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Targeted therapeutics in pancreatic cancer for precision medicine

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal solid malignancies and the 4th leading cause of cancer-related deaths in North America. The survival rate remains less than 5% at 5 years taking into account all stages of the disease. In contrast to other cancer types, the mortality rate of PDAC is increasing, with PDAC being predicted to become the second leading cause of cancer-related mortality by 2020. Despite great efforts to improve the treatment and outcome of patients with PDAC, limited progress has been made. Still, current therapeutic options are very disappointing. Genetic mutaions of tumor supperssor genes have been well characterized in pancreatic cancer. However, the pathophysical progression of PDAC doese not always correlate with these genetic changes, suggesting the possibility that unidentified genetic alterations or epigenetic factors might be involved in the progression of pancreatic maligancy. The loss of heteozygosity of lysine demethylase (*KDM6B*) encoding histone demethylase makes pancreatic cancer epigenetically silenced in the downstream target of CCAAT/enhancer binding protein alpha (C/EBPα), strong anti-proliferator by affecting p21, a cyclin-dependent kinase (CDK) inhibitor. The decreased expression of *KDM6B* and C/EBPα is well-correlated through the malignant progression of PDAC. For the precision medicine in pancreatic cancer, to activate the silened gene of C/EBPα for the therapeutics, small activating RNA(saNRA) to C/EBPα is developed. For targeted delivery of C/EBPα, RNA aptamers have been isolated *via* cell-SELEX, that showed the pancratic cancer cell specificity. The isolated RNA aptamers have been conjugated with C/EBPα-saRNA as targeting modalities. The targeted delivery of the C/EBPα-saRNA conjugates showed the increased expressionof C/EBPα *in vitro* with translational and transcriptional level. *In vivo* assay, the targeted delivery of C/EBPα-saRNA conjugates significantly inhibited the tumor growth without toxicity. Using pancreatic cancer specific aptamers, to reduce the non-specific absorption of cytotoxic drugs in normal cells, aptamer-drug conjugates (ApDCs) were constructed with active metabolites of prodrugs, gemcitabine and 5FU, and chemotoxins, MMAE and DM1. The ApDCs with gemcitabine and 5FU showed the significant anti-prolieraction effects by inducing double-strand breask in nuclear without affecting non-targeting cells. Also, The ApDCs with MMAE and DM1 showed the stong anti-prolieraction effects by arresting the cycle without the cytotoxicity in non-targeting cells. Taken together, our studies prove the therapeutic strategies for precision medicine in pancrearic cancer by following firstly, targeting somatic mutaions for therapeutics and secondly, aptamer mediated targeted delivery of theapeutics with minimizing the side effects in normal cells.

Biography

Sorah Yoon has completed her PhD from Seoul National University, South Korea and Post-doctoral studies from Beckman Research Institute of City of Hope, USA. She is Staff Scientist of Department of Molecular and Cellular Biology at Beckman Research Institute of City of Hope. She has published more than 19 papers in reputed journals, one book chapter, and 15 patents including USA patents. She was awarded numerous travel awards including Meritorious Abstract Travel award in ASGCT, 2015 and travel award in OTS, 2016. She was also invited as a speaker to drug delivery conferences in China and Malaysia.

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