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Investigation of 5-FU Nanocarriers Cytotoxicity on HT-29 Cells Cultured in a Biomimetic Tumor-on-a-chip Platform †

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Abstract: Despite the rapid development of numerous drug-delivery systems that hold promise in improving the stability and solubility of their drug payload and enhancing the active concentration of the drug that reaches the tumor tissue, the *in vitro* assessment of treatment safety and efficacy is hindered by the lack of accurate cancer preclinical models that can emulate the 3D hierarchical complexity of *in vivo* tumors and their microenvironment. A solution to this critical issue is represented by implementing the cutting-edge organ-on-a-chip technology that presents numerous advantages compared to other 3D cell culture models. Organ-on-a-chip is microfluidic devices that recapitulate the *in vivo* microenvironment, including the 3D architecture of the tissues. In this view, our study aimed to develop and validate a dynamic biomimetic tumor-on-a-chip platform and employ it to further investigate the response of colorectal tumor cells to 5-fluorouracil (5-FU)-loaded nanocarriers. Thus, adenocarcinoma colorectal tumor cells (HT-29 cell line) were seeded at different initial densities in various extracellular matrices (Matrigel, collagen) in commercially available organ-on-a-chip platforms. At different time points, the cell viability and morphology were assessed by fluorescence microscopy to determine the optimal cell seeding density, extracellular matrix composition, and perfusion parameters. Then, different concentrations of 5-F loaded polymeric nanoparticles were perfused to the validated colorectal cancer tumor-on-chips to determine the lethal dose of 50. More, the impact of 5-FU loaded nanoparticles on cell morphology, health, and proapoptotic potential was further investigated by fluorescence microscopy and flow cytometry assays. Our results showed that HT-29 cells cultured in biomimetic tumor-on-a-chip platforms respond differently to the treatment than 2D cell cultures.

Keywords: organ-on-a-chip; colorectal cancer modeling; drug-delivery systems.

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Conflicts of Interest

The authors declare no conflict of interest.