BREAST CANCER ORGANOIDS AND THEIR POTENTIAL IN PERSONALIZED MEDICINE

Lenka Trnkova[1,2], Svetlana Miklikova[1], Jana Plava[1], Lucia Rojikova[1], Marina Cihova[1]

[1]*Department of Molecular Oncology, Cancer Research Institute, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia*
[2]*Department of Genetics, Faculty of Natural Sciences, Comenius University in Bratislava, Bratislava, Slovakia*

Experimental model of cancer organoids is relatively novel *in vitro* cell culture approach which is getting increased attention in recent years due to its multiple advantages over classic cell line cultures. Cancer organoids are derived from individual patient and thus preserve specific patient characteristics including genetic and histological profile, inter- and intra-tumor heterogeneity and pharmacotherapy response while offering advantages of *in vitro* manipulation. This methodology is currently used in number of cancer types including colorectal, lung, liver, prostate or bladder cancer and the method has been recently adjusted for establishment of organoids from breast cancer. A significant benefit of cancer organoids is their recapitulation of treatment response of individual patient which provides potential for their clinical use and as an approach for personalized medicine. In these settings, cancer organoids can be used for decision of the most appropriate therapy in the cases of progressive disease or in the patients who did not respond to previously selected therapies. Additionally, they can supplement diagnostic approaches and treatment decision that are based on genetic testing and gene expression analysis of the tumor. Some studies have already described cancer organoids as a tool for drug testing either in the form of single case studies or more robust drug screens. However, drug testing with breast cancer organoids has not yet been described in broad extent since number of studies is still limited by the novelty of this model.

Presented work describes derivation of cancer organoids from metastasis located on the ovary of a patient with invasive lobular breast carcinoma. Established breast cancer organoid culture was used for pilot drug testing with potentially effective drugs selected according to the data available from genetic analysis of the patient tumor. Selected drugs consisted of everolimus, crizotinib, exemestane and letrozole applied in adjusted concentration range to breast cancer organoid culture and sensitivity of breast cancer organoids was measured by cell luminescence viability assay. Furthermore, breast cancer organoids were successfully orthotopically transplanted to immunodeficient mice to generate patient-derived xenograft model. Growth of the mice xenograft from breast cancer organoid culture was enhanced by subcutaneous implantation of estrogen pellet on the back of the animal prior to organoid xenotransplantation. Derived mice xenografts were used for pilot testing of *in vivo* response to everolimus. Finally, sensitivity of *in vitro* breast cancer organoids to drug treatment was compared to the sensitivity of classic monolayer cell line culture representing similar hormone receptor-positive subtype of breast cancer.

In conclusion, breast cancer organoids can be successfully established from metastatic sample of breast carcinoma and can be used for *in vitro* applications and *in vivo* mouse xenotransplantation to generate patient-derived xenografts. Moreover, breast cancer organoids represent clinically relevant model suitable for drug testing with potential use in personalized medicine.

This work is supported by VEGA grant No. 2/0138/20, EraCoSysMed project RESCUER, Slovak Research and Development Agency under the contract No. APVV-16-0178, VEGA grant No. 2/0067/22, Grant programme for SAS PhD students no. APP0327, and by the Slovak League Against Cancer.