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Metabolic reprogramming and molecular crosstalk at the cancer–endothelial interface in ovarian carcinoma

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Abstract

Ovarian carcinoma (OC) is the most lethal gynecological malignancy, with high mortality due to late-stage diagnosis and the development of chemoresistance. Tumor progression relies on a complex interplay between cancer cells and the tumor microenvironment (TME), particularly endothelial cells (ECs), which support angiogenesis, nutrient supply, and metastasis. Aberrant neovascularization, driven primarily by VEGF signaling and hypoxia-inducible factors (Hifs), establishes a structurally and functionally abnormal vasculature that enhances tumor growth and dissemination. In the TME, ECs and OC cells undergo metabolic reprogramming, with glycolysis, fatty acid oxidation (FAO), and amino acid metabolism supporting angiogenesis, proliferation, redox balance, and chemoresistance. The bidirectional nutrient exchange establishes a metabolic symbiosis sustaining angiogenesis stimulation, tumor growth and survival under hypoxia and a pro-oxidative TME. Ultrastructural adaptations, including tunneling nanotubes (TNTs), facilitate direct cytoplasmic and organelle exchange, enhancing mitochondrial transfer, metabolic

support, and therapy resistance. The formation of EC TNTs is regulated by stress-responsive pathways, including Hif-1α, VEGF, and Nrf2, which integrate hypoxia, oxidative stress, and metabolic signaling to reinforce vascular remodeling. This intricate network of signaling and metabolic interactions establishes a self-sustaining vascular niche that drives tumor aggressiveness and limits therapeutic efficacy. Understanding these mechanisms provides insight into potential therapeutic interventions, aiming to disrupt the cooperative tumor-EC network and overcome chemoresistance in OC.

Keywords: Ovarian carcinoma (OC), endothelial cells (ECs), angiogenesis, vascular endothelial growth factor (VEGF), hypoxia inducible factor (Hif), nuclear factor erythroid 2–related factor 2 (Nrf2), targeted therapy, metabolic symbiosis, tunneling nanotubes (TNTs).

1. **Introduction**

Ovarian cancer, mainly represented by ovarian carcinomas (OC), remains the most lethal gynecological cancer and a significant clinical challenge[1,2]. Each year, more than 230,000 new cases are diagnosed, with an associated mortality exceeding 150,000 deaths[3]. This high mortality is largely a consequence of the disease´s insidious clinical presentation, as the absence of conspicuous initial symptoms often leads to diagnosis only at advanced stages (III or IV)[2,4]. The treatment of advanced OC involves a combination of primary tumor reduction surgery and platinum-based chemotherapy[2,5]. Although this approach yields high initial response rates, with a substantial proportion of patients achieving remission, the therapeutic benefit is short-lived[1,4,6]. The prognosis for recurrent OC remains unfavorable, with a limited long-term survival for patients with advanced-stage disease,

underscoring the urgent need for therapeutic strategies that target the fundamental drivers of its progression[1].

A deeper understanding of the biological mechanisms underlying OC will enhance our ability to comprehend its development, improve diagnosis, refine prognosis, and optimize clinical management. This review will focus on angiogenesis and cancer metabolism as key hallmarks of OC, exploring both their individual roles and the interplay between them, while also considering the modulatory influence of the tumor microenvironment (TME) and the formation of tunneling nanotubes (TNTs) as ultrastructural modifications facilitating the contact between OC cells and ECs.

2. **Angiogenesis as a motor for ovarian carcinoma (OC) progression**

Central to the progression of all solid tumors, angiogenesis is a core hallmark of cancer[7,8], comprising the formation of new blood vessels from pre-existing vasculature, in a transient and tightly regulated process[3,8] (Figure 1 A). In cancer, a dysregulated angiogenic switch destabilizes the natural equilibrium between pro- and anti-angiogenic factors, leading to sustained and uncontrolled neovascularization (Figure 1)[7–9].

Neovascularization is essential for tumors to achieve sizes exceeding the 1-2 mm^3 diffusion limit, establishing a capillary network that provides oxygen, nutrients and ensures metabolic waste removal[1,4]. A family of molecules, the vascular endothelial growth factor (VEGF) family, in conjunction with its cognate tyrosine kinase receptors (VEGFRs), has been identified as the most critical regulators of this process[1,3] (Figure 1 A). The TME is often characterized by hypoxia, which serves as a potent stimulus for the upregulation of hypoxia inducible factors (Hifs) that, in turn, drive transcription of

VEGF-A (from now on called VEGF) mRNA[1,5,8] (Figure 1 C). High levels of VEGF are expressed by OC cells[4,8], and multiple studies established a direct correlation between elevated serum VEGF levels and adverse clinical outcomes (Figure 1), including the presence of macroscopic residual disease after surgery, a higher risk of disease progression and significantly shorter progression-free survival (PFS) and overall survival (OS)[8,10]. Therefore, the profound reliance of OC in this aberrant vascular network provides a compelling biological rationale for targeting the angiogenic pathway as a core therapeutic strategy[2,3].

Angiogenesis is essential for tumor progression, metastasis and the development of malignant ascites[11,12]. The formation of cancer-associated vessels is driven by a complex interplay of signaling molecules and cellular interactions within the TME, contributing to the aggressive behavior of the tumor[9,12] (Figure 1 C). For OC to grow, an adequate blood supply is required to deliver oxygen, nutrients and to remove metabolic waste[11,13]. The VEGF signaling pathway, particularly the VEGF/VEGFR-2 axis on ECs, is considered the primary mediator of this process[14]. OC cells secrete VEGF, which stimulates ECs and some tumors also express VEGFR-2[14]. Beyond VEGF, other pro-angiogenic factors play critical roles. Angiopoietin-like 4 (ANGPTL-4) and Angiopoietin-like-2 (ANGPTL-2) have been shown to accelerate OC carcinogenesis and angiogenesis by activating signaling pathways like JAK2/STAT3[11]. Platelet-derived growth factors (PDGFRs), especially PDGFR-β expressed in the tumor stroma, are involved in signaling cascades that lead to cell proliferation and survival, and high expression correlates with poorer outcomes[9,14]. The establishment of this neo-vasculature is a prerequisite for subsequent metastatic dissemination[15] (Figure 1 A).

OC spreads primarily through the peritoneal cavity, where angiogenesis plays a crucial role in supporting the survival and growth of metastases[16,17] (Figure 1 B). OC cells shed from the primary tumor

form multicellular aggregates or spheroids in ascites, which then implant on the mesothelial lining of the peritoneal cavity[16,17]. ECs are critical players in this process, co-aggregating with OC cells in ascites, to form organized angiospheres, structures often comprised of a core of AKT- activated ECs surrounded by OC cells[17]. These angiospheres demonstrate increased resistance to therapy and an enhanced ability to invade the peritoneum[17] (Figure 1 B). Analyses of ascitic fluid demonstrate that cysteine is the most abundant thiol, highlighting that this protective mechanism extends beyond structural support[18,19]. This is also reflected systemically, as patients with OC exhibit elevated serum levels of total and free cysteine and homocysteine, with free cysteine distinguishing malignant from benign tumors[19]. This high cysteine bioavailability confers a survival advantage, allowing cancer cells to adapt to hypoxic conditions and resist carboplatin-induced cytotoxicity[19] (Figure 1 B). Metabolism-directed NMR studies have confirmed that cysteine contributes directly to central carbon metabolism through its conversion into lactate, supporting bioenergetic and biosynthetic demands under stress[18].

The TME recruits additional cellular components to sustain tumor progression[17] (Figure 1 C), and actively orchestrates the signals that maintain this process. Cancer-associated fibroblasts (CAFs) act as key contributors to tumor angiogenesis by secreting pro-angiogenic factors such as VEGF, SDF-1, FGF2, and IL-6[12]. These CAFs also play a critical role in resisting the inhibitory effects of anti-angiogenic drugs like lenvatinib[12]. Ascitic fluid accumulation remodels the peritoneal matrix, inducing linear collagen alignment, a structural feature linked to enhanced tumor invasion[16]. Malignant ascites is characterized by increased vascular permeability combined with the obstruction of peritoneal lymphatic drainage by disseminating cancer cells[16]. The resulting ascites contributes to a pro-tumorigenic TME[16]. For instance, prostacyclin (PGI_2) synthase, which is highly expressed by CAFs, promotes PGI_2 secretion that activates its receptor PTGIR on tumor-associated macrophages (TAMs) within ascitic fluid[20]. This

signaling drives TAMs toward an immunosuppressive, pro-tumor phenotype, enhancing tumor migration, adhesion and angiogenesis through factors such as VEGF[20]. A tight interplay between ECs and TAMs is pivotal in the control of angiogenesis; not only can TAMs release signaling molecules to regulate ECs activation, but monocytes can also differentiate into ECs, working as endothelial progenitor cells (EPCs)[21]. ROS promotes monocyte differentiation toward an EC-like phenotype, an effect that is fully suppressed by cysteine as a GSH precursor[21]. Lopes-Coelho *et al.* (2020) reported that exposure to H_2O_2 induces the expression of EC markers vWF, CD31 and CD146 in monocyte-derived ECs, whereas cysteine supplementation fully prevented this effect[21]. Cysteine was shown to restore expression of the monocytic marker CD14 and to suppress the EC transcriptional program, thereby preventing differentiation into functional EPCs[21]. These findings indicate that cysteine, through its antioxidant capacity, regulates immune–endothelial plasticity within the TME.

