Establishing Organoid Cultures to Delineate the Biological Mechanisms of Drug Resistance in a South African Colorectal Cancer (CRC) Cohort

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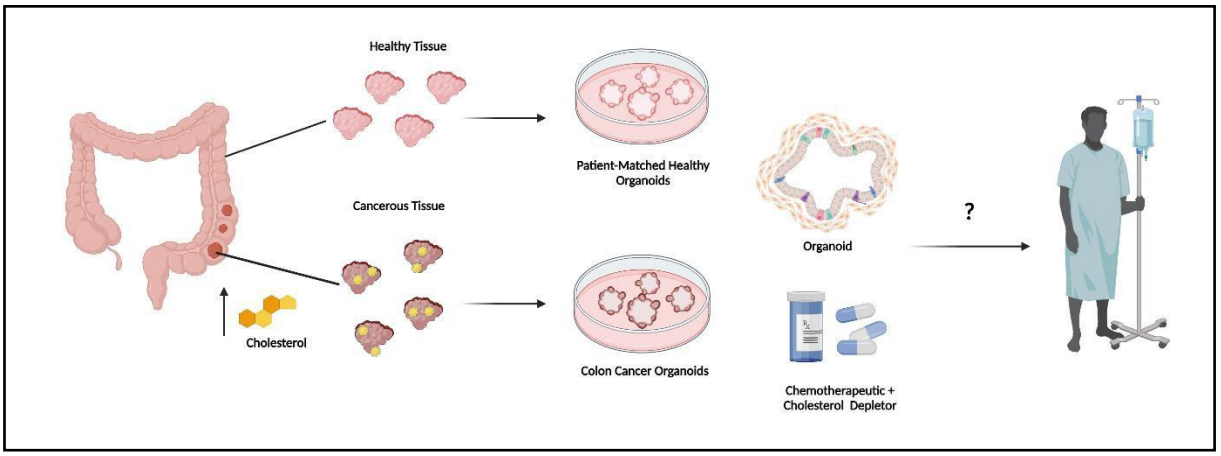

Scientific evidence exists highlighting deregulated cholesterol metabolism in CRC. This study aims to address the molecular link governing cholesterol-mediated drug resistance in CRC. By employing cholesterol depletion in organoids, the role of cholesterol in facilitating aggressive disease phenotype will be delineated. Seeing that human cellular physiology can be mimicked more accurately this will facilitate direct translation to a clinical setting (Figure created using Biorender.com)

Introduction: Colorectal cancer (CRC) presents a significant burden worldwide and is particularly diagnosed at a later stage where administration of chemotherapeutics proves ineffective, due to the acquisition of drug resistance. Previous studies conducted in our laboratory identify a crucial role of cholesterol in mediating drug resistance in breast cancer (BC). In cases of CRC, deregulation of multiple cholesterol homeostasis genes is implicated in disease pathophysiology.

Methodology: Patient-derived tumors, obtained from a South African cohort with colorectal adenocarcinoma, and matched healthy controls were dissociated into crypts employing a combination of chemical and mechanical digestion for the generation of patient-derived organoids. Crypts were subsequently seeded in domes and cultured over a period of 6 days. Optimization of this protocol is being completed with the ultimate intention of elucidating mechanisms governing cholesterol- mediated drug resistance.

Results: The current protocol employed is efficient in yielding colonic crypts. This protocol will be further optimized to ensure dome formation remains intact to facilitate testing of chemotherapeutic and cholesterol depletory agents to delineate the molecular link governing cholesterol-mediated drugresistance as a novel means of treating CRC.

Discussion: Cancer cells adopt intricate mechanisms to mediate drug resistance. Scientific evidence exists highlighting deregulated cholesterol metabolism in CRC. Importantly no study to date has addressed the molecular link governing cholesterol-mediated drug resistance in CRC more so in a South African population. By employing cholesterol depletion in organoids, the role of cholesterol in facilitating aggressive disease phenotype will be delineated and could serve as a novel means of targeting CRC.

Keywords: Cholesterol, Cancer, Drug Resistance, Organoids, Cholesterol Depletion

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