News Release

Title

Publication of the elucidation of novel mechanism of anti-cancer drug resistance in malignant lymphoma ~Anticipation to establish novel treatment strategies~

Key Points

• Malignant lymphoma is most common hematological malignancy, and about 35,000 patients develop the disease annually in Japan. Recent progresses in treatment outcomes have allowed approximately 6 out of 10 patients to overcome their diseases, while the remaining approximately 4 patients cannot defeat the disease with current treatment strategies. The development of novel effective therapies is required for intractable patients.

• In this study, focusing on cancer-associated fibroblasts (CAFs) around lymphoma cells in the tumor microenvironment, we demonstrated that CAFs support proliferation and survival of lymphoma cells. We also demonstrated that exosomes, 30-150 nm diameter nanovesicles, secreted from CAFs play an important role of these functions.

• MicroRNA contained in exosomes secreted from CAFs induces anti-pyrimidine drug resistance through the suppression of its transporter protein, ENT2.

Summary

Shunsuke Kunou and Mika Takai (Graduate Students, Department of Hematology and Oncology, Nagoya University Graduate School of Medicine), Professor Hitoshi Kiyoi (Professor, Department of Hematology and Oncology, Nagoya University Graduate School of Medicine), Kazuyuki Shimada (Lecturer, Department of Hematology, Nagoya University Hospital), Masashi Sanada (Director, Department of Advanced Diagnosis, Clinical Research Centre, National Hospital Organization Nagoya Medical Center), and Chitose Oneyama (Director, Division of Cancer Cell Regulation, Aichi Cancer Center Research Institute and Visiting Professor, Department of Target and Drug Discovery, Nagoya University Graduate School of Medicine) suggested novel anti-cancer drug resistance mechanism in malignant lymphoma, which is induced by exosomes, 30-150 nm nanovesicles, secreted from CAFs.

Malignant lymphoma is one of hematological malignancy known to be quite heterogenous. Recent progress in research in malignant lymphoma indicates the importance of the tumor microenvironment. Various cells in the tumor microenvironment play an important role of proliferation and survival of lymphoma cells.

In this study, focusing on CAFs in the tumor microenvironment, we revealed that CAFs support proliferation and survival of lymphoma cells, and exosomes, major components of extracellular vesicles, secreted from CAFs play an important role of these functions. Furthermore, we also revealed that exosomes derived from CAFs are involved in anti-pyrimidine drug resistance through the inhibition of its uptake by suppressing the expression of the transporter protein, ENT2.

Extracellular vesicles, represented by exosomes, act as messengers that are responsible for cell-to-cell interactions. The present study revealed that CAFs surrounding lymphoma cells are involved in

anti-cancer drug resistance through their derived exosomes. In the future, it is expected that the development of therapies targeting exosomes, such as suppressing the secretion of exosomes, will lead to establish novel treatment strategies with a different mechanism from existing treatments.

The present study has been published in the Oncogene on May 16, 2021.

Research Background

The tumor microenvironment is deeply involved in the process of tumor growth and development. CAFs are one of major components of the tumor microenvironment, however the role of CAFs in the lymphoma microenvironment remains unknown.

Research Results

In this study, we focused on CAFs and their derived exosomes on the lymphoma microenvironment to uncover their clinical significance. CAFs supported the survival of lymphoma cells through increased glycolysis. Exosomes, a major component of the extracellular vesicles from CAFs, also supported the survival of lymphoma cells. The suppression of the secretion of exosomes resulted in decreased survival of lymphoma cells. Moreover, anti-pyrimidine drug resistance was induced in the presence of exosomes through the suppression of its transporter, ENT2, and miRNA in exosomes suppressed the expression of ENT2 and induced the drug resistance.

Future Perspective

The present study suggests that exosomes from CAFs are a potential therapeutic target. In the future, it is expected that the development of therapies targeting exosomes, such as suppressing the secretion of exosomes, will lead to establish novel treatment strategies.

Publication

Oncogene
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