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The role of selected molecular factors in ovarian cancer metastasis

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ABSTRACT

The main reason for treatment failure in ovarian cancer is chemoresistance and the presence of metastasis. Ascites, which allows the physical movement of cancer cells, the lymphovascular pathway, and several molecular factors and signalling axes, are involved in metastasis.

Ascites, with the involvement of cytokines and chemokines, MAPK/STAT1 and NOTCH as well as CXCL12/CXCR4 signaling pathways and circulating anoikis induces cancer dissemination, in particular to the peritoneum and omentum.

The spread of lymphatic and bloodstream cancer cells is a multi-stage process. Tumour infiltration of the stroma and lymphovascular space (LVSI) produces biologically active cancer-associated fibroblasts and macrophages (CAFs, TAMs) that secrete numerous cytokines, chemokines and growth factors, inhibit NK function, induce epithelial-mesenchymal transition (EMT), resulting in an increase of the metastatic potential of cancer cells and the formation of cancer stem cells (CSCs).

Overexpression of some genes, and microRNAs, in LVSI-(LMGS) associated with metastasis has been identified.

The role of extracellular vesicles (EVs) transporting metastasis-associated factors has been described as has the role of cancer stem cells (CSCs) in chemotherapy resistance and metastasis. Sirtuins, enzymes involved in metastasis formation, have also been detected. Certain types of microRNAs (miR-509-3p, microRNA-506-3p) and melatonin have been shown to inhibit metastasis.

Key words: ovarian cancer; metastasis; ascites; CAFs; microRNA; molecular signature

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INTRODUCTION

Ovarian cancer (OC) is the seventh most common malignancy in women worldwide. It is the leading cause of death among all gynaecological cancers. More than 70% of ovarian cancers are diagnosed in advanced clinical stages. After successful primary therapy, approximately 80% of patients are found to have recurrent ovarian cancer with a 5-year survival rate of 25–35%. In 90% of cases ovarian cancer is the cause of death [1–3].

The primary type of OC is epithelial carcinoma with five subtypes, among which high-grade serous ovarian cancer (HGSC) is the most aggressive and associated with a poor prognosis [4–7].

Chemo-resistance and metastasis, in addition to the clinical stage of cancer, are fundamental reasons for treatment failure. Metastasis is a complex process in which cancer cells migrate to different parts of the body, acquire invasive features, and cause the formation of new cancer foci.

The mechanism of metastasis is regulated by specific genes using various cytokines, chemokines, growth factors, signalling pathways and intercellular interactions. Metastasis is associated with high death rates [8–16].

A considerable number of molecular mechanisms involved in metastasis have been described, as well as pathways involved in this process. According to Kim et al. [4],

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the presence of ascites modulates the behaviour of cancer cells released from the tumour, contributing to tumour heterogeneity related to different responses to treatment. Ascites forms a microenvironment containing various factors: cytokines- IL-6 and IL-8, IL-10, pro-angiogenic VEGF, stromal cells — including a fraction of cancer-associated fibroblasts (CAFs) — that promote cancer cell proliferation, migration, invasion, and chemoresistance. Aggregates of cells, spheroids, with typical stem cell expression were isolated from ascites: CD 44 and CD 24 which represent the chemoresistant population and cells expressing metastasis-related genes including TGF-β and integrin [4, 17].

Ascites contains a significant number of proteins and exosomes, the extracellular vesicles (EVs) involved in transferring information between metastatic cells [4, 18].

According to Weidle et al. [17], ascites fluid, in addition to the physical condition that allows the movement of exfoliated cancer cells, promotes the interaction of cancer cells with the microenvironment and the induction of multiple pathways that promote metastasis, including MAPK/STAT1 and NOTCH.

Furthermore, metastasis is favoured by the activation of some chemokines and their receptors, including CXCL12--CXCR4 axes, as well as the overexpression of transmembrane tyrosine kinase C-MET promoting cancer dissemination [19, 20].

In the promotion of ovarian cancer dissemination, attention has been paid to the resistance of anoikis — cells detached from the tumour that have acquired metastatic features and which under non-adherent conditions can circulate as CTCs (circulating tumour cells) participating in metastasis formation [18].

The presence of ascites, as well as tumor-stromal interaction, TGF-α excreted by ovarian cancer cells and CAF--secreted TGF-α together with EGFR, AKT and ERK signalling pathways promote metastasis to the omentum [14].

Lymphatic and vascular dissemination play a key role in the formation of both intraperitoneal and distant metastases [21, 22].

