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Review

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Interconnections within the tumor microenvironment: extracellular vesicles as critical players of metabolic reprogramming in tumor cells

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Abstract

Metabolic reprogramming is an intrinsic characteristic of cancer, contributing to its establishment and progression, survival, high proliferation rates, and increased migratory and invasive potential; tumor cells establish an intimate relationship with the surrounding microenvironment, where sustained communication allows the stromal fraction of the tumor microenvironment (TME) to supply energetic substrates and facilitate the biosynthesis of macromolecules, thereby promoting tumor progression. In this context, extracellular vesicles (EVs) emerge as potential communication vehicles, carrying inside content reflecting the cellular environment of origin and thus modulating the phenotype of recipient cells. The potential of EVs as modulators in the TME has been highlighted and is now consensual; however, most available articles have focused on revealing the effect of EVs in modulating tumor phenotypes and signaling pathways in tumor cells. Regarding the metabolic modulation sustained by EVs, studies have demonstrated the role of cancer cells' EVs as modulators of surrounding cells, like immune cells, fibroblasts, and adipocytes. Therefore, this review aims to: *i.* highlight the most recent studies evaluating the role of cellular vesicles released by those cells within the microenvironment in the metabolic reprogramming of cancer cells; *ii.* compile scientific evidence proposing how EVs could modulate the metabolic profile of tumor stem cells

and lymphocytes, particularly given the lack of studies focused on such approaches; and *iii.* highlight possible effects of vesicles, as the metabolic modulation induced by these vesicles could have anticancer potential.

Keywords: Metabolism, cancer, extracellular vesicles, tumor microenvironment, and metabolic reprogramming

INTRODUCTION

In early 2000, Hanahan and Weinberg provided a solid foundation for understanding the complex biology of cancer in a seminal review article titled "The Hallmarks of Cancer," which comprised six essential alterations in cell physiology - sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis - thus enabling a conceptual framework for understanding the diversity of neoplastic diseases[1]. In 2011, these six acquired characteristics were expanded, incorporating two emerging Hallmarks: energy metabolism and evading immune destruction. Furthermore, a new concept acknowledging tumors as a complex microenvironment composed of multiple distinct cell types interacting, the "Tumor Microenvironment" (TME), has emerged. The TME is constructed along the tumorigenesis and comprises cancer and Cancer stem cells (CSCs), endothelial cells, pericytes, immune-inflammatory cells, cancer-associated fibroblasts (CAFs)[2], and various additional tissue-resident cell types, such as adipocytes[3], as well as the transformed parenchyma and associated stroma[4]. Within the TME, the tumor-supportive environment depends on the heterotypic interactions between cancer cells and resident or recruited noncancerous cells. This signaling network provides intercellular communication, including cell-cell contact and paracrine signaling, through the release of cytokines, chemokines, growth factors, proteases[5], and extracellular vesicles (EVs)[6].

Furthermore, this intricate network, which favors uncontrolled cell proliferation, relies on increased energy production and the synthesis of macromolecules. Thus, malignant cells often reprogram their biochemical pathways to allow rapid absorption and degradation of nutrients to cope with increased metabolic stress, contributing to the disease's transformation, maintenance, and progression[7]. In this scenario, it is now recognized that cancer cells undergo metabolic reprogramming, thus getting adapted to intrinsic or extrinsic cues from the microenvironment due to high flexibility in nutrient acquisition and utilization[8].

The birth of cancer metabolism research dates to the 1920s, when Otto Warburg *et al.* observed that tumors were taking up enormous amounts of glucose compared to what was seen in the surrounding tissue[7,9] and that even in the presence of oxygen, glucose was fermented to produce lactate, a process known as aerobic glycolysis or Warburg Effect[10].

A general view of the cancer metabolism

Metabolic reprogramming allows cancer cells to adapt to intrinsic or extrinsic cues from the microenvironment through plasticity and high flexibility in nutrient acquisition and utilization[8]. Such adaptation allows nutrient acquisition and utilization to support increased proliferation, migration, and invasiveness. This fine-tuning balance between aerobic glycolysis and oxidative phosphorylation - the so-called metabolic reprogramming - occurs differently depending on the tumor type, even in cells within the same tumor[11]. In this context, tumors can broadly be classified into two main groups regarding (adenosine triphosphate) ATP sources: those that primarily rely on glycolytic and those that undergo preferential oxidative phosphorylation[12,13].

