Impact Objectives

- Explore the interactions between cancer cells and normal cells and the communication tools used
- Understand how extracellular vesicles (EVs) mediate cancer cells establishing their comfortable environment at metastasis initiation
- Elucidate molecular mechanisms of cancer cells use to induce EV release to communicate with the surrounding cells

How cancer cells communicate

*Cancer researcher **Assistant Professor Nao Nishida-Aoki** is focused on understanding more about cancer extracellular vesicles in the hopes of facilitating better treatments targeting tumour microenvironments*

How did you embark on your research in molecular biology?

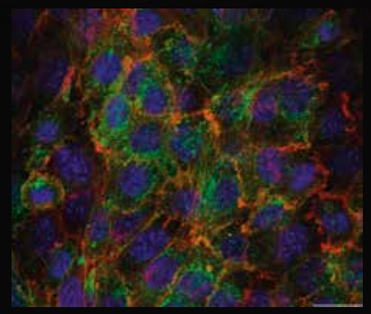
My PhD involved studies of yeast stress signalling pathways and related transcription factors under the supervision of Dr Mitsuyoshi Ueda at Kyoto University. In this work I was studying intracellular signalling pathways within a single cell activated by external stimuli. For the next step I wanted to study intercellular signalling, that is, cell-to-cell interactions. I became fascinated by 'exosomes', also known as extracellular vesicles (EVs), which were emerging intercellular communication tools utilised by almost all cells. The top researcher of EVs in Japan at the time was Dr Takahiro Ochiya at the National Cancer Center and I started my first postdoctoral training at his lab, which brought me to cancer research.

Can you tell us about the investigations you are currently conducting?

My research explores interactions between cancer cells and normal cells and the communication tools they use. One of these communication tools I am focused on is nanosized vesicles called extracellular vesicles (EVs). Despite ongoing research, significant gaps remain in our understanding of EVs, particularly how they work within the physiological tissue environment of cancer patients. I am currently investigating how cancer cells secrete EVs and transfer to the surrounding cells within tissue. My aim is to achieve real-time microscopic observation of EV transfer by cancer cells, but this is particularly challenging due to the nanoscale size of EVs. By leveraging a physiological tissue model called organotypic tissue slice culture (TSC) and by introducing high-sensitive EV labels into cancer cells, I will be able to directly observe the dynamics of EVs within in a context that closely mimics physiological conditions, providing insights that could lead to novel therapeutic strategies.

You are collaborating with several researchers. How important are their contributions to your studies?

My colleagues, Dr Takafumi Inoue and Dr Yoshiki Hatashita, are helping with live imaging of EV transfer under 2-photon microscopy. Dr Takahiro Ochiya, currently of the Tokyo Medical University, is very supportive by providing me with experimental environments, and Dr Yusuke Yamamoto, from the National Cancer Center Research Institute in Tokyo, provides access to animal experimental facilities. Members of the Ochiya lab have been helping me since my parental leave. Put simply, without these people, my research cannot be carried out. In addition, I am collaborating with several researchers to help me to push the technical limitations of the EV field forward to reach the new findings. Dr Takao Yasui, at the Tokyo Institute of Technology is helping develop a new platform to investigate spatial distribution of EVs, and Dr Akimitsu Narita, of the Okinawa Institute of Science and Technology Graduate University, and Dr Xiaomin Liu, from the Max Planck Institute for Polymer Research, are helping observe EVs labelled with super-resolution organic dyes.



A fluorescent microscopic image of cancer cells with labelled EVs (blue = nuclei, green = EVs, red = actin, scale bar: 20 μm)

Cancer cells manipulating their environment

__Dr Nishida-Aoki__, based within the __Waseda Institute for Advanced Study (WIAS)__, is investigating extracellular vesicles transfer in tumour tissues to understand cancer metastasis establishment, ultimately leading to improved cancer therapies

For cancer cells to grow in the human body, they require a comfortable living environment. To do this, cancer cells interact with their surrounding normal cells and modulate them into tumour-supportive phenotypes, accelerating tumour growth and metastasis. This requires the use of communication tools. These tools have been studied by researchers around the world in efforts to help create targeted cancer therapies.

