GRP78 dysregulation: A proposed molecular mechanism linking the tumor microenvironment to sepsis susceptibility in patients with cancer (Review)

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Abstract. Patients with cancer are at a significantly higher risk of sepsis, which is associated with substantially increased morbidity and mortality. However, the intrinsic molecular mechanisms driving sepsis susceptibility in this high-risk population remain unclear. Glucose-regulated protein 78 (GRP78), the master regulator of endoplasmic reticulum stress, is aberrantly overexpressed and is involved in cell membrane translocation and extracellular release driven by the tumor microenvironment and anticancer therapies. To date, no clinical cohort study has directly established a causal link between GRP78 dysregulation and sepsis incidence or mortality in patients with cancer. The present narrative review therefore relied predominantly on indirect evidence from *in vitro* studies, animal models and non-oncologic sepsis cohorts. Despite these limitations, the present study advanced the hypothesis that GRP78 dysregulation may increase sepsis susceptibility through two convergent mechanisms: i) Facilitating pathogen invasion via cell-surface GRP78, which serves as a critical coreceptor for specific viruses and Mucorales fungi and ii) orchestrating immunosuppression through secreted GRP78-mediated dampening of innate immune responses. Direct evidence for the function of cell-surface GRP78 as a bacterial adhesion receptor is limited; its contribution to bacterial sepsis, the predominant clinical form, is primarily indirect and mediated by host inflammatory dysregulation, phagocytic impairment and barrier disruption. The present review provided a preliminary theoretical framework for future investigations into GRP78-mediated sepsis susceptibility in patients with cancer, with hypothetical implications for risk stratification and targeted interventions, pending dedicated clinical validation in oncology-specific cohorts.

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Abbreviations: GRP78, glucose-regulated protein 78; HSPA5, GRP78-encoding gene; UPR, unfolded protein response; ER, endoplasmic reticulum; BiP, immunoglobulin heavy-chain binding protein

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Contents

1. Introduction
2. GRP78: Beyond its role as an ER chaperone
3. Tumor-driven ER stress and GRP78 dysregulation in sepsis susceptibility
4. From membrane surface exposure to pathogen invasion
5. Immunoregulatory role of GRP78 in sepsis
6. Therapeutic approaches for targeting GRP78
7. Current limitations and future directions

1. Introduction

Within the spectrum of populations at high risk for sepsis, patients with cancer constitute a particularly susceptible subgroup that is distinguished by substantially unfavorable clinical outcomes. Contemporary multinational, multicenter epidemiological investigations have uniformly revealed that these patients account for >20% of all sepsis-related hospital admissions and have a markedly increased risk of all-cause mortality (1,2). Historically, clinical research has ascribed the increased sepsis predisposition in patients with cancer to factors that induce acquired immunodeficiency, including neutropenia, chemotherapy-mediated compromise of mucosal

integrity within the gastrointestinal and respiratory epithelia and immunosuppressive antineoplastic interventions (3,4). Undoubtedly, these conventional risk factors represent the most well-recognized and clinically actionable drivers of sepsis in patients with cancer and serve as the primary targets for infection prevention and control in clinical practice (3,4). However, established risk factors explain only a fraction of malignancy-associated sepsis cases. Notably, some patients with advanced cancer develop refractory, life-threatening infections that rapidly progress to sepsis or septic shock despite a lack of severe neutropenia or evident mucosal barrier damage (4), suggesting that the pathophysiological mechanisms are partially independent of conventional risk factors.

In contemporary oncology, chronic stress responses in the tumor microenvironment critically link malignant progression to systemic host dysfunction (5). Among these stress responses, endoplasmic reticulum (ER) stress and its master regulator glucose-regulated protein 78 (GRP78/BiP/HSPA5), a core heat shock protein 70 family member, have attracted significant attention because of their pleiotropic functions (6,7). As the primary ER molecular chaperone, GRP78 orchestrates the unfolded protein response (UPR) to maintain proteostasis, modulate calcium-dependent protein folding and regulate apoptotic signaling under physiological and stress conditions (8). A growing body of basic and translational research implicates dysregulated GRP78 expression in increased infection susceptibility and accelerated sepsis progression among patients with cancer. First, robust experimental evidence has indicated that the tumor microenvironment induces sustained, chronic ER stress, leading to the marked upregulation of GRP78 expression in neoplastic cells, along with aberrant membrane translocation and extracellular secretion that increase the systemic levels of secreted GRP78 (sGRP78) (9). Second, cell surface-localized GRP78 acts as a key entry receptor or cofactor for diverse viral and fungal pathogens while also modulating host immune responses to bacterial components, thereby increasing infection susceptibility (10,11). Preliminary clinical studies further confirmed positive correlations between elevated sGRP78 concentrations, the severity of multiorgan dysfunction and short-term mortality in sepsis patients, supporting its potential utility as a prognostic biomarker (12,13).

While preclinical studies have robustly demonstrated GRP78-mediated pathogen invasion and immunomodulation and studies of non-cancer sepsis cohorts link elevated circulating levels of GRP78 to mortality, no prospective or retrospective study has specifically examined the use of GRP78 as a predictor of the sepsis risk, severity, or outcome in an oncology population. The present review focused specifically on GRP78 dysregulation induced by the tumor microenvironment. It systematically elucidated the pathological pathways through which GRP78 affects sepsis susceptibility in patients with cancer via a dual mechanism: Aberrant GRP78 expression not only facilitates pathogen invasion but also dysregulates inflammatory responses and promotes immunosuppression. Finally, GRP78-targeted therapeutic strategies are explored. The aberrant expression of GRP78 and its functional implications in the tumor microenvironment are shown in Fig. 1.

2. GRP78: Beyond its role as an ER chaperone

GRP78, an ER-resident molecular chaperone, undergoes a subcellular redistribution under stress conditions, resulting in the formation of three functional states: endoplasmic reticulum GRP78 (ER-GRP78), sGRP78 and cell-surface GRP78 (csGRP78) (6,14,15). The dynamic interconversion among these three states constitutes a crucial mechanism by which tumor cells adapt to microenvironmental stress. Fig. 2 depicts the three functional states of GRP78, the central roles of GRP78 in maintaining ER homeostasis under physiological conditions and the GRP78-mediated regulatory mechanism that orchestrates the activation of the unfolded protein response activation to restore ER homeostasis during pathological stress.

ER-GRP78: The canonical guardian of proteostasis in the endoplasmic reticulum. ER-GRP78 represents the canonical functional state of GRP78, which is predominantly localized within the ER lumen (16). Under physiological conditions, ER-GRP78 is maintained within the endoplasmic reticulum through the binding of its C-terminal KDEL (Lys-Asp-Glu-Leu) sequence to KDEL receptors (KDELRs) (17). As the central regulator of the UPR, ER-GRP78 binds to and inhibits transmembrane stress sensors, including protein kinase R-like ER kinase (PERK), inositol-requiring enzyme 1 alpha (IRE1α) and activating transcription factor 6 (ATF6), thereby maintaining these proteins in an inactive conformation (18,19). When unfolded or misfolded proteins accumulate within the ER lumen, GRP78 dissociates from these sensors to bind to the aberrant proteins, initiating the UPR signaling cascade. This response restores proteostasis through three coordinated mechanisms: Inhibition of global protein synthesis, upregulation of molecular chaperone expression and enhancement of ER-associated degradation. Under normal physiological conditions, the vast majority of GRP78 exists as ER-GRP78, serving as the cornerstone of cellular protein quality control.

sGRP78: A systemic messenger in intercellular communication. GRP78 can be secreted extracellularly as sGRP78 and is detected in various body fluids, including blood, urine and cerebrospinal fluid (15). Its secretion occurs through both canonical (ER-Golgi apparatus pathway) and noncanonical (direct release via exosomes or vesicles) mechanisms (20). In the tumor microenvironment, exosomes secreted by GRP78-induced M2 macrophages can transfer GRP78 to colorectal cancer cells, promoting cancer stem cell properties and chemotherapeutic resistance (15,20). Clinical investigations revealed significantly elevated serum sGRP78 levels in lung patients with cancer, with 80.2% sensitivity and 68.9% specificity for an early-stage lung cancer diagnosis and an area under the curve of 0.788, outperforming the conventional biomarker carcinoembryonic antigen (14). sGRP78 levels are positively correlated with the tumor burden, disease stage and a poor prognosis; notably, non-small cell lung cancer (NSCLC) patients with high sGRP78 expression experience significantly shorter overall survival (14).

csGRP78: Stress-driven cell surface translocation. In response to tumor microenvironmental stressors (hypoxia,

