migration assays were conducted on these five treated cell lines. The regulatory mechanism was evaluated using Western blotting, immunoprecipitation, and ELISAs.

Results:
PI3K-activated MSC-derived CM reduced the proliferation (N=5) and migration (N=2) of PDAC ($p < 0.01$). MSC CM was enriched with polyubiquitin C (Ubc), which acted as an extracellular tumor-suppressing protein by interacting with CXCR4. While the anti-tumor efficacy of Ubc differed depending on the CXCR4 expression level of PDAC, MSC CM was commonly effective in the tested cell lines and tissues (N=5).

Conclusion and potential Impact:
Collectively, this study demonstrated that MSC CM can be converted into a tumor-suppressing agent by the activation of PI3K, and a Ubc-CXCR4 regulatory axis is at least in part responsible. The use of MSC CM treatment can potentially serve as an alternative or supplemental treatment to current chemotherapeutic agents in treating pancreatic cancer without inducing life-threatening side effects.