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Modele 3D jako alternatywne metody badań lekooporności nowotworów

Rozprawa na stopień doktora nauk medycznych i nauk o zdrowiu

w dyscyplinie nauki medyczne

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Abstract

Syngeneic animal models are highly valuable tools in cancer therapy research. However, they cannot always be used, due to their high cost or for ethical reasons. Therefore two-dimensional cell culture models are often chosen. This method has many advantages, but does not take into account many important aspects of natural tumor microenvironment. Three-dimensional cultures can be an alternative to these methods. So far, many of them have been developed, but due to various factors, e.g. high cost or the difficulty of recreating, complicated techniques, the wide application of 3D in cell research is limited. The aim of this study was to develop a universal and simple three-dimensional model that will mimic the phenomena occurring in the tumor microenvironment. Emphasis was placed on: three-dimensional tumor shape, proper oxygen pressure and induction of mechanisms increasing tumor aggressiveness (such as: CSC, EMT). In addition, the developed model should be an easy alternative to drug research. In order to verify the universality and usefulness of the proposed model, two animal tumor models with different mechanisms of action were used - melanoma (B16F10) and kidney cancer (RenCa). The developed models were compared with the corresponding syngeneic mouse models and two-dimensional models. A number of tests were performed with the use of therapeutics with different mechanisms of action (everolimus, cisplatin, doxorubicin). It was shown that the melanoma model and kidney cancer in three-dimensional cultures are characterized by different mechanisms related to cancer progression - in renal cancer, the population of CSC cells increased, while in the melanoma model, the EMT phenomenon was induced. It has been proven that the proposed models reflect the tumor microenvironment in terms of the assumed features. It was shown that skin tumor spheroids showed a lower sensitivity to all applied drugs, while renal tumor displayed only a lowered sensitivity to doxorubicin. It was found that the difference in drug sensitivities between 2D and 3D cultures, does not result from the three-dimensional shape of the spheres or by the expression of MDR1 and mTor. The increase in the expression of genes belonging to the cytochrome p450 related pathways was verified by the NGS analysis and qPCR in both spheroids models. Although no changes causing drug resistance in spheroids have been identified, it has been shown that the 3D method of culture can be important for cancer physiology studies. It can be used for patient cell testing as a clinically relevant and easily available mean.