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Visiting Translocons Sec Roles in Antigen Presentation in Breast Cancer

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ABSTRACT

Background: Translocons Sec61, Sec62, and Sec22B occupy a central yet underappreciated position in the regulation of antigen cross-presentation. Rather than serving redundant roles, each contributes a distinct function within endoplasmic reticulum (ER)-associated antigen processing. Sec61 primarily facilitates the translocation of internalized antigens into the cytosol for proteasomal processing, whereas Sec62 enables the selective reentry of processed peptides into the endoplasmic reticulum through mechanisms that can bypass canonical transporter associated with antigen processing (TAP) dependency. In parallel, Sec22B governs ER–phagosome fusion and vesicular trafficking, thereby shaping the spatial and temporal organization required for efficient peptide loading and major histocompatibility complex (MHC)-class I transport. In this review, we synthesize emerging evidence to argue that Sec translocons represent overlooked determinants in antigen presentation and may hold therapeutic relevance in breast cancer.

Methods: Parallel inquiries in the PubMed database were performed with a query of Sec breast cancer. Subsequent assessments were manually conducted considering the relevance of the papers to our area of interest.

Results: A total of 554 publications containing either of the query sets were identified. Following further assessment, 72 publications were included. The original research articles were scarce and the majority of them were in vitro studies.

Conclusion: Sec61, Sec62, and Sec22B form a regulatory axis in bidirectional tumor-peptide trafficking across ER-associated compartments that governs antigen cross-presentation. By shaping antigen availability and immune recognition, these translocons may critically influence tumor behavior and represent promising targets for improving immunotherapeutic strategies in breast cancer.

INTRODUCTION

Despite significant advancements in cancer therapies that have markedly improved patient outcomes, the emergence of resistance remains a formidable challenge.[1] Reports indicate that some breast cancer (BC) patients no longer respond to conventional treatments, particularly chemotherapy[2,3] and radiotherapy,[4] thereby complicating the fight against cancer. This pressing issue has spurred extensive research worldwide, leading to the identification of numerous BC biomarkers and mutagenic pathways.[3–5] Among these, the antigen processing machinery (APM) plays a vital yet often underappreciated role in cancer immunity.[6] The APM comprises a set of genes that encode for antigen presentation, including processes involved in protein folding, chaperoning, proteasome function[6,7], and regulation of translocons.[8] Within this complex, translocons are particularly critical, serving as

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gateways that facilitate the translocation of antigens from endosomes into the cytosol.[9] Their role is crucial in clinical oncology because the effectiveness of immune surveillance heavily relies on the efficient processing and presentation of tumor antigens.[10] Enhancing translocons' function could, therefore, bolster cross-presentation, leading to improved activation of cytotoxic T cells and more effective tumor clearance.[9]This emphasizes their potential as therapeutic targets to overcome resistance in cancer treatment.[11] Consequently, a profound comprehension of these elements is imperative. Despite their identification and characterization nearly 4 decades ago by Raymond J Deshaies and Randy Schekman—who discovered that Sec-mutant-carrying yeast strains were incapable of exporting these Sec proteins into the endoplasmic reticulum (ER)[12]—the number of reports remains limited. This review seeks to clarify the contribution of Sec translocons to the modulation of anticancer immunity mechanisms.

METHODS

We followed the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to systematically identify and select relevant articles for inclusion in our narrative review. We conducted a literature search using the PubMed database using queries: "Sec breast cancer." Relevance was determined manually by reviewing abstracts and discussions. We focused primarily on original research articles. However, given that the topic of translocons in the context of breast carcinoma is underrepresented, we have also included other types of publication including review articles. Our reference collection method is presented in Figure 1.