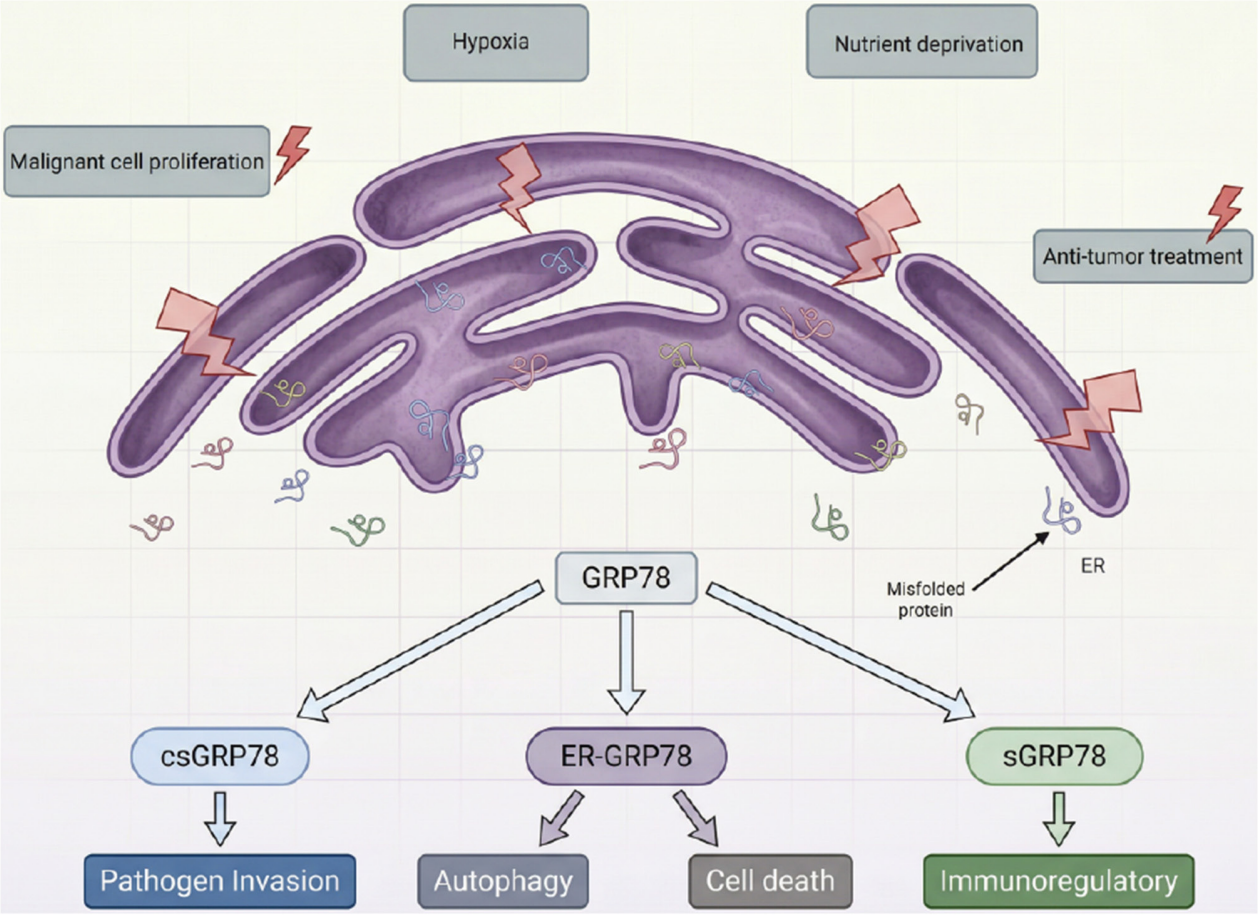


Figure 1. GRP78 dysregulation connects the tumor microenvironment and sepsis susceptibility. Tumor-derived GRP78 drives sepsis pathogenesis through dual mechanisms. i) Pathogen invasion: csGRP78 acts as a critical coreceptor, facilitating the entry of specific viruses (such as SARS-CoV-2, dengue virus and Japanese encephalitis virus) and Mucorales fungi (such as *Rhizopus* spp.), thereby increasing infection efficiency. For bacterial pathogens, the predominant cause of clinical sepsis, direct evidence for csGRP78 as an adhesion or invasion receptor is currently limited to *Mycoplasma hyopneumoniae* (a nonhuman pathogen). In bacterial infections, the predominant cause of clinical sepsis, csGRP78 does not function as a canonical adhesion receptor for major human pathogens. Instead, GRP78 contributes to the progression of bacterial sepsis through the indirect regulation of host inflammatory responses, phagocytic function and epithelial barrier integrity. ii) Immunosuppression: sGRP78 functions as a potent immunosuppressive cytokine, triggering a 'cytokine storm' in early sepsis followed by profound immune paralysis in late sepsis. This immunosuppressive milieu, combined with direct pathogen invasion, compromises host defense mechanisms, leading to uncontrolled infection, vascular leakage, multiorgan dysfunction and ultimately septic shock. The figure was constructed using the Figdraw 2.0 tool (https://www.figdraw.com/#/), with official authorization obtained by the authors (authorization no. PPPIU1c449). GRP78, glucose-regulated protein 78; cs, cell-surface; s, secreted.

nutrient deprivation and therapeutic stress) or ER stress induction, GRP78 translocates to the cell surface to form csGRP78 through the following four primary mechanisms.

First, the ER retention and recycling system is saturated. Under pathological stress conditions, sustained GRP78 overexpression exceeds the retrograde transport capacity of KDEL receptors (KDELRs) (16). Consequently, substantial quantities of unretrieved GRP78 enter the anterograde secretory pathway via COPII-coated vesicles and are ultimately trafficked to the plasma membrane through post-Golgi secretory vesicles (21).

Second, KDELRs are dysfunctional. Pathological conditions induce the aberrant activation of the tyrosine-protein kinase SRC, which mediates the phosphorylation of ASAP1 and the accumulation of Arf1-GTP, leading to the dispersion of KDEL receptors from the Golgi complex (17,22). This process downregulates their retrograde transport activity, impairing the effective retrieval of escaped GRP78 and facilitating its entry into secretory pathways (22).

Third, vesicular trafficking and secretory pathway-mediated mechanisms are involved. GRP78 is trafficked through two routes: One subset follows the canonical secretory pathway and is transported from the ER to the Golgi apparatus via COPII vesicles and subsequently to the plasma membrane through secretory vesicles (22). A second subset utilizes exosome-mediated pathways, potentially bypassing Golgi apparatus processing through alternative routes (23).

Fourth, plasma membrane anchoring occurs. GRP78 is trafficked to the plasma membrane and stably anchored to the outer membrane leaflet through interactions with cell surface glycoproteins, phosphatidylserine and other lipid moieties, resulting in the formation of functional csGRP78 (23). Following membrane anchoring, csGRP78 undergoes specific conformational rearrangements that expose its substrate-binding domain to the extracellular milieu, significantly increasing ligand accessibility (24). This structural adaptation confers the capacity to specifically bind extracellular ligands, pathogen structural proteins and cell surface receptors (17).

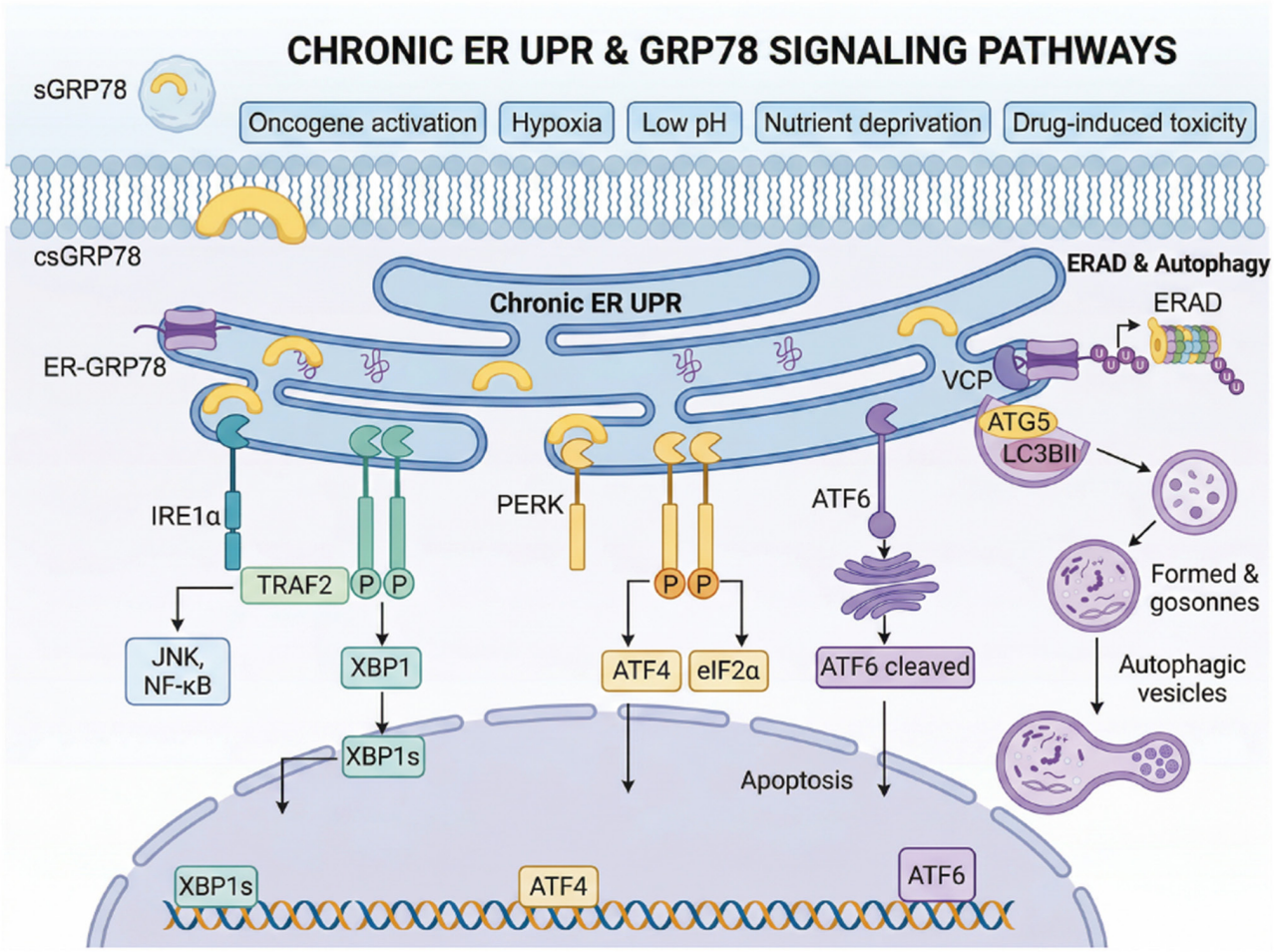


Figure 2. Schematic of GRP78-mediated maintenance of ER homeostasis and the UPR regulatory feedback loop under physiological and stress conditions. GRP78 is expressed in three well-characterized functional states: the ER-resident form (ER-GRP78) with intrinsic protein-folding chaperone activity, the cell surface-localized form (csGRP78) that acts as a transmembrane signaling receptor and the soluble extracellular form (sGRP78) that acts as a secreted intercellular signaling factor. Under resting conditions, ER-resident GRP78 maintains cellular homeostasis through three key functions: preserving ER proteostasis through its molecular chaperone activity; indirectly inhibiting apoptosis through the suppression of CHOP and caspase activation; and negatively regulating the UPR by binding to and repressing three core ER stress sensors (PERK, IRE1 and ATF6). Upon exposure to pathological stress, unfolded/misfolded proteins that accumulate in the ER compete for binding to GRP78, leading to the differential activation of three interconnected UPR branches: The PERK-eIF2α-ATF4, ATF6 cleavage-nuclear translocation and IRE1-sXBP1 pathways. The ATF6 and IRE1-XBP1 pathways primarily converge to upregulate GRP78 transcription, whereas PERK signaling contributes indirectly, resulting in the formation of a negative feedback loop to restore ER homeostasis. The figure was constructed using the Figdraw 2.0 tool (https://www.figdraw.com/#/), with official authorization obtained by the authors (authorization no. RPWUW59df5). GRP78, glucose-regulated protein 78; ER, endoplasmic reticulum; ER-GRP78, endoplasmic reticulum-resident GRP78; csGRP78, cell-surface GRP78; sGRP78, secreted GRP78; UPR, unfolded protein response; PERK, protein kinase R-like ER kinase; IRE1, inositol-requiring enzyme 1; ATF6, activating transcription factor 6; CHOP, C/EBP homologous protein; eIF2α, eukaryotic initiation factor 2 alpha; ATF4, activating transcription factor 4; sXBP1, spliced X-box binding protein 1; XBP1, X-box binding protein 1.

Notably, the expression of csGRP78 is markedly increased on the surface of multiple solid tumor cells but is minimal on cells in normal tissues, establishing it as an ideal target for tumor-specific therapeutic interventions.

3. Tumor-driven ER stress and GRP78 dysregulation in sepsis susceptibility

Aberrant expression patterns of GRP78 across different tumor types. Tumorigenesis and progression are accompanied by persistent ER stress driven by malignant cell proliferation, hypoxia, nutrient deprivation and antitumor treatment, which are the core drivers of aberrant GRP78 overexpression, subcellular redistribution (especially membrane translocation) and extracellular release (6,25). Unlike total intracellular GRP78, which acts primarily as a chaperone to regulate tumor progression and therapeutic resistance, csGRP78 and sGRP78 represent plausible molecular mediators that may link tumor pathology to increased sepsis susceptibility in patients with cancer, but these findings require direct clinical validation.

Notably, most existing studies have focused on the correlations between GRP78 expression and the tumor stage, chemotherapy resistance and overall survival, while direct clinical evidence verifying the causal association between GRP78 dysregulation and sepsis incidence/prognosis in patients with cancer remains scarce. Table I systematically summarized the changes in GRP78 expression directly related to the infection/sepsis risk across common human malignancies, with a focus on membrane expression and secretion features that are closely associated with sepsis pathogenesis (15,26-61).

Table I. GRP78 dysregulation in human malignancies: Expression features, underlying mechanisms and implications for sepsis susceptibility.

