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| **No.** | K22-2056 | |
| **研究課題名** | Functional polarization of tumour-associated macrophages by tumor microenvironment | |
| **研究代表者** | 何 暁東 ( 山東大学・講師 ) | |
| **研究組織** | **受入教員** | 中西 真 ( 東京大学医科学研究所・教授 ) |
| | **分担者** | Xiao-dong He ( Shandong University・Lecturer ) |
| | **分担者** | Hai Yu ( Shandong University・Graduate student ) |
| | **分担者** | Tian-shu Liu ( Shandong University・Graduate student ) |
| | **分担者** | Makoto Nakanishi ( Cancer Cell Biology, Institute of Medical Science, University of Tokyo・Professor ) |

(Form 2)

| Principal Investigator |
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| HE XIAODONG |

## IMSUT International Joint Usage/Research Center Project <International>

## Joint Research Report (Annual/Project Completion)

**Project Completion Report**

### Report

**Summary of Research Activities (FY2022–FY2024)**

Over the past three years (FY2022–FY2024), our project investigated the polarization mechanisms of tumor-associated macrophages (TAMs) under acidic tumor microenvironments and tumor-derived exosomes (TDEs). TAMs are key innate immune cells in the tumor microenvironment (TME), and their functional polarization plays a crucial role in tumor progression or suppression. This study focused on exploring how acidosis and TDEs drive macrophage polarization toward an immunosuppressive M2-like phenotype through transcriptomic, molecular, and functional analyses.

**Research Process and Achievements**

- **FY2022:** Established in vitro models of acidic and lactic acid-enriched environments mimicking the TME. Mouse peritoneal macrophages were stimulated with low pH (6.0), 25 mM lactic acid, and supernatants from HGC-27 gastric cancer cells. RNA was extracted for high-throughput transcriptome sequencing.
- **FY2023:** Focused on acid-sensing G protein-coupled receptors (GPCRs) such as TDAG8 (GPR65) and OGR1 (GPR68). We analyzed M1 markers (TNF-α, IL-6) and M2 markers (Arg1, Mrc1) and confirmed the acidic environment induces M2-type polarization. Key findings were shared at:
  - The 10th National Conference on Computational Biology and Bioinformatics (NCCBB)
  - The Biomedical Big Data and Artificial Intelligence Forum

  In the same year, we published a peer-reviewed paper acknowledging IMSUT support.
- **FY2024:** Extended analysis to tumor-derived exosomes (TDEs) obtained from HGC-27/RAW264.7 co-cultures. Transcriptomic data revealed exosome-driven immunosuppressive transcriptional changes. RNA splicing analysis using PSI-Sigma identified condition-specific splicing events in immune-related genes. Functionally, exosome-treated macrophages showed reduced capacity to stimulate T cell proliferation.

**Research Outputs**

- Scientific Contributions:
  - Identified gene and splicing signatures of macrophage polarization under acidic and exosome-rich TME conditions.
  - Highlighted proton-sensing GPCRs (TDAG8, OGR1) as regulators of immune adaptation in tumors.
  - Proposed a potential cooperative mechanism between TAMs and myeloid-derived suppressor cells (MDSCs).
- Academic Publications:

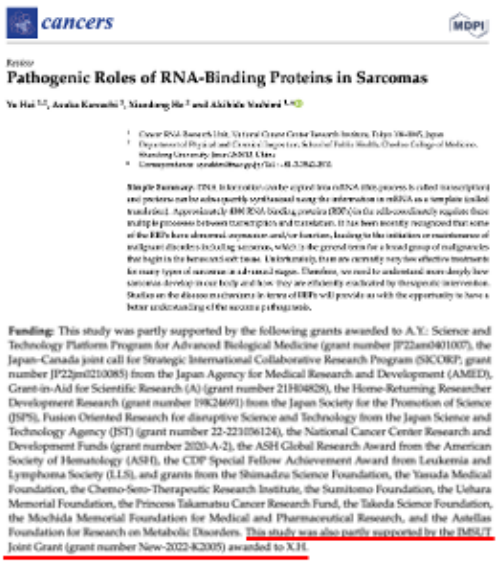
  We have published two academic papers and expressed our gratitude to the University of Tokyo (for detailed information, please refer to the figure below).
- Conference & Seminar Organization:
  - Organized two academic symposia on tumor immunology and computational transcriptomics (2023, 2024).
- Human Resource Development:
  - Trained 2 master's students and 1 PhD student.
  - One PhD student selected for overseas study in Japan.