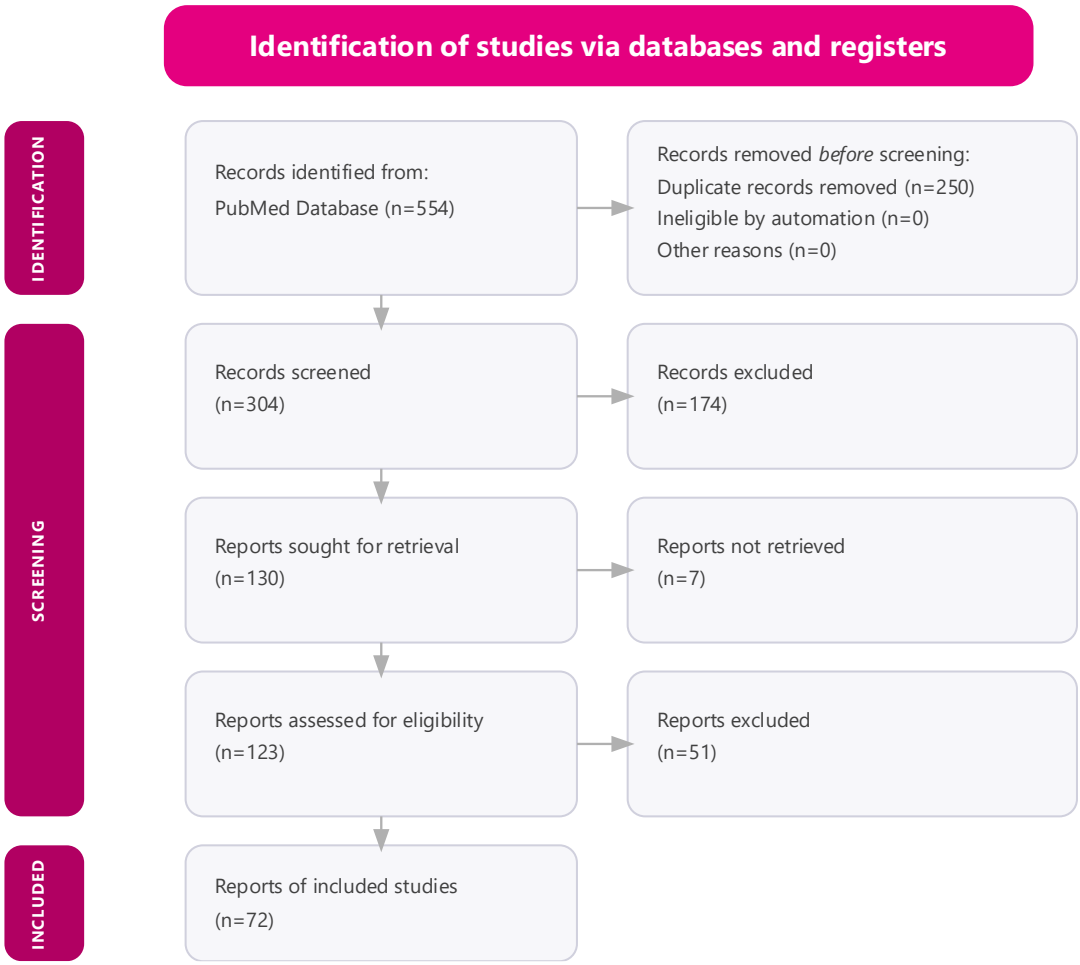

Figure 1. PRISMA Flowchart of Study Inclusion
Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

RESULTS

We aimed to attain a more thorough understanding of the role of Sec in antigen presentation pathways, mainly cross-presentation. This holds importance in the realm of cancer immunotherapy, wherein antigen presentation and

recognition become the main challenges. Recognizing that the scientific domains concerning Sec, particularly Sec61, Sec62, and Sec22B, remain inadequately explored, we initiated comprehensive inquiries with the aim of aggregating the most contemporary and relevant findings. Our database inquiries resulted in 554 initial matches. We did not apply any filter because imposing filters on research articles would have overly restricted our search, potentially making us overlook valuable sources. Ultimately, our review comprised 72 reports—consisting of research articles and metadata analyses as well as review articles. Original and experimental studies on the role of Sec in the context of BC are presented in Table 1.

