Impact Objectives

- Discovery of natural products that regulate the activity of glycosaminoglycans, which play important roles in the pathogenesis of cancer and neurological disease
- Development of glycan-cleaving drugs that can overcome drug resistance in cancer cells

A biochemical approach to drug resistance

***Dr Masao Nakamura** is working on developing glycan-cleaving drugs that will contribute to overcoming therapeutic antibody resistance in refractory cancers*

What inspired you to become involved in functional biochemistry research?

In 2008, I began researching the mechanisms of action of signalling molecules involved in metabolic regulation and discovered that glycosaminoglycans (a type of glycan) facilitate the formation of active receptor complexes. In 2011, my research activities were halted due to the Great East Japan Earthquake. My supervisor informed me about RIKEN's disaster victim support program. I was fortunate enough to be accepted into this program and continued my research by joining a laboratory specialising in the organic synthesis of glycans for 10 months. During this period, I had many discussions with chemists specialising in synthetic organic chemistry and I recognise the benefits of gaining a chemical understanding of biological functions. This gave me an opportunity to explore the molecular biology and cell biology approaches that I had been pursuing up until that point, and to incorporate a biochemical perspective into my research on the mechanisms in which glycans are intrinsically involved.

Can you talk about the research underway in your department at the Sasaki Institute?

The Department of Peptidomics began by developing peptidomics methodologies and developed a method for identifying the physiological cleavage sites of membrane proteins. This method was used in a recent project that sought to develop antibodies that can be used to treat pancreatic cancer from a new perspective of cleaving membrane proteins. In recent years, glycans involved in mediating the interaction between various bioactive molecules and receptors have been found to inhibit the access of therapeutic antibodies to target molecules expressed on the surface of cancer cells. However, little progress has been made in the use of glycans as therapeutic targets. To overcome cell resistance to therapeutic antibodies, I am developing glycan-cleaving drugs that regulate the interactions of various molecules. Therefore, we are developing new analytical methods to elucidate the mechanisms of action in which glycans play a key role.

In general, what challenges have you faced in your studies?

It was originally hoped that enzymatic cleavage of glycans on the surface of pancreatic cancer cells would have an antiproliferative effect by inhibiting the mechanisms of action of growth factors such as fibroblast growth factor and hepatocyte growth factor; however, no substantial effects were observed. Nevertheless, with the development of methods for identifying membrane proteins with cleaved glycans, it has become possible to analyse the relationship between glycan cleavage and the efficiency of drug access, thereby enabling the development of therapeutic drugs targeting drug resistance mechanisms.

Are you collaborating with other researchers in these investigations?

Currently, I have started a project in collaboration with overseas chemists specialising in glycan synthesis to develop a method for suppressing the synthesis of specific glycan in the Golgi apparatus. I am proceeding with the development of glycan-cleaving drugs based on low-molecular-weight compounds using a biochemical approach that combines western blotting and mass spectrometry (CDR-WB-MS) that we have developed to analyse changes in glycans and the membrane proteins that contain these glycans.

A CDR-WB-MS method for identifying proteoglycans with cleaved glycans

New methods to treat pancreatic cancer

*Scientists at the **Sasaki Institute** are working to develop therapeutic antibody enhancers for pancreatic cancer cells, with the aim of overcoming drug resistance acquired by cancer cells and significantly improving patient outcomes*

Pancreatic cancer has one of the most unfavourable prognoses and the number of deaths from this disease has quadrupled in the past 40 years. By 2030, pancreatic cancer is projected to overtake colorectal cancer and emerge as the second leading cause of cancer-related deaths. Dr Masao Nakamura explained that there are currently no effective treatment options for pancreatic cancer and that the anticancer drugs used as adjuvant therapy cannot be continued long-term due to their serious side effects. There is thus a clear need to develop therapeutic drugs that incorporate new approaches and researchers worldwide are working to achieve this goal.

THE IMPORTANCE OF GLYCANS

It is with this in mind that Nakamura has embarked on his latest research project, which focuses on glycans that play important roles in cancer and neurological diseases as therapeutic targets. 'Glycans are closely associated with a wide range of medical conditions, including cancer, central nervous system diseases, immunity and infectious diseases. Glycans present on the cell surface serve as markers that indicate the cell type and disease status. In clinical practice, they are widely used as diagnostic markers such as tumour markers,' describes Nakamura. 'I am focusing on chondroitin sulfate (CS), a glycosaminoglycan involved in cancer invasion and metastasis.'

The CS subtype is known to change in instances of malignant cancers and central nervous system damage. Therefore, Nakamura is developing drugs that can be used to control specific CS subtypes secreted by inflammatory cells. 'Glycans play an important role in the emergence of therapeutic antibody resistance,' he explains. 'Therefore, our goal is to develop enhancers that can increase the effectiveness of anticancer drugs and therapeutic antibodies by modifying glycans on the cell surface whose expression increases as cancer develops.'

ENHANCING THERAPEUTIC ANTIBODIES

Antibody drugs are highly selective therapeutic agents that are effective against hematopoietic tumours, colorectal cancer and breast cancer. However, none of the therapeutic antibodies developed to date are expected to be effective against most pancreatic cancers; the exception being approximately 1 per cent of pancreatic cancer cases that are characterised by specific fusion genes. 'To maximise the high specificity and affinity of antibodies, I am developing therapeutic antibody enhancers that can overcome cancer cell resistance mechanisms that prevent antibodies from accessing their targets,' Nakamura observes. 'We are also developing analytical methods including new approaches that will enable comprehensive analysis of the changes in glycans and proteins necessary for the development of therapeutic antibody enhancers.'

> *'Our goal is to develop enhancers that can increase the effectiveness of anticancer drugs and therapeutic antibodies by modifying glycans on the cell surface'*

Therapeutic antibody enhancers contribute to enhancing the efficiency with which therapeutic antibodies access target molecules by cleaving or modifying glycans on the surface of cancer cells that are associated with drug resistance. Ultimately, this approach could lead to a breakthrough in overcoming the drug resistance acquired by cancer cells through sustained drug delivery, thereby improving outcomes in patients with pancreatic cancer and the treatment of a wide range of other cancers and diseases.

Project Insights

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BIO

Dr Masao Nakamura has been working as a Research Scientist in the Department of Peptidomics at the Sasaki Institute since 2020. He has previously worked as a technical trainee at the National Institute of Advanced Industrial Science and Technology (AIST), a Research Scientist at the RIKEN Brain Science Institute, an Assistant Professor at Tokyo University of Technology and a Lecturer at the AIST Innovation School. Nakamura is interested in promoting research on the discovery of natural products that regulate cancer progression and neurological functions by acting on glycosaminoglycans, and the development of highly functional molecules.

科研費 KAKENHI

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