Cellular interactions within the TME play a crucial role in promoting angiogenesis associated with OC. Assessing the rate of angiogenesis and evaluating specific biomarkers can provide valuable insights into disease progression and serve as tools to monitor treatment response (Figure 1).

2.1. **Angiogenic markers as prognostic indicators and anti-angiogenic therapy in ovarian carcinoma (OC)**

Beyond its role in OC progression, angiogenesis provides clinically valuable prognostic information, as the intensity of neovascularization strongly correlates with patient outcomes[22,23]. The expression levels of key pro-angiogenic factors, both in tumor tissue and in circulation, serve as powerful independent prognostic indicators in patients with OC[23,24].

VEGF is the most studied and validated prognostic angiogenic biomarker in OC[23]. A high expression of VEGF in tumors is associated with adverse clinicopathological features, including advanced FIGO

(*Fédération Internationale de Gynécologie et d'Obstétrique*) stage, high histologic grade, and the presence of macroscopic residual disease[25]. Patients with high tumoral or circulating VEGF levels exhibit a poorer prognosis, with shorter PFS and OS[8,22,23]. A comprehensive literature review confirmed that elevated preoperative serum VEGF is one of the best independent prognostic markers for OS when compared with other established clinical factors[8]. However, some studies have noted complexities, one analysis found that low expression of VEGF in primary tumors was associated with poor OS, suggesting that the TME and cellular context can influence its prognostic role[26].

The prognostic value of VEGF is further amplified in the context of metastatic disease[23,27]. Omental metastases often exhibit significantly higher protein expression of VEGF, VEGF-D, and VEGFR1 compared to their matched primary tumors, indicating that angiogenesis is more active in disseminated cancer[26]. A significant increase in VEGF expression from the primary tumor to the metastatic lesions is associated with a poor 24-month OS rate, underscoring the role of VEGF in driving the aggressive phenotype of advanced disease[27].

Other members of the VEGF family that primary regulate lymphangiogenesis, such as VEGF-C and VEGF-D, also hold significant prognostic value in OC[28]. Elevated serum and tissue levels of VEGF-C and VEGF-D are correlated with lymph node metastasis, peritoneal dissemination and reduced OS[22,28,29]. In multivariate analyses, both serum VEGF-C and tumoral VEGF-D have been identified as independent predictors of poor patient outcomes[28,29], with an increase in poor prognosis of 8.2 for patients with high VEGF-D expression[29]. Recent evidence suggests that blood levels of VEGF-C may be more reliable biomarkers than tissue expression. Specifically, elevated pre-operative plasma VEGF-C levels were predictive of disease recurrence and poor prognosis, whereas VEGF-C tissue expression, although markedly upregulated, did not show a significant association with

prognosis[30]. Therefore, both angiogenesis and lymphangiogenesis are critical drivers of OC progression[28,30]. The pro-angiogenic TME is complex, and other signaling molecules contribute to prognosis[3,31]. High levels of ANG-2, ANG-4, and interleukin-8 (IL-8) in serum and tumor tissue have been demonstrated to correlate with advanced tumor stage and are considered indicators of poor prognosis[11,31]. This suggests that a comprehensive evaluation of the tumor´s angiogenic profile offers a more accurate prognostic assessment[32].

While the levels of these soluble factors are robust prognostic markers, the utility of microvascular density (MVD), an anatomical measure of neovascularization, has yielded more varied results[24]. Although MVD is significantly higher in invasive OC compared to benign tumors, some studies have found that MVD does not independently correlate with clinicopathological parameters or patient survival, especially after accounting for factors like VEGF expression[8,33]. Functional activity of pro-angiogenic signaling represents a more clinically relevant biomarker than MVD alone[8]. These prognostic data provide a strong rationale for the incorporation of anti-angiogenic agents into therapeutic strategies for OC[3]. However, the prognostic value of a biomarker does not always translate to predictive value for a specific therapy. Analysis of OC patients treated with the anti-VEGF agent bevacizumab revealed that expression of key angiogenic markers, including tumoral VEGF and VEGFR-2, lacked significant prognostic value[34]. The same study also suggested that the combined high expression of miR-484 and VEGF-B might have predictive value for bevacizumab activity[34]. The ongoing challenge is to identify robust biomarkers that can not only predict a patient´s general prognosis but also contribute to their stratification to select who can most benefit from specific anti-angiogenic treatments[1].

The robust association of high angiogenic tumor profile with the prognosis of aggressive disease and poor outcome in OC[1,8,23]

reinforces the biological rationale of targeting neoangiogenesis pathways[2,5,25]. Anti-angiogenic agents impair tumor vascularization by disrupting existing vessels and inhibiting the formation of new ones, which limits the supply of oxygen and nutrients to malignant cells[2]. Currently in OC, the anti-angiogenic therapy presents some benefits when applied in combination with chemotherapy and targeted therapy[35]. Across multiple clinical studies, the addition of anti-angiogenic agents to standard chemotherapy or maintenance regimens has been associated with improved clinical outcomes. Bevacizumab in combination with chemotherapy prolongs PFS in platinum-resistant disease and improves outcomes when administered as maintenance therapy following primary debulking[35]. When combined with the PARP inhibitor olaparib, bevacizumab yields substantial extensions in PFS in patients with deficient homologous recombination, an effect that has translated into regulatory approval for frontline maintenance therapy[35]. Re-challenge with bevacizumab plus chemotherapy provides additional benefit in later-line settings. Combination strategies pairing anti-angiogenic agents with immune checkpoint inhibitors, for example, bevacizumab plus nivolumab, or integrating anti-angiogenesis with both PARP inhibition and checkpoint blockade, have shown high response rates and durable clinical benefit, underscoring the synergistic potential of multimodal anti-angiogenic approaches contributing to improved OS, PFS, and objective response rate (ORR)[35].

A systematic review and meta-analysis of randomized clinical trials, conducted in accordance with PRISMA guidelines, identified 13 eligible studies that together enrolled 3953 women with recurrent OC[2]. The pooled analysis demonstrated that adding anti-angiogenic drugs to standard treatment improved PFS, OS, and ORR compared with control regimens[2]. These efficacy gains were most evident when anti-angiogenic inhibitors were combined with chemotherapy or other targeted agents. Trials evaluating anti-angiogenic monotherapy alone failed to demonstrate a significant OS benefit, whereas combination

therapy yielded a marked survival advantage[2]. Subgroup analyses stratified by molecular target revealed that agents targeting the VEGFR pathway conferred an OS advantage, whereas inhibitors of VEGF or angiopoietin prolonged PFS without a clear OS benefit[2]. Controversially, the use of anti-angiogenic agents was associated with a higher incidence of severe (grade ≥ 3) adverse events, a toxicity profile attributed to drug-induced vascular abnormalities, including vasoconstriction and increased peripheral resistance[2]. Methodological limitations inherent to trial-level meta-analyses include heterogeneity among studies, potential industry-related bias, and the inability to assess dose dependence or perform extensive subgroup analyses[2]. The available evidence supports the incorporation of anti-angiogenic therapy, particularly in combination with chemotherapy or other target agents, to improve key clinical outcomes in recurrent OC, while highlighting the need for vigilant monitoring and management of serious adverse events[2].

3. **Signaling and metabolic mechanisms promoting the symbiosis between ovarian carcinoma (OC) cells and endothelial cells (ECs)**

Tumor angiogenesis is not a passive adaptation to hypoxic stress but a dynamic crosstalk between cancer cells and the stromal components of the TME, particularly ECs[36].This symbiosis is orchestrated by a complex network of signaling pathways and metabolic adaptations that collectively create a pro-tumorigenic vascular niche, driving tumor growth, metastasis and therapeutic resistance[37–39]. Within this framework, ECs transition from a quiescent state to a highly activated, pro-angiogenic phenotype, which is governed by canonical signaling cascades that are hijacked by the tumor[39].