Table 1. Overview of Expression Patterns of Sec Translocons in Breast Cancer as Documented in Experimental Studies

Research objectives	Experimental strategy	Results	References
To explore molecular aberration which might highly correlate with clinical outcomes of Sec22B	Paired end transcriptomics analysis of 89 breast cancer cell lines	Sec22BSec22B fusion with NOTCH2 occurs post cleavage of γ-secretase. This fusion leads to aggressive behavior and survival of cancer cells.	[13]
To investigate the function and expression patterns of Sec61 in breast cancer	In vitro with sevrral breast cancer cell lines Ex vivo with Nanjing Medical University BRCA cohort	Sec61G promotes the progression and metastasis of BC via glycolysis pathways which are transcriptionally governed by E2F1.	[14]
To investigate the expression patterns of Sec61 in breast cancer	Bioinformatics with The Cancer Genome Atlas cohorts In vitro using several cell lines	Upregulated Sec61G improves breast cancer cell proliferation and metastasis by modulating epithelial-mesenchymal transition.	[15]
To develop targeted therapies against HER3	In vitro with several breast cancercell lines	Cotransin molecule CT8, upon binding with Sec61, obstructs signal peptide of the nascent HER3 protein from initiating its cotranslational translocation, which results in the degradation of HER3 while sparing the other HER proteins.	[16]
To study the function of Sec62 as a significant contributor to the pathogenesis of breast cancer	In vitro Ex vivo with University of Saarland Mammary Carcinoma Cohort	Sec62 serves as a predictive marker for treatment response, and acts as a prognostic indicator for survival in triple-negative breast cancer (TNBC) and invasive ductal BC. These findings may be of therapeutic significance for patients with TNBC.	[17,18]
To elucidate the process of cross-presentation of Her2/neu antigen	In vitro	Sec61 and Sec22B retrotranslocate misfolded proteins from endoplasmic reticulum into cytosol. This enhances the sensitivity of antigen cross-presentation to proteasome inhibitors which indicates that the antigen fragments are directed into the cytosol for subsequent proteasomal processing.	[19]

DISCUSSION

Cross-presentation: a cornerstone of effective immune-oncology strategies

Cross-presentation, the process by which dendritic cells (DCs) present exogenous antigens on major histocompatibility complex (MHC)-class I molecules to activate $CD8^+$ T cells, plays a crucial role in cancer immunity.[20,21] This mechanism is governed by a set of genes referred to as APM.[6,7,22,23]

Figure 2 illustrates the 2 pathways of antigen presentation—classical MHC-class I processing and cross-presentation of exogenous antigens, which intersect in the display of processed peptides to $CD8^+$ T lymphocytes. In the canonical MHC-class I pathway, endogenous antigens are loaded onto MHC-class I molecules prior to activation of effector mechanism by $CD8^+$ T lymphocytes.[24] These antigens encompass a broad spectrum, including misfolded or damaged proteins generated under cellular stress conditions, viral proteins synthesized during infections[25], as well as tumor-associated antigens derived from mutated or abnormal cellular proteins, including neoantigens.[26]

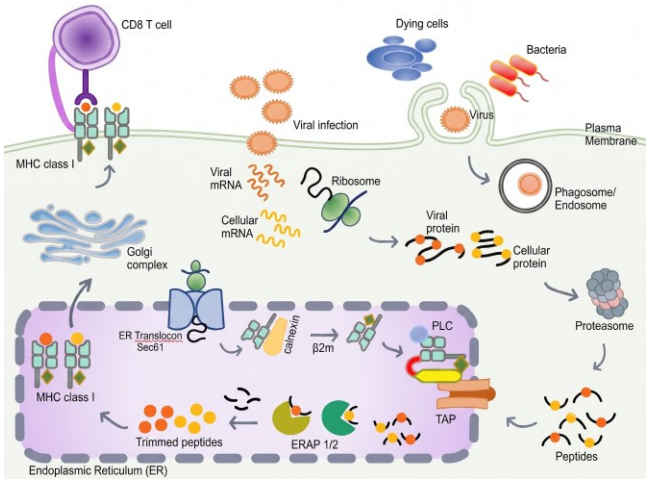

Figure 2. Canonical MHC-class I vs Cross-Presentation Pathway (Adapted from Blander, 2018)[27]

