Original Article

Molecular and Biochemical Alterations Underlying Ovarian Cancer Progression

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Abstract

Background: Ovarian cancer is characterized by complex biochemical and cellular processes that drive transformation from normal cells to malignant phenotypes and promote widespread metastasis. Unlike most solid tumors, ovarian cancer primarily spreads via intraperitoneal dissemination rather than hematogenous or lymphatic routes. At the primary tumor site, cancer-associated fibroblasts (CAFs) remodel the tumor microenvironment by secreting proteins such as versican (VCAN) and microfibrillar-associated protein 5 (MFAP5), which activate TGF-β and NF-κB signaling, enhance integrin-mediated cytoskeletal reorganization, and increase cell motility. Additional CAF-derived factors, including CXCL12 and fibroblast growth, further promote invasion, proliferation, and angiogenesis. In contrast, vascular permeability factor/VEGF establishes a vascular niche that sustains tumor growth and potential systemic spread. At metastatic sites such as the omentum, adipocytes and macrophages secrete cytokines (TNF-α, IL-6, IL-8) and growth factors that provide metabolic support and accelerate tumor colonization. Moreover, ovarian cancer cells evade anoikis through adrenergic receptor-mediated FAK signaling. Metastatic suppressor genes (MSGs), including KAI1, Nm23, KISS1/KISS1R, OGR1, BRMS1, E-cadherin, and MKK4, play critical roles in regulating adhesion, apoptosis, and epithelial–mesenchymal transition (EMT). Loss or downregulation of these genes correlates with poor prognosis, enhanced invasion, and reduced survival. Collectively, ovarian cancer metastasis is orchestrated by tumor–stromal interactions, signaling cascades, and suppression of metastasis-regulating genes, underscoring the tumor microenvironment as a pivotal driver of disease progression. Targeting CAF-mediated signaling, EMT regulators, and angiogenic pathways offers promising strategies for therapeutic intervention in ovarian cancer metastasis.

Keywords: Ovarian cancer, epithelial mesenchymal transition, extracellular matrix, vascular endothelial growth factor.

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Introduction

Cancer development involves protein products or molecular changes in a cell that cause a normal cell to transform into a cancer cell. Ovarian cancer metastasis involves multiple biochemical and cellular mechanisms, including epithelial–mesenchymal transition (EMT), resistance to anoikis, microRNA regulation, and the influence of growth factors and cytokines within the tumor microenvironment. During EMT, epithelial cells lose their polarity and intercellular adhesion, while acquiring migratory properties that enable invasion and motility, leading them to adopt mesenchymal-like characteristics. Evidence also indicates that cancer stem cells may contribute to this transition. Unlike many other cancers, ovarian tumors most commonly metastasize via intraperitoneal dissemination rather than through the bloodstream or lymphatic system.[1]

Cellular Events in Ovarian Cancer Metastasis

In ovarian cancer progression from the primary site to the omentum site:

Primary Tumor Site: In ovarian cancer, the ovary is the primary tumor site, where cancer cell motility is significantly influenced by proteins secreted by cancer-associated fibroblasts (CAFs). These CAF-derived proteins are central to remodeling the tumor microenvironment and promoting cancer progression. The expression of CAFs is markedly upregulated by versican (VCAN), a proteoglycan, by activating the transforming growth factor-beta (TGF-β) signaling pathway. Versican, in turn, activates the nuclear factor kappa B (NF-κB) signaling cascade within ovarian cancer cells, which enhances tumor cell motility and invasive potential. This is achieved by upregulating key molecules such as CD44, hyaluronan-mediated motility receptor (HMMR), and matrix metalloproteinase-9 (MMP9), all contributing to extracellular matrix degradation, adhesion, and migration. In addition, microfibrillar-associated protein 5 (MFAP5), another protein secreted by CAFs, binds to αVβ3 integrin receptors on the ovarian cancer cell surface. This interaction triggers Ca^{2+}-dependent activation of the FAK/CREB