3.1. **Major signaling pathways involved in angiogenesis and in metabolic control**

At the core of tumor neovascularization is a network of regulated signaling pathways that mediate the communication between cancer cells and ECs[39]. The dysregulation of these pathways transforms the tumor vasculature into an abnormal active network that sustains the evolution of the tumor[36]. The VEGF signaling axis is one of the principal drivers for this process[8,40]. Tumor-derived VEGF binds to its cognate receptor VEGFR-2, which is highly expressed on ECs triggering receptor dimerization and autophosphorylation[8,39]. This event initiates a cascade of downstream signaling pathways essential for the angiogenic phenotype. Activation of the PLCγ–PKC–Raf–MEK–MAPK pathway promotes EC proliferation and DNA synthesis, while the parallel activation of the PI3K/Akt pathway is critical for enhancing EC survival and migration[8]. The cumulative effect is the upregulation of genes that orchestrate EC proliferation, migration and assembly into new vessels, alongside a marked increase in vascular permeability, which facilitates tumor cell intravasation and metastatic dissemination[8,39]. The VEGF and VEGFRs form a key signaling axis that mediates pathological angiogenesis in solid tumors, especially in OC[41]. When dysregulated, this system forms a feedback network that enhances tumor growth, metastasis and resistance to treatment[42–44]. The VEGF ligands engage specific VEGFRs on ECs, triggering receptor activation and intracellular signal transduction [8,42 1,8,45]. Upon ligand binding, VEGFRs dimerize, leading to autophosphorylation of intracellular tyrosine-kinase (TK) domains[46]. This activation initiates essential downstream signaling cascades, including PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways, promoting EC proliferation, migration, survival and increasing vascular permeability[8,45,46] (Figure 2).

In OC, the clinical significance of this axis is well established, as previously stated. The pathological intensity of the VEGF:VEGFR axis is linked to tumor hypoxia, which stabilizes Hifs, particularly Hif-1α[42]. Hifs act as transcription factors that upregulate VEGF expression, creating a stimulus for neovascularization[42,45]. Beyond prognosis,

VEGF levels track systemic oxidative stress: circulating VEGF levels correlate positively with malondialdehyde (MDA), a ROS marker, supporting a model in which angiogenic imbalance reflects metabolic dysregulation in OC[8] (Figure 2).

The Notch signaling pathway is a central regulator of vascular development and serves as a key mediator of direct, contact-dependent communication within the tumor vascular niche[37,47]. This pathway plays a decisive role in EC fate, particularly in specifying migratory “tip cells” *vs* proliferative “stalk cells” during angiogenic sprouting[47]. Tip cells, which lead the migrating vascular sprout, are characterized by high VEGF signaling and express the Notch ligand Delta-like 4 (DII4)[38,47]. DII4 activates Notch receptors on adjacent ECs, suppressing the tip cell phenotype and promoting their differentiation into stalk cells, which elongate the nascent vessel[36,38]. In OC, this pathway is co-opted to establish a pro-tumoral angiocrine niche[17]. Tumor-activated ECs often exhibit an activated PI3K/Akt pathway, which upregulates the Notch ligand Jagged1[17](Figure 2). This EC-derived Jagged1 engages Notch3 receptors on adjacent OC cells, triggering a signaling cascade that enhances OC cell proliferation, survival and resistance to chemotherapy[37] (Figure 2). This juxtacrine loop establishes a self-reinforcing circuit where the endothelium directly fosters the aggressive traits of the cancer cells it supports[37].

The Endothelin-1 (ET-1) signaling axis represents another crucial communication network that integrates tumor and stromal cell responses[40] (Figure 2). High levels of ET-1 in the TME, acting through its G-protein coupled receptors ETAR and ETBR, unleash autocrine and paracrine signals that promote tumor growth, invasion and neovascularization[40,48]. ET-1 signaling is directly intertwined with the VEGF axis. ET-1 can induce VEGF expression via Hif-1α, creating a potent feed-forward loop[40]. Hif-1α drives the transcription of glycolytic and VEGF genes[49,50]. The nuclear factor erythroid 2–related

factor 2 (Nrf2) orchestrates an antioxidant program by inducing the cystine transporter xCT and driving biosynthesis, thereby coupling cysteine metabolism to metabolic adaptation and the regulation of angiogenesis[51–53]. Together, Hif-1α and Nrf2 coordinate cysteine metabolism with metabolic reprogramming and pro-angiogenic signaling, thereby reinforcing tumor growth and sustaining malignant cell survival. This feed-forward loop is active across cancer cells, ECs and CAFs: ET-1 stimulation not only augments its own expression but also induces VEGF, establishing a self-amplifying pro-angiogenic and pro-survival signaling network[40]. Activation of this axis triggers downstream pro-survival pathways, including p42/44 MAPK and AKT in both cancer cells and ECs, further solidifying the supportive vascular niche[40].

These distinct signaling cascades often converge on the PI3K/AKT/mTOR pathway, a central hub that regulates cell growth, proliferation and metabolism[54]. In OC, this pathway is one of the most frequently activated, integrating signals from growth factors like VEGF and ET-1 to modulate the metabolic state of ECs[54]. AKT activation is a characteristic of the pro-angiogenic EC phenotype, promoting increased glucose uptake via the transporter GLUT1 and enhancing glycolytic flux in ECs[8,37,54]. This metabolic reprogramming supports the high energetic and biosynthetic demands of activated ECs during rapid vessel formation[54] . By regulating glycolysis, lipid synthesis and oxidative phosphorylation (OXPHOS), the PI3K/AKT/mTOR pathway serves as a master regulator that translates pro-angiogenic signals into the metabolic and functional adaptations required for tumor neovascularization[54].

3.2. **The metabolic reprogramming of ovarian carcinoma (OC) cells and endothelial cells (ECs)**

Metabolic reprogramming is a central driver of tumor progression, immune invasion and therapy resistance in OC[55,56]. This rewiring extends beyond cancer cells, shaping complex metabolic crosstalk

within the tumor TME, including stromal, immune and ECs[38,55,57,58]. In the next sections, an integrative view of core metabolic pathways will be presented highlighting symbiosis between OC cells and ECs (Figure 3).

3.2.1. **Nrf2 is a central player linking metabolic remodeling, oxidative stress, hypoxia and angiogenesis, in ovarian cancer (OC)**

The metabolic plasticity of OC cells is increasingly recognized as a central determinant of their ability to survive hostile microenvironmental conditions and resist chemotherapy. Among the metabolites that shape this adaptive landscape, cysteine plays a particularly critical role (Figure 3 A). A growing body of literature indicates that cysteine reliance supports OC cell survival under stressors such as hypoxia, nutrient limitation, and exposure to cytotoxic agents[59–61]. By fueling antioxidant defenses and redox-buffering systems, cysteine enables tumor cells to endure oxidative damage that would otherwise limit proliferation or trigger cell death[59–61].

Cyclic or intermittent hypoxia—a hallmark of poorly vascularized OC tumors—intensifies this selection pressure. When fluctuating oxygen availability occurs in a cysteine-rich milieu, cancer cells with enhanced capacity for cysteine uptake and utilization gain a metabolic advantage. Over time, this fosters a population of cells more adept at coping with redox stress and, consequently, more tolerant to platinum-based chemotherapeutics[18,19,62]. Accordingly, interfering with cysteine-dependent metabolic pathways and inducing GSH depletion resensitizes OC cells to platinum salts[63,64]. Clinically, this evolutionary trajectory is especially concerning given that cysteine is abundant in the peripheral blood and exceptionally enriched in the ascitic fluid of OC patients[19]. In line with this and reinforcing the relevance of cysteine reliance on chemoresistance, a prolonged inhibition of cysteine uptake induces ferroptosis-resistant phenotypes by activating

the one-carbon metabolism-diverted reverse transsulfuration pathway, allowing the endogenous synthesis of cysteine[65]. The TME, therefore, acts as a continuous selective filter, favoring cysteine-dependent phenotypes that display chemoresistance and heightened aggressiveness.

Central to this cysteine-driven adaptation is the Nrf2 pathway, a master regulator of the antioxidant response with emphasis on cancer metabolic remodeling[52,66,67]. A comprehensive review recently summarized how Nrf2 activation contributes to antioxidant defenses, drug resistance (e.g. to platinum salts), and survival in OC[68]. This contextualizes Nrf2 as a major mediator of redox adaptation in OC, as Nrf2 activates the expression of xCT, the primary route for cystine (cysteine dimer) import in many OC cells, and glutathione-peroxidase 4 (GPX4), a crucial suppressor of lipid peroxidation and ferroptosis[69,70]. The role of xCT in platinum resistance was demonstrated more than 20 years ago in OC lines, supporting the link between cystine uptake and chemoresistance[63]. Through these mechanisms, Nrf2 orchestrates a redox defense machinery that depends heavily on cysteine availability. The dual inhibition of Nrf2 and GPX4 in OC cells robustly suppresses proliferation, spheroid formation, and peritoneal spread, highlighting that the Nrf2/xCT/GSH/GPX4 axis is critical for OC survival and chemoresistance[71]. Importantly, the functional interplay between Nrf2 and Hif-1α further integrates oxygen sensing with metabolic rewiring and deserves to be deeply explored.