Cellular stress responses further induce the formation of defective ribosomal products (DRiPs) which are subsequently degraded by proteasome into smaller peptide prior to their loading onto MHC-olecules.[28] These peptide-MHC-class I complexes facilitate recognition by $CD8^+$ T cells, thereby activating cytotoxic effector mechanisms aimed at eliminating cancer cells.[29] Tumor antigens are processed via cytosolic or vacuolar pathways, distinguished by their reliance on proteasomal degradation and TAP-mediated transport. In the cytosolic route, substrates are either cleaved into immunogenic peptides or transiently stabilized by Hsp90, thereby regulating their availability for MHC class I presentation.[30] Recent findings indicate that MHC-class I molecules are likely derived from secretory pathways.[31,32] Within the vacuolar pathway, internalized antigens are processed by lysosomal proteases inside endocytic compartments and loaded onto recycling MHC class I molecules that return to the plasma membrane via early endosomes.[33] Antigen properties shape pathway usage, as soluble or low-molecular-weight antigens preferentially access cytosolic processing, whereas particulate or Hsp-associated tumor antigens follow more heterogeneous presentation routes.[34]

Cross-presentation is also dictated by antigen-presenting cell identity: CD8-like DCs favor cytosolic processing, inflammatory DCs access both cytosolic and vacuolar routes, while B cells and bone marrow-derived DCs may rely on autophagy for antigens.[35] Effective cancer immunotherapy depends on efficient cross-presentation.[36] These processes implicate tightly-regulated antigen-processing networks by APM, including the underappreciated Sec translocon system.[37]

Critical yet underexplored translocons in antigen processing

Despite their central role in protein trafficking, Sec translocons, such as Sec61, Sec62, and Sec22B have been relatively underrepresented in cancer immunology research compared with classical antigen processing components like, MHC, TAP, or the proteasomes.[9] Accumulating evidence suggests that the translocons Sec61, Sec62, and Sec22B contribute to antigen processing and cross-presentation through complementary trafficking and translocation functions.[9,13,17,18] However, their direct mechanistic integration has never been demonstrated, particularly in the context of BC. This absence of integrated analyses leaves unresolved the fundamental question of whether these translocons operate concurrently to sustain efficient cross-presentation, or whether their contributions are context- or compartment-specific. Addressing this question has been challenging, as no existing study has examined these components within a single experimental framework. Nevertheless, given that other elements of APM function as interdependent modules[8,20,23,29,43,47,48,51], it is reasonable to hypothesize that disruption of any one of these Sec components may compromise the downstream immune outcomes. Because available studies have examined Sec61, Sec62, and Sec22B largely in distinct experimental frameworks, it remains unresolved whether these translocons act in a coordinated manner during antigen processing. Drawing on convergent evidence from independent lines of research, we propose that these Sec proteins constitute a spatially and temporally compartmentalized trafficking system, in which each

component contributes a nonredundant yet complementary function to antigen translocation and cross-presentation rather than operating as a singular linear pathway.[9,54,55] This conceptual integration provides a framework to reconcile prior discrepancies and highlights a previously underappreciated layer of regulation with potential relevance for antitumor immune competence.[56] Below, we examine the Sec proteins that underpin this proposed antigen translocation framework.

