



How Autophagy Shapes the Tumor Microenvironment in Ovarian Cancer

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Ovarian cancer (OC) is characterized by a high mortality rate due to the late diagnosis and the elevated metastatic potential. Autophagy, a lysosomal-driven catabolic process, contributes to the macromolecular turnover, cell homeostasis, and survival, and as such, it represents a pathway targetable for anti-cancer therapies. It is now recognized that the vascularization and the cellular composition of the tumor microenvironment influence the development and progression of OC by controlling the availability of nutrients, oxygen, growth factors, and inflammatory and immune-regulatory soluble factors that ultimately impinge on autophagy regulation in cancer cells. An increasing body of evidence indicates that OC carcinogenesis is associated, at least in the early stages, to insufficient autophagy. On the other hand, when the tumor is already established, autophagy activation provides a survival advantage to the cancer cells that face metabolic stress and protects from the macromolecules and organelles damages induced by chemo- and radiotherapy. Additionally, upregulation of autophagy may lead cancer cells to a non-proliferative dormant state that protects the cells from toxic injuries while preserving their stem-like properties. Further to complicate the picture, autophagy is deregulated also in stromal cells. Thus, changes in the tumor microenvironment reflect on the metabolic crosstalk between cancer and stromal cells impacting on their autophagy levels and, consequently, on cancer progression. Here, we present a brief overview of the role of autophagy in OC hallmarks, including tumor dormancy, chemoresistance, metastasis, and cell metabolism, with an emphasis on the bidirectional metabolic crosstalk between cancer cells and stromal cells in shaping the OC microenvironment.

Keywords: cancer, cell metabolism, dormancy, cytokines, chemoresistance, autophagy, cancer associated fibroblasts, inflammatory stroma

INTRODUCTION

Ovarian cancer (OC) emerges as the eighth most commonly diagnosed cancer among women worldwide and the leading cause of death among gynecological malignancies (1). Epithelial ovarian cancers are characterized by extensive genomic instability with mutations in several oncogenes and tumor suppressor genes including *BRAF*, *KRAS*, *TP53*, *BRCA1/2*, and *PTEN*, among others, that identify different subtypes with different behaviors and prognoses (2). The current therapy for OC

consists in surgical debulking followed by multi-agent chemotherapy regimens with platinum-based or taxane-based compounds (3). Unfortunately, despite the initial efficacy of the treatment, the majority of OC recurs with the development of drug-resistant and metastatic tumors (3). Metastatic dissemination of OC cells predominantly occurs through direct cell spreading from the primary tumor site into the intra-abdominal cavity of OC patients that is full of malignant ascitic fluid (4). Cancer cells distribute into the cavity, broadly seed in and invade through the peritoneum, and resume secondary tumor growth in distant abdominal and pelvic organs (5). Together with chemoresistance, these phenomena not only denote the emergence of more aggressive tumor clones, but also reflect the dynamics and plasticity that occurred within the tumor microenvironment.

For a long time, cancer stroma has been considered as a passive by-stander in carcinogenesis, subjected to modification associated with the reactive inflammation. It is now recognized that the tumor stroma composition (in terms of vascular structures, cell components, and secreted factors) and its dynamic changes play a fundamental role in cancer progression (6).

Alterations in the expression profiles of genes and signaling pathways lead to aberrant stroma activation, resulting in intense extracellular matrix remodeling along with the synthesis and release of factors involved in metastasis, angiogenesis, and drug resistance (7). Overall, the stroma can either hamper or sustain the proliferation and spread of OC cells depending on its composition. Hence, targeting cancer microenvironment could be an effective therapeutic strategy to limiting OC aggressiveness and relapse, and to this end a deeper understanding of the metabolic crosstalk between OC cells and tumor stroma is crucial. In this context, autophagy, as a catabolic pathway that provides substrates for the carbohydrate, nucleotide, protein and lipid metabolisms (8), plays a pivotal role in the exchange of metabolites between cancer cells and stromal cells, thus impacting on the evolution of the tumor microenvironment.

