委員会企画　国際委員会

国際学会報告（SABCS2023，GBCC2023，TIBCS2023）

委員会-国際-1

Expression and co-expression patterns of TROP2 and HER2 in breast cancer: implications for bispecific antibody-drug conjugate therapy

[1]国立がん研究センター中央病院　腫瘍内科、
[2]国立がん研究センター中央病院　病理診断科

大西　舞[1]、下井　辰徳[1]、小島　勇貴[1]、矢崎　秀[1]、山中　太郎[1]、
北台　留衣[1]、河知あすか[1]、大熊ひとみ[1]、齋藤亜由美[1]、伊藤　宗洋[1]、
喜多　昭介[1]、前嶋　愛子[1]、西川　忠曉[1]、須藤　一起[1]、野口　瑛美[1]、
藤原　康弘[1]、吉田　正行[2]、米盛　勧[1]

Introduction: Antibody-drug conjugates (ADC) targeting trophoblast cell surface antigen 2 (TROP2) , such as sacituzumab-govitecan and datopotamab-deruxtecan, have recently been developed. Preclinical study has reported the efficacy of anti-human epidermal growth factor receptor 2 (HER2) and TROP2 bispecific ADCs in treating HER2 and TROP2 co-expressing tumors, including HER2-low tumors in various solid tumors (Chengzhang Shang et al: AACR 2023) . In this study, we aimed to evaluate the expression of TROP2 by immunohistochemistry (IHC) at different sites and investigate the changing status and co-expression of HER2 and TROP2 among breast cancer patients.
Methods: ・We collected 244 archival paired samples of primary tumorsand metastatic sites from 111 breast cancer patients treatedin our hospital from 2000 to 2018. Surgical specimens and specimens from one or more recurrent sites were required. Estrogen receptor (ER) , progesterone receptor (PgR) , and HER2 status were determined from previous pathology reports. HER2 low was defined as HER2 IHC score of 1+ or 2+ with negative fluorescent in situ hybridization. In addition, we determined the expression of TROP2 stained with Anti-Human TROP-2 (Clone77220) for IHC assays and categorized the results based on the histochemical score (H-score) .
Results: Among the samples, ER+HER2- was 139, ER+HER2+ was nine, ER-HER2+ was eight, and triple-negative (TN) was 88. The median TROP2 H-score was 10, with a mean of 37.5 (range: 0-265) . Overall, 27% of the samples had H-score of 0, 73% had H-score 1<, 47% had H-score 10<, and 12% had H-score 100<. No statistically significant association was observed between TROP2 expression and breast cancer subtypes (ER+HER2-; H-score =0 24%, H-score 1< 76%, H-score 10< 44%, H-score 100<14%, TN; H-score =0 30%, H-score 1< 70%, H-score 10< 54%, H-score 100< 11%) . On the other hand, samples from the metastatic site showed a higher rate of TROP-2 expression compared to the primary site (primary site; H-score =0 36%, H-score 1< 64%, H-score 10< 35%, H-score 100< 7%, metastatic site; H-score =0 18%, H-score 1< 82%, H-score 10< 59%, H-score 100< 17%; p<0.01) . The rates of TROP2 expression varied among the metastatic sites, with 100% in the liver, 92% in the brain, 89% in lymph nodes, 64% in the lung, and 60% in the bone. Regarding the co-expression of HER2 and TROP2, among HER2-positive samples, 35% were TROP2-negative, 24% had TROP2 H-score <1, and 41% had TROP2 H-score <10. while among HER2 low samples, 21% had TROP2 H-score 0, 27% had TROP2 H-score <1, 39% had TROP2 H-score <10, and TROP2 H-score <100 was found in 13% of patients. Based on the definition of co-expression such as TROP2 <1 and HER2-low or HER2-positive, overall, 40% of the samples had co-expression of HER2 and TROP2 and the metastatic site had a higher rate of co-expression than the primary tumor. (49%, 33% respectively, p=0.002)
Conclusions: Metastatic sites and specific organs show higher rate of TROP2 expression. Additionally, 49% of the samples from metastatic site had the co-expression of HER2 and TROP2, suggesting a potential target for future bispecific ADC therapy.

委員会-国際-2

Selective elimination of CD169$^+$ macrophages in lymph nodes invaded by breast cancers

[1]京都大学医学部附属病院　乳腺外科、[2]京都大学　医生物学研究所、
[3]岩手医科大学　病理学講座、[4]京都大学医学部附属病院　病理診断科、
[5]東京大学　新領域創成科学研究科、[6]関西医科大学　乳腺外科学講座、
[7]京都大学大学院医学研究科　医学統計生物情報学、
[8]東京都立病院機構東京都立駒込病院　乳腺外科、[9]東北大学　加齢医学研究所、
[10]三重大学医学部附属病院　乳腺外科／乳腺センター

前島佑里奈[1,2]、片岡　竜貴[3]、Alexis Vandenbon[2]、平田　勝啓[4]、
竹内　康英[4]、鈴木　穣[5]、福井由紀子[1]、川島　雅央[1]、髙田　正泰[1,6]、
揖斐裕実子[7]、羽賀　博典[4]、森田　智視[7]、戸井　雅和[1,8]、河岡　慎平[2,9]、
河口　浩介[1,10]