Sec61: a core translocation hub shaping antigen entry into the cross-presentation pathway

Sec61 complex, which consists of 3 subunits (Sec61α, Sec61β, and Sec61γ), plays a key role in facilitating antigen transfer between endosomes and the cytosol.[19] This complex has the ability to influence the expression of MHC-class I molecules in tumor cells, thereby affecting their immunogenic visibility.[57] Sec61γ enhances the phosphorylation of the epidermal growth factor receptor (EGFR), which then activates downstream signaling pathways such as mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)-Akt. This signals the synthesis of cell cycle regulators, which subsequently inhibit the phosphorylation of cyclin-dependent kinase 2 (CDK2). This inhibition facilitates the G1/S phase in the intracellular Ca^{2+} gradient mediated by calmodulin and dependent on its concentration.[56,58,59]

Most Ca^{2+} efflux is facilitated by the Sec61 heterotrimeric complex, which also mediates the translocation of newly-formed polypeptide chains into the lumen of the ER.[46] The main physiological regulators of Ca^{2+} flux through Sec61 are the cytosolic Ca^{2+}-calmodulin (CaM) complex and the luminal Hsp70-type chaperone-binding immunoglobulin protein (BiP), which interact directly with the Sec61α pore-forming subunit around tyrosine 344 to limit ER Ca^{2+}.[59,60] Another role of BiP is the regulation of Sec61-mediated Ca^{2+} leakage during cellular processes such as the unfolded protein response and apoptosis. Although the exact correlation between Sec61 and Ca^{2+} has not been definitively established, existing reports suggest that in the oncology framework of cancer, alterations in Sec61 and Ca^{2+} may represent a viable approach for anticancer treatment.[56,58,59]

To explain the regulatory mechanism of Sec61G in BC, Ma and colleagues (2021) performed bioinformatic analysis using the JASPAR database and Matrix Profile tool. They identified two transcription enhancement domain-associated (TEAD) binding elements (TBEs) suspected to be located within approximately 1 kb of the Sec61G promoter region. By engineering luciferase reporter constructs, containing wild-type or mutated E2F1 binding sequences, which were transfected together with control vectors or E2F1 overexpression vectors into HEK293 cells, they showed that E2F1 overexpression significantly increased luciferase activity, while TBE mutations reduced this effect. Moreover, using RNA immunoprecipitation (RIP) assays, they demonstrated that the downregulation of E2F1 significantly diminished the mRNA and protein levels of Sec61G in MCF-7 and MDA-MB-231 cell lines. Conversely, the upregulation of E2F1 corresponded with increased Sec61G expression. This finding suggests that E2F1 directly binds TBE region within the promoter of Sec61G, thereby influencing its transcriptional regulation.[14]

Reduction of Sec61G expression via shRNA significantly disrupted cisplatin-induced calcium release from the ER and decreased activation (phosphorylation) of the ERK1/2 and AMPK pathways. The acquisition of cancer stem cell (CSC) characteristics—such as increased expression of CSC markers, spheroid and colony formation, and invasive behavior—induced by cisplatin— can be effectively suppressed through Sec61G suppression and treatment with chloroquine, an autophagy inhibitor.[15]

Downregulation of Sec61 expression results in reduced cross-presentation of soluble ovalbumin (OVA) in the IFN-β-inducing adaptor (TRIF)-dependent signaling pathway containing the toll-like receptor/interleukin-1 (TIR) domain.[9] When Sec61 release from the ER to endosomes is blocked using antibodies that fuse with the ER retention signal, there is a disruption in cross-presentation and antigen export to the cytosol. Experimental blocking or downregulation of Sec61 disrupts endosomal antigen export to the cytosol in DCs, reducing cross-presentation to CD8+ T cells, and tumor-associated regulators can exploit Sec61-related pathways to suppress MHC class I assembly and presentation.[57]

Sec62: complementary function in the TAP-independent pathway

Sec62 represents another translocon component functionally aligned with Sec61, sharing its posttranslational protein translocation pathway while exerting distinct biological effects.[61] Located at chromosome 3q26, Sec62 is frequently amplified in BC, where its overexpression correlates with invasive behavior and unfavorable prognosis.[17,18] Mechanistically, Sec62-driven cellular transformation depends on its interaction with the RNA helicase DDX3X, a process mediated by the amino-terminal region of Sec62—a domain also implicated in ribosome association. DDX3X independently constitutes a component of poly-A-binding protein (PABP), which has been identified as

a binding partner of Sec62. Consequently, the interaction between Sec62 and DDX3X influences a specific subset of mRNAs.[62,63]