The tumor microenvironment (TME) has been described as hypoxic, nutrient deprived, energy limited, acidic, and inflammatory (9, 10). This scenario can induce autophagy in cancer cells (11). As a further layer of complexity, autophagy in cancer and stromal cells contributes to the remodeling of the extracellular matrix and reshaping of the cellular composition in the TME (12). Since stromal cells in the TME and cancer cells influence reciprocally the regulation of autophagy in a dynamic manner that favors cancer cell persistence and progression (13, 14), interrupting this metabolic complicity could be of therapeutic value (15).

Abbreviations: OC, ovarian cancer; miRNA, microRNA, lncRNA, long non-coding RNA; EMT, Epithelial-to-Mesenchymal transition; CAF, cancer-associated fibroblast; CAA, cancer-associated adipocyte; TAM, tumor-associated macrophage; MSC, mesenchymal stem cell; TME, tumor microenvironment; ECM, extracellular matrix; AAs, amino acids; FAs, fatty acids.

THE OVARIAN CANCER MICROENVIRONMENT

Ovarian cancer is composed of organoid-like structures in which epithelial OC cells interact with the stroma composed of cancer-associated fibroblasts (CAFs), cancer-associated adipocytes (CAAs), tumor-associated macrophages (TAMs), and other immune and inflammatory cells, mesenchymal stem cells (MSCs) and endothelial cells embedded in a mixture of amorphous components forming the extracellular matrix (ECM) (16). A schematic representation of OC TME composition is illustrated in **Figure 1**.

Cellular and molecular crosstalk between stromal and cancer cells significantly affects OC tumorigenesis and progression through the establishment of a malignant *liaison* that results in a tumor-promoting and immunosuppressive microenvironment (17). In addition, the inflammatory stroma could also favor the awakening of dormant OC cells, thus causing cancer recurrence (17). Moreover, oncogene-induced inflammatory pathways facilitate metabolic changes in the tumor stroma resulting in the secretion of metabolites that are used as alternative nutrient source by cancer cells to sustain their increasing energy needs for growth and anabolic functions (18).

These bidirectional communications have a great impact on biological processes, the metabolic reprogramming of the various components of tumor stroma, and their phenotypic features *via* autocrine, paracrine, endocrine, and contact-dependent cell signaling, thus reflecting the changes driving OC relapse (19, 20).

The bioactive soluble factors secreted into the extracellular space and the malignant ascitic fluid include metabolites (amino acids, fatty acids, *etc.*), proteases (MMP1, MMP2, MMP9, uPA, collagenases), phospholipids (LPAs), chemokines (CXCL1, CXCL-11, CXCL-12, CCL5), growth factors (IGF-1, M-CSF, VEGF, HGF, FGF), and cytokines (IL-4, IL-10, IL-6, IL-1 α , IL-1 β , TGF- β , IL-8, TNF- α). Additionally, OC microenvironment is greatly affected not only by soluble factors, but also by epigenetic mechanisms, such as non-coding RNAs (miRNAs and lncRNAs), histone modifications, DNA methylation, and chromatin remodeling (5).

Tumor-derived metabolites accumulate in the microenvironment in consequence of an accelerated and imbalanced metabolism. Among the pathways involved in the metabolic rewiring, here we focus on autophagy, a mechanism acting as an active supplier of nutrients/energy source for cancer cell survival.

AUTOPHAGY AND OVARIAN CANCER

Autophagy, literally “self-eating”, is a dynamic catabolic process that ensures cellular quality control through the degradation of cytoplasmic damaged, harmful, aged, redundant or unnecessary cellular self-constituents (11, 21).

Autophagy starts with the recruitment of key initiating complexes resulting in the nucleation of the isolation membrane, followed by the elongation of the vesicle that captures cytosolic material, forming the autophagosome.

