Title of Research:

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Development of the Novel Method with iPSCs to Assess Chemical Compounds for the Risk of CSC Induction

Principal Investigator:

Masaharu Seno, PhD (Professor, Graduate School of Natural Science and Technology, Okayama University) 3.1.1 Tsushima-Naka, Kita, Okayama 700-8530, Japan.

Collaborators:

Tomonari Kasai, PhD, Akifumi Mizutani, PhD, Jyunko Masuda, PhD, Akimasa Seno, PhD, Aun Ko Ko Oo, PhD, Hideki Minematsu, MS, Eman Ahmed Taha, MS (Graduate School of Natural Science and Technology, Okayama University)

Yoshiaki Iwasaki, MD, PhD (Center of Healthcare, Okayama University)

Summary of Research:

The risk assessment for the cancer development caused by chemical compounds has long been made by mutagenicity or repeated dose toxicity study, by which it generally takes long time to get results. However, cancer is currently recognized consisting of heterogeneous population of cells and cancer stem cells (CSCs). This is altering the idea that a cancer tissue consists of a homogeneous population of clonal cells continuously proliferating due to the oncogenic mutations. It appears necessary to develop a novel method to identify chemical compounds that may induce cancer stem cells. In this study, we established a simple method to assess the risk of chemical compounds inducing CSCs employing mouse iPSCs, which have been reprogrammed from the embryonic fibroblast derived from a transgenic mouse carrying the Nanog promoter integrated with GFP gene. This method allows the assessment in 8 days by judging the increase of spheres and the fluorescence of GFP enhanced by Nanog gene expression. We evaluated 147 chemical compounds and 30 were judged as positive. Further, we tried to analyze the molecular mechanism inducing CSCs from miPSCs by microarray, CpG methylation, lipid component, bioinformatics and so on. As the results, the relationship of some chemokine and its receptors, some specific cytoplasmic signal transduction pathway, inflammatory factors were implied to be importantly involved. Collectively, it should be possible to find out the key relationships between the cancer risks and the mechanism of action of chemical compounds in the future.

Timeline:

March 1, 2012 – February 28, 2018

Topics:

Poster presentation entitled “Development of the Novel Method with iPSCs to Assess Chemical Compounds for the Risk of CSC Induction” at 2017 Annual Meeting of LRI.

Publications:

Nair N, Calle AS, Zahra MH, Prieto-Vila M, Oo AKK, Hurley L, Vaidyanath A, Seno A, Masuda J, Iwasaki Y, Tanaka H, Kasai T, Seno M. A cancer stem cell model as the point of origin of cancer-associated fibroblasts in tumor microenvironment. Sci Rep. 2017;7(1):6838.

Ninomiya T, Ohara T, Noma K, Katsura Y, Katsube R, Kashima H, Kato T, Tomono Y, Tazawa H, Kagawa S, Shirakawa Y, Kimura F, Chen L, Kasai T, Seno M, Matsukawa A, Fujiwara T. Iron depletion is a novel therapeutic strategy to target cancer stem cells. Oncotarget. 2017;8(58):98405-98416.

OoA, Calle AS, Nair N, Mahmud H, Vaidyanath A, Yamauchi J, Khayrani AC, Du J, Alam MJ, Seno A, Mizutani A, Murakami H, Iwasaki Y, Chen L, Kasai T, Seno M. Up-Regulation of PI 3-Kinases and the Activation of PI3K-Akt Signaling Pathway in Cancer Stem-Like Cells Through DNA Hypomethylation Mediated by the Cancer Microenvironment. Translational Oncology. 2018;11(3), 653-663.

Seno A, Seno M. Commonly expressed genes among cancer stem cells induced from hiPSCs and

Development of New Risk Assessment Methods with iPSCs
obtained from cancer tissues or cell lines. Tumor and Microenvironment. 2018 *in press*.