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REVIEW

Molecular mechanisms of metastatic peritoneal dissemination in gastric adenocarcinoma

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Abstract

Peritoneal dissemination portends a dismal prognosis in patients with gastric adenocarcinoma in the context of limited effective treatments. The underlying cellular processes that drive gastric peritoneal carcinomatosis remain unclear, limiting the application of novel targeted therapies. In this comprehensive review, we aimed to identify and summarize all existing context-dependent molecular mechanisms that have been implicated in peritoneal dissemination and peritoneal carcinomatosis establishment from primary gastric adenocarcinoma. We applied a multilevel examination including data from *in vivo* murine models using human gastric cancer cell lines, *in vitro* technique-based studies, *ex vivo* models, and genomic/proteomic and molecular profiling analyses to report on various aspects of gastric cancer peritoneal metastasis biology. Mechanisms promoting peritoneal dissemination were grouped into three main functional categories: (1) intrinsic cancer cell biology, (2) cancer cell-peritoneal surface adhesion, and (3) peritoneal tumor microenvironment. We identified significant overlap among the three categories, indicating a complex interplay between multiple molecular mechanisms. By interrupting these pathways, peritoneal-directed therapies have the potential to improve quality and length of life in patients with high-risk primary gastric cancer.

Keywords Gastric cancer · Peritoneal carcinomatosis · Tumor progression · Microenvironment · Biomarker

1 Introduction

Gastric adenocarcinoma is one of the leading causes of cancer death worldwide; Approximately 40% of patients present with synchronous distant metastases and are considered upfront incurable. Of the 60% of patients who are eligible for curative resection of their primary tumor, 20–40% will develop recurrent cancer that involves the peritoneal surface [1]. Peritoneal metastasis is associated with limited treatment options and poor prognosis, portending a 5-year overall survival of $<5\%$ [2], and a poor quality of life secondary to symptoms related to ascites, ureteric, and bowel obstruction [3].

The peritoneal metastatic cascade has been proposed to occur in five steps (Fig. 1): (1) gastric cancer cells invade through the layers of the gastric wall, penetrate the serosa, and exfoliate into the peritoneal cavity; (2) cancer cells survive and move within the peritoneal cavity itself, adapting to the hypoxic, acidic, and hypoglycemic environment; (3) cancer cells attach to the mesothelial layer of the peritoneum, in an adhesive interaction with mesothelial cells; (4) cancer cells invade through this mesothelial cell layer and its underlying basement membrane, into the submesothelial space; and (5) gastric cancer cells proliferate and attract a blood supply, establishing a distinct peritoneal metastatic lesion [4]. The specific molecular mechanisms contributing to each step of the peritoneal metastatic cascade remain poorly defined. Furthermore, patients who develop peritoneal metastases tend to be younger and have non-cardia, diffuse-type tumors with signet ring cell histology, potentially suggesting a unique mechanism in the

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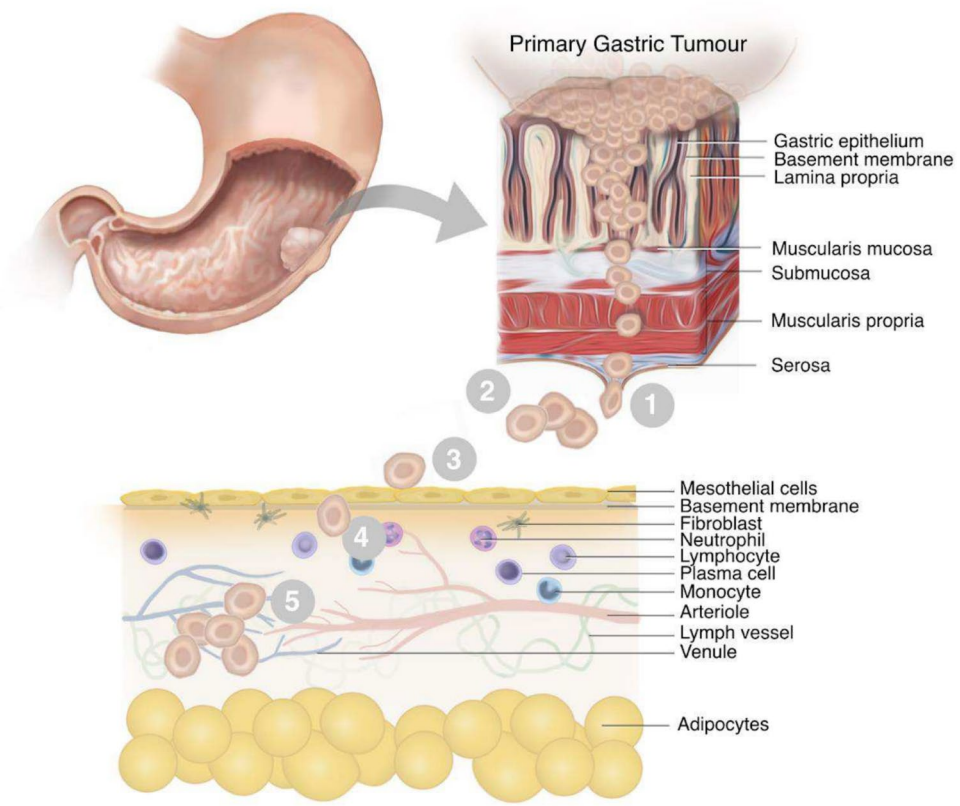

Fig. 1 Key steps in the gastric cancer peritoneal metastatic cascade. Illustration of the five main processes by which gastric adenocarcinoma cells spread and metastasize within the peritoneal cavity: (1) Invasion through the layers of the gastric wall, into the peritoneal cavity; (2) migration through the peritoneal cavity; (3) adhesion to the mesothelial cell lining of the peritoneal surface; (4) invasion through the basement membrane into the submesothelial layer; (5) growth and angiogenesis

development of peritoneal metastasis [5, 6]. These characteristics suggest that the cellular and molecular mechanisms that underpin the development of peritoneal metastases may be distinct from those that drive hematogenous and/or lymphatic metastases and may constitute a "peritoneal metastasis signature" [7]. Nevertheless, clinically relevant specific molecular features that predispose to peritoneal dissemination have been challenging to identify.

While some previous studies have examined specific steps in the peritoneal metastatic cascade, no study has presented a broad overview of all molecular mechanisms involved in peritoneal dissemination, which are likely to demonstrate interplay [4]. Here, we present a scoping review that consolidates the molecular pathways implicated in peritoneal dissemination in the setting of gastric adenocarcinoma, examining how they shape this disease's distinct clinical course. We discuss gastric cancer peritoneal metastasis as a distinct clinical entity, detailing the biologic underpinnings of peritoneal-specific spread. We highlight emerging biomarkers—derived from *in vitro*, *in vivo*, genomic, and transcriptomic studies—that may refine patient stratification and guide personalized therapies. Finally, we propose how integrating molecular insights into current treatment paradigms could inform novel strategies to improve outcomes for patients with gastric cancer peritoneal metastasis.

2 Methods and classification

2.1 Study overview

We conducted a scoping review and report the results in accordance with the standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) guidelines.

2.2 Data sources

We systematically searched three databases (MEDLINE-Ovid, EMBASE, and Cochrane CENTRAL) from inception until March 1, 2024, for studies describing molecular mechanisms of peritoneal spread in gastric cancer. The search strategy was designed through consultation with a research librarian and is presented in Supplementary Table 1. Citations from relevant reviews, as well as the citations and citing articles of included full-text articles, were further screened through the Scopus database to improve the comprehensiveness of the initial search.

2.3 Eligibility criteria and study selection

We included studies describing molecular mechanisms of peritoneal dissemination from primary human gastric adenocarcinoma. Included studies were limited to articles written in English. We excluded editorials, conference posters and abstracts, duplicate studies, and studies that did not address mechanisms of peritoneal metastases.

Study selection was performed in two stages: (1) title and abstract, (2) full-text. All studies were screened independently by at least two authors (DN/DC/SK). Any discrepancies in screening were resolved via consensus.

2.4 Data extraction and synthesis

Following study selection, standardized data extraction forms were used to extract study characteristics, methodologies used, and results. All data were extracted in duplicate by two reviewers.

Results were first summarized descriptively. Study data were then grouped into categories by the steps of the peritoneal dissemination pathway addressed: (1) intrinsic cancer cell biology; (2) cancer cell-peritoneal surface adhesion; and (3) peritoneal tumor microenvironment. Intrinsic cancer cell biology was defined as properties of gastric cancer cells that contribute to epithelial-mesenchymal transition (EMT) (step 1); cell proliferation, migration, and invasion (steps 2–4); and angiogenesis (step 5). Cancer cell-peritoneal surface adhesion was defined as the process by which gastric cancer cells interact with mesothelial cells in the peritoneal cavity or the peritoneum to promote peritoneal adhesion (step 3) [8, 9]. The peritoneal tumor microenvironment refers to the cells and molecules in the abdominal cavity or within the peritoneal tissue that form a unique niche that interacts with gastric cancer cells to promote peritoneal metastasis (steps 2 and 5), Fig. 1. We additionally collected data on the results of genomic and/or proteomic analyses conducted to identify features of gastric tumors associated with higher rates of metastasis to the peritoneum. Given the nature of this review, a narrative synthesis was performed without an attempt at meta-analysis.

Formal risk of bias assessment was not performed, in accordance with scoping review guidelines.

2.5 Literature search

Of the 1525 original database citations, 248 duplicates were removed. After title and abstract screening, 596 unique articles were eligible for full-text evaluation, and 182 articles were selected for inclusion after full-text review (Fig. 2).

2.6 Study characteristics

The majority of studies (98/182) used *in vivo* murine models with human gastric adenocarcinoma cell lines to study peritoneal metastasis. There were 21 studies employing primarily *in vitro* techniques and five *ex vivo* studies. A total of 58 studies employed tissue or cells from primary gastric cancer specimens, ascites, or peritoneal metastasis specimens.

