Investigations of Lipid Droplets Role in Attenuating Chemotherapeutic Responses to 5-FU in Cancer Cells in vitro

Duaa Sabbah

Petra University, Jordan.

DOI: https://doi.org/10.35516/jjps.v16i2.1509

ABSTRACT
Cancer has been considered as a main cause of death worldwide. Despite the effectiveness of traditional anticancer therapies such as 5-Flurouracil (5-FU), poor therapeutic outcomes are reported in many cases, due to tumor recurrence and chemoresistance. Intracellular lipid accumulation as lipid droplets (LDs) is now a well-recognized hallmark of cancer. However, the influence of LDs accumulation in cancer progression and treatment remains to be elucidated. Adjuvant use of non-chemotherapeutic drugs (e.g. NSAIDs and corticosteroids) with anticancer drugs to manage cancer related symptoms, may though serve as factors modulating the therapeutic response to anticancer agents via LDs related mechanisms. The aim of this study is to evaluate possible strategies influencing chemoresistance by attenuating LDs biogenesis and function. LDs levels in eight human cancer cell lines were measured. The existence of correlation between the cellular levels of LDs and cytotoxicity of ten chemotherapeutic agents was evaluated. A moderate correlation between basal LDs levels and the half inhibitory concentration (IC50) values of 5-FU on selected cell lines was established ($r^2 = 0.5235$). Nevertheless, LDs levels were significantly elevated following exposure to 5-FU. A549 human lung cancer cells showed the highest increase in LD accumulation (***P >0.001) compared to their basal levels of LDs. LDs levels were also assessed following exposure to 5-FU in the presence of sub-lethal doses of celecoxib (CXB), dexamethasone (DEX), and simvastatin (SMV). Interestingly, CXB and DEX exposure to 5-FU treated cells resulted in an alleviation in the antiproliferative activities of 5-FU in MDA-MB-468 and HCT116 but not in A549 cells. While, SMV exposure to 5-FU-treated cells resulted in reduced antiproliferative activities of 5-FU in MDA-MB-468 only. These results strongly suggest that increased LDs levels caused by CXB, DEX, and SMV may contribute in the development of a resistance mechanism exist only in some cancer types, which therefor, attenuates responses to 5- FU. The inhibition of phospholipid metabolism by DEX, as well as the inhibition of 3-hydroxy-3- methylglutaryl-CoA reductase (HMGCR) by SMV were expected to result in the up regulation of triacylglycerol (TAG), leading to LDs accumulation. This study highlights the importance of assessing drug-drug interaction before designing integrated therapy regimens for cancer patients receiving 5-FU treatment. Further studies are needed to discover the role of TAG inhibition on the sensitivity of cancer cells against 5-FU.