Exploratory Research and Hypothesis in Medicine **2023** vol. 8(1) | 81–85
DOI: 10.14218/ERHM.2022.00087

Opinion

Trop-2-Cells, Their Exosomal Cargo, and the Potential Impact on Diagnostics and Therapeutics in Breast Cancer: The Expanding Frontiers

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Received: July 18, 2022 | **Revised:** August 07, 2022 | **Accepted:** September 07, 2022 | **Published online:** September 28, 2022

Abstract

Recently, an anti-trophoblast surface antigen-2 (Trop-2) antibody-drug conjugate targeting Trop-2 positive cancer cells has been approved for treating patients with unresectable locally advanced or metastatic triple-negative breast cancer, who have failed two or more lines of systemic chemotherapy. This has renewed the interest in translational research of Trop-2 positive breast cancer, the gene TACSTD2 and microRNAs that interact with it, and the signaling networks sparked by Trop-2 mediated signaling. In addition, this opinion paper argues that exosomes, extracellular vesicles that are released from Trop-2 positive cancer cells, could play a significant role in cancer progression. Furthermore, diagnostic applications using Trop-2-released exosomes, the cargo exosomes carry, which could be any genetic information such as specific miRNAs, adhesion molecules such as integrins, and metabolites, are yet to be explored in breast cancer patients. Most of the evidence and data are obtained from studies in epithelial cancers other than breast cancers, which have been introduced in the current paper. Therefore, this article briefly summarizes previously published data on other cancer types, forms some hypotheses, and proposes research questions and directions that may be explored further.

Endeavors have recently been successful in elucidating the mechanism of trophoblast surface antigen-2 (Trop-2) signaling in various epithelial cancers. Four decades ago, Lipinski and his Stanford University colleagues reported the generation of monoclonal antibodies to normal and malignant trophoblast cells.[1] Trop-2 is one such membrane antigen targeted by anti-Trop-2 monoclonal antibodies. Subsequently, Trop-2 was recognized as a ubiquitous transmembrane glycoprotein in most epithelial cancers. Trop-2, along with Trop-1, which is commonly known as an epithelial cell adhesion molecule, are encoded by genes in the tumor-associated calcium signal transducer (TACSTD) family.[2] Both these proteins are involved in the function of tight junctions regulating epithelial cell-cell adhesion.[2] The Trop-2 protein traverses the cell membrane with a 26-amino acid cytoplasmic tail, which contains a phosphorylatable serine residue by protein kinase C isoforms and a conserved phosphatidylinositol (4, 5) bisphosphate (PIP2) binding site.[2] Compared with the normal tissues, upregulation of Trop-2 mRNA could be found invariably in most solid tumors, including the lung, colon, rectum, breast, ovary, and endometrium.[3,4] Apparently, this Trop-2 gene upregulation provides selective advantages for Trop-2 overexpressing cancer cells. Although further research would be needed to provide more evidence, Trop-2 gene overexpression would correlate with the abundance of the Trop-2 protein on the cell membrane and inside the cytoplasm, which could be detected using immunohistochemical staining of a pathological slide.[5,6] Trop-2 glycoproteins are involved in the cancer cell-cell as well as cell-extracellular matrix communications. As a result, cancer cells could migrate and possess invasive properties within the tumor microenvironment. Furthermore, research in this arena in the past decade has provided some crucial insights that Trop-2 plays a central role in the cleavage by tissue necrosis factor-α-converting enzyme (TACE, also known as ADAM17) and activating Beta-1 (β_1) integrin-dependent migration through extracellular fibronectin of which the main receptors are primarily Alpha 5 beta 1 ($\alpha_5\beta_1$) integrins assembling with the intracellular focal adhesion kinase.[7–10] This cascade of interactions and activations would ul-

Keywords: Triple-negative breast cancer; Trop-2; Exosome; Tumor microenvironment; Anti-Trop-2-targeted therapy.

Abbreviations: ADAM, a disintegrin and metalloprotease 17; ADC, antibody-drug conjugate; FDA, Food and Drug Administration; miR, microRNA; mRNA, messenger RNA; TACSTD, tumor-associated calcium signal transducer; Trop-2, trophoblast surface antigen-2.

