Modulating cellular cholesterol for anticancer therapy

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Cholesterol is a crucial life-supporting molecule, however, cholesterol dyshomeostasis in cancer cells leads to intracellular cholesterol accumulation, which allows cancer cells to evade cell death mechanisms, thus promoting cell division and proliferation. To further facilitate cancer cell proliferation, the accumulated cholesterol may impart drug resistance, leading to failed therapeutic outcomes. This knowledge gained in the past decade through scientific studies suggests to curb the level of intracellular cholesterol in cells, therefore, cholesterol lowering in cancer cells can been envisaged as a potential anticancer strategy. In this direction, two therapeutic strategies have been proposed: (a) to inhibit the biosynthesis of cholesterol in the cells and (b) to deplete excess cholesterol from cancer cells. My lab focuses on the latter and we have generated significant amount of data to demonstrate that depleting cholesterol from cancer cells significantly inhibits their growth both in vitro (in both breast and colorectal cancers) and in vivo (breast cancer). We have identified a cholesterol depletor as a potential anticancer therapeutic molecule, which will be tested in a clinical trial in the next year. We have attempted to understand the role of various molecuar players involved in cancer related pathways that can modulate or regulatecholesterol level in cancer cells. Additionally, by generating new scientific evidences, we conceptualize and argue that the depletion of excess cholesterol could sensitize cancer cellsto available therapeutics, and may also help to alleviate cancer drug resistance, while identifying new potential anticancer therapeutic molecules.

References:

1. Gu L, Saha ST, Thomas J, Kaur M. Targeting cellular cholesterol for anticancer therapy. FEBS J. 2019 Nov;286(21):4192-4208. doi: 10.1111/febs.15018.
2. Monchusi B, Kaur M. microRNAs targeting cellular cholesterol: implications forcombating anticancer drug resistance. Genes Cancer. 2020;11(1-2):20-42. doi: 10.18632/genesandcancer.202.
3. Monchusi B, Kaur M. miRNAs as Modulators of Cholesterol in Breast Cancer Stem Cells: An Approach to overcome Drug Resistance in Cancer. Curr Drug Targets. 2021Oct 8. doi: 10.2174/1389450122666211008140811.
4. Abdulla Naaziyah, Vincent C. Theresa, Kaur Mandeep. Mechanistic Insights Delineating the Role of Cholesterol in Epithelial Mesenchymal Transition and Drug Resistance in Cancer. Frontiers in Cell and Developmental Biology. 2021. 9; 3282, doi=10.3389/fcell.2021.728325.

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