Hypoxia and oxidative stress within the TME are intrinsically interconnected rather than independent phenomena in solid tumors[72], and their combined influence on Hif and Nrf2 signaling is therefore highly complex[72]. These conditions frequently coexist in solid tumors, as hypoxia can trigger transient increases in ROS due to impaired electron flow through mitochondrial complex III[73]. Importantly, oxidative stress is also an integral component of the hypoxic response

itself: elevated ROS can stabilize Hif-1α by inhibiting the activity of prolyl hydroxylase domain (PHD) enzymes, thereby enhancing hypoxia-dependent transcriptional programs[43]. In colon cancer xenograft models, tumors derived from cells with stable Nrf2 knockdown exhibited reduced vascularization, which was associated with decreased expression of Hif-1α[74]. Given the pivotal roles of Hif and Nrf2 signaling in tumor growth and progression, it is essential to understand how these pathways respond to distinct environmental stresses and dynamic changes within the TME. Their mechanistic interplay must coordinate adaptive programs in both OC cells and ECs, fostering angiogenesis, metabolic flexibility, and ultimately the development of more treatment-refractory OC subtypes.

Additionally, cysteine catabolism in cancer cells produces H_2S, which has been proposed to contribute to angiogenesis by acting on ECs[59]. This establishes a parallel interplay between OC metabolic adaptations and vascularization processes required for tumor growth and dissemination[59]. H_2S functions as a pro-angiogenic signaling molecule by activating MAPK signaling in ECs, while increased metabolic demand linked to cystine processing enhances dependence on glucose and glutamine, establishing a competitive nutrient environment that impacts ECs[59,75]. This crosstalk extends to the transcriptional level, where stress-induced factors not only upregulate xCT in cancer cells but also promote the expression of pro-angiogenic genes[75,76]. Continuous cystine/cysteine redox balance contributes to a reducing extracellular environment that supports tumor progression[75].

Adding another layer of complexity, VEGF- related angiogenesis and signaling—one of the most prominent Hif-regulated angiogenic factors—has been shown to be regulated by Nrf2. The activation of Nrf2 in ECs was found to suppress Dll4 expression under both normoxic and hypoxic conditions, thereby inhibiting Dll4-mediated Notch signaling. Additionally, Nrf2 activation interferes with VEGF-

driven VEGFR2–PI3K/Akt signaling and reduces Hif-2α levels in ECs, mechanisms that likely contribute to its inhibitory effects on Dll4 and Notch pathways[77] (Figure 1). Importantly, the sub-lethal inhibition of xCT by erastin triggers a ferroptosis-like response underlying ECs activation—causing GSH depletion, increased ROS and lipid peroxidation, disrupted VE-cadherin junctions, heightened permeability, and upregulated ICAM-1/VCAM-1—effects that are reversed by propranolol, which restores redox balance, junction integrity, and reduces cancer cell adhesion and transendothelial migration [9]. Collectively, these findings identify a role for Nrf2 in promoting an angiogenic, sprouting-competent phenotype in vascular ECs[77]. In glioblastoma samples, elevated Nrf2 expression correlated with increased MVD, while Nrf2 knockdown impaired EC tube formation and inhibited VEGF secretion[78]. In gastric cancer, a significant correlation was found between Nrf2 and VEGF expression, strengthening the role of Nrf2 in VEGF-dependent angiogenesis regulation[79]. In OC, the inhibition of the follicle-stimulating hormone (FSH)–ROS–Nrf2–Hif-1α signaling pathway reduced FSH-induced binding of Hif-1α to the VEGF promoter, indicating that ROS and dysregulated Nrf2 expression play a critical role in FSH-induced VEGF upregulation and angiogenesis[80]. All this evidence suggests that pro-angiogenic signaling can indirectly reinforce redox-adaptive pathways, creating a feedback loop in which hypoxia, cysteine metabolism, and vascular remodeling converge to sustain tumor progression and diminish therapeutic efficacy. Together, these interactions outline a coherent narrative: cysteine availability is not simply a metabolic resource but a selective force that shapes the evolutionary trajectory of OC, interfering with essential phenomena supporting cancer, including angiogenesis, also based on OC cells and ECs symbiosis.

Folate and one-carbon (1C) metabolism, fed by serine and glycine pathways, supply one-carbon units that support nucleotide biosynthesis and methylation reactions, enabling rapid proliferation

and sustaining GSH-dependent redox control[55,81]. This redox control depends on cysteine, which serves as the rate-limiting precursor for GSH synthesis[75,82]. Enzymes like MTHFD2 are essential for this pathway and their dysregulation is noted in OC, supporting tumor immune evasion mechanisms such as PD-L1 upregulation[55]. The increased expression of folate receptor alpha (FR-α) in cancer cells highlights the role of one-carbon metabolism. In OC, overexpression of FR-α is well documented[83,84], and it is considered a therapeutic target[83], with inhibitors currently being evaluated in clinical trials (Phase II SORAYA Trial[85]; Phase III MIRASOL Trial[83]; Phase Ib FORWARD II Trial[86]) with promising results in chemoresistant OC. In metastatic sites, including omental metastatic cancer, the PPP often predominates over glycolysis[87]. This metabolic dependency is linked to cysteine import, as the high NADPH demand imposed by cystine reduction creates a strong reliance on the PPP, which is the primary source of NADPH required to sustain both the antioxidant response and the continuous conversion of cystine to cysteine[75,76,88]. This supports NADPH production for antioxidant defense under oxidative stress.

This metabolic reprogramming is not restricted to cancer cells and affects the TME, including ECs and stromal cells[36,38]. Both cancer cells and ECs must metabolically adapt to the hypoxia and nutrient-deprived conditions of the TME, and the metabolic crosstalk between these compartments is pivotal for tumor progression[38].

3.2.2. **Glucose and lactate metabolic reprogramming driven by VEGF and Hif signaling in ovarian carcinoma (OC)**

The metabolic landscape of OC, and cancer overall, is dominated by enhanced aerobic glycolysis[54,89–91]. This metabolic adaptation is essential for generating biosynthetic intermediates at scale, even in normoxic conditions[57,90] (Figure 3 B). Key glycolytic enzymes, including hexokinase (HK2), phosphofructokinase-2/fructose-2, 6-bisphosphatase 3 (PFKFB3) and lactate dehydrogenase A (LDHA), are

upregulated[55,90] and glucose uptake is increased via glucose transporter (GLUT1) expression, regulated by the PI3K/AKT/mTOR pathway, correlating with platinum resistance and poor prognosis in OC[54,55,57,90]. Lactate, the product of aerobic glycolysis, is exported mainly by monocarboxylate transporter 4 (MCT4), contributing to an acidic TME that supports tumor development[57,90]. Beyond its metabolic role, lactate acts as a multifunctional signaling molecule and epigenetic regulator, fostering angiogenesis, immunosuppression, and therapy resistance[92]. For instance, histone H3K18 lactylation supports M2 macrophage polarization, while RAD51 lactylation enhances homologous recombination, reinforcing platinum resistance [89].

In parallel with the metabolic adaptation of OC cells, ECs undergo a distinct reprogramming that enables them to function and persist within the TME[92]. Quiescent ECs in healthy tissues rely on fatty acid oxidation (FAO) to maintain redox homeostasis and vascular integrity, while tumor-associated ECs (TECs) adopt a glycolytic phenotype to meet the energetic and biosynthetic demands of angiogenic signals such as VEGF [38,57,92,93]. This metabolic rewiring enables TECs to generate ATP for migration and proliferation, while diverting glucose intermediates into biosynthetic pathways, including the pentose phosphate pathway (PPP) and the serine synthesis pathway (SSP), to support nucleotide production and macromolecule synthesis required for new vessel formation[92].

TECs also import lactate from OC cells via MCT1, converting it to pyruvate for the TCA cycle and OXPHOS, further sustaining angiogenesis and providing a metabolic link between tumor and vasculature [38,94]. Lactate also acts as a signaling molecule that inhibits PHD2, contributing to Hif-1α stabilization in ECs; in parallel, impaired perfusion generates hypoxic regions that further reinforce Hif-1α-driven glycolytic dependence in cancer cells[38,94]. Stabilized Hif-1α strengthens pro-angiogenic signaling, leading to the formation of

disorganized, hyperpermeable tumor vasculature[38,94]. This abnormal vasculature, a direct consequence of reprogrammed ECs' metabolism that prioritizes rapid growth over structural integrity, provides a reciprocal advantage to OC cells[92]. The disorganized and hyperpermeable vascular network enhances the delivery of glucose, oxygen, glutamine and fatty acids to OC cells, completing a feed-forward loop that sustains their high bioenergetic and biosynthetic demands while reinforcing the glycolytic phenotype and promoting therapeutic resistance. The coupled metabolic adaptation of OC cells and TECs leads to high glycolytic flux, lactate accumulation, and an immunosuppressive TME, consistent with elevated serum lactate observed in OC patients. This interplay also limits T cell infiltration and function, reinforcing tumor immune evasion [38,92,95,96]. Driven by pro-angiogenic signals from hypoxic OC cells, TECs adopt aerobic glycolysis to sustain rapid proliferation and vessel sprouting[59,62,97], while OC cells continue to rely on high glycolytic activity for biosynthesis and survival. This OC–EC metabolic interplay reinforces tumor growth and angiogenesis[94,98].