Tumor category	Tumor type	GRP78 expression features	Core regulatory mechanisms	Implications for sepsis susceptibility	(Refs.)
Hematologic malignancies	AML	High surface expression; high in leukemia stem cells	ER stress and UPR activation	Increases post-chemotherapy sepsis risk	(26)
	ALL	High in high-risk pediatric tumors; co-expressed with CXCR4	ER stress and migration pathway activation	Amplifies immunosuppression and infection risk	(27)
	CLL	High surface expression; elevated in progressive stage	HIF-1α/BAG3 synergistic regulation	Induces immune escape and inhibits anti-infective immunity	(28,29)
	MM	No total difference; elevated in relapsed bone marrow plasma	ER stress from high secretory state	Mediates immunosuppression and infection risk	(30)
	DLBCL	Abnormally high surface expression	ER stress and TGF-β1 synergistic regulation	Promotes immunosuppression and post-chemotherapy infection	(31)
Central nervous system tumors	GBM	High expression; correlates with malignancy/ recurrence; poor prognosis	Hypoxia-driven ER stress and UPR activation	Increases CNS infection and sepsis-associated encephalopathy	(32,33)
	Pediatric brain tumors	Heterogeneous; highest in ependymomas	ER stress and oncogene regulation	Increases CNS infection and systemic immunosuppression	(34)
Thoracic and breast tumors	NSCLC	Upregulated; higher in advanced stages; chemo-resistant	Ubiquitination imbalance, hypoxia/ROS-induced UPR, O-glycosylation	Promotes pulmonary infection progression to sepsis	(35-37)
	Breast cancer	Upregulated; higher in TNBC	TDP-43 activation, ATF6α-AKT pathway, ER stress translocation	Increases post-chemotherapy sepsis risk	(38-40)
	ESCC/ EA	High in 71.7% ESCC; higher in early-stage EA	Hypoxia-induced ER stress and lncRNA-activated MAPK	Impairs gastrointestinal barrier; increases infection risk	(41-44)
Gastrointestinal cancers	Gastric cancer	Overexpressed; linked to stage and poor prognosis	m5C stabilization, hypoxia-MAPK, ER stress-PKM2 feedback	Increases intra-abdominal infection and sepsis	(45-47)
	CRC	Overexpressed; higher in KRAS-mutant tumors	MARylation-UPR, uPA-uPAR translocation	Promotes microbiota translocation and infection	(48,49)
	PDAC	High expression; poor prognosis, chemo-resistant	Sp1 activation, ER stress-UPR	Increases biliary/intra-abdominal infection and sepsis	(50-52)
	HCC	Overexpressed; linked to invasion, metastasis, drug resistance	CYP2E1-ATF6, targeted therapy-induced IRE1α	Impairs intestinal barrier; increases sepsis risk in cirrhosis	(15,53)
Genitourinary cancers	Prostate cancer	Upregulated; elevated after ADT	UPR/AKT/mTOR activation, ADT-induced ER stress	Increases post-treatment sepsis risk	(54-56)
	RCC	Upregulated in tumors and serum	VHL deletion-HIF-α, hypoxia- ER stress	Increases urinary tract infection and sepsis	(57)

Table I. Continued.

Tumor category	Tumor type	GRP78 expression features	Core regulatory mechanisms	Implications for sepsis susceptibility	(Refs.)
	Bladder cancer	Upregulated; linked to progression and poor prognosis	VEGFA/VEGFR2/PI3K/AKT activation	Promotes urinary tract infection progression to sepsis	(58,59)
	UTUC	Controversial expression and clinical significance	Tumor progression pathway-driven	Sepsis risk association unclear	(60,61)

The 'Implications for Sepsis Susceptibility' column presents mechanistic inferences derived from preclinical tumor models (*in vitro* cell lines, animal xenografts) and correlative clinical studies of GRP78 expression in malignancies. No prospective or retrospective clinical study has validated these implications as actual risk factors for sepsis incidence or severity in patients with cancer. These entries should be interpreted as hypotheses for experimental testing, not as established clinical associations. AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; DLBCL, diffuse large B-cell lymphoma; GBM, glioblastoma; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer; ESCC, esophageal squamous cell carcinoma; EA, esophageal adenocarcinoma; CRC, colorectal cancer; PDAC, pancreatic ductal adenocarcinoma; HCC, hepatocellular carcinoma; UTUC, upper tract urothelial carcinoma; UPR, unfolded protein response; HIF-1α, hypoxia-inducible factor 1α; ROS, reactive oxygen species.

Core mechanisms driving GRP78 membrane translocation and extracellular release in tumors. Chronic, persistent ER stress in the tumor microenvironment not only upregulates total GRP78 expression but also, more importantly, specifically increases its membrane translocation and extracellular release (6,8). These two processes represent the primary sources of persistently elevated csGRP78 and sGRP78 levels in patients with cancer, resulting in the formation of an immunosuppressive microenvironment that may contribute to systemic immune dysfunction (62,63). Compared with physiological GRP78 trafficking in normal cells, tumor cells and antitumor treatments increase GRP78 membrane translocation and secretion through multiple nonredundant mechanisms, including SRC-mediated KDELR dispersion and DNAJC3-dependent endosomal transport, with significant heterogeneity across tumor types and treatment modalities (17).

Tumor-intrinsic pathological processes drive constitutive GRP78 dysregulation. The most potent constitutive induction of GRP78 membrane translocation and secretion occurs in highly secretory tumors and tumors with sustained hypoxia/ER stress (26,53). Among these tumors, hematologic malignancies and highly hypoxic solid tumors show the most significant baseline GRP78 membrane localization and secretion (53,64). The core mechanisms include two aspects, which are described below.

Persistent inactivation of the ER retention-retrieval system: Oncogenic activation of SRC kinase in tumor cells disrupts KDEL receptor-mediated retrograde transport by inducing KDELR dispersion from the Golgi apparatus, while the ER stress-induced upregulation of GRP78 promotes its translocation to the cell surface via multiple mechanisms, including the suppression of Golgi-to-ER retrieval (65).

Hyperactivation of noncanonical secretory pathways: Under hypoxic and nutrient-deprived conditions, tumor cells widely utilize exosome-mediated unconventional secretion to release GRP78 into the extracellular space (66). This noncanonical pathway operates alongside classical secretion mechanisms, with ER-stressed tumor cells showing enhanced packaging of GRP78 into exosomes that bypass traditional ER-Golgi quality control checkpoints. This effect is most prominent in GBM, PDAC and other hypoxic solid tumors and is the main source of circulating GRP78 in patients with advanced malignancies (23,53).

Antitumor therapies mediate the secondary amplification of GRP78 dysregulation. Antitumor treatments are the most important exogenous inducers of GRP78 membrane translocation and extracellular release and are the core drivers of the sharp increase in the sepsis risk in patients with cancer during treatment. Among these treatments, myelosuppressive chemotherapy, multitarget tyrosine kinase inhibitors (TKIs) and androgen deprivation therapy (ADT) have the strongest induction effects.

Chemotherapy: Platinum-based chemotherapy and anthracycline-based chemotherapy significantly exacerbate ERS in tumor cells, upregulate GRP78 expression and simultaneously promote its membrane translocation and exosomal secretion (67,68). This process forms a vicious cycle of 'treatment-induced stress-GRP78 dysregulation- immunosuppression-infection susceptibility', which is the core mechanism of postchemotherapy sepsis in patients with hematologic malignancies and solid tumors. Paradoxically, while chemotherapy aims to eliminate tumor cells, it inadvertently amplifies GRP78-mediated immunosuppression, creating a transient 'window of vulnerability' where the host defense against pathogens is severely compromised.

Targeted therapy: Sorafenib activates the IRE1α-mediated unfolded protein response pathway, promoting GRP78 membrane translocation and extracellular release (53). The sGRP78 level measured in patients after targeted therapy can be higher than that at baseline, which is closely related to the increased infection risk during treatment (53). EGFR-TKIs may disrupt ER homeostasis and are associated with an increased infection risk (69).

Hormone therapy: ADT may upregulate GRP78 expression; however, direct clinical evidence linking ADT-induced GRP78 dysregulation to sepsis risk in prostate patients with cancer is currently lacking (55,56).

4. From membrane surface exposure to pathogen invasion

Pathogen infection represents the core pathogenic foundation of sepsis development and progression and spans the entire disease course (70). Current research has progressively established that csGRP78 serves as a critical alternative receptor or coreceptor for pathogen invasion (71), providing a hypothetical pathological mechanism that may underlie the progression of infection to sepsis in patients with cancer, which requires prospective clinical validation. In patients with cancer, csGRP78 detected at sites of pathogen invasion may originate from two distinct cellular compartments with different pathophysiological implications: i) The first is tumor-derived csGRP78. Malignant cells constitutively overexpress csGRP78 because of chronic ER stress driven by hypoxia, nutrient deprivation and oncogenic signaling (6,8). ii) Host-derived csGRP78 in nonmalignant host cells, including mucosal epithelial cells, vascular endothelial cells, alveolar epithelial cells and innate immune cells (macrophages and dendritic cells), is obtained from the *de novo* upregulation of csGRP78 expression in response to infection-induced ER stress, hypoxia and inflammatory cytokines (72). The relative contributions of tumor-derived vs. host-derived csGRP78 to pathogen invasion likely vary by pathogen tropism, the anatomical site of infection and cancer type. Table II summarizes the probable cellular sources of csGRP78 for each major pathogen class discussed in the present review (73-98).

GRP78 as a critical cofactor for viral invasion. Accumulating evidence from *in vitro* and *in vivo* studies confirms that csGRP78 acts as a bona fide functional receptor or critical coreceptor for a broad spectrum of pathogenic viruses (73,74,79). It mediates viral invasion via two core mechanisms: Acting as a primary receptor to directly drive viral adhesion and endocytosis or as an attachment cofactor to increase viral binding affinity to cognate receptors and modulate post-invasion intracellular trafficking, thereby markedly increasing infection efficiency (74). This pro-infective role has been validated across multiple viral families (including *Flaviviridae*, *Coronaviridae*, *Orthomyxoviridae* and *Enteroviridae*), positioning GRP78 as a promising broad-spectrum antiviral target (21).

For *Flaviviridae* members, including dengue virus, Zika virus and Japanese encephalitis virus, GRP78 serves as a key host factor via direct interactions with viral envelope proteins and silencing/knockdown of GRP78 consistently inhibits viral invasion, replication and progeny production (75-80). csGRP78 also acts as a critical coreceptor for Coxsackievirus A9 (*Enteroviridae*), an essential host factor for influenza A virus (*Orthomyxoviridae*) and a key cooperative receptor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, *Coronaviridae*) (81-83). For SARS-CoV-2, in particular, GRP78 directly binds the spike protein receptor-binding domain and forms a functional complex with ACE2 to mediate viral entry, with clinical data linking elevated sGRP78 levels to COVID-19 infection susceptibility (21,73).

The receptor/coreceptor function of csGRP78 in driving viral infection has also been confirmed for retroviruses, filoviruses and other pathogenic viruses (84,86,89,99). Collectively, these findings establish csGRP78 as a core host factor that mediates viral invasion, which underpins the progression to severe disease and sepsis secondary to viral infection (Table III) (73-90,99-104).

Roles of GRP78 in fungal adhesion and invasion. csGRP78 serves as a critical receptor for host cell invasion by certain opportunistic pathogenic fungi, with the most comprehensive mechanistic studies focusing on Mucorales fungi, which represent important pathogens that cause invasive fungal infections that progress to sepsis in immunocompromised hosts.

Mucormycosis is a lethal invasive fungal infection caused by Mucorales fungi such as *Rhizopus*, predominantly affecting individuals with diabetic ketoacidosis (DKA), hematological malignancies, or those undergoing chemotherapy or immunosuppressive therapy, that results in immunocompromised states (92). Mechanistic studies have confirmed that under pathological conditions such as DKA, csGRP78 expression is significantly upregulated in host nasal epithelial cells and vascular endothelial cells. csGRP78 directly and specifically binds to the CotH3 protein on the outer wall of Mucorales fungal spores, mediating spore adhesion to and invasion of host epithelial cells and vascular endothelial cells, thereby leading to vascular invasion and tissue necrosis. This process represents the core mechanism underlying the specific infection of immunocompromised hosts by Mucorales fungi (91,105).