Beyond its key role in ER protein translocation, Sec62 has emerged as a central regulator of recovER-phagy. It integrates protein import with ER quality control mechanisms that are increasingly recognized as critical determinants of tumor cell adaptation and survival.[65]

Due to its intracellular localization, the Sec62 protein exhibits limited accessibility to therapeutic antibodies.[64] Therefore, effective Sec62 inactivation strategies emerge as the most viable strategy for prospective antineoplastic targeted therapy. By facilitating Ca^{2+} efflux from the ER lumen and consequently increasing cellular stress levels, functional blockade of Sec62 exhibits antiproliferative and anti-metastatic properties.[64,66]

Sec22B: SNARE-mediated vesicular trafficking

In addition to Sec61 and Sec62, Sec22B also plays a major role in cross-presentation. This protein is a member of the soluble N-ethylmaleimide-sensitive receptor-associated proteins (SNARE) that facilitate vesicle fusion with membrane-bound organelles, including lysosomes.[67,68] SNARE proteins are primarily involved in autophagy, which includes autophagosome formation, maturation, fusion with lysosomes, and subsequent degradation, all of which require effective membrane fusion. A growing body of evidence suggests that SNARE plays a key role in tumor development and progression, making it a promising target for new cancer therapies.[69,70] In contrast to Sec61 and Sec62 translocons that operate largely in a unidirectional ER-to-Golgi manner, SNARE proteins exhibit dynamic cycling between ER and the Golgi apparatus. Their selective incorporation into coat protein complex II (COPII) vesicles departing the ER and COPI carriers which mediate retrograde Golgi transport is not incidental, but rather central to preserving the compositional and functional asymmetry of the early secretory pathway, a prerequisite for directional protein trafficking and membrane identity maintenance.[71] Wu *et al.*[72] generated a mouse model with targeted Sec22B deletion in DCs using CD11c-Cre Sec22Bfl/fl mice. They found that Sec22B deficiency did not impair the ability of DCs to cross-present these antigens. Both splenic CD11c+ Sec22B−/− DCs and bone marrow-derived DC lacking Sec22B exhibited normal cross-presentation capacity, regardless of tissue origin or culture conditions, suggesting that Sec22B is not critical for this process under these experimental conditions. Conversely, Biscari *et al.*[67] showed that silencing Sec22B in DCs of C57BL/6 mice significantly hampers cross-presentation without impacting other pathways. Mice lacking Sec22B (Sec22B−/−) exhibit impaired activation of $CD8^+$ T cells and, thus, struggle to control tumor progression. Additionally, silencing Sec22B in cancer xenografts mouse models resulted in a marked decrease in metastasis, autophagic activity, and cellular proliferation within the tumors. These findings suggest that Sec22B is crucial to the aggressive behavior of cancer cells. To date, no study has examined Sec61, Sec62, and Sec22B in an integrated framework within a single experimental or clinical context, making it difficult to rigorously assess whether these translocons act in a coordinated or interdependent manner comparable to other components of the APM. Evidence supporting their involvement in antigen handling has instead emerged from independent studies, most of which were conducted outside the BC setting, thereby limiting direct inference about their collective behavior in this disease. Taken together, these fragmented observations support a context-dependent model in which distinct cellular, metabolic, or microenvironmental conditions must be satisfied for individual Sec components to become functionally engaged—an abductive rationale that underpins the hypothesis synthesized in this review.

Proposed complementary model of the 3 major Sec translocons

Recent studies have expanded our understanding of the role played by Sec61, Sec62, and Sec22B in the context of immuno-oncology.[18,45,54,59,61] These translocons are known for their ability to facilitate the presentation of extracellular antigens through MHC-class I molecules, enabling recognition by $CD8^+$ T cells. Their expression has been correlated with unfavorable prognostic outcomes, indicating the existence of a more intricate mechanism that is confined to specific characteristics[14] which necessitate careful consideration.