The initial stage of this process is neoplastic infiltration of the stroma and the presence of cancer cells in the lymphovascular space invasion (LVSI). The tumour-infiltrated lining contains numerous biologically active cells, including the aforementioned fibroblasts — CAFs and tumour-associated macrophages (TAMs). CAFs produce cytokines and chemokines of autocrine and paracrine function as well as growth factors including CXCL1, TGF-α, VEGF1, IL-6, IL-8, COX-2, and overexpress the homeotic gene HOXA9 associated with the promotion of the cancer microenvironment [21, 23].

CAFs also enhance the expression of matrix metalloproteinases (MMPs) and induce epithelial-mesenchymal transition (EMT) associated with the increased metastatic potential of the transformed cell [24]. TAMs secrete many factors such as TGF-β, IGF, and PDGF, inhibiting NK cell function, maintaining the metastatic niche, and helping to maintain CAFs activity [25].

The described activity of CAFs and TAMs facilitates cancer invasion and metastasis. Infiltration of the lining by CAFs is associated with a positive LVSI that correlates with increased serous cancer invasion and worse overall survival ($p = 0.0205$). Results of a targeted therapy study with factors secreted by CAFs and TAMs have been described and appear promising [21].

Numerous other factors are also involved in the metastatic process of ovarian cancer: genetic factors, including microRNAs, extracellular molecules, stem cells, and many others.

METASTASIS-ASSOCIATED GENE SIGNATURE

Yue et al. [21] showed that cancer stromal activation is associated with a differentially expressed gene (DEC). They identified a lymphovascular metastasis gene signature (LMGS) with an increased expression that correlates with an increased risk of metastasis via the lymphatic and circulatory routes. These genes are POSTN, LUM, THBS2, COL3A1, COL5A2, FAP, and FBN1.

It has been shown that there is a relationship between LMGS expression and TGF-β pathway activation. Since TGF-β has been shown to be an essential factor in fibroblast activation and CAFs formation, therefore CAFs also contribute to LMGS overexpression. The cited paper describes the results of a phase I and phase II study of targeted therapies currently under development that are associated with overexpression of the genes under investigation [21].

THE ROLE OF microRNAs IN METASTASIS

MicroRNAs (miRNAs) are a family of small non-coding RNAs that regulate the expression of approximately 50% of protein-coding genes. They play a crucial role in cell cycle regulation, proliferation, differentiation, motility, and apoptosis. In addition, they participate in angiogenesis, epithelial-mesenchymal transition (EMT), and resistance of cancer cells to chemotherapy. According to several studies, they too are involved in metastasis but may also be suppressors of cancer dissemination [8, 11, 26–29].

Braga et al. [11] showed that non-coding RNAs (ncRNAs) are involved in ovarian cancer progression and metastasis by participating in EMT, in which the cell acquires characteristics typical of a stem cell.

Similarly, Ghafouri-Farad et al. [29] showed that a number of microRNAs, including miR-135a, miR-200c, miR-216a, and miR-340 regulate EMT by modulating cell invasiveness through mTOR and PI3K/AKT pathways. According to the authors above, these microRNAs may have applications as biomarkers and provide a therapeutic perspective.

Another paper reported the study of miRNA-205 contained in exosomes, which promotes metastasis by inducing angiogenesis via the PTEN-AKT pathway [28].

Loginov et al. [26] detected 20 abnormally methylated miRNA genes involved in different stages of ovarian cancer development and metastasis to various locations, including the peritoneum. They demonstrated a significant correlation between methylation levels and the presence of microRNAs in metastases. Among the genes studied, thirteen miRNAs were hypermethylated at early stages of cancer development and hypermethylation of MIR-1258, MIR203A, MIR137 and MIR375 was evident in metastatic foci. They also identified three miRNA genes (MIR148A, MIR9-1, and MIR193A) that regulated EMT and were present in macroscopic peritumoral nodules.

A review by Nguyen et al. [8] reported the diverse role of microRNAs in ovarian cancer metastasis. Some microRNAs exhibit metastasis-related activity; these microRNAs showed increased expression and were present in tumour tissues. Their presence correlated with a clinical grade, omental or lymph node metastasis, presence of ascites, or recurrence. Many anti-metastatic miRNAs with decreased expression in ovarian cancer tissues were also detected — e.g., miR-509-3p inhibiting migration, invasion, and steroid formation, positively associated with HGSC survival.

Sun et al. [27] described microRNA -506-3p that inhibits ovarian cancer metastasis by decreasing the expression of EZH2 (enhancer of zeste homolog 2), a key transcription factor in tumour development. Some miRNAs were found to be present in exosomes or circulating body fluids [8].