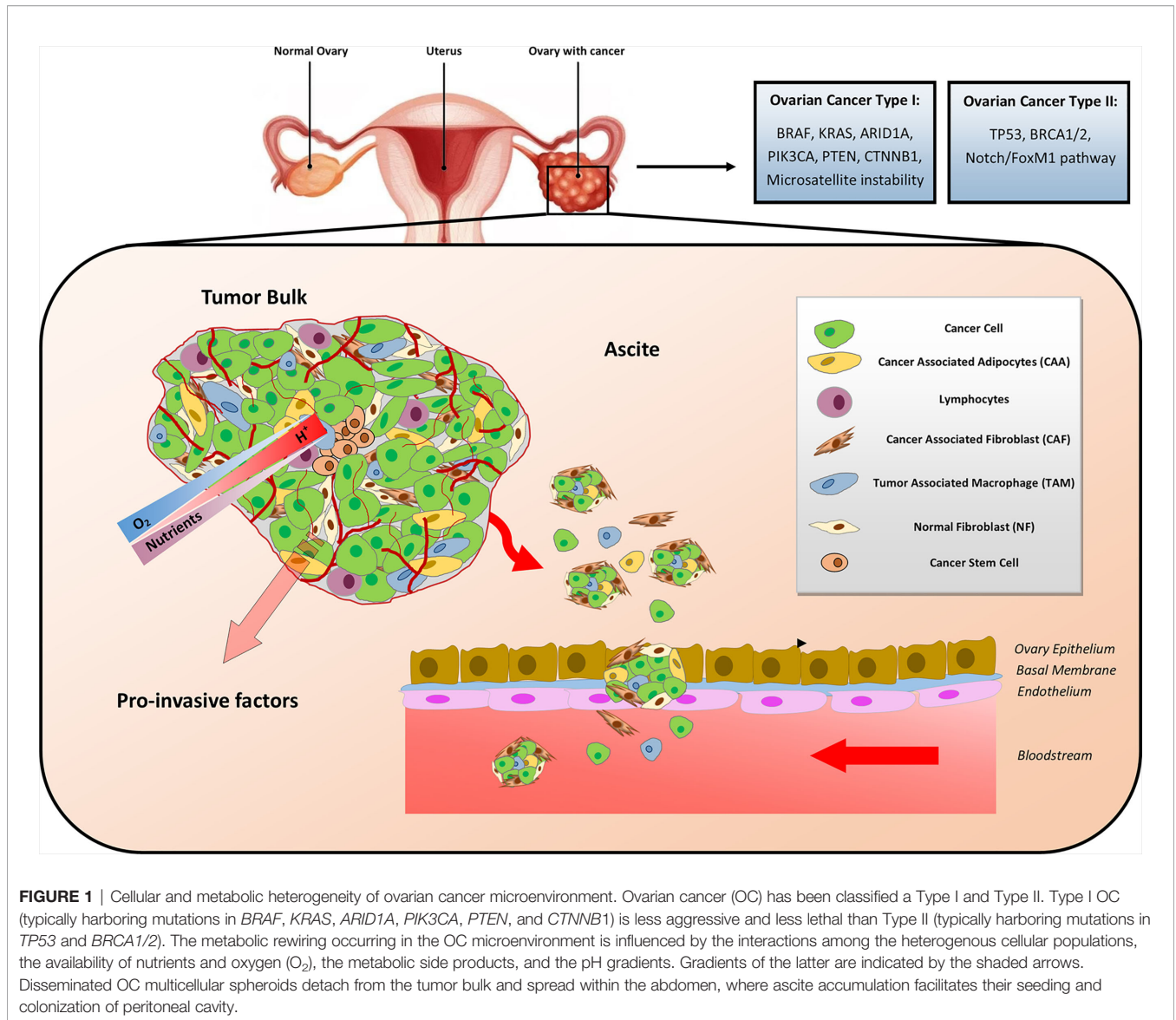
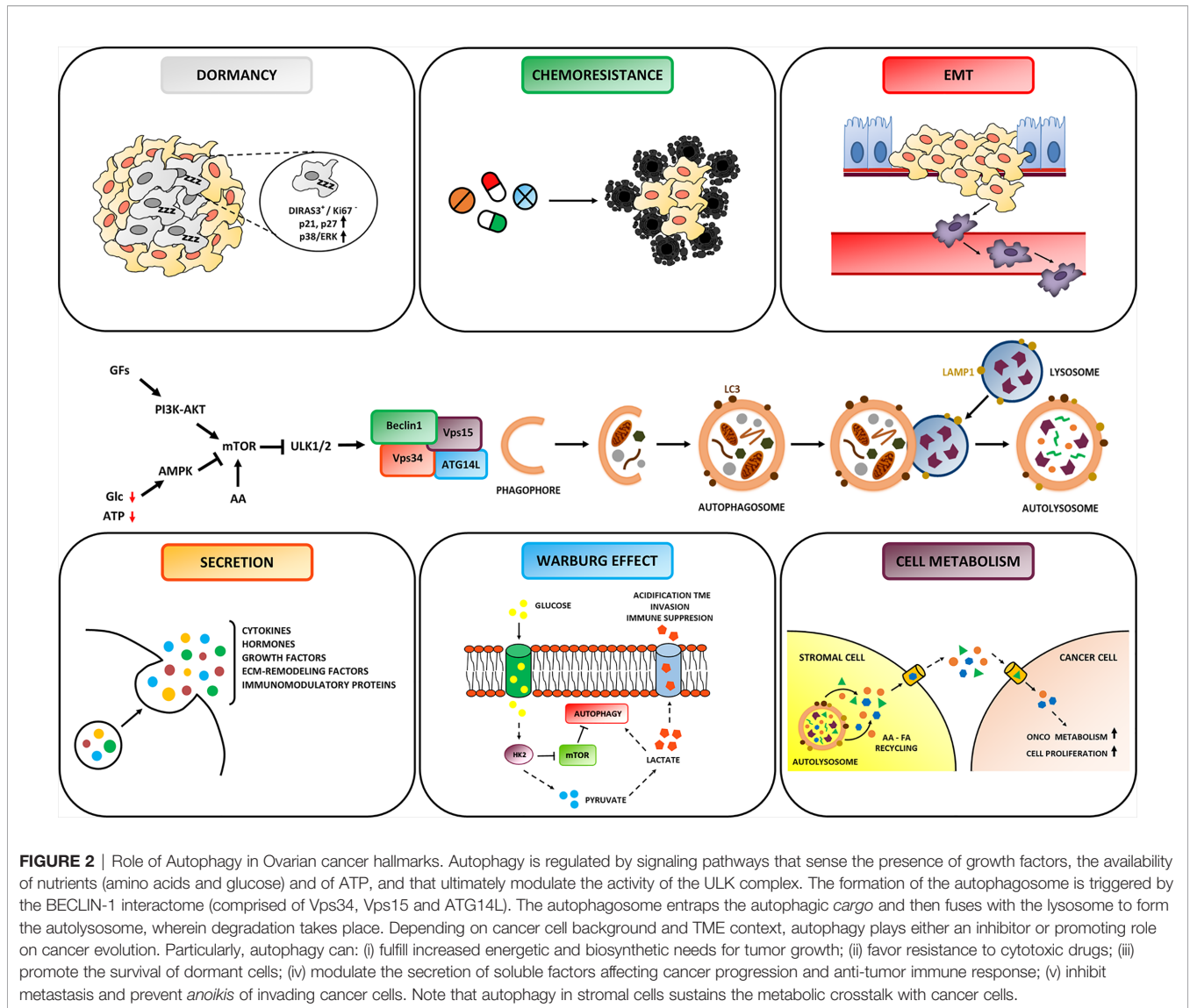