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(cAMP response element-binding protein)/TNNI3 (troponin C type 1) signaling pathway. The downstream activation of this pathway induces reorganization of the F-actin cytoskeleton, thereby facilitating structural changes that promote enhanced cell migration and invasion. These molecular events significantly increase the metastatic potential of ovarian cancer cells within the peritoneal cavity. Alongside these CAF-driven mechanisms, several other signaling molecules and growth factors contribute to tumor progression. For instance, the chemokine CXCL12, secreted predominantly by CAFs, binds to its cognate receptor CXCR4 on ovarian cancer cells, promoting tumor survival, proliferation, and motility. Fibroblast growth factors (FGFs), including FGF1 and FGF18, further accelerate tumor development through autocrine signaling, whereas fibroblast growth factor receptor 4 (FGFR4) enhances cancer progression via paracrine interactions within the tumor microenvironment.

Furthermore, ovarian cancer cells secrete vascular permeability factor (VPF), a potent pro-angiogenic protein produced by diverse cell types. VPF, also known as vascular endothelial growth factor (VEGF), stimulates the formation of new blood vessels within the tumor milieu, creating a vascular network that supplies nutrients and oxygen to the growing tumor mass. These newly formed microvessels sustain tumor growth and provide potential routes for hematogenous dissemination, facilitating distant metastasis of ovarian cancer cells. Taken together, the interplay between CAF-secreted proteins, growth factors, chemokines, and angiogenic signals establishes a highly supportive tumor microenvironment that drives ovarian cancer progression. CAF-mediated activation of TGF-β and NF-κB pathways, coupled with integrin-dependent cytoskeletal remodeling, directly enhances the motility and invasiveness of ovarian cancer cells. At the same time, pro-angiogenic factors such as VPF/VEGF foster neovascularization, ensuring both local tumor expansion and systemic metastatic potential. These findings highlight the critical role of the tumor microenvironment in ovarian cancer biology and underscore the importance of targeting CAF-derived signaling pathways and angiogenesis-related molecules as potential therapeutic strategies.

Omentum Site- In ovarian cancer, the omentum site refers to the omentum, a large, fatty tissue layer in the abdomen that hangs down from the stomach and covers the intestines like an apron. Moreover, the omentum is rich in adipocytes (fat cells), immune cells like macrophages, and blood vessels, creating a supportive microenvironment. Ovarian cancer cells that detach from the primary tumor in the ovary often travel through the peritoneal fluid and preferentially attach to and colonize the omentum. Once there, adipocytes release fatty acids and cytokines (e.g., TNF-α, IL-6, IL-8) that fuel the tumor cells, while macrophages secrete VEGF and TNF, promoting angiogenesis and metastasis. In the omentum (metastatic tumor site), for ovarian cancer, some secretory factors are produced from adipocytes & and macrophages to promote tumor metastasis. Correlation between adipocytes & cancer cells in the omentum increases the tumor metastasis. Adipocytes secrete various cytokines such as TNF-α_, IL-6, and IL-8. These cytokines give energy to ovarian cancer cells. Macrophages build & secrete TNF (tumor necrosis factor) & VEGF into the tumor micro-environment, enhancing tumor metastasis.[2]

Under normal conditions, cells undergo apoptosis when detached from the extracellular matrix (ECM) and surrounding cells, a process known as anoikis.[3] Detachment disrupts normal cell–matrix interactions, leading to programmed cell death, since signals from the ECM and neighboring cells are essential for cellular growth and survival. However, previous research has demonstrated that epinephrine and norepinephrine can protect ovarian cancer cells from anoikis through a FAK-mediated signaling cascade. This pathway is initiated via ADRB2 (the β2-adrenergic receptor gene) and involves Src-dependent phosphorylation of FAK at tyrosine 397.[4]

Many genes have been found in the context of ovarian cancer metastasis,[5,6] and they encode the proteins related to cell-cell adhesion, apoptosis, and cell invasion, and frequently suppress EMT induction.[5] Furthermore, they are indirectly involved in carcinogenesis through loss of function. Based on the mechanism, MSG (metastatic suppressor gene) is related to ovarian cancer, such as:

Genes	Mechanism & Functions
KAI1,[7]	It is a member of type III TM4SF (transmembrane4 superfmily or tetraspanin) and to connect in the regulation of cell motility, morphology, fusion, signaling, fertilization, and differentiation. KAI1 was found as a suppressor of metastatic spread in a rat prostate cancer model,[8] and it is also found that the low expression of KAI1 is directly correlates with poor prognosis in ovarian cancer.[9] It may suppress ovarian cancer progression by inhibiting integrin αvβ3/vitronectin-provoked tumor cell motility and proliferation.[7] These type III transmembrane proteins encompass cytoplasmic N- and C-termini, and traverse the cell membrane four times, thereby forming one small and one large extracellular loop. In the cellular activities of tetraspanins are also involved in the regulation of certain pathologies, including cancer progression.
Nm23,[10]	Nm23 was found by a complimentary DNA (cDNA) & they role as a inhibition of ras signaling and inhibitor of tumor migration. Nm23 affect the cell invasion and not mediated by its NDP kinase activity. The major role is inversely correlated to ovarian cancer.[10-13]
KISS	KISS receptors are 2 types 1) KISS1 2) KISS1R Both are G-protein coupled receptor (GPCR is a plasma membrane receptor with seven transmembrane domains. 1) KISS1 function is maintain dormancy at secondary sites & working like a prohormone. It is also called a Kisspeptins (KP54). They are able to bind the KISS1 receptor and inhibition of metastases in vivo.[14,15] 2)KISS1R function is cell colonization and attached the internal fragments derived from KISS1, And to build an autocrine loop by which the tumor cells suppressed metastasis.[16] Kisspeptin and GPR54 (KISS1R) are the subtypes of clear cell ovarian carcinoma and also the independent prognostic biomarkers specific for ovarian clear cell carcinomas.[14,16]
OGR1 & BRMS1,[17,18]	They both are contribute to MSG. OGR1-Ovarian cancer G-protein coupled receptor (OGR1). This receptor regulates endothelial barrier integrity, proliferation and tube formation, and T-cell migration. In the ovarian cancer, the overexpression of OGR1 which is

	significantly inhibits cell proliferation and migration that results to enhance the cell adhesion into the extracellular matrix. BRMS1- Breast cancer metastasis suppressor 1 (BRMS1) is a nuclear protein and to regulates the expression of multiple genes. The upregulation of CXCR4 through NF-κB activation in ovarian cancer which is regulated by BRMS1.[18]
E-Cadherin,[19]	The loss of E-cadherin cell activity during the epithelial-to-mesenchymal transition (EMT) in many tumors.[20] Loss of E-cadherin correlates with shorter overall survival in ovarian cancer.[19,21] E-cadherin regulated at transcriptional and post-transcriptional levels. There are two zinc finger transcriptional repressors i.e Snail and Slug. They both have been involved in repressing E-cadherin transcription. And loss of activity of E-cadherin cell is a marker of EMT.
MKK4,[22]	The last one but not the least MSG (metastasis suppressor genes). MKK4 (mitogen activated protein kinase kinase 4) gene encode a member of the MAPK family. MKK4 was homozygously absent in some ovarian cancer samples. The activity of MKK4 is loss resulted in the induction of Twist (twist is the zinc finger transcriptional repressors) expression via phosphorylation of NF-κβ and repression of E-cadherin activity.

Discussion

Ovarian cancer metastasis represents a highly coordinated and multifactorial process involving cellular, molecular, and micro environmental interactions that enable tumor cells to detach from the primary site, survive in suspension, and colonize distant organs within the peritoneal cavity. Unlike other cancers that primarily spread through hematogenous or lymphatic routes, ovarian cancer cells exhibit a unique predilection for intraperitoneal dissemination. The transformation of normal epithelial cells into invasive cancer cells is facilitated by epithelial–mesenchymal transition (EMT), during which epithelial cells lose their polarity and adhesion, gaining motility and mesenchymal characteristics. This process is regulated by transcription factors such as Snail, Slug, and Twist, which suppress E-cadherin expression—a hallmark event in EMT that correlates with poor prognosis and increased invasiveness in ovarian cancer.[20] Furthermore, cancer stem cell–like subpopulations may enhance this phenotypic plasticity, contributing to tumor heterogeneity and therapeutic resistance.