3.2.3. **Shared metabolic dependencies on amino acids and fatty acids sustain ovarian carcinoma (OC) and endothelial cell (EC) interactions**

A secondary layer of metabolic symbiosis between OC cells and ECs involves amino acid and lipid handling (Figure 3 C). OC cells show a marked reliance on glutamine to fuel carbon and nitrogen metabolism, sustaining the TCA cycle, energy and biomass production, nucleotide synthesis and redox metabolism[55,57,87]. Glutaminase 1 (GLS1), which converts glutamine to glutamate, is often overexpressed in high-grade serous OC and linked to increased aggressiveness and chemoresistance[55,57]. Glutamate metabolism is tightly linked to redox balance through GSH synthesis[99]. GSH detoxifies ROS and can neutralize platinum agents, with cisplatin resistance mediated

through GSH-cisplatin adduct formation[57,87]. TECs engage glutamine and fatty acid metabolism, highlighting their metabolic plasticity[38,100]. Glutamine is catabolized by glutaminase (GLS) to fuel the TCA cycle and supply nitrogen for nucleotide synthesis, a process that is critical for EC proliferation[38,93]. Additionally, arginine metabolism, which is deeply related to glutamine synthesis, is reprogrammed in OC, and cationic amino acid transporters (SLC7A1/CAT1) overexpression is linked to platinum resistance[101].

Beyond its redox-regulatory functions described in Section 3.2.1, cysteine metabolism further contributes to angiogenic signaling and intercellular metabolic coupling within the OC microenvironment [59] [88]. The contribution of the GSH pathway to platinum resistance is complex in OC, and platinum-resistant cells exhibit reduced GSH levels[102]. This suggests that cisplatin treatment exerts a selective pressure, favoring the survival of cancer cells, which may also be independent of GSH for redox balance[102]. These resistant cells have been reported to exhibit increased reliance on the thioredoxin system, including thioredoxin reductase (TXNRD1)[102]. Clinically, these findings are reflected in patient data showing that low xCT expression correlates with non-response to platinum therapy and poorer PFS, whereas high TXNRD1 expression is likewise associated with inferior PFS[102]. In addition to its antioxidant role, cysteine metabolism supports central carbon metabolism under hypoxic conditions, for example, OC cells can convert cysteine into lactate, demonstrating its direct contribution to central carbon metabolism and bioenergetic support under stress[62]. This process depends on xCT activity, as its inhibition impairs ATP production under hypoxic conditions, an effect that is rescued by cysteine supplementation[62]. Cysteine catabolism also contributes to angiogenesis through the generation of bioactive metabolites. Enzymes such as cystathionine β- synthase (CBS) and cystathionine γ-lyase (CSE), which are frequently upregulated in OC, generate H_2S[59]. This H_2S acts as a signaling molecule that stimulates

ECs migration and proliferation, promoting new blood vessel formation[59,97].

Lipid metabolism is reprogrammed in OC, especially within the adipose-rich omental microenvironment, promoting metastasis, chemoresistance and cancer stemness[55,58,90]. OC cells increase fatty acid uptake via CD36 and augment fatty acid oxidation to meet high energy demands[58]. In addition, elevated CD36 expression in the tumor vasculature correlates with increased metabolic support and poorer patient outcomes[103]. CPT1A, the rate-limiting enzyme of FAO, supports mitochondrial energy production and stem cell survival, making it a viable therapeutic target. Its inhibition can sensitize cells to paclitaxel[55,58]. This metabolic reprogramming is not confined to cancer cells but extends to the stromal compartment, establishing a symbiotic relationship with TECs that supports angiogenesis[59,62,97]. TECs upregulate FAO not only to generate ATP but also to supply carbon backbones for deoxynucleotide (dNTP) synthesis required for DNA replication during vessel sprouting[55,93]. In this context, TECs upregulate the fatty acid scavenger receptor CD36, enhancing the uptake of long-chain fatty acids to further EC metabolism and support vessel hyperpermeability[38,103]. This metabolic interplay establishes a self-reinforcing cycle in which OC cells reprogram EC metabolism to support angiogenesis, while the resulting vasculature supplies the metabolic substrates required to sustain aggressive and chemoresistant tumor phenotypes[96].

The metabolic symbiosis established among different cell types within a tumor is not merely a molecular feature; it also involves ultrastructural modifications that facilitate contact between cancer and non-cancer cells, including ECs.

4. **Tunneling nanotubes (TNTs) in endothelial cells (ECs) and cancer cells are facilitators of symbiosis**

TNTs are thin, dynamic membranous conduits that establish direct cytoplasmic continuity between cells, enabling long-distance transfer of molecular and organelle cargo[104,105]. Structurally distinct from filopodia and gap junctions, TNTs hover above the substratum and are primarily supported by F-actin, with wider variants incorporating microtubules; this architecture underlies their ability to mediate the intercellular exchange of mitochondria, lysosomes, proteins, membrane receptors, ions, and multiple RNA species, including miRNAs[104–106]. Their biogenesis depends on actin-driven protrusions and Rho GTPase–regulated cytoskeletal remodeling, consistent with protrusion-based and cell-dislodgement mechanisms[107]. In cancer, TNTs enable profound transcriptional and metabolic reprogramming, and endothelial–cancer TNTs can facilitate preferential mitochondrial transfer that enhances malignant survival and chemoresistance[108]. These properties define TNTs as a distinct modality of intercellular communication with growing relevance in cancer cells –ECs cross-talk (Figure 4).

4.1. Cancer cells–endothelial cells (ECs) plasticity and TNT-mediated remodeling

TNTs establish a direct communication axis between cancer cells and the ECs, enabling malignant cells to adapt dynamically to the vascular niche. Metastatic cancer cells that form TNTs with EC networks undergo a pronounced morphological transition: instead of remaining as spherical aggregates, they elongate into spindle-shaped forms aligned with endothelial structures, phenotypes strongly associated with enhanced invasiveness and increased transendothelial migration. In contrast, poorly metastatic cancer cells that do not form TNTs retain compact, aggregate-like morphologies[107].

Through selective transfer of cytoplasmic cargo, TNTs facilitate cancer cell adaptation, supporting their capacity to traverse the endothelial barrier while reinforcing local metabolic support[104,107]. TNT formation depends on a coordinated cytoskeletal program

involving actin polymerization and the exocyst–Rho GTPase machinery. Proteins such as Rac1, Cdc42, and Sec3 colocalize with TNTs, indicating that their formation requires spatially controlled cytoskeletal remodeling rather than spontaneous membrane protrusion[107]. Inhibition of these pathways disrupts TNT biogenesis, blocks cytoplasmic transfer, and forces metastatic cancer cells to revert to non-invasive aggregate-like phenotypes. TNT-based communication is bidirectional, and ECs that internalize cancer-derived cytoplasmic material upregulate tumor-associated markers such as CD137, adopting a pathological, tumor-supportive phenotype. When TNT formation is inhibited, ECs no longer acquire tumor-derived cargo and fail to undergo this transformation, demonstrating that EC reprogramming is, in part, TNT-dependent[107]. Beyond local interactions, ECs' TNTs also participate in long-range communication. As shown in EC secretome studies, they facilitate cytoplasmic exchange with distant stromal or immune cells, surpassing the spatial limitations of classical paracrine signaling[109]. Tumors co-opt this pathophysiological system to disseminate supportive cues across the microenvironment, strengthening malignant progression.

A hallmark of ECs' TNTs is their ability to transfer cytoplasmic material and fully functional organelles to cancer cells. Mitochondria are among the most impactful cargo: ECs preferentially donate intact mitochondria via TNTs, which integrate into the cancer cell mitochondrial network and restore OXPHOS during chemotherapeutic stress[108]. This direct organelle donation enhances metabolic fitness and chemoresistance—effects not reproduced by extracellular vesicles or other indirect mechanisms. TNT structural composition shapes their transfer capacity, as microtubule-enriched TNTs exhibit greater stability and are more efficient at transporting large organelles than actin-only nanotubes[104,110]. ECs, capable of assembling hybrid TNTs containing both F-actin and microtubules, thus function as particularly effective mitochondrial donors within the TME. Mitochondrial transfer depends on Miro1-driven coupling to cytoskeletal motors and Drp1-

mediated fission, which generates smaller, transport-competent mitochondrial fragments [111].

Beyond organelles, TNTs enable transfer of calcium ions, membrane components, signaling molecules, and diverse RNA species—including full-length mRNAs—allowing ECs to influence survival pathways, stress responses and transcriptional programs in associated cancer cells [104,105]. Through this high-fidelity communication route, endothelial TNTs provide tumors with metabolic reinforcement and signaling inputs essential for progression, invasion, and therapeutic resistance.

