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研究課題名(和文) 卵巣癌における“hot spot”変異解析に基づく新規薬剤の探索

研究課題名(英文) Investigation of a new drug based on DNA mutation analysis in ovarian cancer.

研究代表者

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研究成果の概要(和文)：卵巣癌において最も予後不良の組織型である卵巣高異型度漿液性腺癌(High-grade serous ovarian carcinoma; HGSOC)について研究を行った。そして、HGSOCの4つの遺伝子発現サブタイプに該当する病理組織分類を樹立し、その分類とタキサン感受性との相関を示した。この結果により、HGSOCの中で、タキサンを含む化学療法レジメンのためのバイオマーカーを明らかにできる可能性がある。

研究成果の概要(英文)：We conducted a research about high-grade serous ovarian carcinoma (HGSOC), poor prognostic histopathological subtype of ovarian carcinoma. We established a novel histopathological classification that correlates with the four gene expression subtypes and taxane sensitivity of HGSOC. This result may identify a biomarker to select a taxane-containing chemotherapeutic regimen in HGSOC.

研究分野：婦人科腫瘍

キーワード：卵巣癌 遺伝子異常 バイオマーカー

1. 研究開始当初の背景

卵巣癌は診断時には進行例が多く、手術のみでは完治せず、化学療法が必須である。しかし、化学療法を行っても、効果がない症例があり、その選別が重要である。またいったんは化学療法が奏功しても、再発し、最終的には薬物療法抵抗性となることが多い。卵巣高異型度漿液性腺癌 (high-grade serous ovarian carcinoma; HGSOc) は、卵巣癌の中でも最も予後不良の組織型で、新規治療法の開発が求められている。

2. 研究の目的

HGSOc に対する、薬物療法感受性のバイオマーカーの探索、および、新規薬物療法の開発を目的とした。

3. 研究の方法

まず、自施設の HGSOc の発現マイクロアレイデータを解析し、さらに病理組織的に再検討した。The Cancer Genome Atlas (TCGA) などの、HGSOc のエクソームシーケンシング、遺伝子発現マイクロアレイ、コピー数データセットを解析した。以上のデータと、薬剤感受性や予後を調べた。

4. 研究成果

卵巣漿液性腺癌は TCGA において、4 つの遺伝子発現サブタイプに分かれるが、それぞれのサブタイプと関連する病理組織細分類を樹立した。そして、その中で Mesenchymal Transition タイプが、タキサン感受性が高いことを示した。この結果は、Mesenchymal Transition タイプでは、dose-dense TC 療法のような、タキサン投与量の多い化学療法レジメンが有用であることを示唆している。

5. 主な発表論文等

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2) シンポジウム口演「卵巣癌の微小免疫環境解析と抗 PD-1 抗体療法の展望」濱西 潤三、万代 昌紀、松村 謙臣、安彦 郁、村上 隆介、馬場 長、山口 建、小西 郁生 上記 2 演題；第 53 回日本癌治療学会、平成 27 年 10 月 29 日～31 日、国立京都国際会館、京都市

3) "Identification through functional genomics screening of factors whose downregulation enhances the side population in ovarian cancer." Noriomi Matsumura, Koji Yamanoi, Susan K Murphy, Junzo Hamanishi, Kaoru Abiko, Ken Yamaguchi, Tsukasa Baba, Masafumi Koshiyama, Ikuo Konishi

4) "Chemoimmunotherapy with PD-1 blockade and paclitaxel induce a potent antitumor immunity in ovarian cancers." Junzo Hamanishi, Jin Peng, Noriomi Matsumura, Kaoru Abiko, Tsukasa Baba, Ken Yamaguchi, Ikuo Konishi, Masaki Mandai

5) "Inhibition of Snail-induced EMT

promotes anti-tumor immune response in ovarian cancer" Mana Taki, Kaoru Abiko, Noriomi Matsumura, Tsukasa Baba, Junzo Hamanishi, Naoki Horikawa, Ikuo Konishi 6) "Expression of VEGF in ovarian cancer suppresses tumor immunity through recruitment of myeloid derived suppressor cells" Naoki Horikawa, Kaoru Abiko, Noriomi Matsumura, Junzo Hamanishi, Susan K Murphy, Tsukasa Baba, Ken Yamaguchi, Masafumi Koshiyama, Ikuo Konishi 以上 4 演題；An AACR Special Conference on Advances in Ovarian Cancer Research, Oct 17-20, 2015, Hyatt Regency Orlando, Orlando, FL

7) シンポジウム英語口演 "Survival and Durable Tumor Remission in Patients with Platinum-resistant Ovarian Cancer Receiving Nivolumab" Junzo Hamanishi, Masaki Mandai, Noriomi Matsumura, Kaoru Abiko, Tsukasa Baba, Ken Yamaguchi, Ikuo Konishi

第 74 回日本学会学術総会、平成 27 年 10 月 8 日～10 日、名古屋国際会議場、名古屋市

8) シンポジウム英語口演 "Genomic Alterations of Ovarian Clear Cell Carcinoma" 松村 謙臣、村上隆介、日笠幸一郎、堤孝信、J. B. Brown、Hisham Abou-Taleb、濱西潤三、山口建、安彦郁、馬場長、越山雅文、山田亮、松田文彦、奥野恭史、小西郁生 第 57 回日本婦人科腫瘍学会学術講演会 平成 27 年 8 月 7 日～9 日、アイーナいわて県民情報交流センター・マリオス盛岡地域交流センター、盛岡市