FIGURE 1 | Cellular and metabolic heterogeneity of ovarian cancer microenvironment. Ovarian cancer (OC) has been classified a Type I and Type II. Type I OC (typically harboring mutations in *BRAF*, *KRAS*, *ARID1A*, *PIK3CA*, *PTEN*, and *CTNNB1*) is less aggressive and less lethal than Type II (typically harboring mutations in *TP53* and *BRCA1/2*). The metabolic rewiring occurring in the OC microenvironment is influenced by the interactions among the heterogenous cellular populations, the availability of nutrients and oxygen (O_2), the metabolic side products, and the pH gradients. Gradients of the latter are indicated by the shaded arrows. Disseminated OC multicellular spheroids detach from the tumor bulk and spread within the abdomen, where ascite accumulation facilitates their seeding and colonization of peritoneal cavity.

Next, the autophagosome fuses with endosomal-lysosomal organelles to form the autolysosome. The sequestered cargo is degraded by lysosomal acid hydrolases into monomeric constituents that are exported across the lysosomal membrane to the cytosol for re-use during cellular renovation and macromolecules turnover (22). Regarding the molecular regulation, the mTORC1 complex appears as the main negative controller of autophagy through the inhibition of the ULK1/2 complex (Figure 2). Both the abundant presence of amino acids, which directly activate mTOR, or of growth factors, which activate mTOR via the PI3KC1–AKT pathway, result in the inhibition of autophagy, while the absence of nutrients (amino acids, glucose) and the lack of oxygen, which causes a reduced production of ATP, trigger the AMPK pathway resulting in the induction of autophagy (Figure 2).