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How to cite this article: Kok VC. Trop-2-Cells, Their Exosomal Cargo, and the Potential Impact on Diagnostics and Therapeutics in Breast Cancer: The Expanding Frontiers. *Explor Res Hypothesis Med* 2023;8(1):81–85. doi: 10.14218/ERHM.2022.00087.

timately mobilize the actin cytoskeletal elements to enhance the mobility of the cancer cells.[11] Moreover, Trop-2 signaling pathways would promote cancer growth and aggressiveness through context-dependent cooperation with cyclin D1, activating RAS, modulating IGF-1R signaling, and apoptosis evasion.[4,12,13]

Different pools of Trop-2 cellular protein could be localized in separate cell compartments: the cell membrane or cytoplasm.[14] Recently, the transmembrane Trop-2 glycoprotein was successfully targeted by several antibody-drug conjugates (ADC) with different chemotherapeutic payloads, particularly camptothecin derivatives. Sacituzumab govitecan-hziy was the first Trop-2 targeting ADC cleared by the Food and Drug Administration (FDA) (Maryland, USA) in April 2020.[15–17] In addition, datopotamab deruxtecan, using a different topoisomerase I inhibitor as a payload, is actively being developed for use in solid tumors.[18] Several other novel Trop-2-targeted ADCs in the early phase of development include STI-3258 (NCT05060276), JS-108-Tub-196 payload (NCT04601285), FDA018 (NCT05174637), and SKB-264-belotecan derived payload (NCT04152499). Thus, 'targeted chemotherapy' could be a viable and practical antineoplastic approach for systemic administration to specifically target Trop-2-bearing cancer cells.[19] Treatment response from single-agent anti-Trop-2 treatment could let us appreciate the magnitude of the impact and efficacy of targeting Trop-2 in a cancer type. For example, a phase 2 trial, called NeoSTAR, in which the single-agent sacituzumab govitecan was administered in a neoadjuvant setting for localized triple-negative breast cancer, yielded a clinical response rate of 62% and a complete pathological response of 30%.[20] Therefore, these successful single-agent therapies would make Trop-2 targeted ADC a good choice for a combination of chemotherapy in various clinical scenarios. Hence, further clinical investigations would be needed to differentiate which molecular or pathological characteristics would be able to predict the response to a Trop-2 targeted agent.

Nevertheless, a literature search on the query of the knowledge gained from the Trop-2 related basic science research in breast cancer has yet to be generated. Initially, investigators at the Roswell Park Comprehensive Cancer Institute, New York, USA determined a very low Trop-2 expression in ER-positive/HER2-negative breast cancer tissues compared to ER-negative/HER2-positive breast cancer tissues using real-time quantitative reverse transcription-PCR analysis.[21] However, additional data would still be needed to determine the differential expression of Trop-2 by the intrinsic breast cancer subtypes. A recent study showed that high expression of the Trop-2 gene, TACSTD2, in invasive breast carcinoma was associated with higher cyclin D1, p53 aberration, lymph node involvement, and distant metastases.[4] Nevertheless, the mechanisms underlying these associations were not completely clear; TACSTD2 overexpression could be correlated with the abundance of specific miRNAs that would affect the expression of other genes. According to the MiRTarBase search, 58 experimentally validated miRNA–TACSTD2 gene interactions in humans were retrieved with annotated functional changes.[22] Notably, in a study of a head and neck squamous cell carcinoma cell line, loss of miR-125b-1 activated TACSTD2 expression resulted in the dysfunction in the mitogen-activated protein kinase pathway, thus contributing to cancer progression.[23] Hence, further research on miR-125b-1 as well as the other miRNAs and TACSTD2 interactions in breast cancer would need to be performed. Moreover, it would be particularly interesting to investigate specific miRNAs or the miRNA signature of the cargo carried by the Trop-2-positive cell-released exosomes.[24]

The tumoral heterogeneity of membrane-bound Trop-2 could play a role in the intrinsic resistance to Trop-2-targeted agents. Recent research also revealed structural changes in the transmembrane Trop-2 glycoprotein through cleavage in the first thyroglobulin domain loop at residues R87–T88, such as by ADAM10 to activate cancer cell growth and progression.[8] In addition, Remšík *et al*. reported a mechanism of the Trop-2 expression determined epigenetically or by epithelial-to-mesenchymal transition transcription factors.[25] Their research findings indicated the need for caution in clonal selection of Trop-2-containing cancer cells with a mesenchymal phenotype, which could result in an acquired resistance from single-agent anti-Trop-2 treatment.