3 Mechanisms of gastric intraperitoneal dissemination

3.1 Intrinsic cancer cell biology

Several studies identified cancer cell-intrinsic mechanisms of peritoneal dissemination. Primary mechanisms identified included epithelial-mesenchymal transition ($n = 23$); cell proliferation, migration, and invasion ($n = 77$); and angiogenesis ($n = 2$) (Supplemental Table 2).

3.1.1 Epithelial-mesenchymal transition (EMT)

Tumor dissemination is a multistep process. Detachment of cancer cells from the primary tumor is largely considered the first step in peritoneal metastasis. Detachment can occur via several mechanisms, including exfoliation of cancer cells from the primary tumor that have invaded the gastric serosa, and secondary mechanisms such as EMT. EMT is a highly conserved and fundamental dynamic program of cell plasticity where cells are transformed from an epithelial to a mesenchymal phenotype characterized by a loss of apico-basal polarity, epithelial tight junctions, and desmosomes that contribute to cell–cell adhesion, and enhanced invasive and migratory properties [1]. In the 2015 Asian Cancer Research Group Classification, primary gastric cancers of the EMT subtype were found to develop peritoneal metastasis more frequently and to have a worse prognosis than the non-EMT subtypes [10].

EMT can occur in a diverse range of physiological and pathological conditions and is driven by a conserved set of inducing signals, transcriptional regulators, and downstream effectors. It is characterized by epithelial marker repression and aberrant mesenchymal marker upregulation. In three studies, downregulation of expression and function of intercellular adhesion molecules such as epithelial (E)-cadherin, a widely studied epithelial marker encoded by the *CDH1* gene, critical in the maintenance of an epithelial phenotype, has been associated with EMT and gastric peritoneal metastasis [2, 11, 12]. The loss of *CDH1* in gastric cancer cells *in vitro* and *in vivo* results in a more aggressive phenotype [2, 13], and it is one of the most commonly mutated proteins in patient samples of gastric cancer peritoneal metastasis

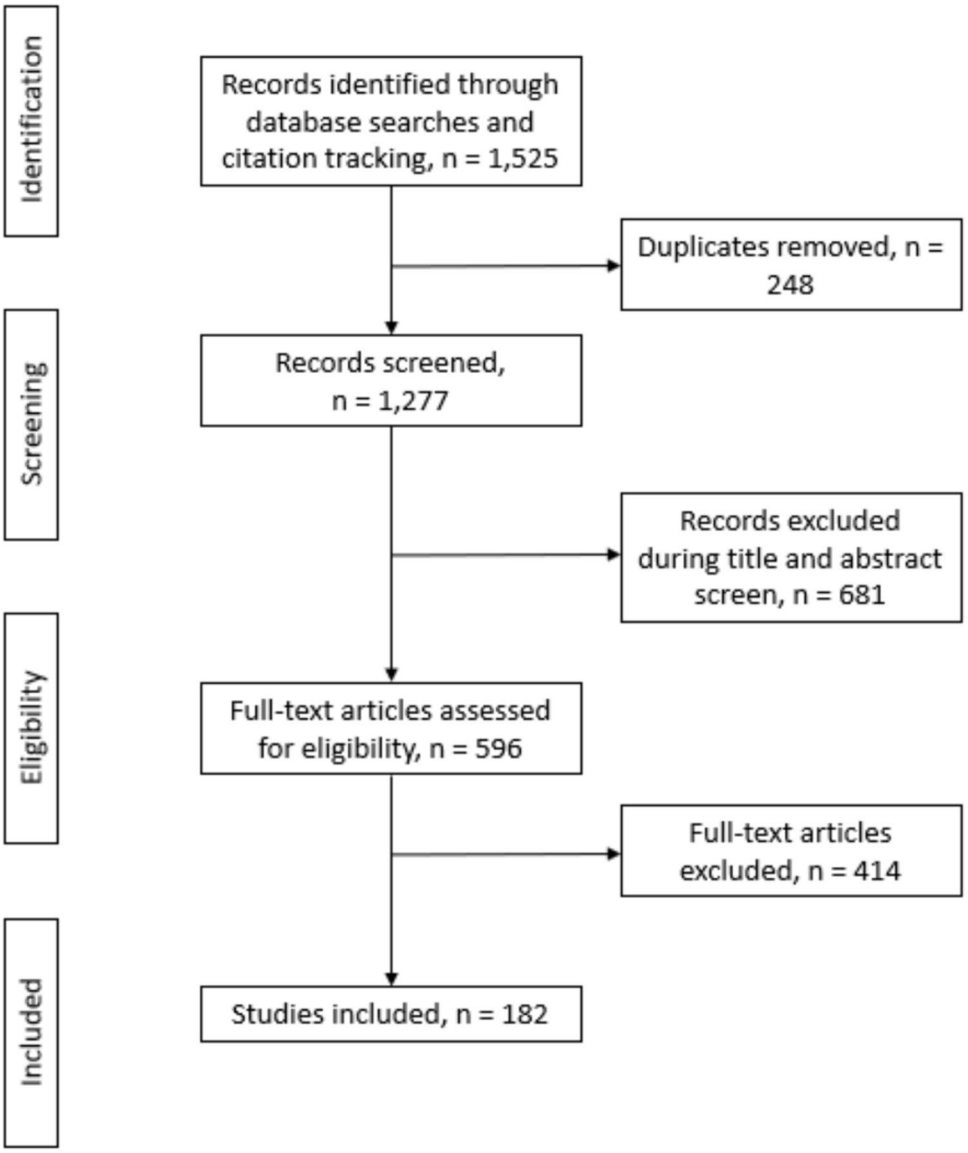

Fig. 2 PRISMA flowchart of study selection process

[12]. Li et al. and Bai et al. identified high expression of S100 calcium binding protein A4 (S1004 A) to significantly correlate with an increase in mesenchymal markers; overexpression of S1004 A, which affects cancer cell motility via the alteration of cytoskeletal dynamics, resulted in decreased CDH1 expression [3, 14]. In turn, gastric cancer cells with downregulated E-cadherin and upregulated S100 A4 expression have an increased probability of undergoing serosal involvement and peritoneal dissemination [15]. In patient samples, decreased expression of Inc-CTSLP4 and miR-200b promoted EMT and peritoneal metastasis, while EMT-promoting FNDC1, RNFT2, and TNNI2 were overexpressed in tissues and were associated with peritoneal recurrence/metastases [16–20]. Shimura et al. identified a peritoneal microRNA signature including miR- 30a- 5p, miR- 659 - 3p, and miR- 3917 that promotes migration and invasiveness through upregulation of EMT-related genes *in vitro* and are significantly overexpressed in the primary tumors of PM-positive as compared to negative patients [21].

Twenty studies identified genes promoting EMT specific to gastric peritoneal metastasis, including *CEACAM6*, *HOTAIR*, and *OSMR* and *Piezo1* [22–25]. CEACAM6, a cell adhesion receptor of the immunoglobulin-like superfamily, expression is upregulated in gastric cancer tissues and is negatively correlated with E-cadherin expression. Overexpression of CEACAM6 induces gastric cancer EMT, characterized by an increase in the mesenchymal markers N-cadherin, vimentin, and Slug expression, while E-cadherin expression is decreased. In nude mice, *in vivo* CECAM6 induces extensive peritoneal spreading, further demonstrating the link between CEACAM6, mesenchymal transition, and peritoneal metastasis [22]. The regulatory role of the

long non-coding RNA HOTAIR in promoting EMT was ascribed to the regulation of miR- 217 that, in turn, impairs the levels of the GPC5 protein. Suppression of HOTAIR *in vivo* reverses the EMT process, significantly reducing invasion and peritoneal dissemination in an orthotopic tumor mouse model [23]. Oncostatin M receptor (OSMR) is a member of the interleukin 6 receptor family that transduces signaling events of Oncostatin M (OSM). In a study by Yu et al., the knockdown of OSMR expression in gastric cancer cells significantly inhibited cell proliferation, migration, invasion, and EMT *in vitro*, as well as peritoneal metastasis *in vivo* [24]. Two studies implicate Piezo1, a mechanosensitive cation channel, in peritoneal metastasis. Wang and colleagues showed increased Piezo1 expression in gastric cancer tissues with omental metastasis, and Piezo1 knockdown significantly inhibited peritoneal metastasis of gastric cancer cells *in vivo* and blocked EMT and angiogenesis [26].

Upregulation of transcription factors and cell differentiation signaling pathways has also been shown to promote gastric cancer EMT in *in vitro* studies [27]. In gastric cancer metastasis, pro-inflammatory cytokines have been shown to activate the JAK2/STAT3 pathway, largely consisting of its receptor and the signaling proteins IL- 6, IFN-α, and IFN-γ [28, 29]. Once activated, JAK2/STAT3 upregulates mesenchymal markers, such as Snail, Twist- 1, and Zeb1.

Overall, in gastric adenocarcinoma, EMT is associated with a diffuse type, a poorly differentiated histology, advanced TNM stage, peritoneal metastasis, and a poor prognosis, suggesting that inhibition of EMT could be promising in the prevention of metastatic progression [30]. Individual molecular mediators of EMT in gastric adenocarcinoma peritoneal metastasis are summarized in Table 1. and Suppl Table 2.