Lymph node metastasis is a prognostically significant factor in breast cancer, though the colonization mechanism of cancer cells in this immune cell-rich organ remains elusive. This study aimed to elucidate the impact of breast cancer on the lymph node immune cell landscape. Multiscale transcriptomic analyses were performed on both metastatic and non-metastatic lymph node samples from breast cancer patients with lymph node metastasis. Twenty laser-micro-dissected sections were obtained from 17 lymph nodes across six breast cancer patients at stages II–III, with each patient contributing both types of lymph nodes for direct comparison.
Comparing the transcriptomes of paired lymph nodes with and without metastasis from the same patients revealed selective downregulation of CD169$^+$ macrophage-related genes in metastatic lymph nodes. The spatial transcriptome indicated a potential depletion of CD169$^+$ macrophages, initiators of anticancer immunity, from their residence (sinuses) in metastatic lymph nodes, while other principal immune cell types were unaltered. Mass spectrometry imaging revealed that the numbers of CD169$^+$ macrophages were smaller in the metastatic lymph nodes than in the non-metastatic lymph nodes, suggesting that cancer cells uprooted CD169$^+$ macrophages from the lymph nodes. Conversely, the count of B, T, Treg, and CD11c$^+$ cells remained comparable in both lymph node types, albeit an enrichment of Treg cells around metastasized cancer tissues was observed.
Additional immunohistochemistry analysis of 315 non-metastatic lymph nodes and 159 metastatic lymph nodes from 58 patients with breast cancer showed that a reduced CD169$^+$ macrophage population was prevalent in various breast cancer subtypes. A subset of metastatic lymph nodes (37 out of 159) displayed a complete absence of detectable CD169$^+$ macrophages. The data also depicted a gradual decline in CD169$^+$ macrophages correlating with the pN classification, while no correlation was identified with pathological tumor size classification (pT) or metastasized cancer volume.
The data suggest precedence of CD169$^+$ macrophage elimination over other reported immune cell abnormalities, such as cell number and metabolic irregularities. CD169$^+$ macrophages are a unique type of resident macrophages in the lymphoid organs that present cancer-derived antigens to CD8$^+$ T cells. The antigen-presenting role of CD169$^+$ macrophages to T cells, a pivotal step in adaptive immunity, signifies the catastrophic implications of their suppression. This study underscores CD169$^+$ macrophage suppression as a pronounced pathological phenotype in lymph nodes with breast cancer metastasis, thereby establishing it as a critical future therapeutic target.

委員会-国際-3

Eribulin Induces Chromosomal Instability and Enhances cGAS Expression in the Nucleus of Triple-Negative Breast Cancer

千葉大学　臓器制御外科学

山田　英幸

Background: Eribulin (ERI) , a microtubule polymerization inhibitor, is approved for locally advanced or metastatic breast cancer. However, its effects on drug-naive cancers are not well understood. In EMBRACE trial, ERI improves overall survival (OS) of the patients with metastatic breast cancer. This result might suggest that ERI could be involved in the immune system. In particular, there are a few reports on the effects of ERI on the innate immune system. This study aimed to investigate how ERI influences the innate immune system, focusing on the cyclic-GMP-AMP synthase (cGAS) .
Methods: Clinical samples from the JONIE-3 trial were analyzed using immunohistochemistry (IHC) . 121 patients were assigned to 2 different neoadjuvant chemotherapy (NAC) groups receive ERI (Group E) or paclitaxel (Group P) followed by FEC. The patients of both groups were performed biopsy before and after chemotherapy. We performed IHC on 56 samples and examined for association with pathological complete response (pCR) , which was defined as no invasive redidual tumor tissue in the breast.
Additionally, 5 different cell lines were established to evaluate the acute and chronic effects of ERI treatment.
The cell lines were as follows: no treatment (control) , PTX for short time (PTX short) , PTX for long time (PTX long) , ERI for short time (ERI short) and ERI for long time (ERI long) .
We evaluated the acute effects of short-term dosing, while the chronic effects of long-term dosing, which mimic resistance to treatment. Protein expression of the cGAS-STING pathway was examined, along with cGAS and IFNβ expression levels and their impact on cell division in the above cell lines. Then at the cellular level, each cell lines were evaluated for differences in cGAS and IFNβ expression and their effects on cell division. The differences in cGAS expression between cytoplasmic and nuclear fractions were verified by the cell fractuation assay. In addition, mitotic abnormalities and cell proliferation were also assessed.
Results: In the clinical trial, ERI did not significantly differ from paclitaxel in terms of pathological complete response (pCR) . However, high cGAS expression in Group E (ERI) correlated with increased pCR rates, while no such correlation was observed in Group P (PTX) . Additionally, High IFNβ expression in Group E also correlated with increased pCR rates, differed from Group P. In vitro, ERI upregulated cGAS, STING, pIRF3, and IFNβ protein expression compared to PTX. Notably, ERI induced elevated cGAS expression in the nucleus, as confirmed by immunofluorescence and cell fracturation assays. Additionally, PTX and ERI differed in their ability to cause mitotic abnormalities. PTX induced more micronuclei cells than ERI, on the other hand ERI induced more micronuclei cells. These results were also verified by live cell imaging.
Conclusion: ERI promoted chromosomal instability, leading to increased cGAS expression. These findings contribute to our understanding of ERI's effects on the innate immune response in triple-negative breast cancer, potentially paving the way for improved therapeutic strategies.