Under normal conditions, autophagy occurs at basal levels and ensures constitutive turnover of cytosolic components by

specifically degrading damaged or redundant organelles and molecules (23). In response to a wide range of extra- and intracellular stress stimuli, autophagy is induced and sustains cell survival by producing metabolites that can be re-used in biosynthetic processes or energy production (11). It has been calculated that autophagy controls the destiny of up to fifty per cent of the cellular proteins (24), and up to four percent of the mitochondria pool is basally degraded by mitophagy every day, while dysfunctional mitochondria are actively and selectively removed on demand (25). Thus, overall autophagy presides to protein and organelle quality control that preserves cell viability and prevents from cancer (26, 27). Additional tumor suppressive mechanisms of autophagy include the elimination of oncogenic substrates and dampening of oxidative stress and inflammation, which contribute to preserve genome stability (28, 29). Yet, these same mechanisms might turn to be pro-tumorigenic when activated in established tumor cells. In fact,



by removing the damaged proteins and DNA, autophagy protects cancer cells from the cytotoxic stress induced by chemo- and radiotherapy (30, 31). Further, autophagy can provide a survival advantage to the cancer cells in the most inner portion of the tumor that face hostile conditions such as hypoxic, growth factor and nutrient-deprived microenvironment due to the scarce vascularization (32). Autophagy is deregulated in OC cells in consequence of genetic and epigenetic mutations (33, 34). The haplo-insufficient tumor suppressor gene *BECN1* (that encodes for the protein BECLIN-1) has been the first autophagy gene that was found to predispose to OC development when mono-allelically deleted (35, 36). Autophagy in ovarian cancer is subjected to epigenetic regulation by histone de-acetylases (37), by hypomethylation (38), and by non-coding RNAs (39–41). Autophagy, being a stress response that can be regulated epigenetically, it is not surprising that the TME can modulate the actual level of autophagy in ovarian cancer cells (10).

AUTOPHAGY-MEDIATED METABOLISM SHAPES THE OVARIAN CANCER MICROENVIRONMENT

Cancer growth requires a complex and orchestrated rewiring of cell metabolism (42). Altered cell metabolism enables cancer cells to sustain their increased energetic and biosynthetic needs for tumor growth, invasion, and progression. To satisfy this abnormal high demand of metabolites the cancer cells must partner with other cells in the TME.

To this end, epithelial cancer cells can reprogram the catabolism of neighboring stromal cells to enhance their secretion of energy-rich metabolites (such as pyruvate, lactate, ketone bodies, amino acids, and free fatty acids) that are uptaken by tumor cells and used to sustain their onco-metabolism (43–45).

The unbalanced availability of these metabolites in the TME affects the regulation of autophagy which in turn has an impact

on cell behavior and destiny. Below, we summarize how autophagy responds to environmental harsh conditions and how this response reflects on the composition and function of the TME and cancer cell fate. As schematically represented in **Figure 2**, autophagy is essentially implicated in the amino acid, glucose, and lipid metabolisms, in the secretion of soluble factors found in the TME, and in cancer cell behavior and fate (that includes cell dormancy, response to chemotherapeutics and metastasization).