Glycolysis

Several oncogenes and tumor suppressors drive the metabolic reprogramming underlying the Warburg effect. In this scenario, the Hypoxia-inducible factor 1-alpha (HIF-1α) is an essential protein for sustained

glycolysis. In noncancerous cells undergoing hypoxia, HIF-1α stabilizes, thus promoting glycolysis and suppressing oxidative phosphorylation[14]. This sustained glycolysis is mediated by the upregulation of glucose transporter (GLUT) 1 and hexokinase (HK) 2, triggering increased uptake and retention of glucose inside the cells, respectively[15]. In cancer cells, HIF-1α is stabilized even in the presence of oxygen in response to several oncogenes like protein kinase B (PK24B/AKT), phosphoinositide 3-kinase (PI3K), Ras, and Von Hippel-Lindau (VHL)[16].

The p53 tumor suppressor protein p53 also has a critical role in limiting glycolysis, though inhibiting transcription of GLUT1, GLUT4, and GLUT12 and the glycolytic enzymes HK1, HK2, glucose-6-phosphate isomerase (GPI), phosphoglucomutase (PGM), and β-enolase; furthermore, p53 can inhibit the rate-limiting step in glycolysis through the inhibition of phosphofructokinase-1 (PFK1) activity, or by inhibiting the transcription of its regulator, the bifunctional enzyme phosphofructo-2-kinase//fructose-2,6-biphosphatase 3 (PFKFB3)[17].

Besides glycolysis, glycogenolysis provides an energy source for tumors under nutrient deprivation conditions independently of cellular replication. Several cancer types display an upregulation in glycogen metabolism, such as breast, bladder, brain, ovarian, renal, skin, and uterine[18]. Such an increase in glycogen accumulation promotes the survival of cancer cells in hypoxic conditions. It occurs via the AKT pathway[19] and the increased expression of the protein phosphatase 1 regulatory subunit 3C (PPP1R3C) in a HIF-1α-dependent manner[20]. Concurrently, suppressing glycogen synthase kinase 2 (GSK2) activity triggered a reduction in prostate tumor growth *in vivo*[21]. Among the glucogenic enzymes playing essential roles in cancer metabolism, both phosphoenolpyruvate carboxykinase 1 (PCK1) and phosphoenolpyruvate carboxykinase 2 (PCK2) can be highlighted; such enzymes can be inhibited by p53, a tumor suppressor[22].

One candidate in this preferential energetic status is the M2 isoform of pyruvate kinase (PKM2), a rate-limiting enzyme in glycolysis, which promotes mitochondrial fusion by interacting with mitofusin 2 (MFN2), attenuating glycolysis and mediating PFK1 degradation, triggering glycolysis inhibition[23]. The inhibition of PFK1 can channel glycolytic carbon into the pentose phosphate pathway (PPP), generating ribose-5-phosphate and Nicotinamide Adenine Dinucleotide Phosphate (NADPH), other than promoting mitochondrial oxidative phosphorylation[13].

Oxidative phosphorylation

Under increased aerobic glycolysis, the excretion of carbon as lactate diminishes glucose's contribution as an anaplerotic repository for biosynthetic pathways. Glutamine and other intermediates can replenish tricarboxylic acid cycle (TCA), thus emerging as an essential source of biosynthetic precursors. This allows the biosynthesis of nucleic acids, amino acids, and lipids, highlighting mitochondrial importance[10,24].

Oxidative phosphorylation (OXPHOS) yields a higher ATP production per glucose unit than glycolysis. It is the preferential ATP source in many types of cancer, being upregulated compared to adjacent normal cells[25], thus contradicting the long-standing belief that OXPHOS is downregulated in cancer.

