Poster

[P25-11] P25-11: Clinical toxicology (1)

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[P25-11-8] In vitro treatment of induced pluripotent stem cells with retinoic acid for the placental drug transport evaluation model

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Background

Although evaluation of placental drug transport is the first step of chemotherapeutic safety evaluations during pregnancy, an *in vitro* model has not been well established. We previously reported that a trophoblast layer model using differentiating choriocarcinoma JEG-3 cells could be used for placental drug transport studies (K. Ikeda, et al., Basic Clin. Pharmacol. Toxicol., Vol. 108, p138, 2011; Pharamazie, Vol. 70, p471, 2015). However, improving the similarities between the syncytiotrophoblast and *in vitro* evaluation model for use as a marker of placental drug transport was necessary. We focused on the *in vivo* similarities of differentiating induced pluripotent stem cells (iPSCs). iPSCs can achieve a syncytiotrophoblast-like form and secrete human chorionic gonadotropin (hCG) after treatment with high levels of bone morphogenetic protein 4 (BMP4) for 5 days. However, the iPSCs differentiated by BMP4 included various mature tissue cells. Retinoic acid (RA) is also a differentiation reagent of iPSCs. The iPSCs differentiated by RA mainly include mature hematopoietic cells. Therefore, the syncytiotrophoblast could be isolated as adherent cells by differentiation with RA. In this study, the conditions required to differentiate iPSCs to syncytiotrophoblasts were investigated using hCG secretion and transepithelial electric resistance of cell layers as markers of syncytiotrophoblast cell layers. Moreover, the advantages of RA stimulation to iPSCs were investigated for the syncytiotrophoblast model.

Methods/Results:

iPSCs secreted hCG after treatment with BMP4 (100 ng/mL) and RA (150 ng/mL) for 5 days, reaching a peak on day 7. After 7 days, hCG secretion from the iPSCs differentiated by BMP4 stimulation and RA stimulation was equivalent. The iPSCs differentiated by RA were reseeded, and these cells reached confluence, and maintained a syncytiotrophoblast-like morphology.

Conclusions

We demonstrated that iPSCs differentiate into syncytiotrophoblasts, characterized by marked hCG secretion after high level BMP4 and RA treatment for 5 days. However, for the placental drug transport model, a dense cell layer is necessary. In future studies, we would establish efficient maintenance culture conditions for placental drug transport evaluation studies with RA treatment to iPSCs.