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）

Study on the metastatic potential of cancer stem cells induced from mouse iPSCs under different microenvironments

異なる微小環境下でマウス iPS 細胞から誘導されたがん幹細胞の転移能に関する研究

学位論文の要旨 Abstract of Thesis

Background:

Cancer stem cells (CSCs) as subpopulation of cancer cells are considered to be responsible of tumor relapse, drug resistance and metastasis. Metastasis is one of major obstacle of tumor treating. Recently cancer stem cells are thought to be responsible for tumor metastasis. On the other hand, our group has developed novel cancer stem cells models derived from mouse induced pluripotent stem cells (miPSCs) in the presence of conditioned media (CM) from different cancer cell line cells. Moreover, we have reported that tumor-derived extracellular vesicles (tEVs) that are secreted from LLC cells induced the transformation of miPSCs into CSCs. Using that methods, we successfully established, lung, liver and breast cancer stem cell models.

Method:

In this study, we focused on evaluating the metastatic potential of CSCs developed in the presence of tumor-derived extracellular vesicles in comparison with CSCs developed in the presence of conditioned medium (CM) of cancer-derived cells using intraperitoneal injection. Cancer stem cells developed from Tumor-Derived Extracellular Vesicles isolated from LLC conditioned medium, BT954 conditioned medium and Huh7 conditioned medium were injected intraperitoneally in node mice. After 6 weeks of injection, the developed metastasis was then excised and analyzed. The

metastasis was investigated in different organs and cells were isolated from metastasis. Gene expression for stemness and metastasis genes were analyzed, and immunohistochemistry staining was done on all metastasis sections.

Results:

Our result shows that cancer stem cells induced by different conditioned media have different metastasis pattern and could give insight on metastasis mechanisms of specific cancer stem cells to preferred sites. Our study could also promote more research in this direction benefiting from cancer stem cells induced from miPSCs.

Although the three types of cancer stem cells showed metastatic potential after injection, cells developed in the Tumor-Derived Extracellular Vesicles showed high metastatic potential when compared to other two type of CSCs in the number of metastasis places, and the aggressiveness which showed by the size of metastasis.

The primer culture cells from all cells showed sustain the expression of CSCs and stemness marker and GFP expression which confirm that our cells were the metastatic cells. The CSCs derived from iPSCs, forming malignant tumors and displaying high metastasis, will provide a good animal model to study the mechanisms of metastasis.

Conclusions:

The CSCs were induced from miPSCs by the treatment with conditioned medium of different cancer cells. Depending on the conditioned medium, CSCs exhibited the ability to form different malignant tumors together with different range of metastatic potential. Since the miPSCs used in this study were derived from single cell source, the iPSCs were demonstrated to be pluripotent to develop different phenotypes of cancers depending on the microenvironment. Studies on the relationship between the heterogeneous potential of developing CSCs and the microenvironments will help understand the mechanism of developing various cancer phenotypes.

Key words

Cancer stem cell, metastasis, microenvironment, conditioned medium, iPSC