Building on the integrated framework above, the available evidence does not support a model in which Sec61, Sec62, and Sec22B function as isolated or mutually exclusive modules, but instead points to a context-dependent convergence shaped by antigen properties and cellular state. All 3 translocons operate at ER-associated stages of antigen processing: Sec61 mediates the export of endocytosed antigens into the cytosol for proteasomal processing[9,56,58], Sec62 enables selective, often TAP-independent reentry of processed peptides into the ER lumen[29,63,65], and Sec22B orchestrates ER–phagosome fusion and vesicular trafficking that governs spatial and temporal compartmentalization of these events.[68,71,72] This division of labor suggests functional specialization rather than redundancy, with pathway usage likely

influenced by factors such as antigen size, peptide composition, intracellular antigen load, and microenvironmental cues, including ER stress.[19,27,29] In this view, antigen presentation emerges from an adaptive network, in which Sec22B-dependent trafficking becomes particularly relevant under conditions of heightened demand or stress, while alternative routes may compensate in other settings, making it difficult to justify the action of these translocons outside their broader contextual interplay.

Future investigations of Sec translocons in antigen cross-presentation should prioritize the identification of genetic and expression alterations that may function as modulators or biomarkers of therapeutic responsiveness in BC, a domain that has received minimal attention to date. Emphasis should be placed on patient-derived and ex vivo analyses, where biologically meaningful patterns can be directly linked to clinical phenotypes. Stratifying Sec translocon alterations into immunologically responsive ("hot") or nonresponsive ("cold") states across individual tumor-specific or tumor-associated antigens may enable correlation with treatment response and survival using annotated clinical datasets. Importantly, such associations will require longitudinal study designs with serial sampling to capture dynamic changes during disease progression and therapy. While current knowledge is derived largely from preclinical in vitro and in vivo models, converging evidence supports the integration of genomic and transcriptomic profiling to establish a clinically actionable framework for understanding how Sec translocons influence tumor immune competence.

CONCLUSION

The functions of Sec61, Sec62, and Sec22B in the realm of antigen presentation are multifaceted. They are essential for facilitating the translocation of antigens from the ER to the cytosol, thereby enabling the recognition by $CD8^+$ lymphocytes, which is crucial for the eradication of cancer. Nevertheless, their applicability in clinical settings may be less than favorable. The enhanced expression of these proteins in BC and their involvement in ER stress responses accentuate their importance in tumor progression and immune evasion. Both in vitro and in vivo investigations indicate their critical role in promoting cross-presentation through various mechanisms. While Sec61 is responsible for exporting processed antigens to the cytosol, Sec62 specializes in importing specific TAP-independent processed peptides back into the ER lumen for loading onto MHC-class I molecules. Sec22B is tasked with regulating the fusion of the ER with phagosomes as well as vesicular transport. Notably, emerging evidence suggests that a deficiency in Sec22B may not universally hinder cross-presentation across all DC subsets; however, other studies highlight its indispensable role in facilitating tumor suppression and the inhibition of metastasis. These apparent discrepancies underscore the possibility that these translocons may operate in a complementary or context-specific manner. Understanding their interplay is imperative for the development of targeted therapies aimed at optimizing antigen presentation, overcoming immune evasion, and ultimately enhancing cancer immunotherapy outcomes for BC.

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ETHICAL CONSIDERATION

Ethical approval was not required for this study.

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial or personal relationships that could have influenced the work reported in this study.

DATA AVAILABILITY

No new data or metadata was produced or examined during this review.

AI DISCLOSURE

The authors state that no artificial intelligence (AI) tools or technologies were utilized in the design, data collection, analysis, or interpretation of this study. We utilized Grammarly free features solely for grammar correction and language refinement. The authors assume full responsibility for the content of the manuscript.

AUTHOR CONTRIBUTION

IN: Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review and editing. DH: Visualization; Writing – original draft. NK: Visualization. SP: Methodology; Writing – review and editing.

All authors reviewed and approved the final manuscript and jointly oversaw the revision and submission processes

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