DOCTORAL THESIS

A novel nucleolin aptamer-celastrol conjugate (NACC) with super antitumor activity on advanced pancreatic cancer

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Abstract

Advanced pancreatic cancer (APC) has a poor prognosis due to the high degree of resistance after systemic chemotherapy. Celastrol (CSL), a quinone methyl triterpenoid monomer extracted from *Tripterygium wilfordii Hook F*, exhibits superior antitumor activity on pancreatic cancer (PC) both *in vitro* and *in vivo*. In addition, CLS counteracts multiple mechanisms involved in multi-drug resistance (MDR) of PC cells. However, CSL induced toxicity to normal tissues (e.g. liver) is the major impediment to its clinical application. Thus, it is desirable to seek strategy to facilitate CSL selectively targeting PC tissues and simultaneously reducing its exposure to healthy tissues (e.g. liver).

Aptamers are single-stranded oligonucleotides which specifically recognize and bind to targets by distinct secondary or tertiary structures. Nucleolin, a protein overexpressed on the plasma membrane of PC cells than that of normal cells (e.g. liver cell), which shuttle between cell surface, cytoplasm and nucleus, work as a cell surface receptor. Nucleolin aptamer is an anti-proliferative G-rich oligonucleotide with high affinity and specificity to nucleolin, which has been proved to be safe in clinical research. Then, nucleolin aptamer, as a target moiety, provide an approach to facilitate CLS selectively targeting PC cells. Taken together, our hypothesis is that the nucleolin aptamer modification could facilitate the conjugated CSL selectively targeting pancreatic cancer cells to achieve higher antitumor activity and less liver toxicity.

In our study, CSL was conjugated to nucleolin aptamer to form Nucleolin Aptamer-Celastrol Conjugate (NACC). A CRO Aptamer-Celastrol conjugate (CACC) was also synthesized as a control for comparison. The water solubility of NACC was significantly higher than that of CSL. Then, the molecular weight of NACC was detected by ESI mass sepectrum (MS). The anti-proliferative efficacy of NACC was higher than CSL *in vitro*. NACC could selectively bind to PANC-1 cells over normal liver cells. The cellular uptake of NACC by PANC-1 cell was stronger than CSL. Moreover, NACC could be taken up by PANC-1 cells mainly via macropinocytosis. Tissue distribution study revealed that NACC could selectively accumulate in pancreatic tumor tissue and reduce the distribution in liver *in vivo*. In addition, NACC demonstrated higher antitumor activity and less liver toxicity *in vivo*, compared with CSL and CACC.

The above results revealed that the nucleolin aptamer modification could facilitate the conjugated CSL selectively targeting PC cells to achieve higher antitumor activity and less liver toxicity.

Table of Contents