学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

A study on radio-resistance mechanism of cancer stem-like cells using a property of low proteasome activity in canine tumor cell lines

（犬腫細胞株におけるプロテアソーム活性を用いて分離したがん幹細胞の放射線耐性機序に関する基礎的研究）

Cancer stem-like cells (CSCs) form a distinct subpopulation of tumor cells with self-renewal capacity, asymmetric cell division, and tumorigenic potential. In addition to the stem-like properties of CSCs, radio-resistance of CSCs makes it difficult to eradicate tumor cells by radiation therapy as survived CSCs after irradiation cause tumor recurrence. Research for targeting canine CSCs has been tried using several methods such as sphere formation or side population, but there are still problems for identification and isolation of the small population. Recently, visualization of CSCs has been realized in human tumor cells using a property of low proteasome activity in CSCs. However, applicability of the system in canine tumor cells is not clear.

Radio-resistance and survival of tumor cells causing recurrence of tumor are main challenges in veterinary radiation therapy. Among heterogenous tumor cells, particularly, CSCs are the main reason of the radio-resistance of tumors. Therefore, radio-resistance related factors were examined in human tumors including degree of DNA double-strand break after irradiation, DNA contents, mitochondrial respiration, level of reactive species accumulation, glutathione (GSH) synthesis, and so forth. Nevertheless, effective molecular target of CSCs for radiation therapy is still vague, especially, in isolated CSCs using the property of low proteasome activity.

Thus, the present dissertation was planned to evaluate the radiosensitivity and radio-resistance mechanism of canine CSCs for targeting CSCs in radiation therapy. The first objective was to visualize canine CSCs using a property of low proteasome activity. The second objective was to assess radiosensitivity of the visualized CSCs and to find a molecular target for radiosensitization of the visualized CSCs.

The first study imaged canine tumor cells with low proteasome activity using canine osteosarcoma cells (HMPOS) and canine transitional carcinoma cells (MegTCC). Subsequently, CSC-like properties of the canine tumor cells with low proteasome activity were evaluated, and the visualized cells exhibited asymmetric cell division, up-regulation of CSC markers, and tumorigenic capacity. In the second study, the visualized canine CSCs were employed, and radiosensitivity and radio-resistance mechanism of the canine CSCs were evaluated. Then, radiosensitizing effects of sulfasalazine which inhibits function of xCT and synthesis of GSH were evaluated using the visualized canine CSCs. The visualized canine CSCs exhibited radio-resistance and high GSH contents compared with non-visualized cells. Application of sulfasalazine effectively radio-sensitized the visualized CSCs in canine osteosarcoma cells by reducing GSH contents.

The conclusion of the current dissertation was that canine CSCs were successfully visualized using low proteasome activity. This visualization system could be a valuable research tool for future CSC research to make CSC-targeting therapeutic approach. Moreover, the radio-resistance and high GSH contents of canine CSCs were revealed owing to high protein level of xCT at low proteasome activity. Also, Sulfasalazine effectively radiosensitized CSCs in canine osteosarcoma cells. These findings suggest the direction of radiation therapy targeting CSCs for successful tumor eradiation.