In OC, TNTs have been shown to represent a hypoxia-induced adaptive communication system that supports tumor cell plasticity and survival[111,112] . TNTs are present in human tumors and are strongly upregulated in chemoresistant variants under hypoxic conditions, a hallmark of the perivascular tumor niche[113–115]. Although this is not proven in OC, it is possible that through TNT-mediated cytoplasmic and organelle exchange, OC cells can engage in metabolic cooperation and stress adaptation, processes that may prime malignant cells for invasion and vascular interaction[116,117]. Importantly, TNT formation in OC is a regulated process dependent on metabolic signaling pathways such as mTOR, highlighting TNTs as potential therapeutic targets within the tumor microenvironment[118,119].

4.2. Hif-1α, VEGF, and Nrf2 Govern Stress-Induced Tunneling Nanotube Formation in Endothelial Cells (ECs)

ECs inherently form long-range membranous contacts, reflecting their central role in vascular adaptation. Among these structures, ECs' TNTs function as active mediators of angiogenesis. They have been observed between EPCs and mature ECs, as well as between ECs and cardiomyocyte populations, demonstrating the vasculature's strong propensity for nanotube-based communication[105].

A defining functional feature of endothelial TNTs is their ability to transport metabolic cargo—most notably lipid droplets—whose abundance within TNTs increases in response to VEGF stimulation[104]. This VEGF-driven enhancement supports the energetic requirements of angiogenesis: by redistributing lipid stores and other metabolites across EC networks, TNTs promote EC proliferation and vascular branching, accelerating vessel growth and expanding vascular complexity[104]. Within tumors—where angiogenesis is continuous and structurally disorganized—TNT-mediated transport acquires increased relevance. ECs' TNTs enable the transfer of cytoplasmic components and organelles to neighboring cells, including cancer cells, influencing tumor metabolism and contributing to therapy resistance through mitochondrial exchange[108]. TNT formation is further amplified by hypoxia, oxidative stress, nutrient deprivation and inflammation, conditions characteristic of tumor-associated vasculature[104]. EC's TNTs also act in concert with pericyte-derived TNTs, which structurally guide EC sprouting and help organize nascent vascular loops in both physiological and tumoral angiogenesis. Together, these networks reinforce vascular expansion and remodeling, contributing to the development of a tumor-supportive vasculature marked by high proliferative capacity, aberrant branching and metabolic interdependence[104].

Emerging evidence suggests that TNT formation is an adaptive response to microenvironmental stress in tumors, including hypoxia and oxidative stress. As described in Section 3.1, hypoxia stabilizes Hif-1α. In OC and other cancer models, the hypoxia-induced Hif-1α expression correlates with enhanced TNT formation, likely facilitating metabolic cooperation, mitochondrial transfer, and survival under stress[119]. It is also demonstrated that cancer cells transfer mitochondria to stromal cells in the TME to control oxidative stress[120]. Building on this, the hypoxic conditions not only promote TNT formation but also facilitate the intercellular transfer of Hif-1α and VEGF, thereby enhancing angiogenic signaling between connected

cells. In cancer, TNT can also contribute to the TME-dependent metabolic remodeling supporting cancer development and progression[112,121].

VEGF, as a primary target of Hif-1α and a key driver of angiogenesis, may indirectly influence TNT formation by modulating the TME and promoting EC activation. On the other hand, there is evidence that TNTs promote angiogenesis by facilitating the intercellular transfer of materials, including lipid droplets, thereby supporting vascular proliferation and branching[122,123]. In OC cells, macrophage-induced TNTs mediate the intercellular transfer of molecules, thereby increasing tumor cell invasiveness, angiogenic capacity, proliferation, and therapy resistance[124]. Although a direct mechanistic link between VEGF signaling and TNT induction has not yet been conclusively demonstrated, the well-documented VEGF-driven changes in cellular behavior and cytoskeletal dynamics involving actin rearrangement [127–129] could provide conditions favorable for TNT development.

Similarly, Nrf2, as the master regulator of cellular redox homeostasis, may contribute to TNT regulation under conditions of oxidative stress. TNT formation is often observed in cells experiencing elevated ROS[125,126], and Nrf2-dependent antioxidant responses can modulate cytoskeletal dynamics and cell survival [127–129], creating an environment conducive to TNT formation. While direct evidence linking Nrf2 activation to TNT formation is limited, current data suggest an indirect role, particularly in the context of stress-adaptive intercellular communication.

Overall, these observations position Hif-1α, VEGF, and Nrf2 as central components of the cellular stress-response network that may regulate TNT formation. TNTs, in turn, enable cancer cells to adapt to hostile microenvironments, promoting metabolic cooperation, resistance to therapy, and aggressive phenotypes. While Hif-1α emerges as the most directly implicated factor, VEGF and Nrf2 likely

act as modulators of TNT formation, highlighting a complex interplay between hypoxia, oxidative stress, and intercellular communication in tumors. Together, these interconnected functions position ECs' TNTs as critical facilitators of tumor progression, unifying angiogenesis, metabolic support, EC remodeling, and metastatic dissemination within a single nanotubular communication system. As such, TNTs represent not only a structural hallmark of the tumor–vascular interface but also a potential therapeutic target for disrupting the cooperative interactions that enable malignant growth and resilience.

5. Conclusions

OC remains a highly lethal malignancy due to late diagnosis, aggressive progression, and frequent chemoresistance. Central to its pathophysiology is the intricate crosstalk between OC cells and the TME, particularly ECs, which drives angiogenesis, metabolic adaptation, and tumor dissemination. Dysregulated VEGF signaling, stabilized by Hifs, orchestrates abnormal vascular networks that supply oxygen, nutrients, and metabolic substrates, while promoting metastasis. Metabolic reprogramming within both OC cells and ECs—encompassing glycolysis, fatty acid oxidation, and amino acid metabolism—establishes a symbiotic network that supports redox balance, bioenergetics, biosynthesis, and chemoresistance. Cysteine emerges as a pivotal metabolite, enabling antioxidant defense, H_2S-mediated angiogenesis, and integration with one-carbon metabolism and GSH pathways. Ultrastructural adaptations, notably TNTs, facilitate direct intercellular transfer of organelles, metabolites, and signaling molecules, strengthening metabolic symbiosis and promoting therapy resistance. TNT formation is tightly regulated by stress-responsive pathways, including Hif-1α, VEGF, and Nrf2, integrating hypoxia, oxidative stress, and vascular remodeling. Collectively, these mechanisms define a self-sustaining vascular-metabolic niche that fuels OC progression and therapeutic refractoriness. Exploring this interconnected network—angiogenic

signaling, metabolic dependencies, cysteine-driven redox adaptation, and TNT-mediated intercellular communication—offers a promising avenue for finding novel therapeutic alternatives and improving clinical outcomes in OC, highlighting the need for combinatorial strategies that disrupt tumor homeostasis by targeting OC-EC symbiosis.

Declarations

Ethics, Consent to Participate, and Consent to Publish declarations

Not applicable.

Competing Interest declaration.

The authors declare no Competing Interests.

Data Availability

Not applicable, as it is a review paper, no new data was generated.

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Figure legends

Figure 1. Angiogenesis an essential process in ovarian cancer (OC) progression.

Angiogenesis is a transient and tightly regulated process, and in cancer there is an imbalance between anti-angiogenic factors and pro –angiogenic factors favoring angiogenesis. Pro-angiogenic factors have been shown to be good prognostic indicators of OC patients. A high angiogenic tumor profile is correlated with adverse clinical outcomes. **(A)** Primary tumor recruits new blood vessels providing O_2 and nutrients and allowing the release of metabolic waste, favoring tumor progression. **(B)** OC cells can form multicellular aggregates conferring ability to invade the peritoneum, firstly by adhesion to the mesothelial lining, migration and invasion of peritoneum. **(C)** In the ascitic fluid, on peritoneal cavity, high levels of cysteine are associated with malignancy and chemoresistance. In a pro-tumorigenic TME, cellular interactions between cancer cells, CAFs, TAMs, monocytes and ECs favor cancer growth and survival by stimulating angiogenesis. Abbreviations: cancer-associated fibroblasts (CAFs), endothelial cells (ECs), endothelial progenitor cell (EPC); hypoxia-inducing factor (HIF), Prostaglandin I2 receptor (PTGIR), reactive oxygen species (ROS), tumor-associated macrophages (TAMs), tumor microenvironment (TME) and vascular endothelial growth factor (VEGF). Images were based on Servier Medical Art tools (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Figure 2. Metabolic and signaling pathways within the ovarian cancer (OC) cells and tumor microenvironment (TME).