3.1.2 Invasion, proliferation, and migration

Candidates implicated in subsequent steps of peritoneal metastasis include anti-apoptotic factors that enable survival of exfoliated cells, proteolytic factors that allow for degradation of the extracellular matrix (ECM), and molecular and cellular mechanisms that allow invasion of the layers of the stomach wall and migration into the peritoneal cavity. Anoikis resistance is the key phenotype that cancer cells develop to permit survival in the peritoneal cavity upon detachment from the primary tumor [193]. Gastric cancer cells develop anoikis resistance through several mechanisms, including modifying surface molecules and activation of transcription factors and genes, such as through C/EBPβ-mediated PDGFB autocrine and paracrine signaling and nuclear MYH9-induced CTNNB1 transcription [57, 88]. ECM degradation is subsequently required for invasion of gastric cancer cells into the submesothelial surface of peritoneal tissue, furthering the progression of the peritoneal metastatic cascade. Matrix metalloproteinases (MMPs) are central to this process in gastric tumors, as discussed in five independent studies, functioning as pro-enzymes activated by proteolytic cleavage to degrade collagen and other ECM proteins. Tissue inhibitors of metalloproteinases (TIMPs) regulate MMPs, and an imbalance favoring MMP activity correlates with enhanced invasion [86, 194]. Yonemura et al. showed that patients with MMP- 7 mRNA-positive tumors have a 9.9-fold higher relative risk for peritoneal metastasis. Specific antisense oligonucleotides that inhibit MMP7 suppressed the invasive ability of gastric cancer cells without modifying cell proliferation in a mouse xenograft peritoneal dissemination model [86]. Cabourne et al. and Oku et al. showed that MMP- 2 and − 9 increase gastric cancer cell invasiveness *in vitro* and peritoneal metastasis *ex vivo* [84, 85]. In another study by Zhu and colleagues, DJ- 1 was shown to upregulate MMP- 2 and MMP- 9 expression, increasing gastric cancer cell migration, invasion, and peritoneal metastasis *in vitro, in vivo*, and in patients [61]. Moreover, several genes expressed by gastric adenocarcinoma cells and implicated in invasion were found to increase the activity of MMPs and/or decrease the activity of TIMPs, including *AEG1*, *CEACAM6*, *DJ1*, *PRL3*, and *TBL1XR1* (Table 1., Supplemental Table 2) [22, 48, 61, 95, 106]. Most recently, Ajani et al. have found that YAP1 was highly upregulated in peritoneal carcinomatosis tumor cells, conferred cancer stem cell properties, and appeared to upregulate the invasiveness of gastric cancer cells [110].

Ex vivo models of the peritoneal metastatic cascade have been developed in an attempt to overcome the limitations of our current understanding of the mechanisms of peritoneal carcinomatosis that are typically based on artificial *in vitro* cellular representations of the human peritoneum or *in vivo* immunodeficient models [195]. Cabourne et al. used peritoneum removed as part of a hernia sac during elective hernia repair to create an *ex vivo* model, where gastric adenocarcinoma cells were seeded directly onto the peritoneum and showed that MMP- 2 and − 9 promoted gastric adenocarcinoma cell invasion and peritoneal invasion [84].

Dysregulation of protective pathways limiting uncontrolled cell proliferation in gastric adenocarcinoma has also been identified in peritoneal metastases. For example, miR- 466 expression is significantly downregulated in gastric cancer cell lines, primary tumor tissues, and peritoneal metastasis tissues compared with respective controls [41]. *EGFR*, *MET*, *HGF*, and *VEGF* have also been shown to be directly implicated in gastric cancer cell invasion and migration *in vitro* [13, 55, 67, 79]. However, these also have broad effects and are implicated in other routes of cancer metastasis, including hematogenous and lymphatic spread [195]. Some therapeutics have been proposed to target these molecular mechanisms, including those specific to genes implicated in peritoneal metastasis, such as MMP7

Table 1. Genes involved in peritoneal metastasis in gastric cancer

Mechanism	Genes	
Cell intrinsic regulation of tumor biologic processes		
Epithelial mesenchymal transition	Inhibitory	*CDH1* [2, 11, 12], *lnc-CTSLP4* [16], *miR- 200b* [17], *ZIC1* [31]
	Contributory	*AEG- 1* [32], *BTF3* [28], *CEACAM6* [22], *FNDC1* [18], *GPBAR1* [33], *HGF* [34], *HOTAIR* [23], *IL6* [29], *IL33* [35], *microRNA signature* [21], *OSMR* [24], *Piezo1* [25, 36], *RNFT2* [19], *S100 A4* [3, 14], *STEAP1* [37], *TNNI2* [20]
Angiogenesis	Inhibitory	*IRX1* [38]
	Contributory	*VEGF* [39]
Invasion, proliferation, migration	Inhibitory	*β-Ala* [40], *miR- 21–5-p* [41], *miR- 466* [42], *miR- 495* [43], *miR- 551a* [43], *TRPV1* [44], *CEACAM1* [45], *LINC00589* [46], *NF2* [47], *RASA1* [47]
	Contributory	*AEG1* [48], *AnxA1* [49], *APOC2* [50], *ARID1 A* [51], *ARL4 C* [52], *BAFT2* [53], *BGN* [54], *CTSL* [55], *CEACAM6* [22, 56], *C/EBPβ* [57], *CD45* [58], *CD90* [58], *DDR2* [59, 60], *DJ- 1/PARK7* [61, 62], *EGFR* [55], *EGR1* [63], *ELF3* [64], *FXYD5* [55], *GLI1* [65], *GRK3* [66], *HGF* [55, 67], *HOXA11* [68], *LAMC1* [69], *LAMP5* [70], *LIMK1* [71], *LINC00924* [72], *LMGN* [73, 74], *LMOD1* [75], *LPPR4* [76], *MCM6* [29, 77], *MELK* [78], *MET* [79], *MGAT5* [80], *miR- 106a* [81], *miR- 214* [82], *miR- 93 - 5p* [83], *MMP2* [84, 85], *MMP7* [86], *MMP9* [84, 85], *MSRB3* [87], *MYH9* [88], *NSUN2* [89], *PAI1* [90], *PGK1* [91], *PLEKHA5* [79], *POLB* [92], *POSTN* [93], *PRL3* [94, 95], *PTPRT* [96], *RhoA* [97], *Rho-ROCK* [98], *SALL4* [99, 100], *SEMA3B-AS1* [101], *ST6GAL1* [102], *SYT8* [103, 104], *SYT13* [103, 104], *TAGLN2* [105], *TBL1XR1* [106], *THBS1* [107], *TLR4* [108], *UCA1* [109], *VEGF* [13, 55], *YAP1* [110], *ZIC3* [111]
Tumor cell-mesothelial cell adhesion		
Adhesion molecules on gastric cancer cells	Inhibitory	*CDH1* [2, 13], *IL6* [13], *ITGB4* [2, 55, 112]
	Contributory	*sialyl Le* [113], *1-ITGA* [114], *1-ITGA (2,3)* [115–117], *αvβ5-ITGA* [117–119], *6-ITGA* [117], *αvβ3-ITGA* [65, 118], *ALCAM* [120], *BAX* [121], *Bcl- 2* [121], *CADM1* [122], *CCR5* [123], *CD44* [55, 112, 116, 124], *CD155* [13], *CDCP1* [125], *CEACAM6* [56], *COL3 A1* [126], *COL4 A1* [126], *COL4 A5* [127], *CLDN18.2* [128], *CTNNB1* [3], *Cx43* [129], *EpCAM* [130], *FN1* [131], *LAMC1* [131], *LGALS4* [132], *HOXA11* [68], *L1 CAM* [133], *LFA- 3* [134], *MYH2 A* [88], *MYH9* [88], *MUC1* [135], *sTn* [136], *SDC1, 2* [13]
Adhesion molecules on peritoneum	Contributory	*α1–2, α1–3, α1–4 FUT* [113], *CD44* [137], *ICAM1* [137, 138], *VCAM1* [137]
Mediators of gastric cancer cell-peritoneal interaction	Contributory	*Bax* [139], *Bcl- 2* [139], *Caspase- 3* [139], *Caspase- 8* [139], *CCN1* [140], *CTGF* [141], *IL- 1β* [137], *NF-Kβ* [142], *P38 MAPK* [143], *REG4* [144–146], *SPHK1* [147], *TGF-β1* [148–154], *TNFα* [137], *uPA* [155, 156]
Tumor microenvironment related factors		
Ascites and tumor exosomes	Inhibitory	*CASP9* [157], *PLZF* [158]
	Contributory	*CXCL5/CCL2* [159], *FN1* [131, 159], *ICAM- 1* [159], *IL- 6* [159], *IL- 8* [159], *OSM* [159], *L1 CAM* [131], *miR- 10b- 5p* [160], *miR- 21 -5p* [161], *miR- 544* [158], *MMP9* [159], *p-ERK* [162], *STAT3* [163]
Hypoxia	Inhibitory	*HIF- 1α* [164]
	Contributory	*ANGPTL4* [165], *CDH1* [166], *HIF- 1α* [167–169], *VEGFA* [170], *PLOD2* [171]
Peritoneal milky spots	Contributory	*CCL22* [172], *CDH1* [173], *HIF- 1α* [167], *TNF-α* [174]
Adipocytes	Contributory	*CXCL2* [175], *DGAT2* [176]
Cancer-associated fibroblasts	Inhibitory	*EZH2* [177], *miR- 200* [17]
	Contributory	*ANXA6* [178], *IL- 6* [179], *IL- 33* [35], *ITGA α-β1* [180, 181], *LUM* [182], *MMP- 2, − 7 − 9, MT1-MMP* [183], *ROCK/Src/Abl* [184], *Spondin- 2* [185]
Macrophages, cytokines, NETs, mast cells	Inhibitory	*ICAM- 2* [186]

Table 1. (continued)

Mechanism	Genes	
	Contributory	*CD66* [187], *IL- 8* [188], *IL- 10* [189], *IL- 17 A* [190], *TGF-β* [189], *LINC00924* [191], *TIM- 3* [192], *PD-L1* [192], *CTLA- 4* [192], *TLR4* [192]

inhibitors. The majority of therapeutics, however, including irinotecan and gemcitabine, have wide-ranging effects on both hematogenous and lymphatic metastasis [196].