**Research Support and Grants**

This project was supported by:
- IMSUT International Joint Usage/Research Center Grant, The Institute of Medical Science, The University of Tokyo
- National Natural Science Foundation of China
- Outstanding Innovation Fund, Shandong University

**Acknowledgements**

We sincerely thank Prof. Makoto Nakanishi and the IMSUT team for collaborative support and advanced research facilities. The IMSUT joint research program provided essential infrastructure and academic exchange opportunities, which contributed significantly to our project's success.



cancers

MDPI

Review

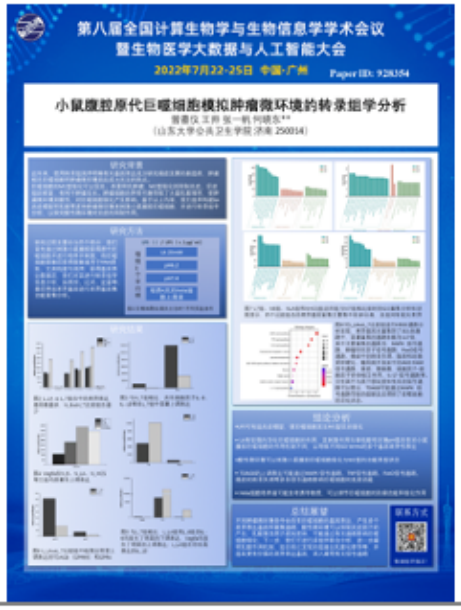
**Pathogenic Roles of RNA-Binding Proteins in Sarcomas**

Ye Hai [1,2], Asuka Kawashi [3], Xiaodong He [1] and Akihide Yoshida [1,4]*

1 Cancer RNA Research Unit, National Cancer Center Research Institute, Tokyo 104-0045, Japan
2 Department of Physical and Exercise Therapy, Graduate School of Public Health, Osaka College of Medicine, Shandong University, Jinan 250012, China
4 Correspondence: akyoshida@ncc.go.jp; Tel.: +81-3-3542-2511

**Simple Summary:** DNA information can be copied into mRNA through a process called transcription, and proteins can be subsequently synthesized using the information in mRNA as a template (called translation). Approximately 400 RNA-binding proteins (RBPs) in the cell coordinately regulate these multistep processes between transcription and translation. It has been recently recognized that some of the RBPs have abnormal expression and/or function, leading to the initiation or maintenance of malignant disorders (cancers). Sarcomas, which are the general term for a broad group of malignancies that begin in the tissues of soft tissue. Unfortunately, there are currently very few effective treatments for many types of sarcomas at advanced stages. Therefore, we need to understand more deeply how sarcomas develop in our body and how they are efficiently eradicated by therapeutic intervention. Studies on the disease mechanisms in terms of RBPs will provide us with the opportunity to have a better understanding of the sarcoma pathogenesis.

**Funding:** This study was partly supported by the following grants awarded to A.Y.: Science and Technology Platform Program for Advanced Biological Medicine (grant number JP22am0401007), the Japan–Canada joint call for Strategic International Collaborative Research Program (SICORP; grant number JP22jm0210085) from the Japan Agency for Medical Research and Development (AMED), Grant-in-Aid for Scientific Research (A) (grant number 21H04928), the Home-Returning Researcher Development Research (grant number 19K24691) from the Japan Society for the Promotion of Science (JSPS), Fusion Oriented Research for disruptive Science and Technology from the Japan Science and Technology Agency (JST) (grant number 22-2231061241), the National Cancer Center Research and Development Funds (grant number 2020-A-2), the ASH Global Research Award from the American Society of Hematology (ASH), the CDF Special Fellow Achievement Award from Leukemia and Lymphoma Society (LLS), and grants from the Shimadzu Science Foundation, the Yasuda Medical Foundation, the Chemo-Sero-Therapeutic Research Institute, the Sumitomo Foundation, the Uehara Memorial Foundation, the Princess Takamatsu Cancer Research Fund, the Takeda Science Foundation, the Mochida Memorial Foundation for Medical and Pharmaceutical Research, and the Astellas Foundation for Research on Metabolic Disorders. This study was also partly supported by the IMSUT Joint Grant (grant number New-2022-K2005) awarded to X.H.



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小鼠腹腔原代巨噬细胞模拟肿瘤微环境的转录组学分析

Nutrition & Metabolism

RESEARCH Open Access

Chondroitin sulfate alleviates osteoporosis caused by calcium deficiency by regulating lipid metabolism

Abstract

**Additional file 1: Table S1.** MRPP analysis showed significant differences in microbial community structure between group N and group C and between group C and group CS and between group CS and group Ca.

**Additional file 2: Table S2.** The differential metabolites of fecal metabolomics between the N group and the C group. The differential metabolites of fecal metabolomics between the C group and the Ca group. The differential metabolites of fecal metabolomics between the C group and the CS group. The differential metabolites of fecal metabolomics between the CS group and the Ca group.

**Additional file 3: Table S3.** The differential metabolites of plasma metabolomics between the N group and the C group. The differential metabolites of plasma metabolomics between the C group and the Ca group. The differential metabolites of plasma metabolomics between the C group and the CS group. The differential metabolites of plasma metabolomics between the CS group and the Ca group.

**Acknowledgements**

The authors want to thank Translational Medicine Core Facility of Shandong University for consultation and instrument availability that supported this work. This study was supported by a Grant from International Joint Usage/Research Center, the Institute of Medical Science, the University of Tokyo.

The results were presented at the 8th National Conference on Computational Biology and Bioinformatics (NCCBB) and The Biomedical Big Data and Artificial Intelligence. At the same time, we published a review paper and a research paper. These are written: "This study was partly supported by a Grant from the International Joint Usage/Research Center, The Institute of Medical Science, the University of Tokyo."