Research on other common pathogenic fungi indicates has not produced definitive evidence that currently confirms that *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*, or *Histoplasma capsulatum* directly utilize host csGRP78 as an invasion receptor. Only studies on *Pneumocystis jirovecii* suggest that it may bind to GRP78 on the surface of lung epithelial cells, with csGRP78 potentially serving as a putative receptor for host cell adhesion, although the relevant mechanisms require further validation (93). A summary of the differential roles of GRP78 in the invasion of various pathogenic fungi is presented in Table IV (91-93,105-110).

Role of GRP78 in bacterial infections. Compared with viruses and fungi, the current evidence regarding the direct role of csGRP78 in mediating bacterial adhesion and invasion remains relatively limited. The existing research focuses primarily on bacterial infection-induced ER stress and changes in GRP78 expression in host cells, with only a few pathogens confirmed to directly interact with csGRP78 to promote the infection process (94); meanwhile, the indirect regulatory role of GRP78 in bacterial sepsis, which is equally important, has been underemphasized.

The membrane protein Mhp271 of *Mycoplasma hyopneumoniae* can directly and specifically bind to the NBD of host cell csGRP78, promoting mycoplasmal adhesion to and invasion of host cells, which represents an important mechanism in its infection process (94). Although *Mycoplasma hyopneumoniae* is a rare cause of severe sepsis in humans, this interaction provides a proof-of-concept that csGRP78 can function as a bacterial receptor. Research on other common sepsis-causing pathogens has shown that infections with *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella*, *Mycobacterium tuberculosis*, *Helicobacter pylori* and *Streptococcus pneumoniae* can induce ER stress in host cells and upregulate GRP78 expression (95-98,111-113). However, no definitive direct evidence

Table II. Probable cellular sources of csGRP78 mediating pathogen invasion in cancer-associated sepsis.

Pathogen class	Pathogen	Primary target cell type	Predominant csGRP78 Source	Evidence basis
RNA viruses	SARS-CoV-2	Alveolar epithelial cells, monocytes	Host-derived (VeroE6-ACE2, THP-1)	Carlos *et al* (73) used VeroE6-ACE2 cells for mechanistic studies; Han *et al* (74) used THP-1 monocytes and primary CD14+ monocytes for clinical translational validation
	DENV	Hepatocytes	Cancer cell line-derived (HepG2, Huh-7)	Alhoot *et al* (75) and Jindadamrongwech *et al* (76) used HepG2 cells; Chumchanchira *et al* (77) used Huh-7 cells. All cell lines are derived from hepatocellular carcinoma
	ZIKV	Lung epithelial cells	Cancer cell line-derived (A549)	Khongwichit *et al* (78) explicitly used A549 cells for all experiments, including infection, co-immunoprecipitation, immunofluorescence, flow cytometry, antibody inhibition and siRNA knockdown
	JEV	Lung epithelial cells, kidney cells	Cancer cell line-derived (Neuro2a, 293T, Huh-7, BHK-21)	Nain *et al* (79) used Neuro2a and Huh-7 cells; Wu *et al* (80) confirmed that the ER stress response protein GRP78 is co-opted by JEV
	CVA9	Kidney cells, rhabdomyosarcoma cells, cervical carcinoma cells	Host-derived (GMK)	Triantafilou *et al* (81) primarily used GMK cells for infection experiments
	IAV	Lung epithelial cells	Cancer cell line-derived (A549)	Rashid *et al* (82) and Feng *et al* (83) both used A549 cells. No evidence from primary respiratory epithelial cells or macrophages is available
	HIV-1	T lymphocytes, macrophages	Host-derived (BSC-1)	Earl *et al* (84) used BSC-1 cells for gp160 studies; Elshemey *et al* (85) provided computational evidence. Direct binding of csGRP78 in primary cells has not been confirmed
	EBOV/ MARV	Endothelial cells, monocytes, macrophages	Cancer cell line-derived (primary human GBM cells, A549)	Booth *et al* (86) used multiple tumor cell lines for *in vitro* mechanistic studies, not primary endothelial cells or monocytes
	CHIKV	Epithelial cells, fibroblasts, endothelial cells	Host-derived (THP-1 cells)	Gupta *et al* (87) did not explicitly detect direct GRP78 binding; evidence is limited to UPR pathway modulation
	VEEV	Neural cells, endothelial cells, macrophages	Host-derived (Vero, 293T)	Barrera *et al* (88) confirmed the interaction between VEEV E2 protein and GRP78 via co-immunoprecipitation and colocalization
	MV	Human airway epithelial cells	Cancer cell line-derived (HEp-2)	Bolt *et al* (89) confirmed that measles virus infection upregulates GRP78 expression
DNA viruses	HBV	Hepatocytes	Cancer cell line-derived (Huh-6, HepG2, HepAd38)	Suwanmanee *et al* (90) suggested that GRP78 interacts with the preS2 domain via its ATPase domain
Fungi	*Rhizopus* spp./ Mucorales	Nasal epithelial cells, vascular endothelial cells	Mixed (CCL-30, A549)	Gebremariam *et al* (91) suggested that endothelial cell GRP78 binds to the fungal CotH3 protein; Alqarihi *et al* (92) identified the specific interaction between nasal epithelial cell GRP78 and fungal CotH3
	P. jirovecii	Alveolar epithelial cells (type II pneumocytes)	Host-derived (rat primary alveolar & airway epithelial cells)	Kottom *et al* (93) suggested that GRP78 mediates organism attachment

Table II. Continued.

Pathogen class	Pathogen	Primary target cell type	Predominant csGRP78 Source	Evidence basis
Bacteria	*M. hyopneumoniae*	Respiratory epithelial cells	Host-derived (293T, PTEC)	Pan *et al* (94) suggested that Mhp271 interacts with host GRP78
	S. pneumoniae	Alveolar macrophages	Host-derived (BMCs)	Cho *et al* (95) did not directly detect GRP78; the study focused on the NLRP3 inflammasome
	P. aeruginosa	Bronchial epithelial cells	Host-derived (16HBE)	van 't Wout *et al* (96) used the 16HBE human bronchial epithelial cell line. No direct GRP78 binding has been confirmed
	M. tuberculosis	Macrophages	Host-derived (BMDMs)	Lim *et al* (97) suggested that tuberculosis infection induces ER stress-mediated apoptosis. No direct GRP78 binding has been confirmed
	H. pylori	Gastric epithelial cells	Cancer cell line-derived (AZ-521)	Akazawa *et al* (98) suggested that VacA toxin induces ER stress contributing to apoptosis. No direct GRP78 binding has been confirmed

Cell line sources (alphabetical order): 16HBE, immortalized human bronchial epithelial cell line; A549, human lung adenocarcinoma cell line; AZ-521, human gastrointestinal adenocarcinoma cell line); BHK-21, baby hamster kidney cell line; BMCs, mouse bone marrow cells; BMDMs, mouse bone marrow-derived macrophages; BSC-1, African green monkey kidney cell line; CCL-30, human nasal epithelial cell line; GBM, human glioblastoma multiforme cell; GMK, green monkey kidney cell line; 293T, human embryonic kidney cell line; HEp-2, human laryngeal epidermoid carcinoma cell line; HepAd38, HepG2-derived human hepatoblastoma cell line with tetracycline-inducible HBV replication; HepG2, human hepatocellular carcinoma cell line; Huh-6, human hepatoblastoma cell line; Huh-7, human hepatocellular carcinoma cell line; Neuro2a, mouse neuroblastoma cell line; PTEC, primary porcine tracheal epithelial cells; RLE-6TN, rat lung epithelial type II cell line; THP-1, human monocytic leukemia cell line; Vero, African green monkey kidney cell line; VeroE6-ACE2, Vero E6 cell line stably expressing human ACE2 receptor. CHIKV, chikungunya virus; CotH3, spore coating protein H3; CVA9, coxsackievirus A9; DENV, dengue virus; EBOV, Ebola virus; ER, endoplasmic reticulum; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIV-1, human immunodeficiency virus type 1; IAV, influenza A virus; JEV, Japanese encephalitis virus; MARV, Marburg virus; Mhp271, *Mycoplasma hyopneumoniae* membrane protein 271; MV, measles virus; NLRP3, NOD-like receptor family pyrin domain containing 3; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; spp., species (plural); UPR, unfolded protein response; VEEV, Venezuelan equine encephalitis virus; ZIKV, Zika virus; H., *Helicobacter*; M., *Mycobacterium* or *Mycoplasma*; P., *Pneumocystis* or *Pseudomonas*; S., *Streptococcus*.

currently confirms that these bacteria utilize host csGRP78 as an adhesion or invasion receptor.

Notably, the contribution of GRP78 to bacterial sepsis is not dependent on its role as a direct receptor; instead, its indirect regulatory effects on host inflammatory responses, phagocytic function and barrier integrity constitute a temporally ordered, functionally interdependent pathogenic sequence that drives bacterial sepsis progression. It is hypothesized that GRP78 functions as a systems-level coordinator of the failure of the host response through the following integrated sequence.

Phase I: Barrier disruption and bacterial translocation. Bacterial infection-induced ER stress contributes to the downregulation of tight junction proteins in intestinal epithelial cells, disrupting barrier function and creating an anatomical portal for bacterial translocation (111,112). *Escherichia coli*-derived LPS aggravates ER stress and ER stress-mediated apoptosis in ER stress-responsive IPEC-J2 cells; the crosstalk between nuclear GRP78 and p53 triggers this LPS-induced increase in apoptosis (112). *Salmonella* infection activates the IRE1α-UPR signaling axis via curli proteins, upregulating GRP78 expression (113). In patients with cancer, chemotherapy and radiotherapy pre-compromise mucosal integrity, while tumor-derived sGRP78 may further impair barrier repair by suppressing local immune surveillance, increasing the width of the anatomical portal and decreasing its defense.

Phase II: Innate immune dysregulation and delayed clearance. As bacteria translocate, host macrophages upregulate GRP78 in response to infection-induced ER stress. However, this upregulation paradoxically impairs rather than enhances antimicrobial function. *Streptococcus pneumoniae* infection induces the significant upregulation of GRP78 expression in aged lungs, which is associated with decreased NLRP3 inflammasome activation and impaired bacterial clearance by senescent macrophages (95). Additionally, ER stress-mediated GRP78 overexpression can trigger macrophage death through the PERK/ATF4/CHOP pathway, further reducing the phagocytic capacity (114).

Phase III: Inflammatory amplification and tissue injury. When the bacterial burden exceeds the blunted clearance capacity of Phase II, sustained ER stress drives the dissociation of GRP78 from UPR sensors, activating the NF-κB, MAPK and AP-1 signaling pathways and triggering excessive proinflammatory cytokine secretion (18,115). In the context of persistent ER stress, CHOP activation downstream of the PERK-eIF2α axis induces apoptosis, exacerbating tissue damage and systemic inflammation (114). *Staphylococcus aureus* infection activates the GRP78-EIF2α-ATF4 pathway and ER stress-autophagy axis, leading to host cell apoptosis (111). In patients with cancer, chemotherapy-induced tumor cell death releases damage-associated molecular

Table III. Core roles and underlying mechanisms of GRP78 in infection by diverse pathogenic viruses.

