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研究課題名（英文）Identification of early stage malignancy changes in the structural and biophysical proporties of exosomes by atomic force microscopy (AFM)-based nano-mechanical measurements

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研究成果の概要（和文）：本研究では、3次元原子間力顕微鏡（3D-AFM）フォースマッピングにより、数種類の異なるタイプの細胞から放出されたエクソソームの生理条件下での構造とナノ力学特性を高い空間分解能で計測した。その結果、これまで同定されていなかった個々のエクソソームの部分構造を観察し、膜表面から膨出したナノドメインの存在と、その外表面に関連する膜タンパクを確認した。更に、転移性がん細胞由来エクソソームと非転移性がん細胞由来エクソソームのナノ力学特性の違いを示した。

研究成果の学術的意義や社会的意義
Cancer is a leading cause of death due to late diagnosis. Distinguishing between metastatic and non-metastatic malignant cell-derived exosomes is crucial. This differentiation aids in understanding exosome functions and enhances their use as biomarkers, improving early cancer detection and outcomes.

研究成果の概要（英文）：We employed 3D-AFM to reveal the structural and associated-nanomechanical properties of exosomes. 3D-AFM showed the presence of distinct nanodomains bulging out from the membrane surface, which can be attributed to the heterogeneous presence of membrane-associated proteins exposed on the vesicles’ outer surfaces. Our results further showed differences between the nanomechanical properties of metastatic and nonmetastatic cancer cell-derived exosomes.

研究分野：Scanning probe microscopy (SPM), AFM, Nanoscience

キーワード：Exosomes　3D-AFM　Nanomechanics

１．研究開始当初の背景

Extracellular vesicles, particularly exosomes, have recently gained interest due to their emerging role as mediators of cell-cell communication and as novel biomarkers for cancer cells and other diseases and have potential as drag delivery vehicles **(Nat. Rev. Immunol. 14, 195 (2014)).** Exosomes are nanosized (30-150 nm) lipid bilayer-enclosed membrane vesicles released from a wide variety of cell types into the extracellular space, and can be found in most body fluids, such as blood, saliva, breast milk, and urine. They are suggested to serve as important vehicles for transporting different types of functional cargos from one cell to another through direct interactions with the recipient cell membrane, i.e., mediating intercellular communication. Cargoes in exosomes are diverse, and contain a specific mixture of proteins, lipids, receptors, and nucleic acids, which can vary depending on the type of the cells and their metabolic status (see **Fig.1**). Therefore, the composition and morphology of exosomes can harbor specific information associated with the physiological and the pathological states of parental cells.

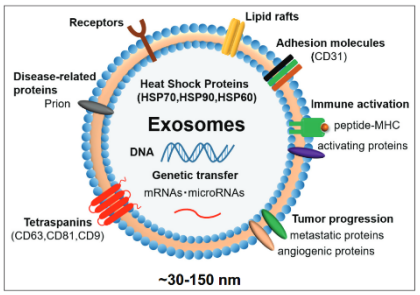

Fig. 1 Schematic showing the typical structure and biomolecular content of exosomes. The payload of exosomes can include proteins, receptors, adhesion molecules, lipids, miRNAs, mRNAs, DNAs, and other bioactive substances.

Several lines of evidence have also suggested that exosomes play an essential role in cancer progression and metastatic spreading through the transfer of their molecular cargos **(Nat Cell Biol. 10, 1470–1476 (2008), Nature, 523,177–182 (2015), Nature Comm., 9, 4284 (2018))**. Since exosomes contain cell type specific adhesion molecules (see **Fig.1**), it has been suggested that tumor-derived exosomes may differ from healthy ones in terms of the structural, molecular, and mechanical characteristics. The physical/biochemical characterization and analyses of these vesicles would thus allow early detection of changes associated with the presence of cancers and other diseases.

２．研究の目的

The main objective of this research project was to reveal the detailed structural and nanomechanical properties of exosomes derived from normal and cancer cells using AFM under near-physiological conditions. To elucidate the potential differences in the structural and mechanical characteristics of exosomes related to malignancy, exosomes derived from healthy (non-malignant) and malignant cells will be characterized using 3D-atomic force microscopy (3D-AFM) force mapping method together with other biochemical methods. In addition to this, to investigate the possible differences in specific biomolecular composition of exosomes between normal and cancer-derived exosomes, we aim to perform force mapping experiments to probe the surface receptors, proteins, lipids, and other biomolecular contents on individual exosomes using AFM probes that are functionalized with biomolecules specific to exosome surface proteins and receptors, i.e., ligands and/or antibodies. Furthermore, internal contents of exosomes will also be elucidated by rupturing the exosomes using AFM probe. Thus, this research proposal aimed to obtain high-resolution images of exosomes and to reveal their mechanical properties, for better understating of the bio-physical and bio-molecular variations between normal and cancer-derived exosomes.

