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Review

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Molecular mechanism of peritoneal dissemination in gastric cancer

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Abstract

Peritoneal dissemination (PD) is the most common cause of metastasis in gastric cancer (GC). Because there are no standard treatments for PD, it is associated with a poor prognosis. Although clinicians have performed intraperitoneal chemotherapy for GC with PD, the outcome remains unsatisfactory. Therefore, the development of novel treatments and diagnostic tools for PD is expected to improve the prognosis of GC patients with PD. Notably, it is essential to elucidate the molecular mechanisms involved in the development of PD in GC. In this review, the molecular mechanisms of PD (three steps: detachment from the primary tumor, adaptation to the microenvironment of the peritoneal cavity, and attachment to peritoneal mesothelial cells) and new topics in GC are highlighted.

Keywords: Gastric cancer, peritoneal dissemination, molecular mechanism

INTRODUCTION

Gastric cancer (GC) is one of the most prevalent cancers worldwide and is associated with a high mortality rate[1]. The malignant potential of GC is characterized biologically by the dissemination of cancer cells from the primary site throughout the peritoneal cavity. Almost 50% of recurrence was peritoneal dissemination in GC, and GC patients with peritoneal dissemination (PD) had a poor prognosis[2]. Although molecularly-targeted therapy has improved the prognosis of advanced and recurrent GC, the outcome remains unsatisfactory particularly in GC patients with PD[3,4]. Therefore, clarification of the

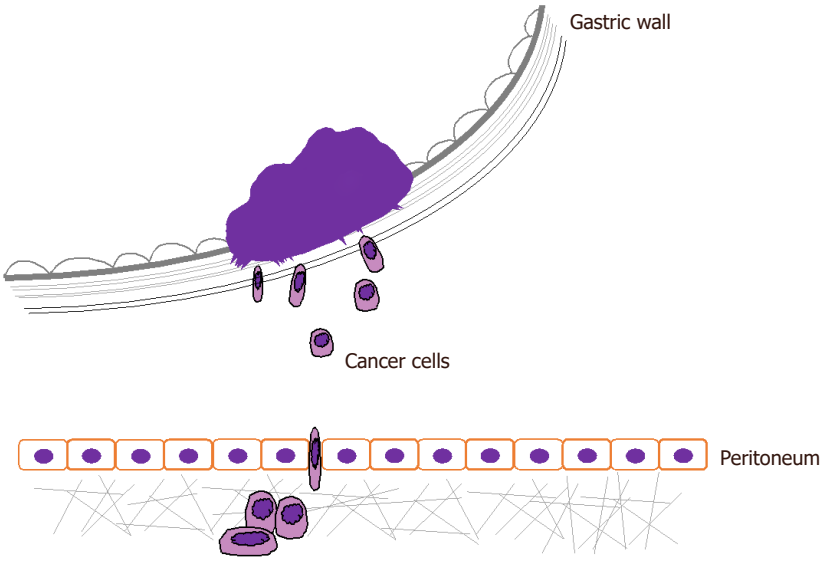

Figure 1. The metastatic cascade of peritoneal dissemination in gastric cancer

Table 1. The major molecules involved in development of peritoneal dissemination in gastric cancer

	Molecule	Biological function	Associated molecules/ pathways	References
Detachment from the primary tumor	E-cadherin	Cell-cell adhesion	Wnt, Rho GTPase, NF-κB pathway, EMT	[14-19]
	ARL4C	GTP-binding protein	Rho GTPase, EGF, Wnt	[23,24]
Adaptation to the peritoneal cavity microenvironment	HIF1α	Regulation of cellular and systemic homeostatic responses to hypoxia	EMT, NF-κB pathway, Glucose metabolism	[39-42]
	LOX	Lysyl oxidase	EMT	[43]
	ANGPTL4	Resistance to anoikis	FAK/Src/PI3K/Akt/ERK	[46]
	CXCL12	Chemokine ligand	EMT, CXCL12/CXCR4	[55,56]
	Akt	Serine-threonine kinase	PI3K/Akt, PTEN/PI3K/ NF-κB/FAK	[50-54]
	FAK	Tyrosine kinase	Fak/Src	[53,54]
Attachment toperitoneal mesothelial cells and tumor growth	Integrin a3b1	Cell adhesion	Lamine-5	[63]
	VEGF	Vascular endothelial growth factor	Angiogenesis	[61,65-67]

molecular mechanisms of PD is important for developing novel therapies and improving the clinical outcomes of GC patients.

The metastatic cascade of GC consists of lymphatic metastasis, hematogenous metastasis, and PD. Although the lymphatic metastasis and hematogenous metastasis are the major dissemination processes in solid cancers, PD is the most frequent metastatic type in GC patients, according to the annual report 2009 from Japanese Gastric Cancer Association. Unlike the lymphatic metastasis and the hematogenous metastasis, the peritoneal dissemination is initially driven by direct invasion from gastric wall to the peritoneal cavity.