Several chemokines and their axes detected in malignant ascites, including CXCL12/CXCR4 and CCL22/CCR4, are also of particular importance in migration, chemotaxis, adhesion, and peritoneal metastasis [197]. The expression of chemokine receptors on gastric cancer cells, particularly C-X-C motif chemokine receptor 4 (CXCR4), is associated with cancer cell migration and metastasis. CXCL12, the only known ligand for CXCR4, activates the CXCR4 receptor and attracts circulating CXCR4-expressing cancer cells to peripheral tissues to promote peritoneal lesion formation [198]. In patient tissues, CXCR4 expression in the primary tumors of patients with advanced gastric adenocarcinoma is significantly associated with the development of peritoneal metastasis [197]. In this study, crosstalk between heparin-binding EGF-like growth factor, CXCR4/CXCl12, and tumor necrosis factor-α converting enzyme further amplified gastric cancer peritoneal metastasis through autocrine/paracrine signaling mechanisms. These results suggest that targeting these paracrine factors or inhibiting downstream intracellular signaling pathways through peritoneal targeted therapy, as demonstrated in ovarian cancer [199], may be a useful strategy for gastric cancer peritoneal metastasis therapy.

3.1.3 Angiogenesis

Angiogenesis in the subperitoneal space is another important step in peritoneal carcinomatosis. Vascular endothelial growth factor (VEGF) secreted from gastric cancer cells induces an angiogenic response in the peritoneal microenvironment after gastric cancer cells invade the submesothelial stroma, promoting neovascularization and remodeling of tumor vasculature, establishment of peritoneal nodules, and generation of ascites (Table 1., Supplemental Table 2) [200].

The anti-angiogenic and tumor suppressive function of Iroquois homeobox 1 (*IRX1),* a member of the Iroquois homeobox protein family, was first identified by Jiang et al. [38]. *IRX1* expression effectively suppressed peritoneal dissemination by inhibiting angiogenesis and vasculogenic mimicry—a process where solid tumors reorganize cells to improve blood supply independent of endothelial cells in mouse xenograft models [38]. They noted that BDKRB2 and its effector PAK1 are downregulated by *IRX1* overexpression and explored their role as therapeutic targets. Knocking down BDKRB2 and PAK1 through siRNA inhibited gastric cancer cell proliferation, migration, and invasion. They hypothesized that this was due to reduced blood supply and other survival signals, suggesting the potential role of a BDKRB2 antagonist. The role of tumor angiogenesis in gastric cancer peritoneal dissemination and the potential role of anti-angiogenic targeted therapy was further highlighted by Tokuyama et al. Peritoneal dissemination was reduced with SU6668, an inhibitor of VEGF tyrosine kinase receptors, through its inhibitory effect on tumor angiogenesis [39].

Interestingly, recent studies have provided new evidence that angiogenesis can be an early and enabling step in peritoneal metastasis rather than a later event in metastatic progression driven by the metabolic demands of growing tumor deposits. Findings on pre-metastatic niches indicate that tumors release soluble factors such as VEGF and TGF-β, priming distant sites—including the peritoneum—before metastatic cells arrive. These factors induce vascular remodeling and endothelial activation, facilitating the survival of circulating tumor cells [201]. In gastric cancer models, pre-metastatic angiogenesis in the peritoneum has been observed before tumor cell implantation. Elevated VEGF expression has been observed in peritoneal tissue before detectable metastatic deposits, suggesting that tumors remotely induce angiogenesis [201].

3.2 Gastric cancer cell to peritoneal surface adhesion

Cancer cell to peritoneal surface adhesion refers to the interaction between adhesion molecules on gastric adenocarcinoma cells and receptors on the mesothelial cells of the peritoneal surface. Adhesion of free cancer cells to the peritoneal surface relies on several adhesion molecules, such as integrins, proteoglycans, and the immunoglobulin superfamily (Fig. 3). Molecular mechanisms of tumor cell-mesothelial cell adhesion were subcategorized from the included articles as mechanisms related to (1) adhesion molecules on gastric cancer cells ($n = 33$), (2) adhesion molecules on peritoneal tissue ($n = 3$), and (3) mediators of gastric cancer cell-peritoneal tissue interaction ($n = 19$) (Supplementary Table 3).

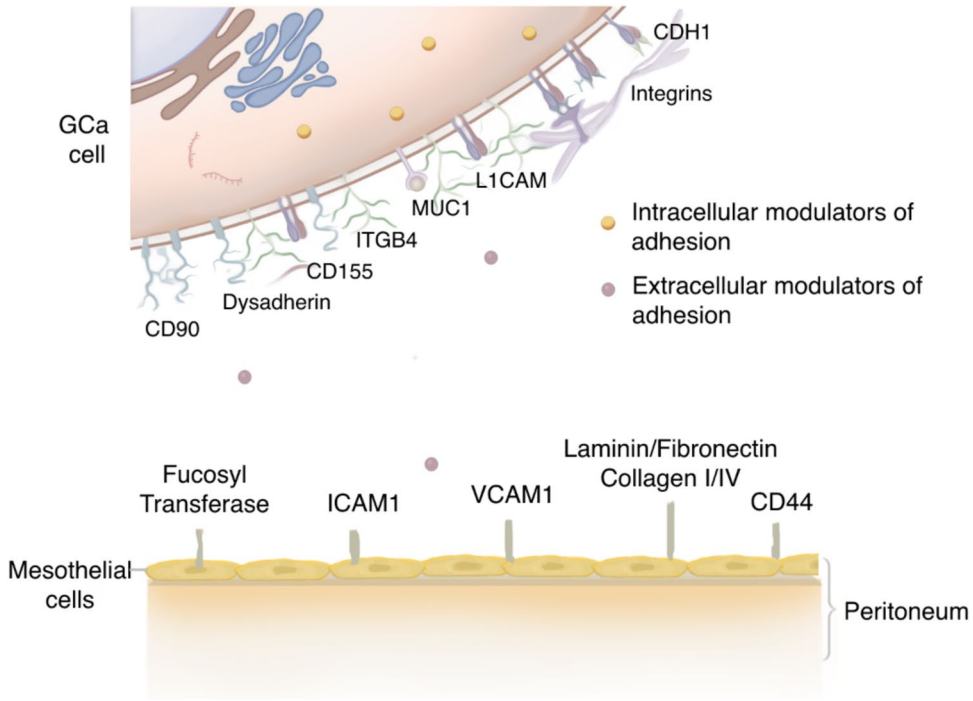

Fig. 3 Mediators and modulators of tumor cell-mesothelial adhesion. Both intra-cellular modulators that alter receptors and proteins on the gastric tumor cell surface and extra-cellular modulators that optimize the structure and environment of the extracellular matrix are involved in gastric cancer cell to peritoneal surface adhesion. GCa = gastric cancer

3.2.1 Adhesion molecules on gastric adenocarcinoma cells and mesothelial cells

Adhesion molecules on gastric cancer cells play dual roles, acting as both inhibitors and facilitators in the development of gastric peritoneal metastatic deposits (Table 1., Supplemental Table 3). Cell adhesion proteins, such as CDH1, discussed above in the context of EMT, and 4-integrin, have been shown in multiple studies to preserve cell architecture, allowing gastric cancer cells to remain anchored to the primary site [2, 13, 55, 112]. Their expression is frequently inversely correlated with the depth of tumor invasion and TNM staging in gastric adenocarcinoma tissues. Moreover, the downregulation of these genes corresponds with increased metastasis to the peritoneum [202]. Notably, germline or somatic mutations in *CDH1* serve as a hallmark of diffuse gastric adenocarcinoma, which is characterized by aggressive disease progression [203].

Adhesion of gastric cancer cells to the peritoneal lining is in turn a crucial step in the process of peritoneal dissemination. Integrins, a class of cell surface adhesion molecules composed of α and β subunits, have been implicated in over eight studies to mediate the direct contact between gastric cancer cells and the ECM [204]. While 4-integrins exhibit protective effects, the α1, α2, α3, and β1 integrin subunits have been closely linked to the peritoneal dissemination of gastric adenocarcinoma [115, 204]. Nishimori et al. [117] selected a gastric cancer cell line with high peritoneal metastatic potential and found that these cells preferentially overexpressed α1 through α6 integrins, compared to its parental cell line which demonstrated limited peritoneal diffusion capacity. In turn, Takatsuki et al. highlighted the critical role of the α3β1 integrin in mediating gastric cancer cell adhesion to laminin [205]. In *ex vivo* studies, monoclonal antibodies specific to integrin α3β1 inhibited gastric cancer cell adhesion to excised peritoneum and suppressed cell growth. Additionally, pretreatment of excised peritoneum with an antibody targeting laminin- 5 significantly reduced gastric cancer cell adhesion.

Both 1-integrin and CD44, a cell surface proteoglycan, have been implicated in promoting gastric cancer cell adhesion to peritoneal mesothelial cells [115–117]. Antibodies have been developed against both these proteins in an attempt to disrupt their binding to mesothelial cells and potentially decrease peritoneal metastasis [206]. In another approach, a recent study identified that connective tissue growth factor (CTGF) effectively blocks adhesion by binding to α3β1 integrin, and the authors hypothesized that recombinant CTGF may have therapeutic potential [207]. While these studies have shown encouraging results *in vitro*, discerning the effects of targeting integrins *in vivo* remains challenging due to the complex interactions and regulatory factors that influence the expression of integrins in both the primary tumor and peritoneal metastatic sites.