３．研究の方法

To achieve these goals, I employed a highly sophisticated AFM-based force mapping method (3D-AFM) in a liquid environment (ACS Nano, 6, 9013(2012)) (**Fig.2**). In this method, the tip is scanned both vertically and laterally to probe the interaction forces acting between tip and surface. The recorded map of 3D force field can then be used to extract the local elastic properties of exosomes, i.e., stiffness/hardness, and Young's modulus. Thus, 3D-AFM enables the simultaneous acquisition of a structural/morphological and nano-mechanical property map, thereby the specific morphological and molecular variations can be correlated to the mechanical property changes. We also used other biochemical measurements to investigate the protein content in exosomes using nano-liquid chromatography mass spectrometry (LC-MS), Western blot, and ELISA measurements.

We applied 3D-AFM, in force mapping mode, to assess the structural and nanomechanical properties of exosomes released from three types of cells in a physiologically relevant environment. The 3D-AFM force maps enabled previously unidentified substructures of individual exosomes to be observed, indicating the presence of distinct nanodomains bulging out from the membrane surface **(Fig.3)**. These protruding features were attributed to membrane-associated proteins exposed on the outer surface. To determine the identity of these features, tip functionalization with antibodies specific to exosomal surface proteins is necessary. This will be our next goal. The nanomechanical properties of exosomes were determined from the 3D-force maps using the Sneddon (conical) model.

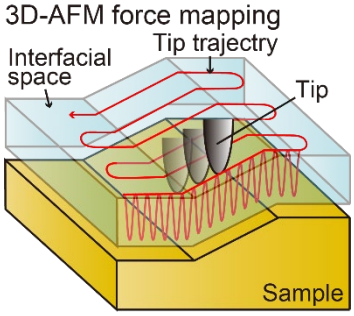

Fig.2: Schematic illustration showing the 3D-AFM Method.

A relatively high Young's modulus value, ranging from 50 to 350 MPa on average, was found compared to that of synthetic liposomes, which signifies a crucial role for membrane-associated proteins in exosome mechanical properties. We revealed malignancy state-dependent changes in the mechanical properties of exosomes and their parent cells, and our results showed differences between the nanomechanical properties of metastatic and nonmetastatic tumor cell-derived exosomes. Highly aggressive metastatic 143B cell-derived exosomes exhibited an increased Young's modulus, 192 MPa, compared with 118 MPa for nonmetastatic HOS cell-derived exosomes. Protein profiling analysis using LC-MS/MS, western blotting, and ELISA indicated that the metastatic tumor cell-derived exosomes were enriched in specific proteins involved in the elastic fiber formation. We thus concluded that these elastic fiber-associated proteins were responsible for the increased vesicle rigidity. We also performed nanomechanical measurements for parental HOS and 143B cells that secreted the exosomes to confirm the general principle that malignant cells tend to be softer than their healthy counterparts. The metastatic tumor cells (143B) had an apparent Young's modulus lower than that of the nonmetastatic ones (HOS). In contrast to their daughter exosomes, cell-based ELISA analysis indicated that the elastic fiber-associated proteins are expressed at significantly higher levels in parental HOS cells than in 143B cells. Based on these findings, it is plausible that metastatic tumor cells may exploit exosomes to release stiffening proteins to preserve their softness. These findings suggest that exosomes stiffness characteristics combined with their easy accessibility almost in all body fluids could have the potential to serve as non-invasive mechanobiological markers for early-stage identification of changes related to the cancers and other diseases, which can, in turn, allow early diagnosis of cancers.

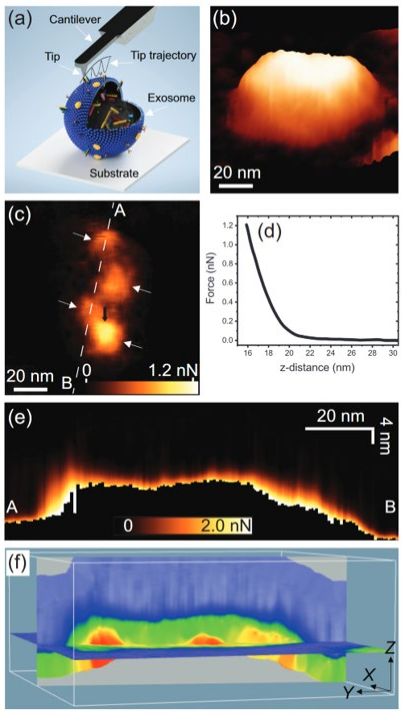

Fig.3: Substructural details of exosomes by 3D-AFM.