Many metastasis-related factors, such as adhesion molecules, matrix proteases, and motility factors, are involved in the development of PD, which is a multistep process[5-9]. The first step involves detachment of cancer cells from the primary tumor, followed by survival of the cells in the microenvironment of the peritoneal cavity. The last step is attachment of circulating tumor cells to peritoneal mesothelial cells and tumor growth. In this review, we highlight the major molecular mechanisms of PD [Table 1 and Figure 1] and new topics in GC.

THE DETACHMENT OF CANCER CELLS FROM THE PRIMARY TUMOR

The development of PD is initiated by penetration of cancer cells through the gastric wall. In this step, cancer cells must have the ability to migrate and invade for successful detachment from the primary tumor and for gaining access to the peritoneal cavity. E-cadherin is a calcium-dependent cell - cell adhesion molecule that plays a crucial role in establishing the epithelial architecture and maintaining cell polarity. Dysregulation of E-cadherin contributes to tumor invasion by promoting cell motility[10,11], resulting in PD. Moreover, E-cadherin and the cadherin - catenin complex may promote invasion and migration by modulating various signaling pathways in epithelial cells, including Wnt signaling[12], Rho GTPase[13,14], and NF-κB pathways[15,16], as well as epithelial-mesenchymal transition (EMT)[13,17].

The activation of Rho GTPases (RhoA, cdc42, Rac) also drives cancer cell motility and invasion by promoting actin cytoskeleton reorganization[18-20]. The formation of lamellipodia and filopodia (resulting in actin cytoskeleton reorganization), which are regulated by Rac and cdc42, respectively, contributes to cancer cell motility[18]. In a previous study, ADP-ribosylation factor-like 4C (*ARL4C*), a downstream factor of EGF signaling and Wnt signaling, was reported to promote cell motility by activating Rho GTPases[21]. We recently found that *ARL4C* is associated with PD in GC, possibly by promoting the invasive capacity of cancer cells via activation of both EMT and actin cytoskeleton reorganization[22]. *ARL4C* is proposed to be a novel biomarker and potential therapeutic target for GC patients with PD.

In the process of cancer cell invasion, overexpression of matrix metalloproteinases (MMPs) is required for degradation of the extracellular matrix (ECM)[23,24]. High expression of MMP-7 is a reported risk factor for PD in GC[25], and MMP-2 and MMP-9 are also associated with the invasive capacity of gastrointestinal cancer cells[24,26,27]. Furthermore, MMP-14 can activate MMP-2 in addition to degradation of ECM[28].

EMT is an essential phenotypic conversion mechanism that has been implicated in the initiation of metastasis and tumor progression in many types of cancers[29]. During EMT, epithelial cells exhibit enhanced motility and invasiveness[30], low expression of E-cadherin, high expression of vimentin, a spindle shape, and reduced adhesion. The major ligands involved in EMT are EGF, TGFβ, Wnt, Notch, and integrin. The major transcription factors that induce EMT via downregulation of E-cadherin expression[13] are Twist, Snail, Slug, Zeb1, and Zeb2[31-33]. We focused on the influence of EMT on PD and found that discoidin domain-containing receptor 2 promoted PD in GC via induction of EMT[34].

CELL SURVIVAL IN THE MICROENVIRONMENT OF THE PERITONEAL CAVITY

The microenvironment of the free abdominal space is hypoxic and deficient in glucose[35]. The cancer cells, which are seeded in the peritoneal cavity, must survive, proliferate, and migrate in this environment. Cell adhesion to appropriate ECM components with integrin and cadherin is essential for cell survival, and loss of this adhesion induces cell death, which has been termed "anoikis". Therefore, anoikis resistance is required for cells surviving in the peritoneal cavity and anchorage-independent growth[36].

HIF1α is reportedly involved in PD in GC, colorectal cancer, and pancreatic cancer[35,37]. HIF1α is induced by hypoxia and functions as a master regulator of cellular and systemic homeostatic responses to hypoxia by activating the transcription of many genes, including those involved in glucose metabolism and other adaptations to hypoxia[38-40]. Interestingly, HIF1α induces EMT by activating the transcription of genes in the *LOX* family[41]. EMT contributes to not only migration and invasion but also anoikis resistance in cancer cells[42,43]. HIF1α also induces angiopoietin-like-4 (*ANGPTL4*), a secreted protein essential for tumor growth and resistance to anoikis in GC cells[44].

Cancer cells develop anoikis resistance via several mechanisms, including changes in integrin repertoire expression, induction of EMT, oncogene activation, and adaption of their metabolism[45-47]. In gastrointestinal

cancers, the PI3K/Akt[48-50] and PTEN/PI3K/NF-κB/FAK pathways[51,52] are involved in the formation of PD and anoikis resistance. FAK is a key integrin signaling molecule involved in cell survival pathways[51,52]. Moreover, the CXCL12/CXCR4 pathway can induce EMT[53,54] and is associated with PD and anoikis resistance[55,56] in multiple human cancers.

