学位論文の要旨

Abstract of Thesis

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学位論文題目 Title of Thesis（学位論文題目が英語の場合は和訳を付記）

Analysis of the effects by signaling inhibitors in the conversion of iPS cells into cancer stem cells

非変異原性物質の影響下においてマウス iPS 細胞が示すがん幹細胞化の解析

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Cancer is a leading cause of death in worldwide, accounting for an estimated 9.6 million deaths in 2018， about 1 in 6 deaths is due to cancer. The most common cancers are: Lung (2.09 million cases), Breast (2.09 million cases), Colorectal (1.80 million cases), Prostate (1.28 million cases), Skin cancer (non-melanoma) (1.04 million cases) and Stomach (1.03 million cases). Meanwhile, the most common causes of cancer death are cancers of: Lung (1.76 million deaths), Colorectal (862, 000 deaths), Stomach (783, 000 deaths), Liver (782, 000 deaths) and Breast (627, 000 deaths). Approximately 70% of deaths from cancer occur in low- and middle-income countries. The economic impact of cancer is significant and is increasing. Therefore, each year billions of funds are allocated towards the research and development of new therapeutic strategies to combat this growing menace. With the advent of new scientific technologies and advancement in molecular cancer research, the future does seem promising. Nevertheless, considerable measures need to be taken in order to solve key issues revolving around this disease such as late presentation of symptoms, development of resistance to available treatments and lack of awareness.

Targeted cancer therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer. Many different targeted therapies have been approved for use in cancer treatment. These therapies include hormone therapies, signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, immunotherapies and toxin delivery molecules. They have improved the disease outcomes in many cancer types but still the most serious challenge often encountered in cancer therapy is the development of drug resistance. It is believed that this acquisition of resistance is typically caused by small population of cells in tumor with pre-existing alterations, which can drive the resistance. Since the concept of Cancer stem cells (CSC) has been introduced in late 1990s, its importance in cancer research and development of novel anti-cancer therapies is widely accepted. CSC which are also known as ‘tumor initiating cells’ represent very small population of tumor sharing common properties with normal stem cells. They are unique cells

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with self-renewing and tumorigenic potential. Current radio and chemotherapies are able to eliminate the bulk of cancer cells but not cancer stem cells since they are endowed with specific resistance mechanisms. They give rise to new tumors and metastases leading to relapse of the disease. The recurring tumors are more malignant, prone to faster metastasis and exhibits enhanced drug resistance. Overall, this leads to therapy failure reducing the survival rate of cancer patients with specific resistance mechanisms. They give rise to new tumors and metastases leading to relapse of the disease. The recurring tumors are more malignant, prone to faster metastasis and exhibits enhanced drug resistance. Overall, this leads to therapy failure reducing the survival rate of cancer patients.

We established a model of CSCs by culturing mouse induced pluripotent stem cells (miPSCs) in the presence of conditioned medium (CM) of Lewis Lung Carcinoma (LLC) cells. Base on this methodology of developing CSCs from miPSCs, we assessed the risk of carcinogenesis of 110 non-mutagenic chemical compounds, most of which were known as inhibitors of cytoplasmic signaling pathways. We treated miPSCs with each compound for one week in the presence of the CM of LLC cells, while one week was too short for the CM to convert miPSCs into CSCs. As the result, miPSCs treated with PD0325901, CHIR99021 and Dasatinib respectively were found to survive and keep growing while the non-treated miPSCs differentiated and slowed their growth. The survived cells after the treatment exhibited the expression of stemness markers and the spheroid formation in suspension culture indicating that the stemness and the self-renewal capacity were significantly maintained for a week. When the cells were subcutaneously transplanted into Balb/c nude mice, they formed tumors, which were histopathologically diagnosed malignant. Collectively, we found the three signal inhibitors accelerated the conversion of miPSCs into CSCs. The expression levels of PI3K related genes were assessed and the expression of pi3kca was found extensively enhanced 10 to 30 folds of that in miPSCs. Simultaneously, pik3r5 and pik3r1 genes were moderately upregulated. These indicated PI3K in either class IA or IB should be enhancing the responsible signaling pathway. Consistently, AKT phosphorylation was found upregulated in the obtained CSCs. Since mTOR expression was recognized in all cells assessed in the experiments, survival of the converted cells might be explained by the sustained pluripotency, which was secured by the expression of stemness markers. Although the mechanism is not clear, inhibition of ErK1/2, tyrosine kinase and/or GSK-3β should closely be involved in the enhancement of PI3K-AKT-mTOR signaling pathway in undifferentiated cells resulting in the sustained stemness, which should lead the conversion into CSCs.