Autophagy in Cell Metabolism

Amino Acid Metabolism and Autophagy

Amino acids play a central role in cell metabolism, as they are the fundamental blocks for protein synthesis and a source for the synthesis of carbohydrates and lipids. Non-essential amino acids could be synthesized endogenously, but if the proliferation rate is fast, these amino acids have to be provided from external sources because the capacity of endogenous synthesis does not meet the increased needs of the highly proliferating cancer cells (46). Amino acid shortage not only impairs the anabolic pathways, it also potently induces autophagy for rescuing amino acids and other metabolites necessary for vital functions (47). Consistently, prolonged amino acid starvation in ovarian cancer cells triggers the expression of several autophagy genes (48). Amino acid availability is sensed by the mTOR kinase, that positively regulates protein synthesis while negatively regulates autophagy (49). In cancer cells, the lack of (conditionally) essential amino acids determines the proteasomal degradation of the mTOR kinase, thus allowing pro-survival autophagy (50). It has been shown that ovarian cancer cells cultivated in arginine-deprived medium and unable to synthesize it, preventing the induction of autophagy eventually leads to cell death (51). Cancer cells are particularly addicted to glutamine, a (conditionally) essential amino acid that fuels the mitochondrial Krebs's cycle, particularly when glucose is not fully oxidized in the mitochondria (52). In cancer cells, there is a cooperative link between the glutamine and the glucose metabolisms (53).

Nutrient addiction displayed by OC cells relies on the availability of different substrates, and these metabolic dependencies are also dependent on cancer stage (44, 54, 55).

Interestingly, low-invasive OC cells are basically glutamine-independent and rely on glucose metabolism for their growth, whereas high-invasive OC cells shift their nutrient addiction from glucose to glutamine (56). Remarkably, to fulfill their increased requirement for glutamine, highly malignant OC cells reprogram their surrounding CAFs to neo-synthesize more glutamine than what normal ovarian fibroblasts would do (56). Glutamine has been shown to stimulate OC cell proliferation through modulation of the mTOR pathway (57), and this likely inhibits autophagy as indicated by the observation that L-asparaginase, which degrades glutamine to glutamate, induces autophagy in OC cells (58).

Glucose Metabolism and Autophagy

Glucose is one of the principal sources of energy, and its lack is sensed by the cell through the Hexokinase 2-mTOR axis to

trigger autophagy as a stress response (59). Cancer cells resident in well-vascularized areas can fully exploit glucose through mitochondrial respiration to sustain their energetic needs (60). However, highly proliferating cancer cells preferably use glycolysis to produce ATP and skip the mitochondrial respiration step despite the availability of oxygen, a phenomenon known as Warburg effect (61). On the other hand, cancer cells located in hypoxic niches are obliged to use glycolysis for the production of ATP because of the lack of oxygen (62). Glycolysis is ten times less convenient than mitochondrial respiration in terms of ATP yield, therefore the tumor mass consumes huge amount of glucose (approximately 10–200 times more) compared to the normal counterpart tissue, and this leads to the production of high amount of lactate (63).

The acidification of the TME due to lactate secretion further contributes to cancer progression promoting (i) cancer cell invasion and metastasis (64), (ii) Epithelial-to-Mesenchymal transition (EMT) and the emergence of stem-like clones (65, 66), (iii) angiogenesis (67), (iv) the survival of cancer cells competing with stromal and immune cells for energy and glucose availability (68, 69), (v) the polarization of tumor-associated macrophages (TAMs) toward an immune suppressive phenotype (70, 71), and (vi) resistance to hypoxia, cytotoxic drugs and immune attack (72).

It has been proposed that the glycolytic shift in glucose metabolism along with upregulation of autophagy occur also in stromal cells, mainly in CAFs (44), that would then supply the cancer cells with amino acids and lactate to sustain the anabolic processes involved in hyperproliferation and cancer progression (73, 74). In the presence of oxygen, cancer cells can oxidize lactate into pyruvate thanks to the lactate dehydrogenase B (LDHB), thus substituting the glucose to fuel the mitochondria (75). Interestingly, this LDHB-dependent metabolism increases the autophagy flux along with increased acidification of the lysosomes in cancer cells (75).

Fatty Acid Metabolism and Autophagy

The bidirectional crosstalk between ovarian cancer cells and adipocytes, that are used as "food donors", is another example of metabolic complicity in the TME that supports OC growth (76, 77).

Lipidomic analysis of malignant OC ascites revealed the presence of high concentrations of linoleic acid, a potent PPAR β/δ agonist that promotes the pro-tumorigenic polarization of ovarian TAMs (78).

When cultured in the ascite microenvironment, ovarian cancer cells undergo a metabolic shift from aerobic glycolysis to β -oxidation and lipogenesis, and this associates with increased aggressiveness (79).