Pathogen	Viral family	Primary role	Key mechanism	(Refs.)
SARS-CoV-2	*Coronaviridae*	Key auxiliary factor for viral entry/ ACE2- independent entry receptor	csGRP78 binds spike protein RBD; forms functional complex with ACE2 to mediate viral entry	(73,74,99)
DENV	*Flaviviridae*	Key host factor for viral entry and replication	csGRP78 is core component of viral receptor complex to mediate entry; infection upregulates GRP78 to promote replication	(75-77)
ZIKV	*Flaviviridae*	Essential host factor for viral entry and replication	csGRP78 binds envelope E protein to mediate entry; intracellular GRP78 stabilises viral proteins and regulates replication/progeny production	(78,100,101)
JEV	*Flaviviridae*	Key host factor for viral entry and replication	csGRP78 binds envelope protein domain III to mediate entry; intracellular GRP78 regulates viral RNA replication, protein synthesis and progeny release	(79,80,102)
CVA9	*Picornaviridae*	Critical co-receptor for viral entry	csGRP78 cooperates with integrin αvβ3 for initial adhesion; forms complex with MHC-I to mediate virus-receptor complex endocytosis	(81)
IAV	*Orthomyxoviridae*	Essential host factor for viral entry and replication	csGRP78 binds hemagglutinin to mediate entry; intracellular GRP78 modulates replication via ER stress pathway regulation	(82,83,103)
HIV-1	*Retroviridae*	Potential auxiliary factor for viral entry/key regulator of viral envelope maturation	csGRP78 may mediate viral adhesion/entry; intracellular GRP78 acts as chaperone for envelope protein folding/maturation	(84,85)
EBOV/ MARV	*Filoviridae*	Essential host factor for viral replication	Regulates viral glycoprotein folding/maturation; modulates host viral receptor expression to enhance infection/ replication	(86)
Alphavirus spp. (CHIKV, VEEV)	*Togaviridae*	Key host factor for viral infection and replication	csGRP78 binds E2 protein to regulate entry; infection activates UPR to upregulate GRP78, further promoting replication	(87,88)
MV	*Paramyxoviridae*	Key chaperone for viral glycoprotein maturation	Intracellular GRP78 acts as molecular chaperone for viral glycoprotein folding, maturation and trafficking	(89)
HBV	*Hepadnaviridae*	Auxiliary factor for viral entry/ regulator of antigen secretion	csGRP78 facilitates viral adhesion/entry; intracellular GRP78 regulates viral antigen folding and secretion	(90,104)

ACE2, angiotensin-converting enzyme 2; CVA9, Coxsackievirus A9; csGRP78, cell surface glucose-regulated protein 78; DENV, Dengue Virus; EBOV, Ebola Virus; ER, endoplasmic reticulum; HBV, Hepatitis B Virus; HIV-1, Human Immunodeficiency Virus Type 1; IAV, Influenza A Virus; JEV, Japanese Encephalitis Virus; MARV, Marburg Virus; MHC-I, major histocompatibility complex class I; MV, Measles Virus; RBD, receptor-binding domain; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; spp., species (plural, standard taxonomic abbreviation); UPR, unfolded protein response; VEEV, Venezuelan Equine Encephalitis Virus; ZIKV, Zika Virus.

patterns, which may synergize with bacterial pathogen-associated molecular patterns to amplify the inflammatory cytokine storm beyond the threshold observed in non-cancer sepsis.

Phase IV: Endothelial dysfunction and multiorgan failure. The sustained inflammatory milieu drives the translocation of GRP78 to endothelial cell surfaces, where csGRP78-mediated signaling disrupts vascular integrity. GRP78-induced O-GlcNAcylation of VE-cadherin compromises endothelial junctions, whereas the activation of the PERK/IRE1α pathway promotes NF-κB binding to the iNOS promoter, driving excessive nitric oxide production that induces vasodilation,

Table IV. Core roles and underlying mechanisms of GRP78 in pathogenic fungal infection.

Pathogen	Fungal taxonomy	Functional category	Primary role	Key mechanism	(Refs.)
Mucorales fungi	Order *Mucorales*	Host GRP78 core function	Essential host functional receptor for fungal invasion	Host csGRP78 directly binds to fungal CotH3 protein to mediate spore adhesion to and invasion of host epithelial and vascular endothelial cells	(91,92,105)
Pneumocystis jirovecii	Family *Pneumocystidaceae*	Host GRP78 core function	Potential host receptor for fungal adhesion	Host csGRP78 mediates fungal adhesion to host lung epithelial cells	(93)
Candida albicans	Family *Saccharomycetaceae*	Other host regulatory function	Host cytoprotective factor against fungal-induced cell damage	Sustained expression of host GRP78 attenuates fungal-induced epithelial cell death	(106)
Aspergillus fumigatus	Family *Aspergillaceae*	Other host regulatory function	Regulator of host inflammatory and stress responses	Host GRP78 participates in the regulation of fungal-induced ER stress and inflammatory signaling in host cells	(107,108)
Cryptococcus neoformans	Family *Cryptococcaceae*	Fungal-encoded GRP78 homolog function	Essential molecule for fungal pathogenicity	Fungal-encoded Kar2/BiP (GRP78 ortholog) regulates the virulence of the pathogen	(109)
Histoplasma capsulatum	Family *Ajellomycetaceae*	Host response marker	Biomarker of host stress response to fungal infection	Fungal infection induces significant upregulation of host GRP78 expression	(110)

csGRP78, cell surface glucose-regulated protein 78; GRP78, glucose-regulated protein 78; ER, endoplasmic reticulum; BiP, Immunoglobulin heavy-chain binding protein.

hypotension and tissue hypoperfusion (114,116,117). These vascular and barrier effects culminate in the hemodynamic collapse and multiorgan dysfunction characteristic of septic shock.

Fundamental mechanistic distinction: Thus, unlike in viral and fungal infections, where csGRP78 functions as a canonical adhesion or coreceptor, csGRP78 does not appear to serve as a primary bacterial receptor for major pathogens causing sepsis in humans. Instead, GRP78 modulates host inflammatory responses, phagocytic function and epithelial barrier integrity through an indirect, temporally ordered, four-phase mechanism that coordinates the failure of the host response from the initial bacterial encounter to terminal organ dysfunction. This systems-level role represents a fundamental mechanistic distinction across pathogen classes.

A summary of the roles of GRP78 in different bacterial infections is presented in Table V (94-98,111-113,118-124), which highlights that the indirect regulatory effects of GRP78 on host immunity and barrier function are far more extensive than its direct role as a bacterial receptor and that these indirect effects are crucial for the progression of common bacterial infections to sepsis.

In summary, the existing research has fully confirmed that csGRP78 serves as a critical receptor or coreceptor for host cell invasion by multiple viruses and Mucorales fungi. Its abnormal overexpression can directly increase host susceptibility to these pathogens, providing the core pathological foundation for the subsequent progression of infection to sepsis. Although direct evidence that csGRP78 acts as a bacterial receptor is currently limited, the role of GRP78 in the progression of bacterial sepsis, the primary cause of clinical sepsis, through its indirect regulation of inflammatory responses, phagocytic function and barrier integrity is indispensable.

5. Immunoregulatory role of GRP78 in sepsis

Based on preclinical evidence, in addition to its proposed role in mediating pathogen invasion, the inflammatory and immunoregulatory functions of GRP78 are hypothesized to be critically governed by two determining factors: Cellular origin (tumor-derived vs. host-derived) and the temporal phase of sepsis (early systemic inflammatory response syndrome vs. late immunosuppressive phase) (115,125). Specifically, tumor-derived GRP78, which predominantly exists as

Table V. Core roles and underlying mechanisms of GRP78 in bacterial and mycoplasma infection.

Pathogen	Bacterial taxonomy	Functional category	Primary role of GRP78	Key mechanism	(Refs.)
Mycoplasma hyopneumoniae	Order *Mycoplasmatales*, Family *Mycoplasmataceae*	Direct receptor for pathogen adhesion and invasion	Key interacting molecule mediating mycoplasma adhesion and invasion	Host csGRP78 directly binds to mycoplasmal Mhp271 protein via its NBD to facilitate pathogen adhesion and host cell invasion	(94)
Clostridium butyricum	Order *Eubacteriales*, Family *Clostridiaceae*	Therapeutic target and immune regulatory function	Regulatory target of tumor immune microenvironment	Binds to host csGRP78 to inhibit pro-inflammatory signaling and improve the efficacy of tumor immunotherapy	(118)
Chlamydia pneumoniae/ *Chlamydia psittaci*	Order *Chlamydiales*, Family *Chlamydiaceae*	Host stress and autophagy regulatory function	Regulator of host autophagy and stress response	Pathogen infection activates the ER stress pathway to upregulate GRP78 expression, which further modulates host autophagy	(119,120)
Streptococcus pneumoniae	Order *Lactobacillales*, Family *Streptococcaceae*	Host immune regulatory function	Regulator of macrophage immune function	Modulates inflammasome activation in senescent macrophages during infection	(95)
Staphylococcus aureus	Order *Bacillales*, Family *Staphylococcaceae*	Host cell death and inflammatory regulatory function	Regulator of host cell death and inflammatory response	Activates the GRP78-EIF2α-ATF4 pathway and ER stress-autophagy signaling axis; mediates ferroptosis and apoptosis of host cells via downstream CHOP activation, exacerbating tissue damage	(111,121)
Pseudomonas aeruginosa	Order *Pseudomonadales*, Family *Pseudomonadaceae*	Host stress response regulatory function	Regulator of host stress response	Pathogen infection activates the host UPR pathway to upregulate GRP78 expression	(96)
Escherichia coli	Order *Enterobacterales*, Family *Enterobacteriaceae*	Host epithelial apoptosis and inflammatory regulatory function	Regulator of intestinal epithelial apoptosis and inflammation	Nuclear GRP78-p53 signaling axis mediates LPS-induced intestinal epithelial cell apoptosis	(112,122)
Salmonella spp.	Order *Enterobacterales*, Family *Enterobacteriaceae*	Host stress response regulatory function	Activator of host UPR pathway	Bacterial curli protein activates the IRE1α-UPR signaling axis to upregulate GRP78 expression	(113)
Mycobacterium tuberculosis	Order *Mycobacteriales*, Family *Mycobacteriaceae*	Host cell death and autophagy regulatory function	Regulator of macrophage apoptosis and autophagy	Modulates apoptosis and autophagy of infected macrophages via ER stress signaling	(97,123)
Helicobacter pylori	Order *Campylobacterales*, Family *Helicobacteraceae*	Host cell apoptosis and carcinogenesis regulatory function	Regulator of host cell apoptosis and carcinogenesis	Modulates ER stress-mediated cell apoptosis and intracellular ROS levels during infection	(98,124)

csGRP78, cell surface glucose-regulated protein 78; GRP78, glucose-regulated protein 78; ER, endoplasmic reticulum; UPR, unfolded protein response; IRE1α, inositol-requiring enzyme 1α; LPS, lipopolysaccharide; NBD, N-terminal nucleotide-binding domain; ROS, reactive oxygen species; spp., species (plural, standard taxonomic abbreviation).

sGRP78, establishes a baseline immunosuppressive state that increases the vulnerability of patients with cancer to infectious complications (115). By contrast, host-derived GRP78, encompassing both csGRP78 and intracellular pools, exhibits stage-specific bidirectional immunomodulatory effects: it amplifies proinflammatory responses during early sepsis but subsequently drives immune exhaustion and paralysis in the late immunosuppressive phase (125). These ontologically and temporally distinct mechanisms collectively establish GRP78 dysregulation as a pivotal link between cancer pathophysiology and sepsis progression. Table VI comprehensively summarizes the regulatory effects of GRP78 on key inflammatory cytokines during immune responses (116,126-142), with explicit stratification by the cellular origin of GRP78 and the temporal phase of sepsis.

Regulation of proinflammatory cytokines: Origin- and stage-dependent bidirectional control. The regulation of proinflammatory cytokines by GRP78 is the core of its stage-dependent effects, with distinct roles for tumor-derived and host-derived GRP78.

