News Press Research Release

Title

Targeted Phototherapy for Malignant Pleural Mesothelioma: Near Infrared Photoimmunotherapy Targeting Podoplanin

Key Points

- The development of new treatments for malignant mesothelioma has not been advanced so far, and its development is awaited.
- The development of molecular targeted drugs and treatments for malignant mesothelioma is especially expected.
- We succeeded in developing Near Infrared Photoimmunotherapy targeting podoplanin, a molecule specifically expressed in malignant mesothelioma.
- This study proposed a new therapeutic method for malignant mesothelioma, which has limited therapeutic means, and specifically destroys target cells.
- Since NIR-PIT is under an international phase III clinical trial, Podoplanin-targeted NIR-PIT is thought to be easy translatable into the clinic.

Summary 1

Graduate student **Yuko Nishinaga (1st author)** at the department of Respiratory Medicine, Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu), Assistant Professor **Kazuhide Sato (corresponding author, co-first author)**, at Institute for Advanced Research, Nagoya University (Director: Yoshiyuki Suto), Associate Professor Hiroshi Yukawa and Professor Yoshinobu Baba at Department of Biomolecular Engineering, Professor Toyofumi F. Chen-Yoshikawa at the department of Thoracic Surgery, Yoshinori Hasegawa in Nagoya Medical Center, and their collaborators succeeded in developing near-infrared photoimmunotherapy targeting podoplanin for malignant mesothelioma by collaborative research with Hisataka Kobayashi at Molecular Imaging Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health and Yukinari Kato at Department of Antibody Drug Development, Tohoku University Graduate School of Medicine.

Malignant pleural mesothelioma has a poor prognosis, and the number of patients is thought to be increased worldwide in the future. However, effective chemotherapy for malignant pleural mesothelioma is very limited (only 1 regimen has been used as a chemotherapy), thus, development of new drugs and treatment methods is highly wanted. Podoplanin is a transmembrane glycoprotein that has been reported to

be expressed in malignant mesothelioma and has been used as a positive marker in pathological diagnosis. Prof. Yukinari Kato (co-author) and colleagues at Tohoku University have established anti-podoplanin antibody, NZ-1, as an antibody drug targeting human podoplanin.

Near Infrared Photoimmunotherapy (NIR-PIT) is a recent-developed cancer therapy that developed by Dr. Hisashi Kobayashi (co-author) and colleagues at the National Cancer Center (NCI / NIH). NIR-PIT combines the specificity of intravenously injected antibodies for targeting tumors with the toxicity induced by photosensitizers after exposure on near infrared (NIR) light. It is now in international Phase III clinical trial against locoregional, recurrent head and neck squamous cell cancer (LUZERA-301), and expected to be clinically licensed in near future.

In this study, we investigated the expression of podoplanin in surgically resected human malignant pleural mesothelioma specimens, and then we demonstrated the effect of NIR-PIT on malignant mesothelioma targeting podoplanin using NZ-1. This study suggests that NIR-PIT targeting podoplanin could be a promising new treatment for malignant pleural mesothelioma.

Summary 2

Research Background

Malignant mesothelioma is a malignant tumor that arises from mesothelial cells and is rarer than lung cancer, however, the number of MPM patients is thought to be increased further in the future. In addition, the prognosis is poorer than that of lung cancer, and the 5-year survival rate is only about 10% regardless of treatment, which is even worse outside the indication for surgery. There are few treatment options for unresectable cases, and clinical trials of various drugs have been conducted so far, but the efficacy has not been proved. Therefore, the development of effective new drugs and treatments is highly wanted. Podoplanin is a useful target molecule for malignant mesothelioma, which has been used as a specific diagnostic marker for malignant mesothelioma. A group led by Professor Yukinari Kato (co-author) in the field of antibody drug discovery, Graduate School of Medicine, Tohoku University, has developped antibodies against podoplanin.

Near infrared Photoimmunotherapy is a cancer treatment method developped by Dr. Hisataka Kobayashi (co-author) at the National Cancer Institute, National Institutes of Health (USA). A complex of an antibody that specifically recognizes a protein expressed on cancer cells and IR700, a photosensitizer, is synthesized, and the irradiation with NIR light around 690 nm destroys cells when the complex is bound to the target protein on the cell surface. Recently, Dr. Kazuhide Sato (corresponding author) and his colleagues have elucidated the new cell death mechanism induced by NIR-PIT (*ACS Cent. Sci.,* 2018 Nov 28*4* (11), pp 1559–1569). This time, we tried to apply this NIR-PIT and anti-podoplanin antibody in order to the

treatment of malignant mesothelioma.