Representation of the ovarian cancer tumor microenvironment illustrating metabolic and signaling pathways between ovarian cancer cells, pro-angiogenic stromal cells and endothelial cells. Ovarian cancer (OC) cells display metabolic reprograming characterized by increased xCT, ROS and GSH turnover, and enhanced lactate export through MCT4. Hypoxia and low pH stabilize HIF1-α, which heterodimerizes with HIF-1β and together with the transcriptional co-activador p300, induces the expression of VEGF. VEGF activates VEGFR2 on ECs, while ET-1 signals through ETA and ETB, with both pathways converging in PI3K-AKT-mTOR signaling to promote EC activation, metabolic reprogramming and angiogenic sprouting. During new vessels growth, ECs express DLL4, which activates Notch signaling in adjacent cells, enforcing a stalk cell through lateral inhibition. Jagged1-Notch3 signaling in OC cells further modulates tumor-endothelial communication. Abbreviations: protein kinase B (AKT); angiopoietin-like proteins 2 and 4 (ANGPTL-2/4); delta-like ligand 4 (DLL4); endothelial-1 (ET-1), endothelial receptor A/B (ETA/ETB); glutathione (GSH); hypoxia-inducible factor- α (HIF- α); hypoxia-inducible factor- β (HIF-1β); Delta-like ligand 4 (DLL4); Notch ligand Jagged1 (Jagged1); monocarboxylate transporter 4 (MCT4); mammalian target rapamycin (mTOR); Notch signaling receptor/3 (Notch/Notch3); phosphoinositide 3-kinase (PI3K); transcriptional co-activator p300 (p300); Ras GTPase (Ras); receptor associated kinase (Rak); reactive oxygen species (ROS); vascular endothelial growth factor (VEGF); vascular endothelial growth factor receptor-2 (VEGFR-2), and light chain of Xc- cystine:glutamate antiporter (xCT). Images were based on Servier Medical Art tools (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

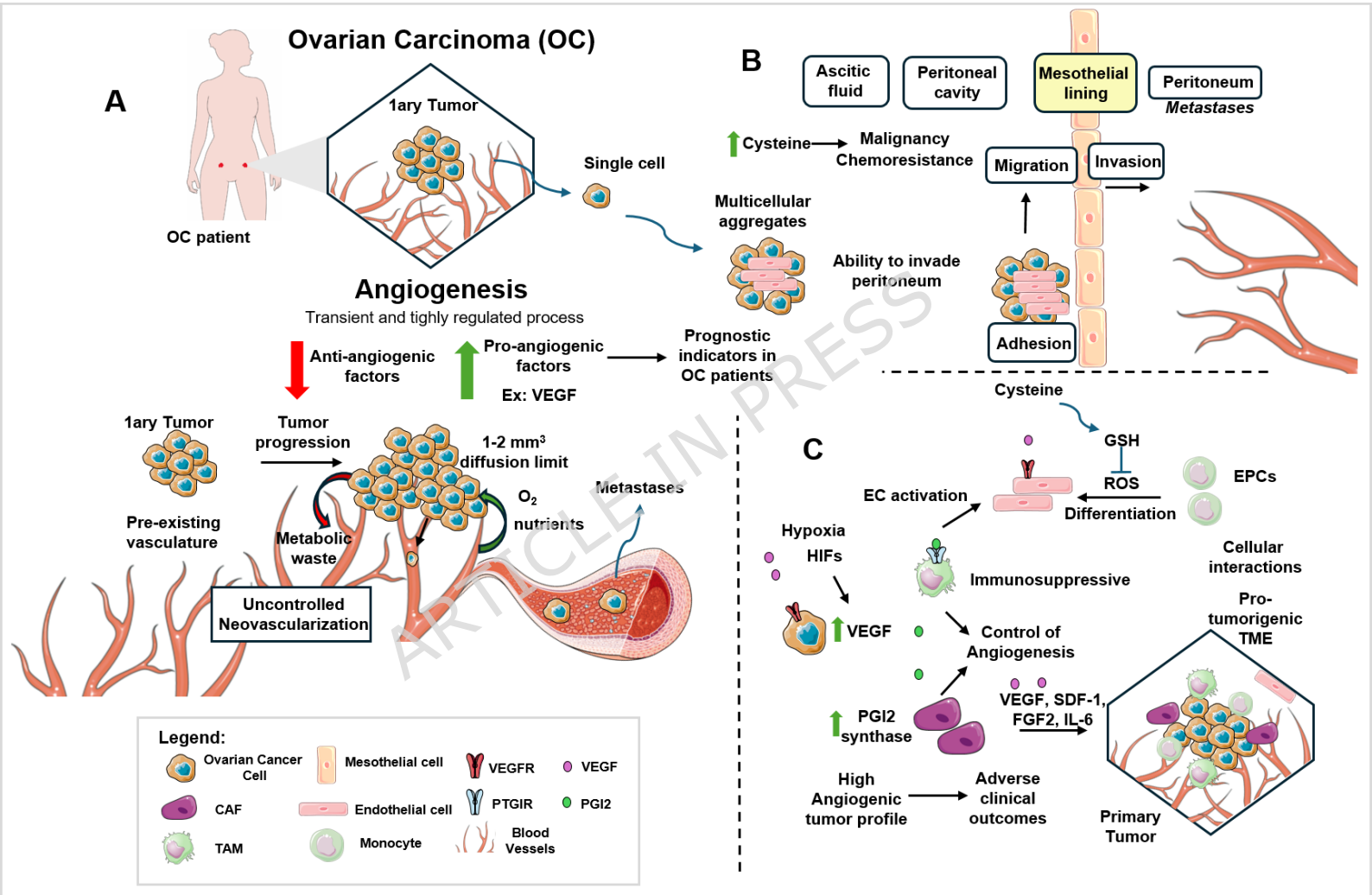
Figure 3. Metabolic interplay and symbiotic signaling between ovarian cancer (OC) cells and endothelial cells (ECs) in the tumor microenvironment (TME).

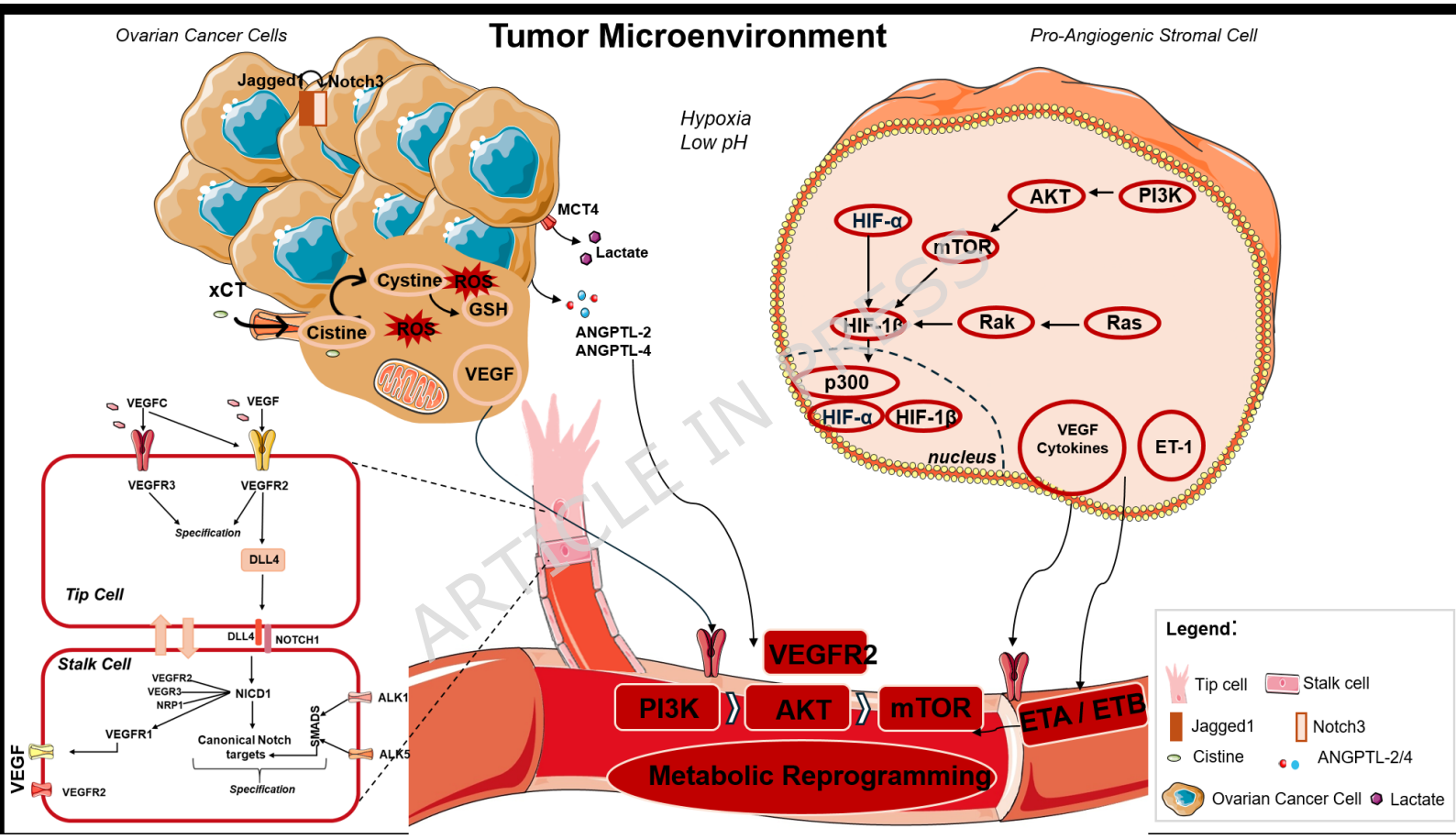
(A) NRF2-dependent redox and angiogenic signaling in ovarian carcinoma. The cystine/glutamate antiporter system Xc^- (xCT) imports cystine in exchange for glutamate. Intracellular cystine is reduced to cysteine in an NADPH-dependent manner, supporting GSH synthesis. GSH acts as a cofactor for GPX4, preventing lipid peroxidation and ferroptosis and promoting OC cell survival. Under oxidative stress, ROS activate NRF2, which upregulates xCT, reinforcing redox homeostasis. Increased ROS activats NRF2 and subsequently HIF-1α, which binds to the VEGF promoter to stimulate angiogenesis. In parallel, cysteine metabolism generates hydrogen sulfide (H_2S), which enhances cellular bioenergetics and promotes angiogenesis via MAPK signaling. **(B)** Remodeling of glucose and lactate metabolism regulated by VEGF and HIF-1α. Glucose uptake occurs via GLUT1 and is phosphorylated by HK2 to fuel glycolysis. Pyruvate is converted to lactate by LDHA and exported through MCT4, contributing to TME acidification. Under hypoxia, lactate can be re-imported via MCT1. Lactate inhibits PHD2, stabilizing HIF-1α in mitochondria and nucleus, which drives VEGF expression and angiogenesis, enabling metabolic adaptation to hypoxia. **(C)** Metabolic crosstalk involving glutamine, cysteine, and fatty acid metabolism. Glutamine is converted to glutamate by GLS1, supporting the TCA cycle and redox balance. xCT imports cystine, which is reduced to cysteine for H_2S production via CBS and CSE, promoting angiogenesis and bioenergetics. TECs uptake fatty acids via CD36, which are transported into mitochondria by CPT1A for β-oxidation, generating ATP and dNTPs required for proliferation. Abbreviations: glutathione (GSH); reactive oxygen species (ROS); glutathione peroxidase 4 (GPX4); and light chain of Xc- cystine:glutamate antiporter (xCT); vascular endothelial growth factor (VEGF); hypoxia-inducible factor-α (HIF- α); nuclear factor erythroid 2-related factor 2 (NRF2); tumor