Another protein implicated in the adhesion of gastric cancer cells, particularly in the context of peritoneal metastasis, is REG4. Overexpression of REG4 has been shown to significantly enhance the adhesion of gastric cancer cells to the murine peritoneum *ex vivo* [144–146]. Additionally, *in vivo* studies have demonstrated that REG4 overexpression

significantly increases the accumulation of ascites and serves as an independent prognostic factor for peritoneal recurrence-free survival [146]. As anticipated, several adhesion molecules on the mesothelial surface that contribute to gastric adenocarcinoma peritoneal metastasis have also been identified in other malignancies that frequently metastasize to the peritoneal cavity, such as ovarian and colorectal cancers. Notable among these are ICAM- 1 and VCAM- 1 [134, 137, 138]. These adhesion molecules, which are expressed on the surface of various cell types, including vascular endothelial cells, fibroblasts, and epithelial cells, play a crucial role in facilitating tumor cell adhesion, mediated by cytokines such as IL- 6 or TNF-α [208]. Fucosyltransferase, a distinct adhesion molecule on mesothelial cells, has been shown to specifically interact with gastric adenocarcinoma cells, highlighting its potential as a target for anti-adhesion therapies. Such therapies could involve the use of substrates for α-fucosyltransferases to disrupt peritoneal dissemination [209].

3.2.2 Promoters of adhesion between gastric cancer cells and the peritoneum

Many mediators of adhesion are cytokines that share similar signaling pathways, such as TNF-α-, TGF-β1, and p38 MAPK [137, 143, 148–154]. TNF-α, along with other inflammatory cytokines such as IL- 6 and IL1β, is found in malignant ascites and has been shown to increase the expression of adhesion molecules, such as intercellular adhesion molecule- 1 (ICAM- 1) and vascular adhesion molecule- 1 (VCAM- 1), on mesothelial cells [210]. Gastric cancer peritoneal metastases further secrete IL- 6 and IL- 8, which enhance cell motility, invasiveness, and resistance to chemotherapy [159].

TGF-β1, a member of the TGF-β superfamily, plays a crucial role in regulating proliferation and differentiation in a variety of cell types. The TGF-β pathway is notably upregulated in gastric cancer cells, with elevated levels of TGF-β1 being detected in peritoneal wash samples from patients with gastric cancer peritoneal metastasis [211]. Through activation of the SMAD signaling pathways, TGF-β1 upregulates collagen and fibronectin deposition, leading to peritoneal fibrosis and increased gastric cancer cell adhesion [211]. Several regulatory factors modulate the function of TGF-β1, including protein-bound polysaccharide K (PSK) [212]. Shinbo et al. demonstrated that PSK inhibits the transformation of human peritoneal mesothelial cells into myofibroblast-like cells induced by TGF-β1, as well as tumor-associated fibrosis in xenograft models. Furthermore, PSK has shown potential to prolong survival when used in combination with adjuvant chemotherapy in some studies [213, 214].

These mediators collectively increase the expression of adhesion molecules on either gastric adenocarcinoma cells or mesothelial cells, promoting peritoneal metastasis. A detailed overview of adhesion molecules on the peritoneum and mediators within the peritoneal environment implicated in gastric cancer peritoneal metastasis is provided in Table 1. and Supplemental Table 3.

3.3 Tumor microenvironment (TME)

Aspects of the tumor microenvironment addressed in studies included (1) ascites and tumor exosomes ($n = 8$); (2) hypoxia ($n = 8$); (3) peritoneal milky spots ($n = 4$); (4) adipocytes ($n = 2$); (5) cancer-associated fibroblasts ($n = 11$); and (6) macrophages, cytokines, NETs, and mast cells ($n = 8$) (Supplemental Table 4).

3.3.1 Physiology of the peritoneum: ascites, tumor exosomes, hypoxia, peritoneal milky spots, adipocytes

In order for gastric cancer cells to successfully migrate from the primary tumor site to metastatic sites on the peritoneum, the surrounding peritoneal microenvironment needs to provide hospitable conditions favoring survival and proliferation (Fig. 4). Key features that have been described to allow for an ideal metastatic milieu unique to the peritoneal environment include ascites, cancer-derived exosomes, a state of local hypoxia, peritoneal milky spots, and adipocytes.

Malignant ascites represents an adipocyte-rich microenvironment comprising differentiated preadipocytes stimulated by cancer cells that release free fatty acids, enhancing cancer cell proliferation and EMT [69].

Cancer-derived exosomes are 30- to 100-nm membrane-bound vesicles that are formed and excreted by cancer cells or adipocytes into the peritoneal cavity [215]. Found in malignant ascites, they promote peritoneal metastasis through various intercellular signaling processes. Arita et al. demonstrated that exosomes increase the adhesive and migratory ability of gastric cancer cells and normal mesothelial cells through increased FN1 expression [131]. Similarly, Kersey et al. found that exosomes secreted from adipocytes in omental tissue increased gastric adenocarcinoma cell growth, motility, and invasiveness through increased expression of IL- 6, IL- 8, MMP9, FN1, and CXCL- 5 [159].

The peritoneal cavity is a hypoxic environment, with low oxygen tension fostering conditions favorable for EMT, invasion, and metastasis. The transcription factor HIF- 1, a key regulator of the cellular response to hypoxia, has been shown to increase expression of angiogenic and growth factors, including VEGF [167, 168, 170]. Miyake et al. used orthotopic implantation and conventional intraperitoneal injection models to investigate peritoneal dissemination of gastric cancer [216]. They demonstrated that HIF- 1α plays a critical role in peritoneal dissemination through the activation of

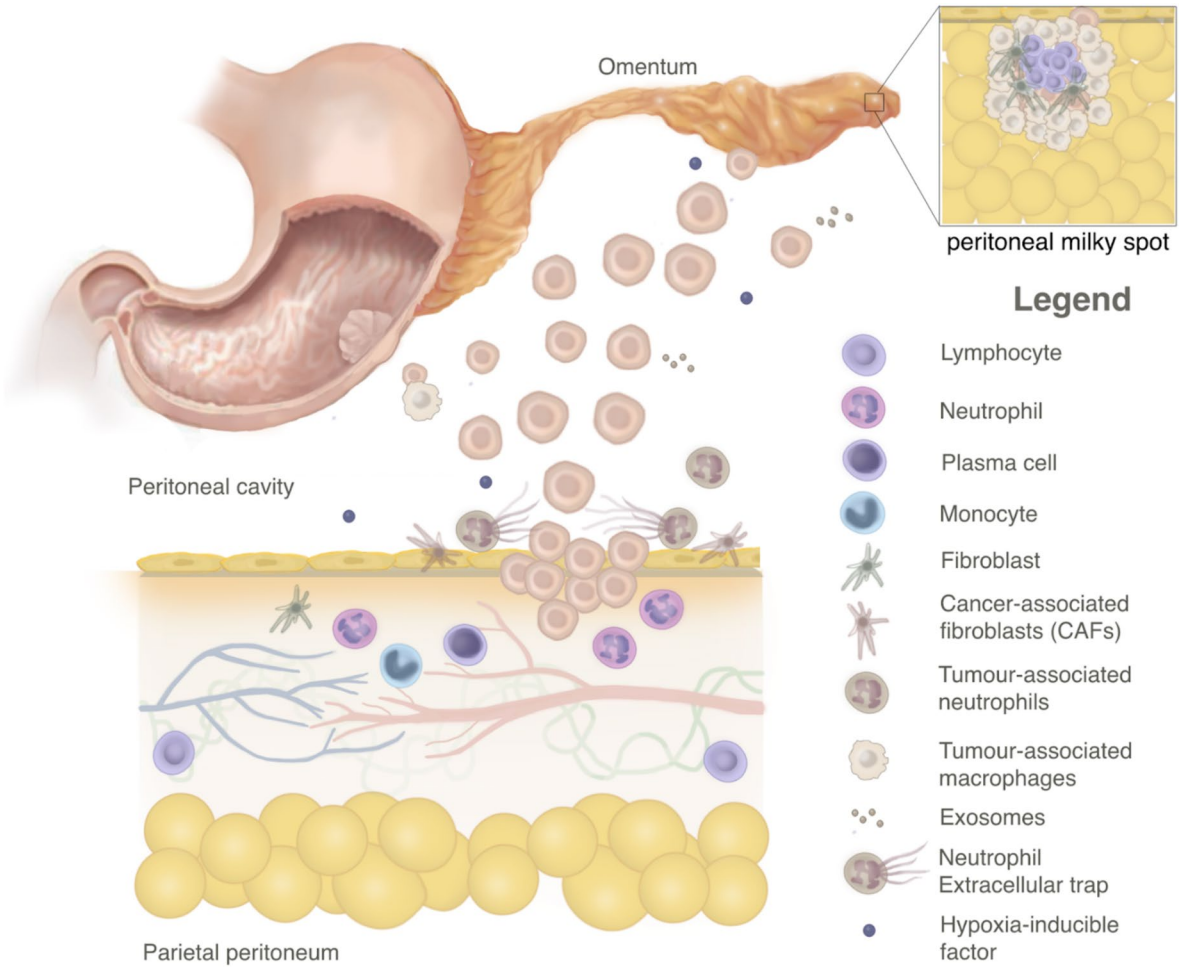

Fig. 4 Factors within the tumor microenvironment (TME) that influence gastric cancer peritoneal metastasis. This schematic highlights key components within the TME implicated in gastric cancer peritoneal metastasis. Peritoneal milky spots, lymphoid-rich regions within the greater omentum, serve as major implantation sites for metastases. They consist of mesothelial-covered mesenchymal cells, macrophages, lymphocytes, and mast cells, facilitating tumor cell adhesion. Cancer-associated fibroblasts (CAFs) are a heterogeneous and plastic population of activated fibroblasts within the tumor stroma that support extracellular matrix deposition, remodeling, and reciprocal signaling with cancer cells, thereby enhancing metastasis. Exosomes, vesicles released from gastric cancer cells and omental adipocytes into malignant ascites, promote EMT, invasion, migration, and adhesion. Neutrophil extracellular traps (NETs) consist of condensed extracellular fiber scaffolds that can shield the tumor from host immune responses and promote growth and proliferation. Hypoxia-inducible factor- 1α (HIF- 1α), a transcription factor stabilized under the hypoxic conditions in the peritoneal cavity, regulates cell proliferation, apoptosis, and energy metabolism, contributing to the aggressiveness of gastric cancer cell spread

angiogenesis and vascular invasion in the orthotopic model, although it had an inhibitory effect in the intraperitoneal injection model. Furthermore, HIF- 1 responds to hypoxic stimuli to promote peritoneal metastasis through regulating pathways involved in cell proliferation and invasiveness, and increasing the expression of gastric cancer stem/progenitor cells [168]. Interestingly, a study by Hiraki et al. described a paradoxical role for HIF-1α- where it resulted in less invasive phenotype of gastric adenocarcinoma cells, through its effect on MMP- 1 [164].

