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Tumor Cell Behavior in Porous Hydrogels: Effect of Application Technique and Doxorubicin Treatment

M. H. Zoughaib, D. T. Luong, Z. Y. Siraeva, A. A. Yergeshov, T. I. Salikhova, S. V. Kuznetsova, R. G. Kiyamova, and T. I. Abdullin

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The effect of porosity on diffusion characteristics of scaffolds and invasive capacity of MCF-7 and PC-3 tumor cells was studied for gelatin hydrogels. According to MTS test results, the efficiency of population of a macroporous cryogel by cells applied by different techniques increased in the following order: migration from the monolayer<surface adhesion<<injection. Tumor cells in the cryogel differed by the migration and aggregation activity; injection route ensured a more uniform and dense population. In the cryogel-based culture, the cytotoxic effect of doxorubicin was 3-lower than in monolayer culture, which can be explained by supporting effect of the scaffold on cell growth and clustering. The results are of interest for the creation of tumor models and grafts with controlled properties.

Key Words: *3D models of tumors; porous hydrogels; tumor cells; scaffold population and analysis; doxorubicin resistance*

Creation of informative models for the study of the properties of tumor cells and tissues, detection of their drug resistance, and screening of anticancer drugs is an urgent problem of cell technologies. Traditional cultures of adhesion cells grown on plastic are often used in fundamental and applied studies [9,21]. It is known that these cultures undergo significant phenotypic changes due to reduction of cell—cell and especially cell—scaffold interactions, which often limits their application for creation of relevant models of human tumors [4,13,30].

A promising approach is the use of tissue-like materials consisting of extracellular scaffold components that form native microenvironment for tumor cells [12]. These materials usually represent cross-linked macromolecular hydrogels corresponding by their physical and chemical properties to soft tissues [2]. Hydrogel scaffolds for tumor cells have been developed based on collagen [3], fibrin [8], laminin [28], hyaluronic acid [10], and other polysaccharides [23], as well as their combinations with synthetic polymers [6]. These scaffolds differ by their properties and fabrication techniques. However, collagen-containing hydrogels remain the most popular reference biomaterial used both in pharmacological analysis and for strengthening the oncogenic potential of tumor cells intended to *in vivo* implantation [5,29].

The typical disadvantages of most biomaterials, extracellular scaffold derivatives, are variability and anisotropy of the structure/properties of hydrogels [3], potential immunogenicity of biopolymers [25], and significant hypoxia [22] limiting the growth of incorporated living cells and the formation of tissue-like structures. Therefore, technologies of designing improved biomaterials characterized by high availability for mammalian cells and allowing effective control over structural characteristics and regulation of cell activity became a new trend in this field [23,30].

A promising "platform" for the creation of these biomaterials are cryogels. *i.e.* hydrogels with well-developed system of interconnected pores resulting from cryopolymerization [17,20,23]. Recent studies have demonstrated significant potential of single-component and composite cryogels in the creation of

Kazan (Volga region) Federal University, Kazan, Republic of Tatarstan, Russia. ***Address for correspondence:*** tabdulli@gmail.com. T. I. Abdullin

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