Trop-2-containing cancer cells are also involved in intercellular or cellular-matrix communication via an exosome release and transport.[26–30] The findings of research related to Trop-2-containing exosomes in cancer pathogenesis and progression or therapeutic applications from other epithelial cancers were helpful for generating hypotheses in breast cancer. For example, it would be interesting to investigate the details, functionality, and impact on breast cancer progression of different exosomes with specific cargo payloads released from Trop-2 positive cells. Specific organotropism in cancer metastasis would be partly but significantly facilitated by different expression patterns of integrin in cancer cells.[24] Furthermore, cancer cells could establish a pre-metastatic niche in a specific organ, as a hallmark of cancer, as determined by the integrin subunit carried by integrin-containing exosomes released from the tumor. In a prostate cancer transgenic mouse model, transmembrane Trop-2 glycoprotein was preferentially bound to the integrin α5 subunit and not α3.[9] A recent cell-line study of the EMT-associated integrin β3 showed the suppression of integrin β3 in mesenchymal subtype triple-negative breast cancer-induced EMT reversion and inhibited cancer progression.[31] Therefore, further studies of the interactions and dissemination of specific oncogenic integrins through exosomes in various intrinsic subtypes of Trop-2-overexpressing breast cancer cells would be needed.

The phenotype transformation of Trop-2-negative recipient cells into Trop-2-positive cancer cells could occur via migration, release, and transfection of Trop-2-containing exosomes released from a tumor.[32] Moreover, increased interest in understanding the cancer biology of the EMT, MET (a reversal of EMT), clonal selection of immune evasion from immunotherapy, and metastasis dissemination therapy in breast cancer would initiate further research on the breast cancer cells-derived exosomes, thus investigating the cargo payload carried in exosomes derived from Trop-2-containing cancer cells.

The diagnostic challenge in analyzing Trop-2-cell-released exosomes and their cargo payloads, such as miRNAs or integrins would involve the same technical issues as the current bottleneck in exosome research and augmented intelligence analysis in areas of exosome isolation from biofluids, characterization and molecular profiling of cancer-derived exosomes. Nevertheless, understanding the intricacies of the exosomal cargo may provide insights useful for patient management. For example, Joshi *et al*. reported that compared to patients achieving a pathologically complete response, patients with breast cancer who presented a residual disease after neoadjuvant chemotherapy showed 2.52-fold higher plasma exosome levels of metabolic signatures enriched in the citrate cycle, porphyrin metabolism, glycolysis, gluconeogenesis, and urea cycle pathways.[30]

In addition, clinically relevant issues affected Trop-2-related diagnostics. In early human studies, the immunohistochemical staining of archival tissue blocks was categorized into 4-tier positivity

