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Research project L4-4565

Development of new *in vitro* 3D mono and co-culture models of high grade serous ovarian cancer for drug testing and development of new targeted and stratified therapies

Principal investigator: Ivana Jovchevska

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Project group: SICRIS

Project description:

Ovarian cancer (OC) is one of the most devastating and lethal malignancies, occurring primarily in postmenopausal patients. It is diagnosed at an advanced stage due to unspecific symptoms and the cure rate remains approximately 30%. This is mainly due to the late diagnosis of OC in the stage of metastasis (stage III or IV) or the recurrence of cancer after the beginning of treatment. During metastases, individual cells or clusters of cells originating from the tumor spread with peritoneal fluid through the abdominal cavity, forming multicellular tumor spheroids or aggregated tumors. This is difficult to reproduce *in vitro* using traditional, oversimplified 2D monolayer cell cultures because they do not express the cellular surface proteins (cadherins and integrins) required for metastasis. What is more, the pre-clinical screening of new compounds using traditional 2D cultures and animal models are also associated with low correlation of the data obtained in clinical trials as well as ethical aspects. These factors may lead to inaccurate prediction of drug responses *in vivo*. There is also plenty of evidence that the tumor microenvironment is critical for tumor physiology and pharmacological responses to drug treatments *in vivo*. Most patients with OC develop recurrence after first line treatment, which depends on the tumor complexity and also surrounding tumor microenvironment.

Around 70% of all OC cases are high grade serous ovarian cancers (HGSOC) that can be further subtyped by molecular genetic characteristics to proliferative, immunoreactive, mesenchymal and differentiated subtype. While personalized and targeted therapies still need to be implemented, molecular characterizations studies of HGSOC have also shown that patients with mesenchymal and proliferative subtype would benefit from Bevacuzimab, a monoclonal antibody against the vascular endothelial growth factor, while did not support the use of this drug in other two types of HGSOC. Moreover, Nivolumab, an anti-programmed cell death protein 1 monoclonal antibody that works as immune checkpoint inhibitor, could be used for treatment of immunoreactive subtype. It has also been suggested that patients with mesenchymal subtype of HGSOC would benefit from PPAR inhibitors.

The aim of our study is to establish and characterize *in vitro* 3D models of HGSOC cell lines and compare them to 2D cell models. We will also investigate the effects of different chemotherapeutics on cell proliferation, migration, and invasion of cells. Model cell lines of HGSOC Kuramochi, COV362, OVCAR-4 and OVSAHO will be employed. Prepared sferoids will next be bioprinted together with mesenchymal cells or fibroblast and components of extracellular matrix to form co-culture models that will allow us to better capture tumor microenvironment. Prepared 3D models would be ideal for screening a big number of drug targets, they could be used as a high-throughput screening platform or for studies of tumor microenvironment.

The phases of the project and their realization:

Months 1-27: Establishment and characterization of *in vitro* 3D models of HGSOC cell lines with different preparation techniques and comparison with 2D cell models. Investigation of the effects of various drugs.

Months 11-36: Establishment and characterization of a 3D co-culture cell model of OC for the studies of cytotoxicity and /or invasion upon treatment with various drugs.

Bibliography: **SICRIS**