Peritoneal milky spots are secondary submesothelial lymphoid structures that have been described as an ideal hypoxic niche linked to tumor metastasis. These structures consist of aggregates of mesenchymal cells covered by a mesothelial layer, containing macrophages, lymphocytes, type 2 innate lymphoid cells, and mast cells. While milky spots contribute to the immune homeostasis of the peritoneal cavity, they also allow cancer cell access to the submesothelial space [217]. It is in these milky spots that the transcription factor HIF- is upregulated, enhancing the self-renewing capacity of gastric cancer stem/progenitor cells [167, 172, 173, 218].

In addition to areas of hypoxia, gastric adenocarcinoma cells have also been found to favor areas of the peritoneum with high adiposity, such as the omentum [175]. This preference has been attributed to the favorable conditions offered by cancer-associated adipocytes (CAP). CAPs communicate

with cancer cells, releasing factors that can lead to changes in cell behavior, such as through *CXCL2* and *DGAT2,* enhancing tumor progression [175, 176]. Further details on these mechanisms are provided in Table 1. and Supplemental Table 4.

3.3.2 Cancer associated fibroblasts, macrophages, cytokines, neutrophil extracellular traps, mast cells

The peritoneal metastatic niche is characterized by fibrosis and the recruitment and activation of cancer-associated fibroblasts (CAFs) and tumor-associated macrophages (TAMs) (Fig. 4). These components, along with other immune and stromal cells, create a tumor microenvironment that supports gastric cancer progression and peritoneal metastasis.

CAFs are a key component of the gastric cancer TME, exhibiting diverse functions that support a favorable metastatic niche. They secrete various growth factors, cytokines, chemokines, MMPs, and ECM proteins that promote tumor progression. Key CAF functions include stimulating angiogenesis via VEGF secretion, promoting cancer cell proliferation through CXCL12, and reducing tumor cell death via metabolic reprogramming and growth factor production. Additionally, CAFs secrete TGF-β, which exacerbates immune suppression and enhances the adhesion of gastric cancer cells to mesothelial cell surfaces [189]. CAFs also contribute to ECM remodeling, matrix deposition, reciprocal signaling with cancer cells, and secretion of exosomes that increase cancer cell motility [219]. Notably, certain CAF-secreted factors, such as annexin A6, have been linked to drug resistance, highlighting potential targets for combination therapies [178].

Peritoneal metastases are characterized by severe stromal fibrosis resulting from the interplay between the mesothelial-to-mesenchymal transition process that is induced by gastric cancer cells characterized by the accumulation of CAFs, and the release of fibrosis-inducing cytokines and growth factors such as IL- 17 A and TGF-β [190]. In a study by Gunjigake and colleagues using patient samples, mast cells were shown to produce IL- 17 A in the peritoneal tumor microenvironment, inducing a pro-fibrotic phenotype in mesothelial cells. Fibrosis, which increased intratumoral pressure, was suggested to act as a barrier to effective tumor cell elimination by encapsulating tumor implants [190].

Tumor-associated macrophages (TAMs) are immunosuppressive cells that are abundant in the gastric tumor microenvironment. Flow cytometry analysis by Yamaguchi et al. revealed increased total macrophage numbers in peritoneal metastases compared to primary tumors [220], while Fujimori et al. demonstrated significantly higher numbers of $CD163^+$ macrophages in peritoneal metastases [221]. Functionally, TAMs isolated from peritoneal metastases exhibit an M2-like, or activated, phenotype [220–222]; RT-PCR analysis confirmed increased expression of M2-like gene expression markers such as IL- 10 A, VEGF-A, VEGF-C, matrix metalloproteinase (MMP)− 1, and amphiregulin [220]. TAMs play a pivotal role in angiogenesis, as evidenced by Song et al., who found overexpression of CD34 + progenitor endothelial cells in the surgical margins of gastric tumors and adjacent peritoneal tissue in patients with peritoneal metastases [222]. Additionally, TAMs release cytokines and growth factors, including IL- 8, IL- 10, and IL- 17 A, which promote cancer cell proliferation, migration, and survival [188–190].

Tumor infiltrating lymphocytes (TILs) are also considered key factors in gastric cancer peritoneal metastasis. Yamaguchi et al. analyzed peritoneal metastatic lesions by immunohistochemistry to assess the prognostic significance of TILs (effector CD4 + T cells, CD8 + cytotoxic T cells, regulatory T cells [Tregs]), and myeloid-derived suppressor cells (MDSCs). Both higher infiltration of $CD8^+$ T cells and an increased ratio of $CD8^+$ T cells vs MDSCs were significantly associated with overall survival [220]. However, another study using paired primary and peritoneal metastasis samples found reduced CD8 + T cell infiltration in metastatic lesions compared to primary tumors, with no differences in $CD4^+$ T cell infiltration, suggesting impaired cytotoxic immune responses at metastatic sites [221].

Transcriptomic techniques have further differentiated immune signatures within gastric cancer peritoneal metastases. Zhang et al. generated a peritoneal recurrence related immune score (PRIs) composed of ten immune cells, including Th2 cells, mast cells, T cells, and dendritic cells. The high-PRI, as compared to low-PRI, group had a greater risk of peritoneal recurrence with upregulation of focal adhesion signaling [192]. Additionally, immune profiling of 44 peritoneal carcinomatosis patient samples, based on whole exome and transcriptomic sequencing by Wang and colleagues, revealed two groups: a T cell "exclusive" and T cell "exhausted" phenotype. In the "exhausted" subtype, high levels of immune-related genes, including cytotoxic T cell markers (CD8) and macrophage markers (CD68, CD163) and increased expression of immune checkpoint marker TIM- 3, its ligand galectin- 9, and TGF- β were identified. Other classical checkpoints (PDL- 1, PD- 1, or CTLA4) were not found to be highly expressed in this subgroup, suggesting potential therapeutic targets [12].

Neutrophil extracellular traps (NETs), in turn, are net-like structures composed of DNA-histone complexes and proteins released by activated neutrophils that have been implicated in cancer progression and metastatic dissemination, both in patients and animal models. NETs are a relatively new mechanism that have been proposed to explain how gastric cancer cells circumvent host immune responses. NETs can entrap and serve as an adhesion substrate for gastric cancer cells and can protect the tumor from host immune

responses, thus promoting metastases formation and proliferation [223]. Kanamaru et al. demonstrated that CD66 expressed on gastric cancer cells contribute to NET formation and protection from host immune response *in vivo*. This may contribute to the poor response to treatment associated with targeting peritoneal metastasis, as NETs are thought to impede the delivery of chemotherapeutic agents to the tumor deposits [187].

These mechanisms collectively create a supportive TME for gastric cancer peritoneal metastasis, promoting tumor growth, immune evasion, and resistance to therapeutic interventions. The roles of these processes are further detailed in Supplemental Table 4.

3.4 Molecular biomarkers predictive of peritoneal metastasis

More recently, investigators have sought to characterize the genomic and transcriptomic landscapes of primary tumors, resulting in the identification of genomic profiles or subtypes of primary gastric cancer that predict peritoneal metastasis and treatment resistance, and describing new molecular-guided therapeutic strategies [111]. Wang et al. conducted whole exome sequencing (WES) on 70 patients with gastric cancer and identified four genomic subtypes; subtypes 3 and 4 included genomically stable tumors with a propensity for peritoneal metastasis [51]. Similarly, Takeno et al. developed a 22-gene expression profile associated with peritoneal relapse, demonstrating 76.9% overall accuracy in predicting peritoneal-relapse-free survival [111]. Other studies leveraging RNA sequencing (RNA-Seq) data of gastric cancer primary tumors showed a significant association between increased expression of SYT8 [103], SYT13 [104], and TNNI2 [20] and the risk of metachronous gastric cancer peritoneal metastasis. In another transcriptome-based analysis, a 12-gene panel was identified that is predictive of both synchronous and metachronous peritoneal metastasis [224]. This signature included genes such as *CAVIN2*, part of the TGF-β pathway and associated with EMT, again emphasizing an overlap in mechanisms of peritoneal dissemination and substantiating *in vitro* findings [225]. If successfully validated, these molecular signatures could meaningfully improve early detection, guide adjuvant therapy decisions, and ultimately enhance patient outcomes by identifying high-risk individuals who may benefit from more aggressive treatment approaches.