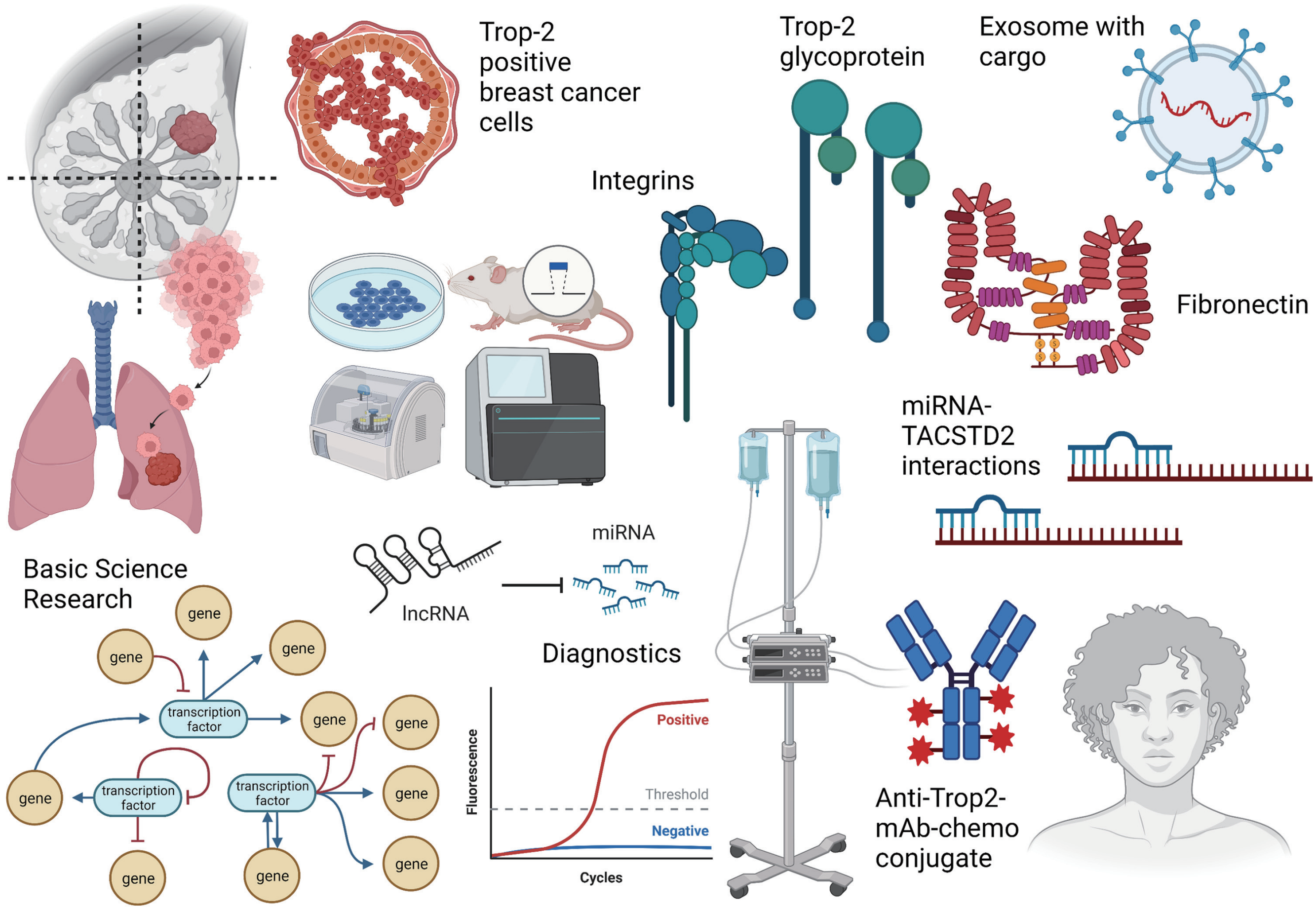

Fig. 1. A conceptual schematic diagram of abstractions of the expanding frontiers of basic science research specifically on Trop-2 positive breast cancer. The future direction of translational research of Trop-2 positive breast cancer could include studies focusing on the co-expressing genes of TACSTD2 and microRNAs that interact with it, as well as the signaling network sparked by Trop-2 mediated signaling. In addition, exosomes and extracellular vesicles that are released from Trop-2 positive cancer cells could play a significant role in cancer progression. Furthermore, diagnostic applications using Trop-2-released exosomes, the cargo exosomes carry, which could be any genetic information such as specific miRNAs, adhesion molecules such as integrins, and metabolites, are yet to be explored in breast cancer patients. lncRNA, long non-coding RNA; mAb, monoclonal antibody; miRNA, micro-RNA; TACSTD2, tumor-associated calcium signal transducer; Trop-2, trophoblast surface antigen-2.

from 0 (no staining or <10% of the cells stained), 1+ (weak staining in the cell membrane and sometimes also cytoplasmic, of >10% of cells), 2+ (clear and moderate staining in >10% of cells) to 3+ (most intense staining of >10% of cells).[33,34] The tumor response rate and progression-free survival seemed to correlate positively with the magnitude of positive Trop-2 immunostaining. In later clinical trials, evaluation of Trop-2 expression in a breast tumor specimen was based on the histochemical score (H-score) derived from a study of papillary thyroid cancer. The H-score ranged from 0 to 300 and was calculated using a formula.[35] To date, the median progression-free survival of patients treated with sacituzumab govitecan is 5.6–6.9 months in those with medium/high H-scores (100–300), whereas patients with low Trop-2 (<100) and the chemotherapy control arm have shown similar median progression-free survival. Consequently, additional research would be needed to transfer and implement this clinical trial's centralized digital pathology H-score into laboratory practice. Moreover, because of the small number of participants in the low H-score subgroup, further studies would be needed to confirm the efficacy to avoid dismissing patients who could benefit from treatment.

