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

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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.

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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timately mobilize the actin cytoskeletal elements to enhance the mobility of the cancer cells.\textsuperscript{31} 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.\textsuperscript{4,12,13}

Different pools of Trop-2 cellular protein could be localized in separate cell compartments: the cell membrane or cytoplasm.\textsuperscript{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.\textsuperscript{15-17} In addition, datopotamab deruxtecan, using a different topoisomerase I inhibitor as a payload, is actively being developed for use in solid tumors.\textsuperscript{23}

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.\textsuperscript{24}

The mechanisms underlying these associations were not completely validated miRNA–TACSTD2 gene interactions in humans other genes. According to an MiRTarBase search, 58 experimental 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.\textsuperscript{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 an MiRtarBase search, 58 experimentally validated miRNA–TACSTD2 gene interactions in humans were retrieved with annotated functional changes.\textsuperscript{25} Notably, in a study of a head and neck squamous cell carcinoma cell line, loss of an miR-125b-1 activated TACSTD2 expression resulted in the dysfunction in the mitogen-activated protein kinase pathway, thus contributing to cancer progression.\textsuperscript{21} 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.\textsuperscript{24}

The tumor 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.\textsuperscript{8} In addition, Remšík \textit{et al.} reported a mechanism of the Trop-2 expression determined epigenetically or by epithelial-to-mesenchymal transition transcription factors.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3} 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.\textsuperscript{31} Therefore, further studies of the interactions and dissemination of specific onco- genetic 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.\textsuperscript{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 payload, 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 \textit{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.\textsuperscript{38} 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.
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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. 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. 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 specifically on Trop-2 positive breast cancer.

**Figure 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. IncRNA, long non-coding RNA; mAb, monoclonal antibody; miRNA, micro-RNA; TACSTD2, tumor-associated calcium signal transducer; Trop-2, trophoblast surface antigen-2.

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 micro-RNAs 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.

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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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