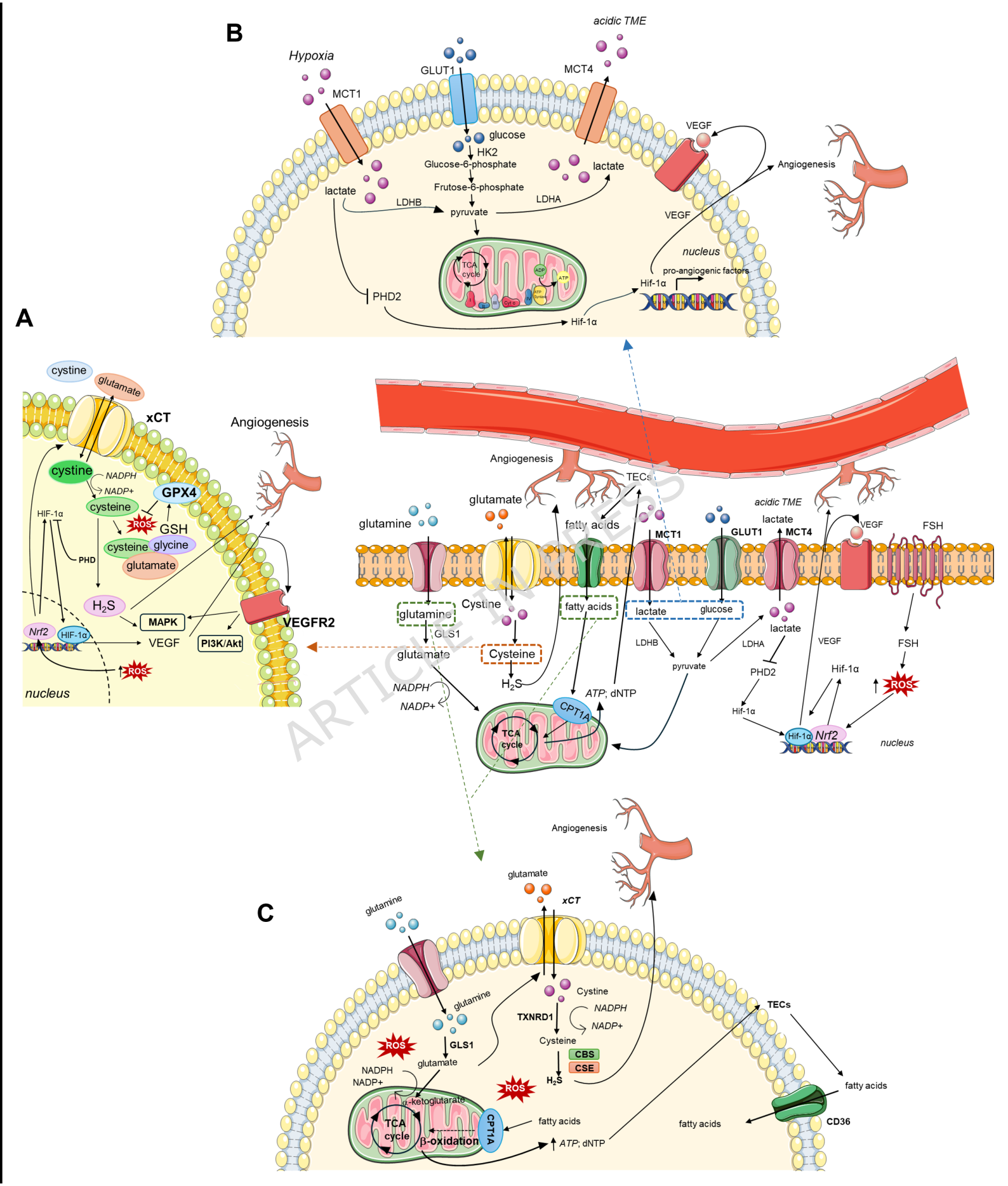
endothelial cells (TECs); Glucose transporter 1 (GLUT1); lactate dehydrogenase A (LDHA); monocarboxylate transporter 1 (MCT1); monocarboxylate transporter 4 (MCT4); hexokinase 2 (HK2); tumor microenvirnment (TME), and mitogen-activated protein kinase (MAPK). Images were based on Servier Medical Art tools (https://smart.servier.com), licensed under CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

Figure 4. Tunneling nanotubes (TNTs) mediate symbiotic communication between ovarian cancer (OC) cells and endothelial cells (EC) within the tumor microenvironment (TME).

(A) Schematic model of TNT induction in OC cells exposed to TME stressors, including hypoxia, chemotherapy, oxidative stress (ROS), and nutrient deprivation. Activation of stress-responsive pathways such as HIF-1α, mTOR, and Nrf2 promotes metabolic rewiring toward increased oxidative phosphorylation (OXPHOS) and drives the acquisition of aggressive and pro-angiogenic phenotypes. Under these conditions, TNTs are formed, establishing direct cytoplasmic connections between cancer cells and ECs within the perivascular niche. **(B)** Magnified view of TNT-mediated bidirectional cargo transfer between OC cells and ECs. TNTs enable the direct exchange of proteins, ions, mRNAs, miRNAs, vesicles, and mitochondria. Mitochondrial transfer supports metabolic adaptation and survival under stress, while ECs receiving tumor-derived material acquire a tumor-supportive phenotype characterized by CD137 expression, increased VEGF signaling, EC activation, and angiogenesis. Abbreviations: tunneling nanotubes (TNTs); endothelial cells (ECs); hypoxia-inducible factor 1 alpha (HIF-1α); reactive oxygen species (ROS); nuclear factor erythroid 2–related factor 2 (Nrf2); mammalian target of rapamycin (mTOR); oxidative phosphorylation (OXPHOS), and vascular endothelial growth factor (VEGF). Images were based on






A
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C
Hypoxia
acidic TME
GLUT1
MCT1
MCT4
glucose
HK2
Glucose-6-phosphate
Frutose-6-phosphate
lactate
LDHB
LDHA
pyruvate
TCA cycle
PHD2
Hif-1α
VEGF
Angiogenesis
nucleus
pro-angiogenic factors
cystine
glutamate
xCT
NADPH
NADP+
GPX4
cysteine
ROS
GSH
cysteine
glycine
glutamate
HIF-1α
PHD
H2S
MAPK
PI3K/Akt
VEGFR2
Nrf2
glutamine
fatty acids
TECs
FSH
Cystine
GLS1
Cysteine
ATP; dNTP
CPT1A
glucose
TXNRD1
CBS
CSE
α-ketoglutarate
β-oxidation
CD36