Understanding of cancer heterogeneity and chemoresistance using patient-derived spheroid models

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In order to devise an effective therapeutic strategy against refractory cancers, it is important to develop model systems which faithfully recapitulate *in vivo* tumors and serve as platforms to validate efficacies for novel therapeutic agents. However, it has been reported that conventional cell lines often fail to mimic clinical effectiveness against anti-tumor agents. We have developed long-term spheroid culture system from clinical specimens of colon and ovarian cancer (ref. 3, 5). The established spheroids seem to retain characteristics of the original tumors, as they can generate tumors that faithfully mimics histology of the original tumor after xenograft formation in immunodeficient mice. Hence these spheroids may serve as invaluable systems to investigate nature of cancer chemoresistance.

Using the established spheroids. several experiments are in progress to understand malignant nature of these cancers. Because accumulating reports indicate that cancer cells are composed of heterologous populations with different chemosensitivity, we perform RNA-seq gene expression analyses of colon cancer xenograft at single-cell levels to understand biological features of the chemoresistant cells. Exposure to chemotherapeutic agents revealed that there exists chemoresistant slow-growing cancer cells in xenograft tumors. The precise nature of the chemoresistant cells are under investigation.

As another strategy to understand mechanism of chemoresistance, we combined transcriptome analyses and systematic investigation of chemoresistance in a panel of patient-derived spheroids from ovarian cancer. We found that the spheroids showed a varied effectiveness toward platinum-based compounds. Further investigation revealed that expression of several glycolytic genes was associated with cisplatin chemoresistance.

[References]

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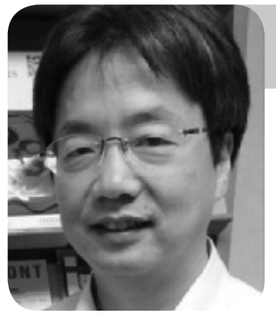

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