In the TME, cancer-associated adipocytes (CAAs) release fatty acids (FAs) that are used by cancer cells as an energetic source, and adipokines that stimulate cancer progression (80). Interestingly, the uptake of (long chain) FAs present in the TME is higher in hypoxic cancer cells due to HIF-1 α -induced expression of CD36, also known as FA translocase (81). To be noted, CD36 is over expressed in ovarian cancer cells and associates with ovarian cancer progression and metastasis (82). In hepatocarcinoma cells, over-expression of CD36 has been

shown not only to increase the long-chain FA uptake but also to inhibit autophagy, and particularly lipophagy (83). Whether this also occurs in OC cells remains to be demonstrated.

Again, recent evidences suggest that lipophagy, the autophagic degradation of lipids, has a role in the release of free fatty acids that constitute an alternative source of energy as well as metabolic intermediates involved in cell signaling and macromolecule biosynthesis (84).

During energy stress condition, CAAs upregulate autophagy and supply fatty acids that are transported to cancer cells and can be used for building cell membranes or are catabolized by β -oxidation (85). The latter process may also generate ketone bodies that represent a useful substrate for ATP generation in fast-growing cancer cells, since ketone bodies provide more ATP with less oxygen consumption than glucose (86). This aspect leads to speculation that cancer cells growing in an adipocyte-enriched microenvironment, like OC, specifically rely on mitochondrial β -oxidation to fuel high bioenergetic demand of cancer cells, suggesting that adipocytes promote a metabolic switch to favor fatty acids over glucose and amino acids as mitochondrial substrate due to a tissue-specific feature of this cancer (80, 87).

In particular settings, lipophagy has shown to exert a tumor-suppressive role. The lack of lysosomal acid lipases, the enzymes involved in lipophagic degradation, results in the promotion of cancer growth and metastasis through the mTOR-dependent activation of myeloid-derived suppressor cells (88).

Further characterization of lipophagy perturbation in the TME is needed to fully understand its role in OC development and progression and to determine its potential as a target for novel cancer therapeutic approaches (89).

The Role of Secretory Autophagy in Shaping the TME

Peptides, proteins, and hormones that lack the leader/secretion peptide and fail to enter the conventional secretory system, normally operating *via* the endoplasmic reticulum–Golgi pathway, can be secreted in an autophagy-dependent manner (90). Thus, autophagy actively participates in remodeling of TME *via* unconventional secretion of soluble factors involved in intercellular communications (91). Autophagy knockdown in stromal and/or in cancer cells results in the reduction of cytokine and chemokine release (including IL-1 β , IL-18, IL-6, IL-8, IL-2, CCL2, CCL20, TNF α , LIF), indicating an autophagy-dependent secretion of pro-inflammatory and pro-invasive factors that collectively modulate tumor growth, immune evasion, stemness maintenance, angiogenesis, and metastasis (91–97). Additionally, the autophagy-dependent tumor secretome includes extracellular matrix remodeling proteins (*e.g.* MMP2, MMP9), angiogenic stimuli (VEGFA) and growth factors (b-FGF, TGF β 1) (95, 98, 99). Further, autophagy impairment hampers the secretion of IFN- γ , CXCL9, CXCL10, CXCL11 that are involved in T cells and dendritic cell recruitment, resulting in immune surveillance escape (100).

On the other hand, autophagy promotes the release of immunomodulatory proteins known as DAMPs (damage-

associated molecular patterns) that elicit anti-tumor immunity by activating immune cells, thus limiting tumor progression (101, 102).

AUTOPHAGY-MEDIATED CROSSTALK WITHIN THE MICROENVIRONMENT AFFECTS OVARIAN CANCER PROGRESSION

The TME has been described as inflammatory and desmoplastic, recalling a wound that never heals (103). In normal tissues subjected to environmental injuries, the inflammatory and autophagy pathways cross-communicate and cooperate to re-establish homeostasis (104). In the tumor niche, several pro-inflammatory factors and pro-tumorigenic metabolites could directly or indirectly impinge on autophagy in cancer and stromal cells, thus affecting cancer evolution (105, 106). On the other side, autophagy plays a role in the release of pro-tumorigenic cytokines (107). IL-6, one such inflammatory and pro-tumorigenic cytokine released by CAFs, is particularly secreted in the OC TME and accumulates abundantly in the ascitic fluid of OC (17). This cytokine has been shown to promote EMT and the migration of OC cells (108). Recently, we have shown that the pro-EMT and pro-migratory effect of IL-6 on OC cells is dependent on the epigenetic regulation of autophagy (40).

