PCSK9 conjugated paclitaxel loaded liposomes to target the cancer cells

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Statement of the Problem: There is an unmet need for anti-cancer drugs to be directed at tumors to kill cancer cells selectively. We need systems that target cancer cells to reduce the side effects seen with conventional treatments. Anti-cancer drugs may be packaged within nanoparticle-based drug-delivery vectors that transport them towards their therapeutic targets. In this research, we have developed a Proprotein convertase subtilisin/kexin type 9(PCSK9) conjugated Paclitaxel-loaded Liposomes (PCSK9-PTX-liposomes) for targeting cancer cells. This work is based on the hypothesis that liposomes linked to PCSK9 will recognize LDL-receptors (LDLR) on cancer cells. PCSK9 is expressed in several organs, particularly the liver and also the intestines and the kidney. PCSK9 acts on the LDLR primarily as a secreted factor and promotes the reduction of LDLR protein concentrations. Cells internalize cholesterol from circulating LDL through the LDLR on the cell surface. Increased LDLR expression to support the continuous proliferation of the cancer cells has been linked with poor patient survival. Elevated LDLR expression on tumor cells ensures site-specific delivery of the drugs via PCSK9-Linked-Liposomes. On recognition, the liposomes will deliver the drugs to the cell interior where their targets lie.

Findings: The results of *in-vitro* studies indicated that PCSK9-PTX-liposomes had shown favorable cytotoxicity activity when compared with the PTX-liposomes not conjugated with PCSK9. In comparison with PTX-liposomes, the cell treated with the PCSK9-PTX-liposomes has shown to have higher accumulation of PXT and better cytotoxic effects. The cytotoxic effect of the PCSK9-PTX-liposomes was found to be lower in the non-cancerous cells when compared with the cancerous cells. This was because of the fact that they express less LCLR compared to the cancerous cells.

Conclusions: These results suggest that PCSK9-PTX-liposomes would serve as a potent PTX delivery vehicle for future cancer treatment and represent a suitable platform for the development of targeted-liposomal-PTX systems.

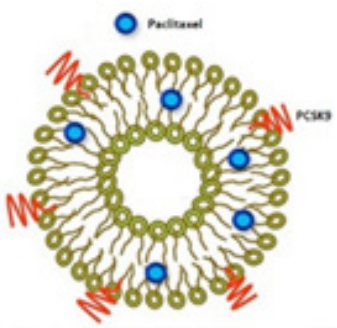

Figure 1. PCSK9 Conjugated Paclitaxel Loaded Liposome

Recent Publications

1. Gallagher E J, Zelenko Z, Neel B.A, Antoniou I M, Rajan L, Kase N, LeRoith D (2017) Elevated tumor LDLR expression accelerates LDL cholesterol-mediated breast cancer growth in mouse models of hyperlipidemia. Oncogene 36: 6462–6471.
2. Harisa GI, Alanazi FK, 2014. Low density lipoprotein bionanoparticles: From cholesterol transport to delivery of anti-cancer drugs. Saudi Pharm. J. 22, 504–515.
3. Kwon HJ, Lagace T, McNutt, M.C, Horton J.D, Deisenhofer J (2008) Molecular basis for LDL receptor recognition by PCSK9. Proc Natl Acad Sci U S A. 105:1820–5.
4. Lambert G, Charlton F, Rye KA, Piper DE (2009). Molecular basis of PCSK9 function. Atherosclerosis: 203, 1–7.
5. Sobot D, Mura S, Rouquette M, Vukosavljevic B, Cayre F, Buchy E, Pieters G, Garcia-Argote S, Windbergs M, Desmaële D, Couvreur P (2017) Circulating Lipoproteins: A Trojan Horse Guiding Squalenoylated Drugs to LDL-Accumulating Cancer Cells. Mol Ther 25: 1596–1605.

Biography

Nitin B. Charbe is a Conicyt Postdoc Fellow at the Pontificia Universidad Catolica de Chile, Santiago, Chile. He received his PhD. in Pharmacology in 2016 from University of Milan, Italy. His PhD. work examined the usefulness of the therapeutic drug monitoring of antiretroviral drugs in optimizing HIV treatment. In March 2018 he joined the Department of Pharmacy and Chemistry at the Pontificia Universidad Catolica de Chile as a CONICYT POSTDOC 2018 Fellow (No 3180250) where his research focus is on the development of the nanoparticles for the targeted drug delivery to cancer cells.

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