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Cholesterol conjugated HDAC inhibitor as novel anti-cancer agent

College of Sciences and Health Professions

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Abstract

Histone deacetylase (HDAC) inhibitors are a class of promising new multifunctional anticancer agents. These agents are able to affect multiple epigenetic changes in aberrant cells. In addition to regulating the gene expression and transcription via chromatin remodeling, HDAC inhibitors can also modulate a variety of cellular functions including proliferation, differentiation, and apoptosis. Vorinostat (Suberanilohydroxamic Acid, SAHA), the first HDAC inhibitor approved by FDA, inhibited the metastasis of various cancer cells. However, SAHA distributes in cancer tissue and normal tissue in a similar level. It will be ideal to selectively delivery SAHA into cancer cells. Rapidly growing cancer cells have a great need for cholesterol to generate new membranes. Increased low-density lipoprotein (LDL)-uptake by tumor cells has been found. LDL is the major cholesterol carrier in plasma and its uptake is mediated by the LDL-receptor (LDL-R), a glycoprotein overexpressed on the surface of cancer cells. Cholesterol can be used as a delivery agent to enhance anti-cancer drugs penetrating cancer cell membrane via LDL-R. Degradation of LDL particles by endosomal enzymes will result in the release of the conjugates to target cancer cells. Herein, we designed and synthesized SAHA cholesterol conjugate, and tested the anti-cancer activity of SAHA and its conjugate. The results suggest that cancer cells uptake more cholesterol SAHA conjugate when the culture medium does not contain LDL. Based on the information, we will design and generate artificial LDL containing SAHA cholesterol conjugate to enhance the drug delivery.