USING EVS TO MODULATE THE ENVIRONMENT

Assistant Professor Nao Nishida-Aoki is a cancer researcher studying one of these communications tools, extracellular vesicles (EVs), which she explains cancer cells utilise to educate the surrounding cells and make them supportive to cancer cell growth and metastasis. 'Current studies analyse EV content and functions after isolation from 2D cultured cells or clinical specimens. But in patient tumours, EVs are secreted in a complex tissue context comprising densely packed cells and non-cellular components forming a 3D structure,' she describes. Her work studying cancer EVs in physiological tumour tissue environments is essential so that the knowledge gained can be directly applied to real-world healthcare situations.

> *'This research explores the molecular mechanisms by which cancer cells regulate how much they 'talk' with the neighbouring cells'*

Nishida-Aoki is working on uncovering molecular details of how cancer cells manipulate their surroundings and use EVs to establish metastatic lesions. 'I have established ex vivo brain and lung metastatic models utilising a physiological tissue model, known as organotypic tissue slice culture (TSC). By leveraging the metastatic models, I will observe cancer EV transfer within tissue architecture in real time, to observe the EV modalities, determine the target cells that are preferentially affected by cancer EVs and their distribution,' highlights Nishida-Aoki. She intends to further investigate the molecular determinants of EV modalities and targeted delivery with a focus on EV surface molecules and tissue structures.

In addition to these studies, Nishida-Aoki is also investigating the mechanisms of inducible secretion of cancer extracellular vesicles upon cell recognition and contribution to cancer malignancy. 'This research explores the molecular mechanisms by which cancer cells regulate how much they 'talk' with the neighbouring cells using EVs at metastatic initiation, which also reflects tumour tissue context,' outlines Nishida-Aoki. 'I hypothesised that cancer cells should increase communication frequency using EVs when they meet other types of cells in a new environment to benefit themselves.'

NOVEL THERAPEUTIC STRATEGIES

Ultimately, by developing understanding of the molecular basis of cancer-normal cell interactions using EVs, Nishida-Aoki hopes that her studies contribute to the development of novel cancer therapeutic strategies. 'Cell-cell interaction is fundamental to life, understanding EVs-mediated cellular communication is not limited within tumours but contributes to the basic mechanisms of multicellular living organisms.' She explains how by targeting EV-mediated cancer cell modulation of the surrounding cells, the efficacy of treatments will be improved, as it may well prove possible to control and manage cancer EV transfer and prohibit cancer cells establishing a pro-tumoural environment.

Project Insights

FUNDING

JSPS KAKENHI Grant-in-Aid for Scientific Research (C), JSPS KAKENHI Grant-in-Aid for Research Activity Start-up, Mitsubishi fund, The Uehara Memorial Foundation, SGH cancer research grant, The Noguchi Institute research grant

COLLABORATORS

Dr Takafumi Inoue and Dr Yoshiki Hatashita (Waseda University), Dr Takahiro Ochiya (TMU), Dr Yusuke Yamamoto (NCCRI, Japan), Dr Takao Yasui (Tokyo Institute of Technology), Dr Akimitsu Narita (OIST), Dr Xiaomin Liu (Max Planck Institute)

CONTACT

Assistant Professor Nao Nishida-Aoki

T: +81 3 5286 2107
E: nnishida@aoni.waseda.jp
W: https://www.waseda.jp/inst/wias/other-en/2022/04/01/9011/

BIO

Assistant Professor Nao Nishida-Aoki has been based at WIAS, Waseda University since 2022. She gained extensive experience in cancer biology, including working at National Cancer Center Research Institute, Japan, the Tokyo Medical University and the Fred Hutchinson Cancer Research Center, US.