3.5 Strengths and limitations of methodologies

The reviewed studies employ a range of methodologies to provide a comprehensive overview of the current molecular landscape of gastric cancer peritoneal metastasis, the majority employing *in vitro* and *in vivo* approaches. *In vitro* experiments provide controlled environments that allow for the precise dissection of molecular mechanisms, high reproducibility, and the ability to manipulate specific variables with relative ease. However, these models often fail to capture the complexity of tumor-microenvironment interactions, particularly the three-dimensional architecture and immune interactions that occur *in vivo*. In contrast, *in vivo* models such as xenografts offer a more physiologically relevant setting by mimicking tumor behavior within a living organism. Despite this advantage, these models are typically based on immunodeficient mice, limiting the ability to study the role of immune modulation in peritoneal metastasis. Furthermore, the heterogeneity observed in human tumors is often not fully recapitulated in these animal models. Recent advances, including the use of *ex vivo* peritoneal explant models, have provided a middle ground by allowing researchers to study tumor-peritoneal interactions in a human-derived, biologically relevant environment. Nonetheless, challenges remain in standardizing these models for broader application. In turn, molecular biomarkers identified through large-scale genome and transcriptome profiling hold significant promise in refining risk stratification for peritoneal metastasis in gastric cancer, offering the potential for more tailored treatment strategies. Nevertheless, challenges remain in their clinical translation. Many of these studies are retrospective, with inconsistent definitions of recurrence endpoints, necessitating prospective validation to establish their true predictive value. Further, these biomarkers require standardization across different patient cohorts to ensure reproducibility and clinical applicability. Overall, a critical evaluation of these methodologies is essential for contextualizing findings from different studies and guiding future experimental designs that more accurately reflect peritoneal metastases.

4 Bridging molecular pathways and clinical therapies

4.1 Systemic treatment strategies

Both synchronous and metachronous peritoneal metastasis from gastric cancer portend a poor prognosis, with median survival ranging from 3 to 15 months in the synchronous setting and 3 to 9 months in patients with metachronous peritoneal metastasis [6, 226–230]. Treatment algorithms and clinical guidelines for gastric cancer with peritoneal metastasis or positive peritoneal cytology fall under the broader category of stage IV disease, with an emphasis on systemic therapy. Over recent decades, advances in systemic treatments—including combination chemotherapies [231–233], targeted agents such as ramucirumab (targeting VEGFR2) [234], trastuzumab for HER2-positive tumors [235],

zolbetuximab for CLDN18.2-positive tumors [236, 237], and immune checkpoint inhibitors like nivolumab for patients with PD-L1 combined positive score ≥ 5 [238, 239]—have resulted in clinically meaningful survival improvements. However, two large-scale cohort studies have demonstrated that, despite increased use of systemic therapies, survival outcomes for patients with both synchronous and metachronous gastric cancer peritoneal metastases have not significantly improved [6, 240]. This discrepancy likely reflects challenges related to inadequate drug penetration into the peritoneum and the adverse effects of symptoms (e.g., intestinal obstruction and ascites) on patient performance status, limiting the ability to tolerate treatment [241–245]. Nevertheless, subset analyses from the limited randomized controlled trials that stratified by the presence or absence of peritoneal metastasis indicate that patients with peritoneal disease do derive benefit from systemic therapies, albeit to a lesser degree than patients without peritoneal metastasis [234, 246–248].

When considering the recent practice-changing SPOTLIGHT [237] and GLOW [236] phase III studies evaluating zolbetuximab (monoclonal antibody that targets CLDN18.2) plus capecitabine and oxaliplatin (CAPOX) as first-line treatment for CLDN18.2-positive metastatic gastric/GEJ adenocarcinomas, subset analyses focusing on patients with peritoneal metastasis were not detailed in the primary publications. Given that peritoneal metastasis frequently correlates with diffuse-type histology, it is notable that in both the SPOTLIGHT and GLOW trials, the OS benefit for patients with diffuse gastric cancer did not reach statistical significance in the prespecified subgroup analyses (SPOTLIGHT HR 0.76 [0.51–1.13]; GLOW HR 0.73 [0.49–1.07]). Therefore, the efficacy of zolbetuximab in patients with peritoneal metastases remains uncertain [236, 237]. Notably, immunohistochemical analysis in a cohort of 42 patients revealed that while 74% of primary tumors were CLDN18.2-positive, only 35% of corresponding peritoneal metastases expressed CLDN18.2—and merely 5% exhibited moderate-to-strong expression—suggesting that assessment of peritoneal nodules may be necessary to predict responses to CLDN18.2-targeted therapies [249].

These data underscore the urgent need for increased representation of gastric cancer patients with peritoneal metastasis in clinical trials to define effective treatment strategies. This is certainly challenging given that PM-only disease often lacks measurable lesions per RECIST criteria, a common inclusion criterion for most clinical trials.

4.2 Intraperitoneal treatment strategies: HIPEC

An alternative approach to managing peritoneal metastasis is the use of locoregional (intraperitoneal) treatment strategies, such as hyperthermic intraperitoneal chemotherapy (HIPEC) and pressurized intraperitoneal aerosol chemotherapy (PIPAC). These modalities can be applied in conversion strategies to enable surgical resection of both the primary tumor and peritoneal metastasis or as part of palliative regimens in conjunction with systemic therapy.

Evidence for HIPEC in gastric cancer remains heterogeneous. Several studies have suggested a potential survival benefit in select patients. The CYTO-CHIP observational cohort study demonstrated that the addition of HIPEC (using agents such as oxaliplatin, mitomycin, or cisplatin) following complete cytoreductive surgery (CRS) resulted in significantly longer survival compared to CRS alone, without an increase in morbidity [250]. A randomized trial by Yang et al. reported an improvement in median overall survival (OS) from 6.5 months with surgery alone to 11.0 months with CRS plus HIPEC ($p = 0.046$) [251]. Similarly, the phase II GYMSSA trial of 17 patients showed a median OS of 11.3 months in the CRS + HIPEC + chemotherapy arm vs 4.3 months with chemotherapy alone [252]. However, not all studies have shown a clear benefit. A recent European randomized trial (GASTRIPEC-I), which compared CRS + HIPEC (mitomycin C and cisplatin) with CRS alone combined with systemic chemotherapy, found no significant difference in median OS (~ 14.9 months in both arms), although HIPEC patients had better progression-free and metastasis-free survival [253]. Meta-analyses reflect this heterogeneity: a meta-analysis of 32 studies from 2017 indicated that CRS + HIPEC extended median OS by approximately 4–5 months compared to controls, with a clear benefit at 1 year but no significant difference by 3 years [254].

Combining systemic and intraperitoneal chemotherapy has also been explored as a strategy to convert unresectable disease to a resectable state. Several phase II trials have demonstrated high rates (71–86%) of conversion to negative peritoneal cytology with this approach [255]. The PHOENIX-GC phase III trial evaluated the addition of intraperitoneal paclitaxel to standard systemic chemotherapy (S- 1 + cisplatin) in patients with peritoneal metastasis. Although the trial did not achieve its primary endpoint of improved median OS—largely due to treatment imbalances and crossover—subgroup analyses suggested that patients with lower-volume peritoneal disease might derive a greater benefit from the combined approach [256]. Other studies have reported successful downstaging of peritoneal metastasis (no macroscopic peritoneal nodules and conversion to negative cytology), with conversion gastrectomy feasible in select patients, leading to improvements in median OS [257–259].

Prophylactic HIPEC has also been investigated as a strategy to prevent metachronous peritoneal carcinomatosis. Early trials suggested that adjuvant HIPEC could reduce peritoneal recurrence and improve survival [254, 260]. However, more recent data are less convincing. A meta-analysis of 1810 patients without overt peritoneal carcinomatosis

found no significant overall survival benefit from prophylactic HIPEC compared to surgery alone [254]. The ongoing multicenter phase III GASTRICHIP trial is currently evaluating the role of adjuvant HIPEC with oxaliplatin in patients with locally advanced gastric cancer without gross peritoneal metastasis undergoing gastrectomy, with results anticipated in 2026 [261].

It is important to note that the benefits of HIPEC are most pronounced in patients achieving complete cytoreduction with low-volume disease; however, this approach must be balanced against an increased risk of morbidity [262].

4.3 Intraperitoneal treatment strategies: PIPAC

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel, minimally invasive technique that administers aerosolized chemotherapy under pressure during laparoscopy. Early studies in gastric cancers with peritoneal metastases report that approximately 69% of patients demonstrate a pathologic response (95% CI 0.60–0.77) [263], with repeated PIPAC cycles enabling some patients to achieve sufficient tumor regression to allow for curative surgery [263]. PIPAC is generally well tolerated, with most adverse events being mild to moderate and severe complications occurring in fewer than 15% of procedures. Although these early-phase results are promising, additional studies are underway to provide more definitive evidence regarding the role of PIPAC in managing gastric cancer peritoneal metastasis.

4.4 Emerging therapies

Oncolytic viral therapy and cellular therapies are also under investigation in early-phase clinical trials. For example, in a Phase I study, intraperitoneal administration of oncolytic vaccinia virus GL-ONC1 in patients with peritoneal metastases—including from gastric cancer—resulted in efficient viral infection, replication, and oncolysis in nearly 90% of cases [264]. Similarly, a Phase I trial of CLDN18.2-targeted CAR T cells reported an overall response rate of 48.6% and a disease control rate of 73% [265]. In preclinical mouse models of gastric cancer peritoneal metastasis, intraperitoneal delivery of targeted agents such as SYT13-specific antisense oligonucleotides (modified with amido-bridged nucleic acids), PGK1 shRNA combined with 5-FU, and the HO- 1 inhibitor ZnPPIX (zinc protoporphyrin IX) inhibited peritoneal nodule growth [103, 266, 267]. These findings underscore the potential of integrating enhanced intraperitoneal drug delivery with molecular targeting to improve outcomes in peritoneal metastasis.

In summary, while novel treatment strategies—including intraperitoneal approaches such as HIPEC and PIPAC—show promise for managing gastric cancer peritoneal metastasis, their optimal use requires further clarification through well-designed clinical trials. Identifying patient subgroups most likely to benefit from these interventions is critical, as is the development of molecularly targeted agents to inhibit peritoneal dissemination. Enhanced molecular characterization and targeting of disseminated gastric adenocarcinoma may ultimately lead to improved therapeutic outcomes.

