News Release

Title

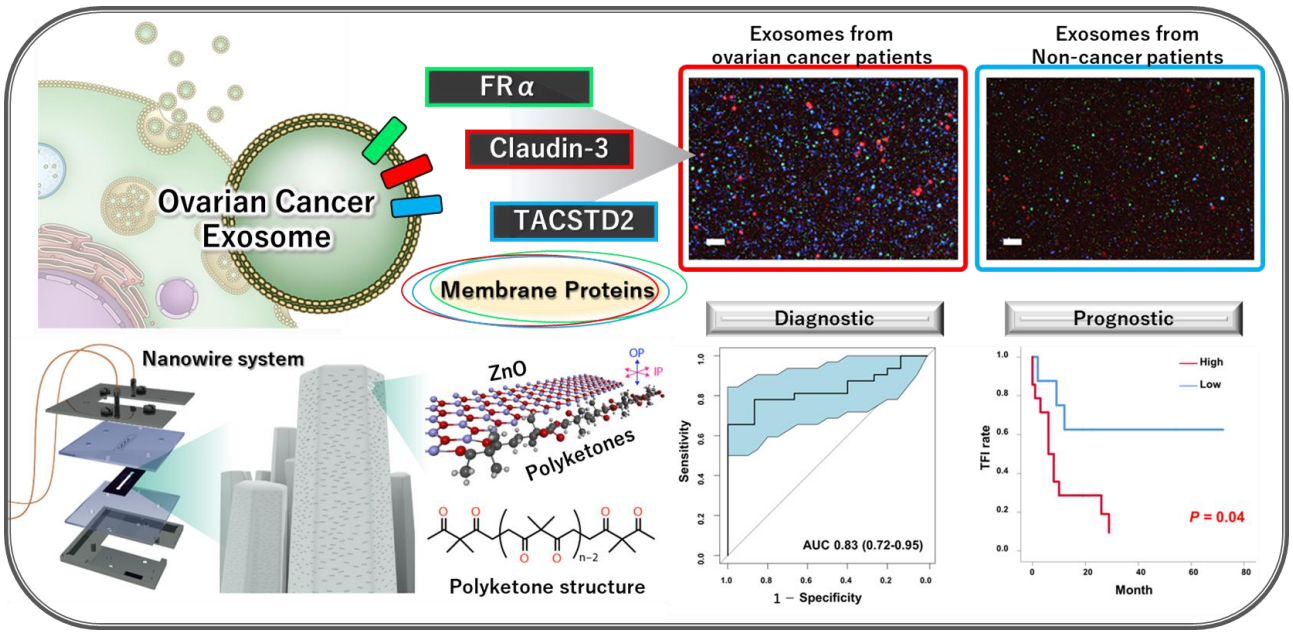
Identifying high-grade serous ovarian carcinoma-specific extracellular vesicles by polyketone-coated nanowires

Key Points

- Revealing the detailed protein information on ovarian cancer EVs and their diversity
- Development of polyketone-coaetd nanowires for simple EV isolation
- Discovery of ovarian cancer specific membrane proteins and reveals their utility
- Expected to be a new EV biomarker strategy to improve ovarian cancer treatment

Summary

Extracellular vesicles (EVs), including exosomes, are present in all human body fluids and have attracted attention as an essential tool for intercellular communication. Membrane proteins on the surface of EVs are necessary to detect specific EVs. They can be used as biomarkers on their own. However, specific EV membrane proteins in ovarian cancer are not known. Ovarian cancer is a female genital malignancy with a poor prognosis. It is one of the leading causes of cancer death among women worldwide. Ovarian cancer is one of the most challenging cancers to detect in its early stages, and the development of a highly accurate and sensitive biomarker is urgently needed. This study identified ovarian cancer EV-associated membrane proteins, FRα, Claudin-3, and TACSTD2, through detailed proteomic analysis in ovarian cancer-derived EVs. In addition, by using nanowire systems, one of the methods to capture EVs, we succeeded in attaching polyketone chains to ZnO nanowires, which enabled to capture EVs with higher performance. Using the new method herein, we have developed a new detection method using EVs in ovarian cancer patients. These findings hold promise as a new biomarker strategy in ovarian cancer.



Research Background

Ovarian cancer is an inferior prognosis cancer that affects about 13,000 people annually in Japan, and almost half of them die. Because early screening is arduous, most cases are diagnosed at an advanced stage, and the 5-year survival rate is said to be less than 45%. Early detection is essential, but currently, there are not enough effective screening methods. There are various types of ovarian cancer, but this study focused on high-grade serous carcinoma (HGSC), the most frequent type. Until now, little was known about HGSC-specific and sensitive biomarkers and membrane proteins associated with EVs.

Among the various bioactive substances contained in EVs, membrane proteins are one of the most important and applicable targets. In addition, understanding the heterogeneity of EVs in body fluids has been recently discussed. For this reason, detailed and sophisticated EV proteomic evaluation has been a significant challenge in this field. For the practical use of EVs as clinical biomarkers, (1) identification of disease-related molecules on EVs and, (2) understanding of EV heterogeneity, (3) simplification of EV supplementation methods are all critical issues to challenge. To address the third point, innovative technologies were promising ways to resolve.

Research Results

The research group concurrently extracted small EVs (sEV) below 200 nm and medium/large EVs (m/lEV) above 200 nm from ovarian cancer cells, noncancerous cells, and blood and ascites fluid from ovarian cancer patients, and analyzed them comprehensively using liquid chromatography-mass spectrometry (LC-MS/MS) was used to analyze the proteins. As a result, it

became clear that sEV and m/lEV were loaded with clearly different molecules. Further validation showed that sEV is a more suitable biomarker target than m/lEV. As a result of rigor selection steps, FRα, Claudin-3, and TACSTD2, membrane proteins strongly associated with HGSCs, were only identified in sEV, i.e., exosomes. For exosome capture, we developed polyketone chain-coated nanowires (pNWs) and demonstrated that pNWs could separate exosomes from serum and ascites fluid in a simple procedure. The results of our pNW-based exosome analysis of ovarian cancer patient exosomes showed that each of the three identified proteins is useful as a biomarker for HGSCs.

Research Summary and Future Perspective

This research has provided new findings to address all issues for the practical use of EV biomarkers: (1) identification of disease-related molecules on EVs, (2) understanding of EV heterogeneity, and (3) simplification of the EV supplementation method. The results of this research will contribute to further understanding of EVs including exosomes, elucidation of the mechanism of ovarian cancer disease progression, and clinical application of ovarian cancer EVs in a broad range of fields. Further investigation and validation are needed to lead to the realization of biomarkers based on ovarian cancer exosomes.

Publication

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Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Sci_230708.pdf

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