Research Results

Immunostaining of podoplanin with NZ-1 was performed on tumor tissue using surgical specimens from Japanese patients who had surgery at Nagoya University Hospital, who agreed to use it for research purposes. When classified by histological type of malignant mesothelioma, podoplanin positive rate in epithelial type was 86.7%, in biphasic type (mixing epithelial type and sarcoma type) was 66.7%, thus podoplanin expression was 83.3% in total. When the expression of podoplanin in malignant mesothelioma cells of Caucasian and Japanese was compared, it was similarly observed in cells of both races, and it was suggested that widely expressed in malignant pleural mesothelioma across races.

An antibody-photosensitizer conjugate consisting of NZ-1 and a phthalocyanine dye, IRDye-700DX, was synthesized and evaluated its specificity. Using NZ-1-IR700, we performed NIR-PIT for human malignant pleural mesothelioma cancer cells. In serial fluorescence microscopic observation, cells were swollen, ruptured, and cell death was observed immediately after irradiation with NIR light. When target cells (podoplanin-positive human cancer cells) and non-target cells (podoplanin-negative human cancer cells) were co-cultured and irradiated with NIR light at the same dish, cell death occurred only in target cells and had no particular effect on non-target cells. In tumor-bearing mice model, the intravenusely injected drug reached the tumor site sufficiently with the study of biodistribution. In addition, as a result of treatment in mice, significant tumor growth inhibition was confirmed, and a remarkable tumor reduction effect was also obtained in the pleural disseminated malignant mesothelioma mice model (Figure1).

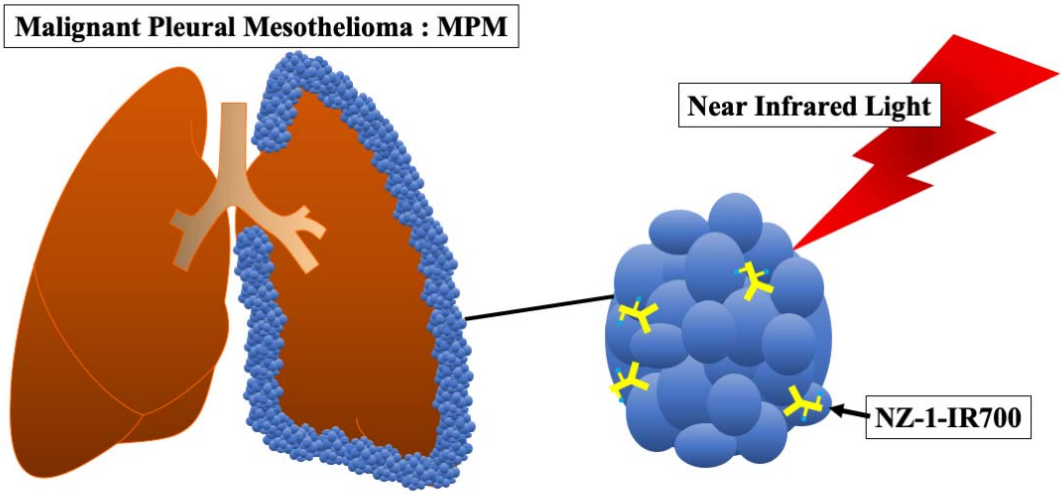

Figure1; Scheme of NIR-PIT for MPM

Future Perspective

The effects of near-infrared photoimmunotherapy on malignant mesothelioma targeting podoplanin were confirmed *in vivo* and *in vitro* experiments. It was also confirmed that podoplanin was widely expressed in Caucasian and Japanese mesothelioma cancer cells across races. This study is expected to contribute as a basic finding when applying NIR-PIT to the treatment of human malignant mesothelioma. In this study, it was proved that the same antibody can be used for tissue diagnosis by immunostaining and treatment with NIR-PIT. And we were able to establish a flow from diagnosis to confirmation of expression of podoplanin in malignant mesothelioma and subsequent treatment. Recently, a new generation of antibody using the cancer-specific monoclonal antibody (CasMab®) technology, which is able to more selectively recognize podoplanin in cancer cells, has been developed by Prof. Yukinari Kato in the field of antibody drug discovery, Graduate School of Medicine, Tohoku University. In the future, we would like to apply CasMab® to NIR-PIT to aim for more selective treatment. Further applications are being investigated in the future, including the development of new NIR-light irradiation devices in thoracic oncology and combined use with conventional treatments.

Publication

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Cells (Apr 20th, 2020)

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DOI：https://doi.org/10.3390/cells9041019

Japanese ver.

https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Ce_200420.pdf