Radionuclide targeting of the Trop-2 surface protein for tumor localization in the body is an attractive diagnostic strategy. In a breast cancer cell line study, an earlier generation of an anti-Trop-2 IgG monoclonal antibody, RS7, showed a fast internalization rate with 50% of the antibody internalized within 70 min.[36] This early result indicated that Trop-2-positive breast cancers could be targeted using a bispecific antibody radionuclide, which could improve tumor localization of Trop-2-positive tumors in the body. With the advent of targeted therapy for Trop-2-positive cancers, the development of a radionuclide anatomic-metabolic fusion scan would be of great clinical relevance and utility. Another area of vital diagnostic importance would be the precision oncology application of exosomes in the diagnosis, disease monitoring, and treatment guidance for patients with Trop-2-positive breast cancer. Figure 1 depicts the expanding frontiers of basic science research on Trop-2 positive breast cancer conceptually. Table 1 highlights some emergent research ideas on Trop-2-containing breast cancer cells for diagnostic and therapeutic purposes.

In conclusion, an anti-Trop-2 antibody-drug conjugate targeting Trop-2-positive cancer cells has been approved for treating pa-

Table 1. Emergent clinically-relevant research ideas or questions focusing on Trop-2-positive cells in breast cancer

1. Standardization of immunohistochemical staining of Trop-2 and the definition of clinically meaningful positive results.
2. Correlation studies of the Trop-2 protein expression with regulated genes or mRNAs.
3. Prevalence and distribution of Trop-2-positive cancer and intratumoral heterogeneity by different intrinsic subtypes of breast cancer.
4. Molecular determinants or any signaling pathways responsible for Trop-2 plasticity.
5. Systems biology and in silico research of genetic data sets on the Trop-2 signaling networks, transcription factors, and multi-omics informatics analyses.
6. Breast cancer subtype-specific Trop-2-related exosomes and their different possible cargo and payload tracking.
7. Diagnostic application of quantifying Trop-2-related exosomes in a liquid biopsy and correlation with clinicopathological features.
8. Further development of radionuclide imaging for tumor localization targeting Trop-2-positive tumors.
9. Breast cancer subtype-specific study of interactions between Trop-2 glycoprotein, integrins, fibronectin, and intercellular communication in the tumor microenvironment.

Trop-2, trophoblast surface antigen-2.

tients with unresectable locally advanced or metastatic triple-negative breast cancer who have failed two or more lines of systemic chemotherapy. This has renewed interest in translational research into Trop-2-positive breast cancer, the gene TACSTD2 and microRNAs that interact with it, and the signaling network on the cell membrane induced by Trop-2 activation. This commentary argues that exosomes, as extracellular vesicles released from Trop-2-positive cancer cells, could play a crucial role in cancer progression. Furthermore, diagnostic applications using Trop-2-released exosomes, the cargo carried by exosomes, which could be any genetic information such as specific miRNAs, adhesion molecules such as integrins, and metabolites, remain to be explored in patients with breast cancer. Most evidence and data were obtained from studies in epithelial cancers other than breast cancers, which were introduced in this paper. Therefore, this opinion paper is intended to motivate oncologists and scientists to consider the importance of this topic, and its potential for accelerating research in the field of Trop-2-targeted therapeutics. Thus, dedicated research would be needed to assist in the further investigation of the Trop-2 signaling network, help broaden the knowledge of Trop-2-associated cancer biology, understand treatment evasion and acquired resistance to Trop-2-directed agents, particularly ADCs, and help deliver antineoplastic payloads to Trop-2-bearing cancer cells using exosomal technologies.

Acknowledgments

None.

Funding

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

The author reports no competing interests.

Author contributions

The author is the sole contributor on the development of the study concept, literature search, data analysis, designing the figures, drafting the manuscript, and revising the manuscript according to the peer review reports.

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