Effects of preparation condition of tumor cell-derived matrices on chemoresistance

T. Hoshiba[1, 2] and M. Tanaka[1].
[1]Graduate School of Science and Engineering, Yamagata University,
[2]International Center for Materials Nanoarchitectonics, National Institute for Materials Science

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Statement of Purpose: Chemotherapy is one of the important treatments for tumor. And anti-cancer drug is a key of chemotherapy. However, it is difficult to develop new anti-cancer drugs because of insufficient *in vitro* screening. Chemoresistance of tumor cells generally gets lower *in vitro* than *in vivo*, leading insufficient in vitro screening. To overcome this problem, there are many efforts to increase chemoresistance of tumor cells cultured *in vitro*. Focusing on extracellular matrix (ECM) is one of the important approaches because ECM regulates various cell functions such as cell survival, proliferation, and chemoresistance.

It has been well known that the matrices mimicking *in vivo* ECM strongly induced cell functions and decellularization technique is useful for the preparation of matrices mimicking *in vivo* ECM[1]. We have previously reported that cells deposit ECM proteins beneath the cells and these deposited ECM proteins can be prepared as the matrices mimicking *in vivo* ECM by decellularization technique. These cell-derived matrices can also induce cell functions as well as the matrices prepared by the decellularization of tissues[1]. And tumor cell-derived matrices can increase their chemoresistance[2]. However, it is unclear how cell sources for matrices preparation influence chemoresistance on tumor cell-derived matrices. Moreover, protein adsorption on the substrates influences ECM formation of cells cultured *in vitro*. Therefore, it is possible to change chemoresistance on tumor cell-derived matrices prepared on different initial substrates. In this study, we compared chemoresistance of tumor cells against 5-fluorouracil (5-FU) cultured on the matrices prepared by tumor cells derived from tumor cells with different tissue sources and malignancy. Also, we compared the chemoresistance on the matrices prepared on initial substrates which exhibit different characteristics of protein adsorption.

Methods: Breast tumor cell lines, MDA-MB-231 (invasive), MCF-7 (non-invasive) and MCF-10A (benign) cells, and colon tumor cell lines, HT-29 (invasive), SW480 (non-invasive), and CCD-841-CoN (a normal colon epithelial cell model) were cultured on tissue culture polystyrene (TCPS) for 2 weeks to prepare tumor cell-derived matrices. In addition to TCPS, the cells were cultured on poly (2-methoxyethyl acrylate) (PMEA) and poly (tetrahydrofurfuryl acrylate) (PTHFA) which showed different characteristics of protein adsorption[3]. After cell culture, the cells were specifically removed from the matrices by decellularization technique. To evaluate chemoresistance against 5-FU on the matrices, tumor cells were seeded on the matrices and cultured. After 1 day culture, the cells were started to be exposed with 5-FU and were cultured for further 3 days. Viable cells were measured by WST-8 after the culture.

Results: The chemoresistance of MD-MB-231 and HT-29 cells against 5-FU increased on the matrices prepared by MDA-MB-231 and HT-29 cells, respectively (Fig. 1). These results suggest that chemoresistance of tumor cells against 5-FU increased on the matrices prepared by the cells derived from original tissue.

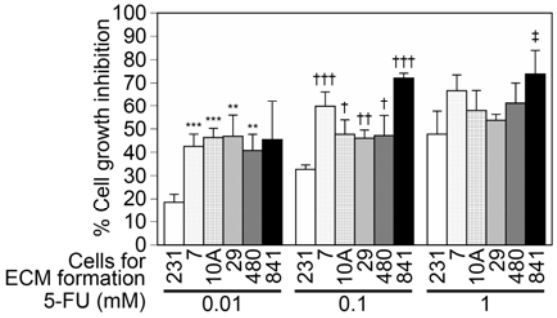

Fig. 1: Chemoresistance of MDA-MB-231 cells against 5-FU on various tumor cells-derived matrices. 231, 7, 10A, 29, 480, 841 indicate MDA-MB-231, MCF-7, MCF-10A, HT-29, SW480, CCD-841-CoN, respectively. Data represent mean ± SD (n=3).

As a next step, we compared the chemoresistance of MCF-7 and SW480 on tumor cell-derived matrices to examine the effects of malignancy of the cells for matrices preparation. The chemoresistance of MCF-7 and SW480 cells increased on the matrices prepared by MDA-MB-231 and HT-29 cells, respectively. These results suggested the chemoresistance of tumor cells increased on the matrices derived from tumor cells at high malignancy. Finally, we compared the chemoresistance on tumor cell-derived matrices prepared on TCPS, PMEA, and PTHFA. The chemoresistance of MDA-MB-231 and HT-29 cells increased on the matrices prepared on PTHFA, indicating that initial substrates for matrices preparation influence the chemoresistance on tumor cell-derived matrices.

Conclusions: In this study, we demonstrated the importance of tissue sources and malignancy of tumor cells for the matrices preparation. In addition, our study clearly demonstrated that initial substrates influenced the chemoresistance on tumor cell-derived matrices, suggesting that selecting adequate initial substrates is one of the methods to improve tumor cell-derived matrices functions.

References:

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