Understanding of the biological functions of exosomes is one of the most critical issues in exosomes research, particularly in cancer, and are not yet fully understood. This is because the previous approaches have been unable to fully characterize these vesicles due to their small size, morphological and compositional heterogeneity. For the first time, we resolve the substructural details of exosomes using 3D-AFM.

Exosomes play a crucial role in cancer development and metastatic spread. They have great potential as novel biomarkers for disease diagnosis. A reliable and accurate method for characterizing their structural, nanomechanical, and molecular properties is required, which will allow us to determine malignancy-dependent changes. We employed 3D-AFM to reveal the structural and associated-nanomechanical properties of exosomes. 3D-AFM showed the presence of distinct nanodomains bulging out from the membrane surface, which can be attributed to the heterogeneous presence of membrane-associated proteins exposed on the vesicles' outer surfaces. Our results further showed differences between the nanomechanical properties of metastatic and nonmetastatic cancer cell-derived exosomes.

Published papers:

16) C. Chen*, **A. Yurtsever**, P. Li*, L. Sun*, Two-Dimensional Layered Nanomaterials Steering Self-Assembly of Dodecapeptides with Three Building Blocks, ***ACS Appl. Mater. Interfaces****, 16, 15,* 19699–19710 (2024).

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4) 3D-AFM investigations of solvation structures on polysaccharide-based nanocrystals and self-assembled peptide nanostructures
Ayhan Yurtsever
IUPAB/NanoLSI Workshop on the computational biophysics of atomic force microscopy, Kanazawa University, JAPAN, Sep 20, 2022 Invited

3) Probing the structural details of cellulose and chitin nanocrystal-water interfaces by 3D-AFM
A. Yurtsever, P. Wang, F. Priante, Y. M. Jaques, K. Miyazawa, K. Miyata, M. J, MacLachlan, A. S. Foster, T. Fukuma
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1) Direct Visualisation of Helical Structures of Poly(diphenylacetylene)s Bearing Chiral Amide Pendants by High-Resolution Atomic Force Microscopy
Sandip Das, **Ayhan Yurtsever**, Tatsuya Nishimura, Rafael Rodríguez, Daisuke Hirose, Kazuki Miyata, Ayumi Sumino, Takeshi Fukuma, Katsuhiro Maeda
Molecular Chirality 2021 (MC2021) in Hiroshima, Japan, Nov 30, 2021

５．主な発表論文等

〔雑誌論文〕　計16件（うち査読付論文　16件／うち国際共著　16件／うちオープンアクセス　7件）

１．著者名 Yurtsever Ayhan、Hirata Kaito、Kojima Ryohei、Miyazawa Keisuke、Miyata Kazuki、Kesornsit Sanhanut、Zareie Hadi、Sun Linhao、Maeda Katsuhiro、Sarikaya Mehmet、Fukuma Takeshi	４．巻 -
２．論文標題 Dynamics of Molecular Self‐Assembly of Short Peptides at Liquid-Solid Interfaces: Effect of Charged Amino Acid Point Mutations	５．発行年 2024年
３．雑誌名 Small	６．最初と最後の頁 -
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オープンアクセス オープンアクセスとしている（また、その予定である）	国際共著 該当する

１．著者名 Chen Chen、Yurtsever Ayhan、Li Peiying、Sun Linhao	４．巻 16
２．論文標題 Two-Dimensional Layered Nanomaterials Steering Self-Assembly of Dodecapeptides with Three Building Blocks	５．発行年 2024年
３．雑誌名 ACS Appl. Mater. Interfaces	６．最初と最後の頁 19699-19710
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1．著者名 Biyani Radhika、Hirata Kaito、Oqmhula Kenji、Yurtsever Ayhan、Hongo Kenta、Maezono Ryo、Takagi Masahiro、Fukuma Takeshi、Biyani Manish	4．巻 15
2．論文標題 Biophysical Properties of the Fibril Structure of the Toxic Conformer of Amyloid-β42: Characterization by Atomic Force Microscopy in Liquid and Molecular Docking	5．発行年 2023年
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1．著者名 Soeta Takahiro、Kurobe Shota、Nirei Yutaro、Kurokawa Naoto、Wei Weilin、Yurtsever Ayhan、Fukuma Takeshi、Ukaji Yutaka	4．巻 29
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2．論文標題 Actin-binding domain of Rng2 sparsely bound on F-actin strongly inhibits actin movement on myosin II	5．発行年 2023年
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2．論文標題 Structural and mechanical characteristics of exosomes from osteosarcoma cells explored by 3D-atomic force microscopy	5．発行年 2021年
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Ayhan Yurtsever

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〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関