9) シンポジウム口演 "Immune checkpoint PD-1 signal; the metastatic promotion of ovarian cancer and the target of new treatment strategy" 濱西潤三、万代昌紀、松村 謙臣、安彦郁、Jin Peng、馬場長、山口建、小西 郁生

第 73 回日本癌学会学術総会、H26 年 9 月 25 日～27 日、パシフィコ横浜、横浜市

10) "HNF1B contributes to resistance to oxidative stress through modification of metabolism in ovarian clear cell carcinoma." K. Yamaguchi, Y. Amano, N. Matsumura, M. Mandai, K. Abiko, J. Hamanishi, Y. Yoshioka, T. Baba, I. Konishi 45th Annual Meeting on Women's Cancer, 2014/3/22-3/25, Tampa convention center, Tampa, FL, USA

11) Symposium "Selection of drugs against ovarian cancer based on gene expression profile." Noriomi Matsumura, Ryusuke Murakami, Masafumi Koshiyama, Tsukasa Baba, Junzo Hamanishi, Ken Yamaguchi, Kaoru Abiko, Yumiko Yoshioka, Ikuo Konishi

12) "Lymph node metastasis in cervical cancer: Novel diagnostic criteria in multi-detector computed tomography" Koji

Yamanoi, Noriomi Matsumura, Aki Kido, Tsukasa Baba, Junzo Hamanishi, Ken Yamaguchi, Yumiko Yoshioka, Hisham Abou, Taleb, Kaori Togashi, Ikuo Konishi

13) "SWI/SNF complex is a novel prognostic factor in clear cell carcinoma (CCC) of the ovary" Hisham A Abou-Taleb, Ken Yamaguchi, Noriomi Matsumura, Yasuaki Amano, Koji Yamanoi, Ryusuke Murakami, Tsukasa Baba, Yumiko Yoshioka, Junzo Hamanishi, Masaki Mandai, Ikuo Konishi

14) "Chemotherapy induces PD-L1 overexpression via NF- κ B signal pathway in ovarian cancer cells" Jin Peng, Junzo Hamanishi, Noriomi Matsumura, Kaoru Abiko, Tsukasa Baba, Ken Yamaguchi, Masaki Mandai, Ikuo Konishi

以上 4 演題 ; The 3rd Asian Society of Gynecologic Oncology meeting,

2013/12/13-15, Kyoto, The Westin Miyako

15) 招待講演「検診対象としての卵巣癌」松村謙臣、小西郁生 第 22 回婦人科がん検診学会学術集会、平成 25 年 11 月 9 日～10 日、熊本市、くまもと県民交流館パレオ

16) シンポジウム「卵巣癌における、がん免疫逃避機構の解明と新規治療戦略～抗 PD-1 抗体を用いた次世代型免疫療法の臨床応用～ / Development of novel therapy targeting immune escape in ovarian cancer~Immuno-therapy using anti PD-1 antibody~.」濱西潤三、松村謙臣、安彦郁、Peng Jin、馬場長、山口建、小西郁生、万代昌紀

第 72 回日本癌学会学術総会、平成 25 年 10 月 3 日～5 日、横浜市、パシフィコ横浜

17) " Induction of PD-L1 expression by cytotoxic agents through activation of NF- κ B signal." Junzo Hamanishi, Noriomi Matsumura, Peng Jin, Kaoru Abiko, Naoki Horikawa, Ken Yamaguchi, Tsukasa Baba, Susan K Murphy, Ikuo Konishi

18) " Functional genomics approach links anchorage-independence with tumor dormancy in ovarian cancer." Noriomi Matsumura, Koji Yamanoi, Yasuaki Amano, Junzo Hamanishi, Tsukasa Baba, Susan K Murphy, Ikuo Konishi

19) 口演 " HNF-1 confers resistance to oxidative stress of ovarian clear cell carcinoma. "

Yasuaki Amano, Ken Yamaguchi, Masaki Mandai, Noriomi Matsumura, Junzo Hamanishi, Tsukasa Baba, Koji Yamanoi, Susan K Murphy, Ikuo Konishi

以上 3 演題 ; An AACR Special Conference on Advances in Ovarian Cancer Research, 平成 25 年 9 月 18 日～21 日、フロリダ州マイアミ市、J.W. Marriott Marquis Miami

20) シンポジウム「遺伝子発現解析に基づく卵巣癌の薬剤選択を目指して」

松村謙臣、村上隆介、山ノ井康二、山村省吾、山口建、濱西潤三、吉岡弓子、馬場長、森誠一、小西郁生、万代昌紀

第 65 回日本産科婦人科学会学術講演会、平成 25 年 5 月 10 日～12 日、札幌市、ロイトン札幌 / ホテル札幌芸文館 / 札幌プリンスホテル / 札幌市教育文化会館

〔図書〕(計 0 件)

〔産業財産権〕出願状況 (計 0 件)

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