Tumor-derived sGRP78: Baseline immunosuppression (pre-infection stage). Tumor cells secrete large amounts of sGRP78 into the systemic circulation, which predominantly exerts anti-inflammatory/immunosuppressive effects to establish a baseline state of immune hyporesponsiveness in patients with cancer (62,115); this key factor increases the susceptibility of these patients to bacterial/viral infection. Specifically, sGRP78 binds to CD14 on macrophages/neutrophils, promotes TLR4 endocytic degradation and inhibits TLR4 dimerization, thereby suppressing LPS-induced TNF-α and IL-6 production (126). Qin *et al* (126) showed that 40 μg/ml sGRP78 almost fully abolished TNF-α release in bone marrow-derived dendritic cells, mimicking the effect of TLR4 knockout; this phenomenon is particularly prominent in patients with cancer and with high circulating sGRP78 levels, reducing their ability to mount an effective early inflammatory response against invading pathogens. This tumor-induced baseline immune suppression creates a 'predisposed' state: Even in the absence of traditional risk factors such as neutropenia, patients with cancer with high sGRP78 levels are more likely to develop persistent infections that progress to sepsis.

Host-derived GRP78: Stage-dependent bidirectional regulation (post-infection stage). Upon infection, host cells (immune cells, epithelial cells and endothelial cells) upregulate GRP78 expression and induce its subcellular redistribution, with effects varying significantly between early and late sepsis.

Early sepsis: Intracellular GRP78 and csGRP78 (host-derived) predominantly exert proinflammatory effects to eliminate pathogens. Intracellular GRP78 activates the PERK pathway to promote TNF-α secretion, whereas csGRP78 activates the NF-κB/MAPK pathway to upregulate IL-6 expression; these responses are necessary for pathogen clearance, but their excessive activation can amplify the inflammatory cytokine storm (143). For example, in a sepsis-related acute kidney injury (AKI) model, LPS-induced ER stress upregulated intracellular GRP78 and TNF-α levels and inhibiting the GRP78/PERK axis reduced renal TNF-α levels and tissue injury (143). With respect to IL-1β, intracellular GRP78 initially activates the NLRP3 inflammasome to promote IL-1β maturation, enhancing the early inflammatory response against pathogens (144).

However, when an infection persists and ER stress remains unresolved, secondary remodeling of GRP78 expression and subcellular localization occur in host cells (62,115). The functional of GRP78 subsequently shifts from 'driving effective inflammation to clear pathogens' to 'excessively suppressing immune responses to mitigate tissue damage,' ultimately precipitating the development of immune paralysis (62,125).

Late sepsis: Sustained ER stress and excessive sGRP78 accumulation lead to the functional exhaustion of GRP78, shifting its role to anti-inflammatory/immunosuppressive effects. *In vitro* studies using human coronary artery endothelial cells demonstrate that chronic ER stress promotes GRP78 secretion (145). The GRP78 released into the conditioned medium subsequently attenuates ER stress and endothelial inflammation (145).

GRP78 also orchestrates Th1/Th17-related cytokine networks in a stage-dependent manner. In the pre-infection stage, tumor-derived sGRP78 suppresses the expression of IL-12 (an M1 macrophage marker) and promotes M2 polarization, impairing Th1 anti-infective immunity and increasing the risk of sepsis (129). In early sepsis, host-derived GRP78 is positively correlated with IFN-γ secretion, enhancing Th1-mediated pathogen clearance (128); it also activates the p38 MAPK pathway to upregulate IL-18, driving M1 microglial polarization and exacerbating inflammatory injury (127). In late sepsis, sGRP78 negatively regulates IL-17 by targeting the CCR6/IL-17A axis in γδ T cells, mitigating tissue damage but further weakening anti-infective immunity (130). Additionally, GRP78 indirectly regulates IL-2 by maintaining immune homeostasis: hematopoietic cell-specific GRP78 knockout leads to hematopoietic stem cell apoptosis, reduced numbers of lymphocytes and a compensatory increase in IL-2 levels, disrupting sepsis resolution (131).

Regulation of anti-inflammatory mediators: Amplifying immune paralysis in late sepsis. The regulation of anti-inflammatory mediators by GRP78 primarily serves to amplify immune suppression in late sepsis, with consistent effects observed for tumor-derived and host-derived GRP78.

IL-10: A key mediator of GRP78-induced immune paralysis. GRP78 promotes IL-10 production in a cell type-specific manner, predominantly by driving M2 macrophage polarization, a core mechanism of immunosuppression in late sepsis. In macrophages, both tumor-derived sGRP78 and host-derived csGRP78 upregulate IL-10 expression: GRP78 overexpression significantly increases IL-10 release, while GRP78 knockdown markedly suppresses it (129). This effect is particularly pronounced in late sepsis, in which sustained GRP78 activation drives extensive M2 polarization, further inhibiting proinflammatory responses and impairing pathogen clearance. By contrast, GRP78-induced tolerogenic dendritic cells exhibit an immature phenotype but show no significant alteration in IL-10 production (146); this exception reflects the cell type specificity of the anti-inflammatory effects of GRP78.

TGF-β and IL-4/IL-13: Synergistic amplification of immunosuppression. The role of GRP78 in regulating TGF-β

Table VI. Regulatory roles and core mechanisms of GRP78 in inflammatory immune mediators.

Major mediator category	Inflammatory mediator	GRP78 origin	Core role of GRP78	Key regulatory mechanism	(Refs.)
Pro-inflammatory cytokines	TNF-α	Host-derived (DC)	Negative regulation	sGRP78 inhibits the TLR4 signaling pathway to suppress TNF-α production	(126)
	IL-1β	Host-derived (pSGC)	Bidirectional regulation	Modulates the maturation and activation of the NLRP3 inflammasome	(127)
	IL-6	Host-derived (DC)	Negative regulation	sGRP78 inhibits the TLR4 signaling pathway to suppress IL-6 production	(126)
	IFN-γ	Host-derived (PBMCs)	Positive regulation	IFN-γ levels positively correlate with the frequency of GRP78-positive clones in PBMCs	(128)
	IL-12	Host-derived (PBMCs)	Negative regulation	Drives M2 macrophage polarization and inhibits IL-12 secretion	(129)
	IL-18	Host-derived (pSGC)	Positive regulation	Regulates the NLRP3 inflammasome to promote IL-18 maturation and release	(127)
	IL-17A	Host-derived (HaCaT)	Negative regulation	Exerts targeted inhibition on the CCR6/IL-17A signaling axis	(130)
	IL-2	Host-derived (BM cells)	Negative regulation	Maintains immune cell homeostasis and regulates compensatory IL-2 secretion	(131)
Anti-inflammatory mediators	IL-10	Host-derived (PBMCs)	Negative regulation	Promotes M2 macrophage polarization and upregulates IL-10 expression in macrophages	(129)
	TGF-β1	Tumor-derived (DLD1, HCT-116, SW480)	Positive regulation	Promotes TGF-β1 expression and secretion and activates the Smad2/3 signaling pathway	(132)
	IL-4	Host-derived (PBMCs)	Positive regulation	Forms a positive feedback loop with M2 macrophage polarization	(129)
	IL-13	Host-derived (BMDMs)	Negative regulation	Inhibits IL-13 signaling transduction	(133)
Chemokines	IL-8/CXCL8	Host-derived (HPAECs)	Positive regulation	Promotes IL-8 transcriptional expression via the ER stress pathway	(134)
	MCP-1/CCL2	Host-derived (human monocytes)	Positive regulation	CCL2 levels positively correlate with the frequency of CD45+sGRP78+cells	(135)
	MIP-1α/β	Host-derived (BMDMs, AMs)	Positive regulation	Promotes chemokine expression via the NF-κB/IRE1 signaling pathway	(136,137)
Vasoactive and endothelial-related mediators	NO	Tumor-derived (RAW 264.7)	Positive regulation	Regulates iNOS expression and NO synthesis via the ER stress pathway	(138)
	ICAM-1/ VCAM-1	Host-derived (hAECs)	Positive regulation	csGRP78 activates the NF-κB pathway to upregulate adhesion molecules	(116)

Table VI. Continued.

Major mediator category	Inflammatory mediator	GRP78 origin	Core role of GRP78	Key regulatory mechanism	(Refs.)
Other key inflammatory mediators	ROS	Host-derived (NRVM, H9c2, rat renal cells)	Bidirectional regulation of oxidative stress	Bidirectionally modulates ER stress and antioxidant signaling pathways	(139-141)
	MMPs	Tumor-derived (SMMC7721, HepG2)	Positive regulation	Promotes MMP-2/MMP-9 transcriptional activation and regulates ECM degradation	(142)

Host-derived GRP78 denotes *de novo* upregulation in non-malignant cells during infection; tumor-derived sGRP78 denotes pre-existing circulating GRP78 secreted by malignant cells. Cell line sources (Alphabetical Order): AM, mouse alveolar macrophage; BMDMs, mouse bone marrow-derived macrophages; BM cells, mouse bone marrow cells; DC, mouse bone marrow-derived dendritic cell; DLD1, human colon adenocarcinoma cell line; HaCaT, human immortalized keratinocyte cell line; HCT-116, human colon carcinoma cell line; HepG2, human hepatocellular carcinoma cell line; H9c2, rat embryonic cardiomyoblast cell line; hAECs, human amniotic epithelial stem cells; HPAECs, human pulmonary artery endothelial cells; NRVM, rat neonatal ventricular myocyte; PBMCs, human peripheral blood mononuclear cells; pSGC, mouse primary submandibular gland cell; RAW 264.7, mouse monocyte/macrophage leukemia cell line; SMMC7721, human hepatocellular carcinoma cell line; SW480, human colon adenocarcinoma cell line. AM, alveolar macrophage; BMDM, bone marrow-derived macrophage; BM, bone marrow; csGRP78, cell-surface GRP78; CCR6, C-C motif chemokine receptor 6; DC, dendritic cell; ECM, extracellular matrix; ER, endoplasmic reticulum; GRP78, glucose-regulated protein 78; hAEC, human amniotic epithelial cell; HPAEC, human pulmonary artery endothelial cell; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; IRE1, inositol-requiring enzyme 1; MCP-1, monocyte chemoattractant protein 1; MIP-1α/β, macrophage inflammatory protein 1 alpha/beta; MMP, matrix metalloproteinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3, NOD-like receptor family pyrin domain containing 3; NO, nitric oxide; NRVM, neonatal rat ventricular myocyte; PBMC, peripheral blood mononuclear cell; pSGC, primary submandibular gland cell; ROS, reactive oxygen species; sGRP78, Soluble GRP78; Smad2/3, SMAD family member 2/3; TGF-β, transforming growth factor beta; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule 1.

levels in patients with sepsis remains unclear, but existing oncological research provides indirect evidence that GRP78 overexpression in colon cancer cells promotes TGF-β1 secretion and activates the Smad2/3 pathway to regulate tissue remodeling (132). In late sepsis, this pathway may contribute to multiorgan fibrotic injury, although direct validation in sepsis models is needed.

With respect to the IL-4/IL-13 axis (key inducers of M2 polarization), GRP78 forms a positive feedback loop with these cytokines to amplify immune suppression: IL-4/IL-13 upregulates GRP78 expression in macrophages (129,147) and GRP78 further promotes M2 polarization via the JAK/STAT pathway, increasing anti-inflammatory signaling (129). Notably, serum IL-13 levels are elevated fourfold in macrophage-specific GRP78-deficient mice, suggesting a negative feedback mechanism by which GRP78 regulates IL-13 secretion (133). This feedback mechanism may prevent excessive immunosuppression in early sepsis but fails in late sepsis because of sustained GRP78 overactivation. The current evidence is primarily derived from tumor-associated macrophage models and the precise role of this axis in sepsis requires further validation (129).

Regulation of chemokines: Stage-dependent modulation of inflammatory cell infiltration. The regulation of chemokines (IL-8, MCP-1 and MIP-1α/β) by GRP78 is closely linked to sepsis-induced tissue inflammation, with the effects varying by the sepsis stage.

Early sepsis: Intracellular GRP78 (host-derived) acts as a positive regulator of IL-8 and MCP-1 levels, promoting endothelial inflammatory responses and leukocyte infiltration to facilitate pathogen clearance. In an LPS-induced acute lung injury model, the cleavage of intracellular GRP78 suppressed IL-8 expression and pulmonary inflammation (134) and Apelin-36 reduced LPS-induced MCP-1 release by inhibiting the GRP78/ASK1/JNK pathway (148), confirming the proinflammatory role of GRP78 in early sepsis.