Due to their heterogeneity, tumors demonstrate a wide range of metabolic phenotypes and flexibility[26]. For instance, gliomas exhibit both OXPHOS and glycolic characteristics, depending on lactate dehydrogenase (LDH) isoforms. OXPHOS is also upregulated in leukemias, lymphomas, pancreatic ductal adenocarcinoma[27], breast cancer, and classical Hodgkin lymphoma. In breast cancer, for example, the activity of Complex I, II, and IV proteins from the electron transport chain (ETC) are upregulated compared to subjacent normal epithelial cells[28].

The tricarboxylic acid cycle

The TCA cycle is a convergence point in the cellular respiration machinery; it integrates a myriad of fuel sources such as glucose, glutamine, and fatty acids. Such cycles produce intermediates required for macromolecule biosynthesis and NADH and $FADH_2$ coenzymes committed to ETC-reducing reactions. Regarding the source of carbons replenishing the TCA intermediates, it is widely accepted that cancer cells shunt pyruvate away from the TCA depending on glutamine and fatty acids[7,29,30].

It is now widely acknowledged that mutations in enzymes of the TCA cycle, such as isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), fumarate hydratase (FH), and aconitase are prevalent in a wide variety of human cancers[7,25,31,32]. For instance, SDH mutations in tumors have been linked to increased aggressiveness and high proliferative rates[33]. These mutations have been associated with several types of cancer, including renal cell carcinoma (RCC), neuroblastoma, gastrointestinal stromal tumors, thyroid cancer, and testicular seminoma[34,35]. Similarly, FH mutations have been reported in uterine fibroids, hereditary leiomyomatosis, and papillary RCC[36]. The reduced expression of FH, leading to fumarate accumulation, results in SDH dysfunction in some cancers, leading to the accumulation of succinate and fumarate, ultimately stabilizing HIF-1α due to the inhibition of prolyl 4-hydroxylases (PHDs). Concurrently, mutations in the IDH, an enzyme converting isocitrate to α-KG, have been observed. The abnormal expression and activity of IDHs result in the loss of the enzyme's ability to catalyze the conversion of isocitrate to α-KG; instead, it gains a new ability to facilitate the reduction of α-KG to D-2-hydroxyglutaric acid (D-2HG), an oncometabolite[16].

Glutamine is an essential nutrient source that feeds into the TCA cycle in numerous cancer types, including MYC-driven cancers[37]. It traverses the cell membrane through amino acid transporters, ASCT2 (alanine, serine, cysteine transporter 2), and system N transporter SN2[38]. Under high proliferative rates, glutamine is often the primary source of energy and is also committed to biosynthesis, a condition known as glutamine addiction. This amino acid is the most abundant within the bloodstream, is converted in α-KG by glutaminases and glutamate dehydrogenase (GDH), fueling the TCA cycle[39], acts as a nitrogen donor to the synthesis of purines and pyrimidines[40], and can be further converted to glutathione, by glutamate-cysteine ligase and glutathione synthetase[41]. Due to its role in neutralizing mitochondrial reactive oxygen species (ROS), it is crucial to cancer cells, which become devastated under the inhibition of the glutamine metabolism due to ROS overproduction[42].

Lipid metabolism

The role of lipid metabolism in tumorigenesis has also received increased attention in recent years[43]. The importance of lipogenesis to cancer cells is undeniable. Some tumor cells show increased levels of enzymes involved in GA synthesis. One example is ATP-citrate lyase (ACLY), whose overexpression in lung adenocarcinoma and acute myeloid leukemia (AML) is directly related to a worse prognosis[44]. The stabilization of ACLY levels is a necessary mechanism for maintaining the viability of lung tumor cells. Any disturbance in this stabilization, such as through the administration of CUL 3, a protein that regulates the ubiquitination of ACLY, leads to a reduction in lipid levels, cell proliferation, and xenograft tumor growth in mice[45].

However, the importance of fatty acid oxidation (FAO) in cancer aggressiveness remains: Are FAO enzymes as dysregulated as those committed in glycolysis and glutaminolysis? An argument against the oncogenic involvement of FAO is that lipogenesis and FAO are mutually exclusive processes coordinated by the level of malonyl-CoA. Malonyl-CoA, an intermediate of fatty acid biosynthesis, acts as an allosteric inhibitor of the FAO rate-setting enzyme carnitine palmitoyltransferase (CPT) 1, presumably preventing FAO from co-occurring with active lipogenesis[46]. Furthermore, little evidence suggests that the FAO is reprogrammed in

cancer due to the activation of specific oncogenes or loss of tumor suppressors.