EXTRACELLULAR VESICLES (EVs) IN METASTASIS

Exosomes are spherical membrane nanobubbles of 30–100 nm in size, which are carriers of various biological molecules, including genetic material. They participate in the modulation of intercellular communication, the immunological activity of fibroblasts, macrophages, and angiogenesis. Proteins and microRNAs are transported in exosomes, thus participating in cancer metastases [13, 28].

In a review by Tian et al. [13], EVs were shown to play a role in drug resistance, as well as the progression and promotion of metastasis. For example, the cell adhesion molecule CD44 is translocated by EVs from cancer cells to peritoneal mesothelial cells, thereby initiating metastasis. CD147-containing vesicles released from ovarian cancer can induce angiogenesis both by expressing E-cadherin on their surface and by using PTEN-AKT and STAT3 signalling to facilitate peritoneal and omental metastasis [28, 30].

Studies show that ascites-derived EVs affect EMT in cells by translocating miR-6780b-5p to target organs, preparing the microenvironment for tumour growth [31].

The promotion of EMT by EV-containing factors is associated with the development of cancer stem cells (CSCs) responsible for carcinogenesis.

CANCER STEM CELLS IN METASTASIS

CSCs are a small subpopulation of cells, accounting for about 2% of tumour mass, but appear to play a key role in chemotherapy resistance and metastasis. They most likely arise from somatic stem cells that have transformed due to genetic and epigenetic factors. They have the ability to self-renew, residing in an inactive state as "dormant cells", and are capable of DNA repair. Ovarian cancer CSC markers have been identified: CD44, CD133, CD24, CD117, Nestin, Nanog, Oct3/4, as have functional markers: ALDHA1 and ABC (associated with cytostatic resistance). They exploit various signalling pathways: PI3K/AKT/mTOR, MAPK, NOTCH, and canonical Wnt [5, 32–35].

Some cells with the CD24 phenotype have been found to have strong renewal properties, are resistant to chemotherapy, play a role in CSCs migration, metastasis and promote interactions between CSCs and the tumour microenvironment [5, 36]. According to Kleinmans et al. [37], CD24 is overexpressed in 70% of solid tumours, including ovarian cancer. It may serve as a preclinical and clinical biomarker of OC and perhaps a future target for therapy. Other studies provided similar data. Tarhriz et al. [38] found CD24 to be an important molecule. Overexpressed in OC, CD 24 is a CSC marker and is associated with ovarian cancer development, invasion and metastasis. According to the above authors, CD24 may be an independent survival indicator for OC patients.

CSCs achieve their metastatic potential through multiple mechanisms. One such mechanism may be the inhibitory effect on the apoptosis pathway and the exploitation of the NF-kB signalling pathway. Inhibitors that reprogram chemoresistance have already been described (e.g., PFKFB3 inhibitor). This issue, however, needs further investigation [12].

Another pathway of metastatic activity of CSCs is the activation of the angiotensin II (ANG II) pathway and its receptor (AGTR1), which enhance spheroid formation and cell migration, thus promoting metastasis, especially to the peritoneum. Studies are underway to influence lipid homeostasis and suppress endoplasmic reticulum (ER) stress which would decrease the formation of spheroids and the CSCs they contain [16].

OTHER MECHANISMS INVOLVED IN METASTASIS

Sirtuin deacetylases (SIRTs) are enzymes that cleave acetyl groups from various proteins. Of the seven groups of SIRTs, SIRT3 has been described to support metastasis, it has been found in ascites and peritoneal metastases in ovarian cancer.

The mechanism that promotes metastasis is the reduction of oxidants induced by oxidative stress. This facilitates the avoidance of anoikis apoptosis, whose detachment from the primary tumour is associated with rapid oxidative stress [9].

MELATONIN

In vitro and in vivo studies have shown that chronic restraint stress (CRS) promotes OC abdominal metastasis and increases the expression of EMT-related markers — including the transcription factor SLUG [39]. Increased expression of β-catenin and norepinephrine (NE) was found to be associated with poor clinical status in ovarian cancer patients. Melatonin (MLT) effectively inhibited tumour burden by inhibiting the complex NE/AKT/β-catenin/SLUG (catecholamine, proliferative-transcriptional) axis.

The authors believe these findings suggest a novel mechanism for CRS-mediated ovarian cancer metastasis, and MLT has potential therapeutic efficacy [39].

Conflict of interest

All authors declare no conflict of interest.

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