Late sepsis: Excessive sGRP78 (tumor and host-derived) inhibits chemokine production, reducing leukocyte recruitment to infection sites and impairing pathogen clearance. For example, the GRP78-specific monoclonal antibody N88 reduces CCL3/CCL4 (MIP-1α/β homologues) expression in LPS-stimulated macrophages (136), whereas the inhibition of the IRE1/XBP-1 pathway (downstream of GRP78) reduces MIP-1α/β production and alleviated acute lung injury (137); these effects reflect the shift of GRP78 function towards immunosuppression in late sepsis.

This stage-specific switch in chemokine regulation by GRP78 underscores its central role in balancing inflammatory cell infiltration: promoting pathogen clearance in early sepsis but contributing to immune evasion in late sepsis.

Regulation of vasoactive and endothelial function-related inflammatory mediators. GRP78 modulates vasoactive mediators and endothelial inflammation in a stage-dependent manner, contributing to sepsis progression.

Early sepsis: Host-derived csGRP78 and intracellular GRP78 drive vascular dysfunction and inflammatory amplification. Intracellular GRP78 activates the PERK/IRE1α pathway, promoting NF-κB binding to the iNOS promoter and

excessive NO production to induce vasodilation, hypotension and tissue hypoperfusion (138). In endothelial cells, csGRP78 binds anti-GRP78 autoantibodies, activating NF-κB to upregulate ICAM-1/VCAM-1 and promoting leukocyte adhesion and transendothelial migration (116). These effects are necessary for local inflammation but, when they are excessive, contribute to systemic endothelial dysfunction.

Late sepsis: Sustained GRP78 activation exacerbates endothelial barrier disruption and multiorgan dysfunction. Excessive NO production (mediated by GRP78/iNOS) leads to irreversible vascular hyporesponsiveness, whereas persistent endothelial activation (via csGRP78) disrupts barrier integrity, which are key features of septic shock (70,149).

In patients with cancer, tumor-derived sGRP78 further exacerbates vascular dysfunction by disrupting endothelial barrier integrity, increasing the likelihood of developing septic shock compared with patients with non-cancer sepsis. Specifically, sGRP78 promotes angiogenesis and endothelial cell proliferation under physiological conditions (150,151); however, during sustained ER stress in individuals with sepsis, the cell surface translocation of GRP78 induces the O-GlcNAcylation of VE-cadherin and disrupts endothelial junctions, leading to increased vascular permeability and barrier dysfunction (117). This paradoxical shift from proangiogenic to barrier-disruptive functions contributes to the hemodynamic instability characteristic of septic shock in patients with cancer.

Regulation of other key inflammatory mediators. The regulation of ROS and MMPs by GRP78 also follows a stage-dependent pattern.

ROS regulation: In early sepsis, intracellular GRP78 (host-derived) maintains redox homeostasis by suppressing ER stress and increasing the activity of Nrf2/HO-1 antioxidant axis (139,140), mitigating oxidative damage. In late sepsis, persistent ER stress induces GRP78 dysfunction, disrupting oxidative-antioxidant equilibrium and exacerbating cellular injury and decreased GRP78 expression is correlated with the exacerbation of oxidative stress in individuals with sepsis-induced AKI (141).

MMP regulation: In early sepsis, GRP78 upregulates MMP-2/9/14 expression via the FAK-Src-JNK-c-Jun pathway, promoting extracellular matrix degradation and leukocyte infiltration (142). In late sepsis, excessive MMP activation (mediated by GRP78) contributes to tissue remodeling and multiorgan fibrosis; PI3K-γ inhibition attenuates GRP78-related ER stress and MMP-9 expression, improving pulmonary pathology in individuals with sepsis-associated acute lung injury (152).

6. Therapeutic approaches for targeting GRP78

GRP78-targeted inhibitors can be divided into seven categories based on their structural properties and mechanisms of action (Table VII) (88,153-181): i) Natural products, ii) synthetic products, iii) modified bacterial toxins, iv) metal-based drugs, v) monoclonal antibodies, vi) peptide agents and vii) nucleic acid drugs. Accumulating evidence has indicated that the expression and function of GRP78 can be regulated at multiple levels, including transcriptional regulation, post-transcriptional regulation, translational regulation and post-translational regulation, providing multiple actionable targets for the development of GRP78-targeted interventions.

However, a critical 'double-edged sword' dilemma exists when these strategies are applied to cancer-associated sepsis. First, systemic GRP78 inhibition disrupts ER proteostasis in host immune and epithelial cells. GRP78 is essential for maintaining the unfolded protein response in neutrophils, macrophages and intestinal epithelial cells under infectious stress; global suppression of this activity impairs cell viability and exacerbates barrier dysfunction (131,182). Second, nonselective inhibition abolishes the stage-dependent protective role of host-derived GRP78. In early sepsis, intracellular GRP78 attenuates CHOP-mediated apoptosis and preserves the phagocytic capacity, whereas in late sepsis, persistent GRP78 activation paradoxically limits NLRP3 overactivation to prevent excessive tissue injury (114,125,127). Third, *in vivo* studies of sepsis have not been conducted in tumor-bearing animals. The existing preclinical efficacy data are derived exclusively from tumor xenograft models without concurrent infection, suggesting that the net effect of GRP78 inhibition on sepsis outcomes in patients with cancer is entirely hypothetical (88,153-181). Thus, the feasibility of GRP78-targeted therapy hinges on resolving two core questions: 'When to intervene?' and 'how to deliver the drug precisely?'.

Transcriptional and post-transcriptional regulation of GRP78. The transcriptional activation of the GRP78-encoding gene HSPA5 is primarily mediated by the ERSE in its promoter region, where ERSE-binding transcription factors such as NF-Y, YY1, general TFII-I and ATF6 play key roles (183), with most transcriptional regulators acting by interfering with the binding of these factors to the HSPA5 promoter. For instance, genistein represses GRP78 transcription by antagonizing NF-Y/CBF binding to ERSE (170). In addition to this canonical ERSE-dependent pathway, ERSE-independent regulatory axes also serve as potential targets for GRP78 transcriptional intervention. Under pathological ER stress, ATF4 activates the HSPA5 promoter by forming a complex with ATF1 and CREB1, but in bortezomib-resistant osteosarcoma cells, ATF4 and its activators can repress GRP78 transcription via alternative mechanisms, reflecting context-dependent bidirectional regulation (158) and agents such as AR12, Kringle 5 (K5), piperine and ribociclib target this axis through distinct pathways (155,158,168).

With respect to post-transcriptional regulation, nucleic acid drugs are the most well-developed targeting agents and an *in vitro* study has confirmed that miR-181a directly targets the 3'-untranslated region (3'-UTR) of the *GRP78* mRNA to inhibit GRP78 translation (181). Notably, transcriptional and post-transcriptional inhibitors non-selectively suppress GRP78 expression in both tumor cells and host immune/epithelial cells, posing significant feasibility risks in treating sepsis. For example, GRP78 is essential for maintaining cellular homeostasis in normal tissues; a global reduction in the level of GRP78 of 50% in whole body or specific tissues potently suppresses tumorigenesis, but requires a careful evaluation of potential side effects on normal organs (182). In the context of sepsis, where host cells rely on GRP78 to manage ER stress and maintain

Table VII. Representative GRP78-targeted agents: Mechanisms and dual therapeutic values in cancer and sepsis intervention.

Drug category	Representative compounds	Precise mechanism of action	(Refs.)
Synthetic small molecules	HA15, CXL146	Target GRP78 ATPase domain; inhibit chaperone activity	(88,153,154)
	AR12 (OSU-03012)	Activate PERK/ATF4 pathway; downregulate GRP78 at transcriptional level	(155)
	Rosuvastatin, Simvastatin	Inhibit GRP78 expression at transcriptional level	(156)
	Sevoflurane	Suppress GRP78-mediated ER stress	(157)
	Ribociclib, Piperine	Negatively regulate GRP78 transcription	(158)
Monoclonal antibodies	SAM-6	Specifically bind to O-glycosylated epitope of tumor- specific csGRP78	(159)
	N88	Target GRP78 NBD	(160)
	C38, C107, anti-CDT	Target GRP78 C-terminal SBD	(161,162)
Peptide agents	Pep42	Specifically bind to csGRP78; mediate targeted endocytosis for drug delivery	(163)
	M4 peptide	Target ER-localized GRP78 via C/F helices	(164)
	Bag-1 peptide, GIRLRG peptide, BC71	Target GRP78 ATPase/SBD domain; inhibit chaperone activity	(165-167)
	Kringle 5	Inhibit pERK1/2 signaling; downregulate GRP78 expression	(168)
Natural products	EGCG, honokiol	High-affinity binding to GRP78 ATPase domain; inhibit chaperone activity	(169)
	Genistein	Antagonize NF-Y/CBF binding; repress GRP78 transcription	(170)
	Triptolide	Induce chronic ERS; downregulate GRP78 expression	(171)
	Plumbagin, DATS, Isoliquiritigenin	Inhibit GRP78 activity or downregulate its expression	(172-174)
Metal-based drugs	NKP-1339 (IT-139)	Inhibit *HSPA5* promoter activity; downregulate GRP78 (Phase II clinical trial)	(175)
	Ruthenium (II) complex 1	Induce ROS production; trigger GRP78 conformational changes	(176)
Modified bacterial toxins	SubAB5	Site-specific cleavage of ER-localized GRP78; abrogate its chaperone function	(177)
	VCD, Prunustatin A, JBIR-04, JBIR-05	Block GRP78 transcription	(178-180)
Nucleic acid drugs	miR-181a	Directly target *HSPA5* 3'-UTR; inhibit GRP78 translation	(181)

GRP78, glucose-regulated protein 78; ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress; csGRP78, cell surface GRP78; ATPase, adenosine triphosphatase; NBD, nucleotide-binding domain; SBD, substrate-binding domain; PERK, PRKR-like endoplasmic reticulum kinase; ATF4, activating transcription factor 4; NF-Y, nuclear factor-Y; CBF, CCAAT-binding factor; ROS, reactive oxygen species; DATS, diallyl trisulfide; EGCG, epigallocatechin gallate; HNK, honokiol; miR-181a, microRNA-181a; UTR, untranslated region; SubAB5, subtilase cytotoxin AB5; VCD, verrucosidin.

barrier function, non-selective inhibition may exacerbate tissue damage and impair immune cell viability (115). This finding is particularly concerning given that GRP78 levels are correlated with disease severity in sepsis patients and that both insufficient and excessive ER stress responses can be detrimental (6). Thus, these non-selective strategies are not suitable for direct application in patients with cancer with active sepsis unless they are combined with tumor-specific delivery systems.

Translational and post-translational regulation of GRP78. The biological function of GRP78 can be modulated at the translational and post-translational levels primarily through direct targeting of the GRP78 protein, including blocking its functional domains, inducing conformational changes, promoting protein cleavage or degradation and inhibiting its subcellular translocation. csGRP78 represents the most feasible target for balancing antitumor and anti-infective effects, as it is selectively overexpressed on the membranes of malignant and

stressed epithelial cells but minimally expressed on normal quiescent cells (17,115). This selectivity arises because normal cells retain GRP78 within the ER through KDEL-mediated retrieval, whereas cancer cells and virally infected cells display significantly higher levels of csGRP78 because of constitutive ER stress and impaired retrograde transport (17,115). This selectivity allows the targeted inhibition of tumor-associated csGRP78 without significantly impairing host GRP78 function.