5 Discussion

Gastric cancer peritoneal metastasis portends a poor prognosis in patients, where 5-year overall survival is less than 10% [268]. Understanding the underlying mechanisms driving gastric cancer peritoneal metastasis represents a significant unmet need, as this process diverges significantly from other metastatic pathways, such as lymphatic or hematogenous spread, which involve directional intra- and extravasation of vessels. This review highlights the unique and multi-faceted mechanisms that specifically drive peritoneal metastasis, including interactions between gastric cancer cells and the peritoneal mesothelium, as well as the role of exosome secretion in malignant ascites. While prior reviews have explored mechanisms of peritoneal adhesion [269], to the authors' knowledge, this is the first systematic scoping review that offers a comprehensive overview of the diverse molecular and cellular processes implicated in gastric peritoneal metastasis.

We classified the identified mechanisms into three major functional categories: (1) intrinsic cancer cell biology, (2) cancer cell-peritoneal surface adhesion, (3) peritoneal tumor microenvironment (Fig. 5). These categories are highly interconnected, underscoring the complex interplay among mechanisms promoting peritoneal metastasis. Most of the identified studies focused on tumor biology, specifically cancer cell invasion, migration, proliferation, EMT, adhesiveness, and angiogenesis. This review also delves into the dynamic interactions between gastric cancer cells and their microenvironment (Fig. 4). In addition, we review and discuss molecular mediators of gastric cancer cell to peritoneal adhesion and metastasis mediators in the peritoneal tumor microenvironment.

Gastric tumor biology in relation to peritoneal metastasis can be difficult to study given limitations in accurately replicating the peritoneal cavity environment. While many studies utilize *in vitro* experiments, which have the advantage of reproducible results, the two-dimensional environment does not reflect tumor interactions *in vivo* where tumors have established cell-to-cell contact in the three-dimensional space. To overcome this barrier, studies utilize *in vivo* xenograft models; however, these are typically immunodeficient mouse models, which preclude an

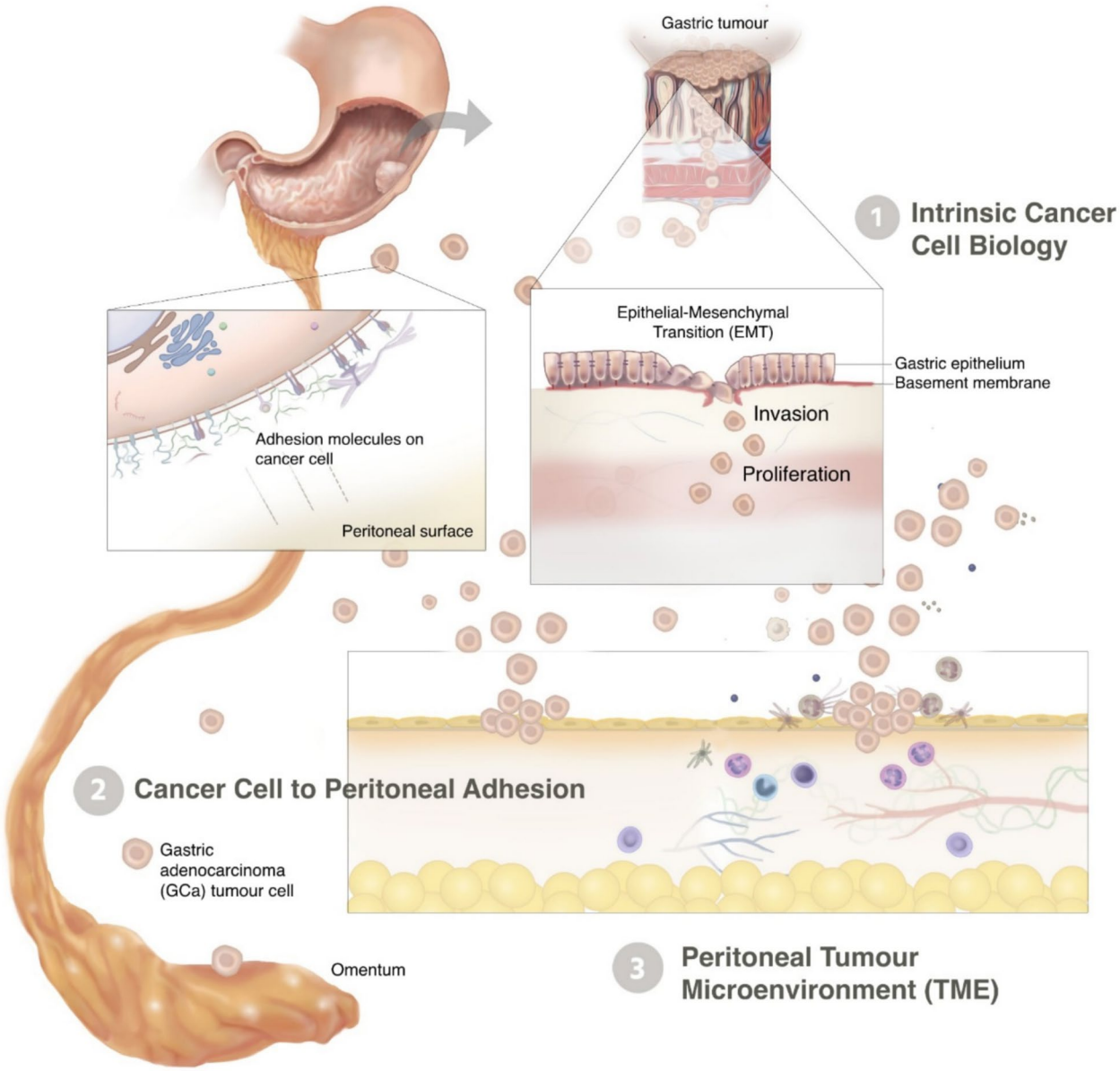

Fig. 5 Summary of key processes implicated in peritoneal metastasis from primary gastric cancer. This schematic illustrates the sequential but interconnected steps involved in peritoneal carcinomatosis, with a complex interplay of molecular interactions and tumor microenvironment components. Gastric tumor cells undergo epithelial-mesenchymal transition (EMT), losing epithelial traits and gaining mesenchymal properties that enable invasion and proliferation ((1) intrinsic cancer cell biology). Once in the peritoneal cavity, free-floating cancer cells interact with adhesion molecules on the peritoneal surface, facilitating cancer cell adhesion ((2) cancer cell to peritoneal adhesion). This adhesion is mediated by integrins, selectins, and other molecular regulators that promote tumor anchoring and colonization. The peritoneal tumor microenvironment (TME) consists of immune and stromal components, including cancer-associated fibroblasts (CAFs), tumor-associated macrophages, neutrophils, and lymphocytes, which contribute to tumor progression by remodeling the extracellular matrix, suppressing immune responses, and promoting angiogenesis ((3) peritoneal tumor microenvironment)

accurate understanding of how immune modulators interact with gastric adenocarcinoma cells. These models fail to fully capture the nuanced tumor microenvironment. These limitations create difficulty in elucidating the specific mechanisms involved in gastric peritoneal metastasis.

In contrast to past reviews, this review also summarizes patient prognostic factors and studies on differential expression. With the recent advances in technology, next generation sequencing is being used with increasing frequency. This allows us the opportunity to investigate mechanisms

in an unbiased way, uncovering novel genes or expression profiles involved in peritoneal metastasis. Some of the more promising and recent studies highlight the utility of assessing differential expression with human samples with primary gastric adenocarcinoma tissue or peritoneal metastasis. However, several limitations also exist with this technique. Most surgical candidates have early disease and patients who proceed with curative resection typically do not have peritoneal metastasis at the time of surgery, making it challenging to obtain matched primary and peritoneal tumor tissue. Some investigators sought to overcome this limitation by using malignant ascites as a surrogate for peritoneal tumor tissues [270]. Another approach was to utilize gastric adenocarcinoma tissue at the time of primary surgery, comparing gene expression patterns of primary tumors that metastasized to the peritoneum with primary tumors that did not metastasize to the peritoneum. This could be accomplished with the development and organization of prospective databases aimed at predicting peritoneal recurrence.

This review summarizes the molecular mechanisms implicated in peritoneal carcinomatosis by way of a systematic and thorough review of the literature. By categorizing these mechanisms into intrinsic cancer cell biology, cancer cell–peritoneal adhesion, and the peritoneal tumor microenvironment, this review underscores the complex interplay of pathways driving metastatic progression. A major strength of this study is its comprehensive integration of *in vitro*, *in vivo*, and genomic analyses, revealing novel insights into the molecular determinants of peritoneal dissemination. The review also identifies emerging biomarkers with potential clinical applications, including their role in risk stratification and therapeutic targeting. While these discoveries pave the way for future translational research, challenges remain, such as the need for prospective validation of molecular signatures and improved preclinical models that better replicate the human peritoneal microenvironment. Further study into these molecular markers may identify clinically relevant prognostic markers that can shape gastric adenocarcinoma management strategies.

Treatment is currently limited in patients with peritoneal disease, where survival remains dismal. Increasingly, novel peritoneal-directed therapies are being evaluated and modestly adopted for gastric cancer peritoneal metastasis (GCPM) [271]. While heated intraperitoneal chemotherapy can potentially reduce the rate of peritoneal recurrence in select patients [272, 273], the benefit is limited and more effective treatments are urgently needed. Current research is exploring combinations of locoregional therapies—such as pressurized intraperitoneal aerosol chemotherapy (PIPAC)—with systemic modalities, while emerging agents like STING agonists are being investigated for intraperitoneal delivery [274, 275]. Several molecular mechanisms reported in this review have promising therapeutic targets that can potentially improve survival and quality of life in patients with peritoneal disease [276]. Overall, integrated strategies represent a promising avenue that warrants further investigation to clarify their potential impact on patient outcomes. With a better understanding of the mechanisms of peritoneal metastasis, we anticipate improved diagnostic and therapeutic intervention.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

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