Another molecule highly secreted within the OC microenvironment is lysophosphatidic acid (LPA). In ovarian cancer, LPA could act either in an autocrine or a paracrine manner to reprogram the glucose metabolism (109), to induce EMT and invasiveness (110), and to promote the secretion of pro-invasive factors (like VEGF, IL-6, IL-8, *etc.*) (111, 112). It is likely that these effects are mediated by modulation of autophagy. Accordingly, LPA has been shown to inhibit autophagy in prostate cancer cells (113, 114). Further, it has been demonstrated that LPA induces a glycolytic shift that associates with the phenocopy of ovarian normal fibroblasts into ovarian CAFs (115), a process that depends on autophagy modulation (74).

Consistent with a role of autophagy in metastatic dissemination, a recent study found that disseminated ovarian cancer cells within the peritoneum over-expressed several autophagy genes (116). However, the relationship between EMT and autophagy is quite intricate: while on one hand it inhibits the early phases of metastasization mainly through the selective degradation of EMT-associated transcription factors such as SNAIL, SLUG, and TWIST, on the other hand it helps cancer cells that already underwent EMT to prevent from *anoikis* and move within the ECM (117), yet it is also involved in the reverse Mesenchymal-to-Epithelial transition process (118, 119).

Tumor dormancy coincides with the period during which disseminated tumor cells can remain in a latent state associated with inhibition of cell proliferation and reprogramming of cell metabolism that sustain cell survival with the least expenditure of energy in presence of reduced source of nutrients and oxygen (120). Hence, dormancy is an important adaptive response to

microenvironmental stresses, and it is the result of an integrated metabolic crosstalk (involving cytokines, chemokines, growth factors, metabolites, and non-coding RNAs) in which autophagy plays a key role (121, 122). Dormancy and autophagy are functionally interconnected at the molecular level. The tumor suppressor gene *ARH-1* (also known as *DIRAS3*), which is epigenetically silenced in a vast majority of ovarian cancers, promotes autophagy in cultured OC cells (40, 123), and its inactivation in the context of a xenografted tumor in mice causes the interruption of dormancy and the rapid re-growth of the tumor (124).

This mechanism of adaptation to a nutrient poor microenvironment favors the survival of chemoresistant OC cells (125). Therefore, autophagy signaling machinery might integrate quiescence and survival signals to promote damage repair, *via* ATG7 regulation of p53 and sustain cancer cell needs by generating an alternative route for amino acid turnover as well as for energetic metabolism and ATP balance (126, 127).

CONCLUSIONS

Here we have briefly described the interplay occurring within the OC tumor microenvironment between OC cells and stromal components, how this influences the dynamic changes in the structure and composition of extracellular matrix and of tumor stroma, the reprogramming of energetic metabolism, and the secretion of soluble factors that, overall, negatively impact on the prognosis of OC patients.

Deregulation of autophagy has been recognized as one of the main hallmarks of cancer. However, while studying the role of autophagy in cancer, we now realize that things are far more complicated than what it was thought some decades ago. In fact, we must consider that autophagy regulation is subjected both to genetic and epigenetic mutations of oncogenes and tumor suppressor

genes, and it is transiently modulated by microenvironmental factors such as metabolites, pro-inflammatory cytokines and pro-oxidant molecules. As a further layer of complexity, we have to consider the level of autophagy in both the epithelial cancer cells, the stromal cells (CAFs, CAAs, TAMs), and probably also of neighboring normal cells, and keep in mind that all these actors can exchange metabolites and factors influencing reciprocally the autophagy level. Interrupting the functional link between autophagy and cell metabolism both in epithelial cancer cells and in stromal cells could be an effective therapeutic approach to slow down OC progression and prevent relapse. To achieve this goal, we need to further investigate the mechanisms of autophagy dynamics and how it shapes the TME.

AUTHOR CONTRIBUTIONS

AF, CG, AE, and CV: drafted the manuscript and iconography. LV and ES: literature search and iconography. DD and CI: conceptualized, supervised, and finalized the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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