Monoclonal antibodies and peptides serve as the primary targeting modalities, with monoclonal antibodies, including SAM-6, C38, C107, anti-CDT and N88, effectively blocking csGRP78 function (159-162). Importantly, these antibodies predominantly target the tumor cell marker csGRP78, inhibiting tumor progression while avoiding the direct suppression of host immune cells to reduce the risk of exacerbating sepsis-related immunosuppression. For example, the GRP78-neutralizing human monoclonal antibody hMAb159 specifically blocks csGRP78-mediated pathogen invasion without affecting the chaperone function of intracellular GRP78 in host cells (73), making it a promising candidate for treating cancer-associated sepsis.

While monoclonal antibodies represent a well-established class of csGRP78-targeting agents, peptide-based therapeutics have also been widely developed for this purpose. Pep42, a 13-amino acid cyclic peptide, specifically binds csGRP78 on tumor cells and mediates its lysosomal internalization, serving as a tumor-targeted drug delivery carrier (163,184), whereas other peptides exert antitumor effects by targeting different csGRP78 or intracellular GRP78 domains (164-167); however, the effects of intracellular GRP78 inhibitors require careful consideration in treating sepsis: Inhibiting intracellular GRP78 in host cells may disrupt ER homeostasis and exacerbate inflammatory dysregulation, particularly in early sepsis, in which host-derived intracellular GRP78 is critical for controlling the inflammatory cytokine storm.

There are two major classes of inhibitors that target intracellular GRP78 that have been developed: Natural products and synthetic small molecules. Natural products and synthetic small molecules are the main inhibitors targeting intracellular GRP78 domains, with honokiol showing promise as a treatment for intracranial diseases because of its ability to cross the blood-brain barrier (153,154,156,157,169,171-174). In addition to inhibitors targeting specific domains, two alternative strategies have been explored to disrupt GRP78 function: inducing protein cleavage and triggering conformational changes. Modified bacterial toxins (such as SubAB) induce site-specific GRP78 cleavage to inactivate it (177), whereas metal-based drugs modulate GRP78 via conformational changes or promoter inhibition, with NKP-1339 entering clinical trials as a treatment for solid tumors (175,176). However, these intracellular inhibitors lack tumor selectivity and may impair host cell function in individuals with sepsis; their clinical application requires tumor-specific delivery systems to reduce off-target toxicity.

Balancing antitumor and anti-infective effects: Timing and precision delivery in patients with cancer-associated sepsis. GRP78 is proposed as a pivotal molecular nexus that may connect tumor progression with increased susceptibility to sepsis in patients with cancer. Targeting GRP78 presents a distinctive dual therapeutic potential within this population, but its clinical feasibility depends on addressing the 'double-edged sword' effect through stage-specific intervention and origin-specific delivery.

Stage-specific intervention: When to target GRP78. The role of GRP78 in sepsis has evolved dynamically and tailored intervention strategies based on the sepsis stage are needed. For instance, prophylactic administration of a csGRP78-neutralizing antibody such as hMAb159 could be evaluated in high-risk patients with cancer prior to chemotherapy-induced neutropenia, with breakthrough infection incidence and dynamic sGRP78 kinetics as primary endpoints, although no such trial has yet been conducted or registered.

Pre-infection stage: Tumor-derived sGRP78 is the primary driver of baseline immunosuppression (62). Targeting tumor-derived csGRP78 or sGRP78 can reduce immunosuppression and the sepsis risk without affecting host GRP78 function; this is the most feasible window for a GRP78-targeted intervention (62). For example, pretreatment with SAM-6 in high-risk patients with cancer has the potential to reduce sGRP78 levels and enhance anti-infective immunity (159).

Early sepsis: Host-derived GRP78 plays a critical role in maintaining cellular homeostasis and ER stress responses during infection (17). In the context of sepsis, GRP78 expression is significantly increased in host immune and epithelial cells, serving as a protective mechanism to manage ER stress and prevent cell death (13). While the proinflammatory role of host GRP78 in pathogen clearance is complex and context dependent, its cytoprotective function in managing ER stress and preventing apoptosis is well established (115). Non-selective inhibition of GRP78 at this stage could exacerbate tissue damage by disrupting ER homeostasis and promoting apoptosis via CHOP activation (185). Thus, intervention strategies should prioritize the selective targeting of tumor-derived GRP78 while preserving host GRP78 function to maintain cellular viability during infection (62).

Late sepsis: The sustained increase in sGRP78 levels contributes significantly to systemic immunosuppression (125). Therapeutic strategies targeting circulating sGRP78, such as neutralization with monoclonal antibodies or blockade of its interactions with immune receptors, represent promising approaches to reverse immunosuppression and restore the pathogen clearance capacity while avoiding the risk of exacerbating the initial inflammatory storm (62). However, careful consideration is needed, as the excessive inhibition of host-derived GRP78 may compromise cellular homeostasis and lead to tissue damage (186). Therefore, achieving an optimal therapeutic balance between alleviating immunosuppression and preserving essential host cell functions remains critical for an effective clinical intervention.

Origin-specific precision delivery: How to target GRP78. Precision delivery strategies are essential to selectively target tumor-derived GRP78 while protecting host-derived GRP78, thus resolving the 'double-edged sword' dilemma.

Tumor-specific targeting carriers: Peptides, antibody-drug conjugates and tumor-specific nanoparticles can deliver GRP78 inhibitors exclusively to tumor cells. For example, a Pep42-conjugated GRP78 siRNA specifically silences GRP78 in tumor cells without affecting host immune cells, achieving

antitumor effects while preserving host anti-infective immunity (163,184).

csGRP78-selective inhibitors: Monoclonal antibodies (such as hMAb159 and SAM-6) that specifically bind to csGRP78 on tumor cells can block tumor progression and pathogen invasion without interfering with the chaperone function of intracellular GRP78 in host cells, making them ideal treatments for cancer-associated sepsis (73,159).

Context-dependent combination therapy: While GRP78 inhibition shows promise in enhancing pathogen clearance in viral infections (187), its combination with antibiotics in treating bacterial sepsis requires further investigation. The inhibition of ER stress combined with conventional sepsis treatments may improve outcomes by modulating immune homeostasis (188).

Proposed priorities for the clinical development of GRP78-targeted therapy for cancer-associated sepsis. The aforementioned mechanistic analysis and stage-origin framework (*Balancing antitumor and anti-infective effects: Timing and precision delivery in patients with cancer-associated sepsis*) can be translated into a concrete, prioritized clinical development roadmap. Three criteria guide the ranking: i) Tumor selectivity (agents must spare host GRP78 to avoid exacerbating the infection); (ii) mechanistic clarity (agents with validated target engagement in human systems are preferred over preclinical leads) and (iii) regulatory feasibility (agents with an existing IND/IMPD status or prior oncology phase I data are prioritized for repurposing as sepsis treatments if their safety profile permits acute administration).

Pre-infection prophylaxis (highest priority). The pre-infection window offers the most favorable risk-benefit ratio because tumor-derived csGRP78/sGRP78 can be suppressed without compromising host ER stress responses. The humanized monoclonal antibody hMAb159 is the lead candidate: It depletes cell surface GRP78 and reduces ACE2 expression in epithelial cells, blocking SARS-CoV-2 entry *in vitro* (73). However, the following critical caveats apply: hMAb159 has not been tested in tumor-bearing models and its epithelial cell target profile may not translate to tumor-specific csGRP78 blockade. SAM-6 is a secondary candidate; this fully human IgM antibody targets an O-glycosylated tumor-specific variant of GRP78 with a molecular weight of 82 kDa, an epitope specific for malignant cells (159). Its fully human backbone reduces the immunogenic risk, but the IgM isotype may limit tissue penetration and pharmacokinetics.

Early sepsis (moderate priority, restricted indication): Early sepsis is the most dangerous window for intervention because host-derived GRP78 is cytoprotective. Tumor-specific delivery systems may facilitate the selective suppression of treatment-induced amplification of GRP78 expression in the tumor. Pep42-drug conjugates represent a proof-of-concept: The cyclic 13-mer peptide specifically binds tumor csGRP78, undergoes clathrin-mediated endocytosis and traffics to lysosomes for drug release (163). In addition to the use of cytotoxic payloads, the Pep42 platform could theoretically be extended to nucleic acid delivery; however, while Pep42 has demonstrated tumor-specific delivery of cytotoxic drugs (doxorubicin and paclitaxel) in xenograft models, siRNA conjugation has not been reported to date (184). A phase I/II trial would require biopsy confirmation of csGRP78 expression prior to enrolment, with real-time pharmacodynamic monitoring of circulating sGRP78.

Late sepsis (moderate priority, immunomodulatory focus: Mechanism re-evaluation required): In late sepsis, sustained sGRP78 accumulation drives immune paralysis. The N88 monoclonal antibody targets the NH_2-terminal domain of GRP78 and inhibits NFκB activation and proinflammatory cytokine expression in LPS-stimulated bone marrow-derived macrophages (136,160). However, the anti-inflammatory activity of N88 presents a paradox for sepsis therapy: While late sepsis is characterized by immunosuppression, N88 further dampens innate immunity via the LRP1/NMDA-R pathway (136).

Agents deprioritized for sepsis indications: Transcriptional inhibitors (genistein, ribociclib and AR12) and global translational inhibitors (miR-181a) are deprioritized due to the risk of nonselective suppression of host GRP78 activity (86,158,170). Inhibitors targeting the intracellular domain (HA15, CXL146 and honokiol) are deprioritized for systemic administration but retained for CNS-specific delivery given their blood-brain barrier penetrance (88,154,169).

7. Current limitations and future directions

Three fundamental constraints limit the conclusions of the present review and the field at large. First, direct clinical evidence is lacking. No study has investigated the link between GRP78 dysregulation and sepsis susceptibility in patients with cancer. Published clinical data on the role of GRP78 in oncology populations address exclusively tumor progression and cancer-specific survival, not infectious outcomes. Furthermore, while sGRP78 expression is related to a poor prognosis in patients with non-cancer sepsis, these findings cannot be extrapolated to patients with cancer-associated sepsis, in which tumor-derived sGRP78 expression creates a unique pathological microenvironment. Second, tumor-bearing sepsis models do not exist. All preclinical efficacy data for GRP78-targeted agents are derived either from tumor xenograft models or from non-tumor sepsis models (such as LPS-induced lung injury and cecal ligation and puncture models) evaluated in isolation. No study has combined an analysis of the tumor burden with polymicrobial sepsis. Consequently, whether GRP78 inhibition prolongs or shortens survival in this context remains unknown. The proposed 'double-edged sword', simultaneous tumor suppression and impaired host defenses, cannot be rigorously assessed without such models. Third, a biomarker threshold has not been defined. The absence of an established sGRP78 cut-off value for sepsis risk stratification or therapeutic monitoring further hinders clinical translation.

Future research should prioritize addressing this gap by launching large-scale, multicenter prospective cohort studies in high-risk patients with cancer to clarify the correlation between baseline sGRP78 levels, dynamic changes during infection and sepsis outcomes, along with nested case-control studies to explore causal relationships. Complementing this approach, efforts should focus on developing tumor-specific delivery systems, establishing stage-specific intervention protocols and validating efficacy in tumor-bearing preclinical sepsis models. In summary, the translation of GRP78 into a viable diagnostic

biomarker and therapeutic target for cancer-associated sepsis hinges on filling the critical gap in research on sGRP78 and sepsis outcomes in cancer-specific clinical cohorts.

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Authors' contributions

HR was responsible for literature collection and the initial draft of the manuscript. MPZ, LJZ and SYL contributed to the analysis and interpretation of experimental data related to vascular smooth muscle cell function in sepsis; they were additionally responsible for image rendering, table processing and the scientific validation of graphical data presentation and critically revised the manuscript for content accuracy. SSL contributed to revising the manuscript critically for intellectual content and approved the final version for publication. Data authentication is not applicable. All authors reviewed the manuscript critically for intellectual content and read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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