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Role of cholesterol transporters, ABCA1 and ABCG1 in Cholangiocarcinoma

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Abstract

Cholangiocarcinoma (CCA) has a high prevalence in Thailand and Southeast Asia. It's abrasive and hasn't been thoroughly researched. The role of cholesterol transporters, ATP-binding cassette (ABC) A1 and ABCG1 in the HuCCA-1 cell line is investigated in this study. The ABCA1 and ABCG1 transporters are thought to be involved in maintaining CCA lipid homeostasis. Methodology: Western blot analysis and immunocytochemistry were used to evaluate the expression and localization of ABCA1 and ABCG1, respectively. To pinpoint cholesterol acceptor and high-density lipoprotein, the characteristics of ABCA1 and ABCG1 in CCA cells were investigated using a cholesterol efflux assay (HDL). The ABCG1 transporter was inhibited by siRNA interference. Wound repair and cholesterol efflux tests, respectively, revealed cell phenotypic alterations such as cell motility and cholesterol export potential. ABCA1 and ABCG1 transporters were found to be expressed in HuCCA-1 cells. ABCA1 was previously found to be localised around the nucleus, whereas ABCG1 was shown to be more distributed throughout the cytoplasm. Furthermore, cholesterol exports to HDL via ABCA1 and ABCG1 were found. While ABCG1 level was down regulated, the retention of ABCA1 expression used to be illustrated. The manipulated and ABCG1 silenced cells were found to be in similar stages of cell migration. Furthermore, there was no difference in cholesterol efflux to HDL across these therapies. The expressions of ABCA1 and ABCG1 in CCA, as well as their cholesterol export activity, were discovered in this study. There were no clear movable phenotypic features like wound healing or cholesterol efflux when ABCG1 was silenced. This establishes the ABCA1 transporter's viability and importance in CCA, which necessitates further investigation. This study gives some light on cholesterol biology and a potential treatment target in CCA. Cholangiocarcinoma (CCA) is a type of adenocarcinoma that starts in the bile duct epithelium and progresses to cancer. CCA can be divided into three types: intrahepatic, perihilar, and distal CCA. CCA's pathogenesis is poorly understood, and more research is needed. Furthermore, CCA's global incidence and mortality rates have improved in recent decades, and it now constitutes for 3% of all gastrointestinal malignancies. Due to the endemic parasite biliary tract infestation, it is also surprisingly widespread in Southeast Asia, particularly Thailand. Early diagnosis of CCA is difficult due to a lack of excellent biomarkers. Symptoms may not appear until the cancer has progressed to a level where it can cause serious consequences. Chronic liver illness, hepatolithiasis, persistent biliary irritation, and cholestasis have all been linked to the development of CCA in previous studies. During liver inflammation, a rise in cholesterol was detected, resulting in significant cell damage. This demonstrates that cholesterol plays a significant role in liver damage. Hepatocytes secrete bile, which contains cholesterol, phospholipids, bilirubin conjugates, bile salts, and toxic compounds and travels down the bile duct to the gallbladder or small intestine. Excess cholesterol is expelled through the bile and expelled in the stool. Cholangiocytes can passively transport certain cholesterols and unconjugated bile acids. Cholangiocytes play an important part in increasing and delivering bile to its destination by secreting bicarbonate and water, which prevents bile acid diffusion and keeps the cell's osmolality stable. Cholangiocytes maintain cholesterol homeostasis and form a connection to protect the hepatic interstitial tissue from toxic substances and bile released by the liver. Cholangiocytes were overexposed to bile lipid contents and hazardous chemicals when cholestasis was caused by bile duct obstruction. Oxysterols have been found to be increased in the bile acids of people who have biliary tract irritation. They're cholesterol oxidation products in human bile and hedgehog signalling pathway activators that help CCA cells proliferate, migrate, and invade. Cholesterol transport is an important part of cellular homeostasis. In a variety of cell types, ATP-binding cassette (ABC) A1 and ABCG1 are well-characterized as cholesterol transporters. ABCA1 carries cholesterol and phospholipids to apolipoprotein A-1 (ApoA-1), whereas ABCG1 delivers cholesterol to mature HDL (HDLABCA1 dysfunction is linked to atherosclerosis in this setting. In macrophages, cholesterol build up lowers the amount of ABCA1, which improves intracellular cholesterol extra. This results in inflammation and cell death, which leads to atherosclerosis. Furthermore, in prostate cancer, epigenetic modification of promoter hyper methylation disrupts the ABCA1 feature. The build-up of intracellular cholesterol is aided by a reduction in ABCA1 export capacity. Prostate cancer development and aggressiveness are linked to large cholesterol pools. This emphasises the importance of ABCA1 and cholesterol in the development of illnesses and malignancies.

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