The tumor microenvironment (TME) plays a central role in promoting ovarian cancer progression. Cancer-associated fibroblasts (CAFs), through the secretion of molecules like versican (VCAN) and microfibrillar-associated protein 5 (MFAP5), activate pro-migratory signaling cascades such as TGF-β, NF-κB, and FAK/CREB/TNNI3 pathways.[21] These interactions promote cytoskeletal reorganization, extracellular matrix (ECM) remodeling, and enhanced motility of tumor cells. In addition, chemokines like CXCL12 and growth factors such as FGFs and VEGF foster a pro-metastatic environment by stimulating tumor proliferation, angiogenesis, and survival. Notably, the secretion of VEGF (also termed vascular permeability factor, VPF) supports neovascularization, ensuring nutrient and oxygen supply to metastatic foci. This interplay of CAF-derived cytokines, growth factors, and integrin-mediated signaling underscores the complexity of stromal–tumor cross-talk in ovarian cancer metastasis and highlights potential therapeutic targets to disrupt tumor–stroma communication.

At metastatic sites such as the omentum, interactions between ovarian cancer cells, adipocytes, and immune cells further facilitate colonization. The omental microenvironment, rich in adipocytes and macrophages, provides both metabolic support and pro-inflammatory signaling. Adipocytes release fatty acids and cytokines including TNF-α, IL-6, and IL-8, supplying energy substrates that promote tumor growth and invasion.[16] Concurrently, macrophage-secreted VEGF and TNF-α enhance angiogenesis and metastatic potential. The crosstalk between these stromal cells and ovarian cancer cells amplifies metastatic behavior while protecting tumor cells from anoikis—cell death induced by detachment from the ECM. Catecholamines such as epinephrine and norepinephrine further inhibit anoikis through β2-adrenergic receptor (ADRB2)-dependent activation of the Src/FAK signaling pathway, demonstrating how systemic stress-related signals can modulate tumor survival.[18]

Metastatic suppressor genes (MSGs) such as KAI1, Nm23, KISS1/KISS1R, OGR1, BRMS1, E-cadherin, and MKK4 serve as key negative regulators of metastasis, and their downregulation or loss is frequently associated with advanced ovarian cancer.[22] KAI1 and Nm23 inhibit integrin-mediated motility and Ras signaling, respectively, while KISS1 and its receptor KISS1R maintain dormancy at secondary sites. Similarly, OGR1 and BRMS1 regulate cell adhesion and NF-κB–dependent gene expression, contributing to metastatic suppression. Loss of E-cadherin promotes EMT, whereas MKK4 inactivation enhances NF-κB activity and Twist expression, further repressing E-cadherin and promoting invasion. Collectively, these findings illustrate how disruption of tumor suppressive networks, coupled with pro-metastatic signals from the microenvironment, orchestrates ovarian cancer progression. Therefore, therapeutic interventions that restore MSG function or target TME-driven pathways such as TGF-β, NF-κB, and VEGF may offer promising avenues to curb metastasis and improve clinical outcomes in ovarian cancer patients

Conclusion

Ovarian cancer metastasis is a multifactorial process driven by intricate biochemical alterations, cellular signaling cascades, and tumor–stromal interactions. Cancer-associated fibroblasts (CAFs), adipocytes, and macrophages within the tumor microenvironment play pivotal roles by secreting growth factors, cytokines, and extracellular matrix–modifying proteins that enhance tumor cell motility, invasion, and survival. Key pathways such as TGF-β, NF-κB, integrin/FAK, and VEGF-mediated angiogenesis orchestrate cytoskeletal remodeling, resistance to anoikis, and vascularization, thereby enabling intraperitoneal dissemination and colonization of metastatic sites like the omentum. Importantly, the downregulation or loss of metastatic suppressor genes (MSGs), including KAI1, Nm23, KISS1/KISS1R, OGR1, BRMS1, E-cadherin, and MKK4, further accelerates disease progression and correlates with poor prognosis. Collectively, these findings highlight the tumor microenvironment as a central driver of ovarian cancer biology. Therapeutic strategies targeting CAF-derived signals, EMT

regulators, and angiogenic pathways hold significant promise for controlling ovarian cancer progression and improving patient outcomes.

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Conflicts of interest
There are no conflicts of interest.

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