On the other hand, although FAO enzyme mutations are not frequent in cancer, studies revealing its overexpression highlight its role in malignancy. The overexpression of CD36, CPT1A, CPT1B, CPT1C, CPT-2, carnitine transporter CT2, and Acyl-CoA synthetase long-chain 3 has been reported. Additionally, the high activity of FAO has been observed in K-Ras mutant lung cancer, triple-negative breast cancer (TNBC), AML, hepatitis B-induced hepatocellular carcinoma, glioma, and low-grade astrocytoma[11].

Camarda *et al*. revealed that triple-negative breast cancer cells overexpressing the oncogenic transcription factor c-Myc presented an increase in FAO enzymes and metabolic intermediates. In the presence of etomoxir, an FAO inhibitor, the tumorigenic potential was inhibited, thus highlighting the crucial role of FAO for triple-negative breast cancer cells[47]. In the same line, Wang *et al*. revealed that FAO inhibition selectively eliminated breast CSCs and increased the cells' sensitivity to paclitaxel chemotherapy, being an essential mechanism for chemoresistance[48].

Some tumor cells show increased levels of enzymes involved in fatty acid synthesis. One example is ACLY, whose overexpression in lung adenocarcinoma and AML is directly related to a worse prognosis[44]. It has already been demonstrated that the stabilization of ACLY is a necessary mechanism for maintaining the viability of lung tumor cells. The administration of CUL 3, which disturbs the stabilization of ACLY through its ubiquitination, reduces lipid levels, cell proliferation, and xenograft tumor growth in mice[45].

EVs within the TME

Previously, studies focusing on the communication between cancer cells' interaction with surrounding cells were limited to soluble mediators. However, EVs have become crucial to tumor formation, progression, and metastasis[49]. Evidence has shown that EVs can facilitate and sustain the bidirectional communication between tumor cells and their microenvironment, which is crucial for tumor occurrence and progression. EVs can be secreted by virtually all cells. Initially, such an effect was adopted to refer to ways cells undergo to eliminate unneeded components[50]. However, it is currently known that EVs sustain cell-to-cell communication by exchanging DNA, mRNAs, miRNAs, proteins, and lipids in a paracrine or systemic manner. The EVs cargo reflects the physiological or pathological microenvironment of its donor cell, allowing cell-to-cell communication through the exchange of its content, thus harboring the potential to regulate proliferation, survival, and immune effector status in recipient cells, through changes in intracellular signaling[49,51,52]. This potential of EVs to regulate critical aspects of cell behavior offers hope for novel therapeutic strategies in cancer.

The term "EVs" is a broad category that includes membrane vesicles of various sizes and origins. These vesicles are classified into main categories based on their biogenesis and size. By origin, exosomes are derived from the endosomal system, while microvesicles originate from the plasma membrane. By size, EVs are further categorized as small EVs (sEVs, ranging from 40 to 150 nm) and medium/large EVs (m/lEVs, ranging from 150 to 1,000 nm) according to the guidelines of the International Society for Extracellular Vesicle (ISEV)[53].

Receptors and ligands on the surface of the EV facilitate specific targeting for biodistribution and can trigger signaling changes within the recipient cell[54]. For example, a breakthrough study conducted by Peinado *et al*. demonstrated the role of EVs released by high metastatic melanomas under the reprogramming of the bone marrow progenitors-derived cells through the Met tyrosine kinase receptor, thus underscoring EV's role upon metastatic dissemination[55].

EVs are essential in communicating cancer cells with surrounding cells within the TME. In this scenario, it is crucial to highlight the bidirectional nature of such communication, which requires active engagement from researchers. For example, when cancer cells undergo a metabolic shift toward an OXPHOS profile, TME cells release lactate - as a result of enhanced glycolysis - thus replenishing carbons to the TCA cycle[56]. Other than that, TME cells also release amino acids and lipids, thus replenishing the TCA and donating build blocks to biosynthesis, favoring cancer progression[57]. This bidirectional communication, where cancer cells influence the TME and vice versa, presents a dynamic and challenging research field for cancer biologists and therapeutics professionals, stimulating their eagerness to contribute to this evolving field.

