High Content Analysis and Targeting Cancer-Specific Pathway in Three Dimensional Breast Cancer Tumor Spheroids

Arora, Arjun

Patients with inflammatory breast cancer (IBC) have a very poor prognosis. Their tumors are not responsive to chemotherapy. Previous studies have suggested that metastasis in IBC is driven by the formation of tumor spheroids, which are specialized multicellular structures that collectively migrate and spread to distant organs. It is therefore critical to understand how cells in the tumor spheroids evade the process of programmed cell death to develop novel anti-cancer drugs to target these mechanisms. The objectives of this study were to: 1) define characteristics of tumor cell spheroids that enable them to resist therapy, 2) use a novel 3D in vitro model of spheroid formation to identify therapeutic strategies to treat them. This study focused on the molecular and phenotypic characteristics that promote their survival by evaluating expression of anti-cell death proteins in breast tumor tissue microarrays, developing a high content assay, and then applying this assay to identify compounds that induce cell death and inhibit tumor spheroid formation. Immunohistochemistry analysis showed that the IBC tumor spheroids express high levels of a potent anti-cell death protein, X-linked Inhibitor of apoptosis protein (XIAP), and the nuclear transcription factor, NFKB, a pro-cell survival protein. The 3D IBC tumor spheroid-high content assay developed was used to identify novel XIAP and NFKB inhibitors that target tumor spheroids. Translation to clinical applications will require further testing of these identified compounds in preclinical drug development models. The 3D tumor spheroid-high content assay can be used to simulate the tumor microenvironment, and facilitate high-throughput drug screening.

Awards Won:
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