Drug screening for intractable cancer and cancer stem cells using 3D cell culture

Although 3D cell culture has been attracting attention in regenerative medicine, it is also gaining interest in drug discovery screening. We interviewed Dr. Hirofumi Nakano, who has been working in the field of cancer research for 30 years at Kyowa Hakko (Kirin) Co., Ltd, and Kitasato Institute for Life Sciences. He is currently at Tokyo Institute of Technology continuing his research on anti-cancer drugs targeting oncogenes Ras and Src.

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3D cell culture technology on the rise

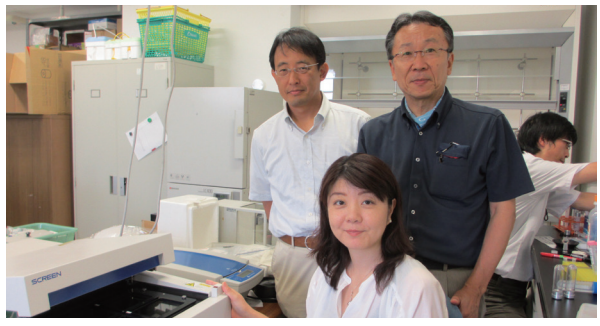
There have been numerous evolutions in the history of cancer drug discovery. During the 1970s, drugs such as Mitomycin, Adriamycin, and 5-FU were found using mice models. Since 1980s, the search for drugs acting on molecular targets such as tyrosine kinases and growth factor receptors intensified, and these drugs were effective treatment for leukemia. The reoccurrence of cancer, however demonstrate that the therapeutic treatments so far are inadequate and additional drugs are needed to eliminate all cancer stem cells. Moreover, pancreatic cancer, colon cancer and lung cancer are extremely difficult to treat since in these cancers, oncogene Ras is activated. The search for new drugs continues.

Three dimensional (3D) cell cultures that retain the original cancer stem cell state of intractable cancers are drawing interest[1), 2)]. Dr. Nakano said that the screening of drug efficacy with 3D cell culture, together with the pharmacokinetic study by animal cancer models, may be the future trend in cancer drug discovery.

New evaluation system in drug discovery

In 2012, under the NEDO innovation commerciali zation venture support project "Development of fibromyalgia drug nerve selective transcription factor targeting", Dr. Nakano screened a chemical library for tumor growth inhibition with the 3D cell culture system of refractory medulloblastoma (a type of brain tumor) that highly expressed NRSF, a transcriptional regulator of neuron-specific genes. At the end of the study, he managed to make stable single spheroids after 6 days when he plated the cells at 1000 cells/well of medulloblastoma on U-bottom plates (PrimeSurface 96 well U shaped-bottom plate, Cat. No. MS-9096U) of Sumitomo Bakelite Co., Ltd. For the rapid evaluation of the growth and morphology of the spheroids, they adopted the Cell^3 iMager from SCREEN Holdings. For screening the potential drug candidates, a PRISM BioLab library containing 3000 types of synthetic compounds were used. The library was made by varying the four side chains of the basic skeleton. Interestingly, they could monitor the growth inhibition of the spheroids according to the specific modification in side chains based on the 4 amino acids of a motif in NRSF. Although it took approximately 3 months to build this evaluation system, the screening of the 3000 compounds was completed in 4 weeks.

Dr Nakano said, "Accurate and rapid three-dimensional cell culture evaluation system is necessary for the screening of anti-cancer agents, and the above mentioned single sphere 3D system is extremely attractive to researchers involved in cell-based drug discovery."



Dr. Nakano (standing right). Sachiko Nishida (sitting front) and Professor Hiroyuki Nakamura (standing back left) Chemical Resources Institute, Tokyo Institute of Technology.

1) Thoma CR, et al. 3D cell culture systems modeling tumor growth determinants in cancer target discovery. Adv Drug Deliv Rev. (2014) 69-70, 29-41.
2) Kenny PA, et al. The morphologies of breast cancer cell lines in three-dimensional assays correlate with their profiles of gene expression. Mol Oncol. (2007) 1(1), 84-96.