THE ATTACHMENT OF FREE TUMOR CELLS TO PERITONEAL MESOTHELIAL CELLS AND TUMOR GROWTH

Cancer cells seeded in the peritoneal cavity attach directly to the peritoneal surface. However, the mesothelium, a membrane composed of simple squamous epithelium that forms the lining of peritoneum, prevents the cancer cells from penetrating into the submesothelial space. The connective tissue under the mesothelium contributes to the formation of a microenvironment (niche) for seeding cancer nodules in the process of PD[6,57,58]. The production of MMPs and integrin is important for the penetration into the submesothelial space[59]. Notably, MMP-7 functions as a key factor in the degradation of ECM, promoting the penetration of cancer cells into the submesothelial space and the formation of PD. Integrins, transmembrane receptors that facilitate cell-ECM adhesion, were found to be overexpressed in GC cell lines with high PD potential[60]. Takatsuki *et al.*[61] reported that inhibition of integrin a3b1 reduced the number of disseminated nodules in GC cells. Laminin-5, a ligand with a high affinity for integrin a3b1, is a major ECM glycoprotein. Inhibition of laminin-5 reduced the adhesion of free cells to parietal peritoneum, suggesting that integrin a3b1 plays a key role in cell penetration into the submesothelial space[61]. Recently, it was reported that mesothelial cells create a novel tissue niche that facilitates GC invasion, resulting in PD[62].

Cancer cells that have attached to connective tissue underlying the mesothelium induce angiogenesis for tumor growth through high expression of vascular endothelial growth factor (VEGF)[59]. VEGF is a well-known signaling protein that stimulates formation of blood vessels. Previous studies suggest that VEGF is associated with PD in GC[63-65]. VEGF receptor antisense therapy inhibited angiogenesis and PD in GC[65]. Targeting VEGF is considered an attractive strategy to inhibit PD in GC.

NEW TOPICS IN GC

Immune checkpoint inhibitors enhance antitumor T-cell activity through inhibition of immune checkpoints such as the programmed death-1 (PD-1) receptor. Recent trials showed that anti-PD-1 receptor antibodies (pembrolizumab evaluated inKEYNOTE-012 and nivolumab in ONO-4538-12) exert antitumor activity in patients with advanced GC or gastro-esophageal junction cancer[66,67]. In a subgroup analysis of theONO-4538-12 trial, there are no interactions between PD and nivolumab treatment, indicating that nivolumab is effective for treatment of GC patients with or without PD. Immune checkpoint inhibitors are expected to improve the outcome of GC patients with PD.

With the accumulation of genomic/epigenomic data, many public data and online analysis tools are now available. The Cancer Genome Atlas (TCGA) is a large cancer genome project that has accumulated RNA sequencing, exome sequencing, SNP array, DNA methylation, reverse-phase protein lysate microarray, and clinical data across multiple cancers, and these data sets can be downloaded easily. Recently, TCGA reported a molecular classification that divides GC into four subtypes [Epstein-Barr virus (EBV)-positive, microsatellite instability (MSI), genomically stable (GS), chromosomal instability (CIN)] based on integrated genomic/epigenomic data (copy number analysis, whole exome sequencing, DNA methylation arrays, RNA sequencing, microRNA arrays, protein arrays)[68]. This classification provides a consistent and unified framework for further clinical and preclinical translational research. Elucidation of the molecular characterization of PD in GC is still needed but is expected to promote the development of novel treatments for GC patients with PD.

Recently, the perinuclear compartment (PNC), a complex nuclear structure associated with metastatic behaviors of cancer cells has drawn much attention[69,70]. Metarrestin, a PNC inhibitor, inhibits invasion in vitro, suppresses distant metastatic development in three mouse models of human cancer[71]. The invasion is required for the formation of PD, suggesting that metarrestin could also disturb the metastatic cascade of PD. Metarrestin will be submitted to the Food and Drug Administration for approval as an investigational drug in the near future.

CONCLUSION

The formation of PD is a multistep process, in which cancer cells must detach from the primary tumor, adapt to the microenvironment of the peritoneal cavity, and develop disseminated nodules. GC is characterized by genome instability and intratumoral heterogeneity, which contribute to the development of cancer by enabling adaptation to any change in environment. The same genomic/epigenomic alterations across all clones maybe an attractive therapeutic target for GC patients with PD. Further elucidation of the molecular mechanism underlying PD is essential for developing novel treatments and improving the outcome of GC patients with PD.

DECLARATIONS

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Authors' contributions

Designed the study, and wrote the initial draft of the manuscript: Hu QJ
Modified the draft of the manuscript: Ito S
Collected and interpreted the data, and critically reviewed the manuscript: Yanagihara K, Mimori K
Approved the final version of the manuscript: All authors

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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