While it is widely accepted that EVs can modulate tumor progression, our understanding of how EVs and their cargo influence metabolic reprogramming in the TME remains limited. In this field, most studies have focused on the role of cancer cell-derived EVs in altering the metabolic profile of TME surrounding cells. In this paper, we highlight cancer metabolism focusing on EVs; furthermore, we have gathered recent evidence on the role of EVs released by TME stromal cells as metabolic modulators in cancer cells, thereby revealing another important communication pathway. Furthermore, considering recent studies, we discuss how EVs could act as modulators of tumor progression and therapeutics.

EVs and the metabolic reprogramming within the TME

EVs play a bidirectional role in the communication between cancer and stromal cells within the TME. EVs are now recognized as critical signal transmitters committed to fine-tuning glucose and lipid metabolism processes. In this scenario, several studies have highlighted how EVs from cancer cells impact the metabolism of non-cancer cells within TME. It was already reported that exosomes from human primary and metastatic colorectal cancer (CRC) cells upregulate GLUT1 expression in fibroblasts in a caveolin-1-dependent manner[58]. Furthermore, miR-155- and miR-210-enriched exosomes from melanoma cells (Mel 1) increased aerobic glycolysis while decreasing OXPHOS in human dermal fibroblasts, thus leading to extracellular acidification[59]. Increased glucose and glutamine metabolism was already observed in fibroblasts exposed to EVs from breast cancer cells in a miR-105-dependent manner[60]; concurrently, both aerobic glycolysis and autophagia are increased in fibroblasts turned into CAFs upon exposure to EVs from nasopharyngeal carcinoma via latent membrane protein 1 (LMP1) nuclear factor kappa B (NF-κB)/p65 pathway[61].

Exosomes from hypoxia-induced tumor cells transfer let-7a miRNA to bone marrow-derived macrophages, enhancing OXPHOS by inhibiting the insulin-Akt-mTOR signaling pathway and thus inducing an M2-like macrophage polarization[62]. Sagar *et al*. demonstrated that endothelial cells exposed to exosomes from AML cells - enriched in vascular endothelial growth factor (VEGF)/VEGFR- displayed a glycolytic profile and undergo glycolysis. Adipocytes exposed to exosomes from Lewis Lung Cancer (LLC) exhibited a lower content of lipid droplets and high levels of glycerol release. Concurrently, exosomes from pancreatic cancer cells induced lipolysis in adipocytes via the ERK1/2 and MAPK p38 signaling pathways[63].

Furthermore, it was already observed that ARG1-containing EVs from ovarian carcinoma suppress T cell proliferation[64]; EVs from cervical squamous cell carcinoma (CSCC) containing miR-142-5p induce the expression of indoleamine 2,3-dioxygenase (IDO) by lymphatic endothelial cells, which in turn trigger $CD8^+$ T cell suppression and exhaustion[65].

While most existing studies have concentrated on the influence of EVs from cancer cells on the metabolism of non-cancer cells in the TME, this review takes a fresh perspective. We delve into the less-explored territory of how EVs from non-cancer cells in the TME stimulate metabolic and phenotypic alterations in

cancer cells. We underscore the pivotal role of EV bioactive charges in these processes, offering a novel angle for your consideration.

EMERGING ROLES OF EVS FROM SURROUNDING TME IN MODULATING CANCER CELL METABOLISM

Macrophage-derived EVs

As phagocytic cells, macrophages play a crucial role in maintaining tissue homeostasis and act as immunological sentinels during infections and in tissue abnormalities such as tumor growth. These cells, distributed in all organs and tumors, exhibit a polarization spectrum dependent on the microenvironment. The extremes of this spectrum are the M1, or classically activated, and M2, or alternatively activated. Tumor-associated macrophages (TAMs), the most abundant leukocytes in the TME, are classified into tumor-killing (M1) or tumor-promoting (M2). Although most TAMs have the M2-like phenotype, they can acquire a range of profiles in response to stimuli, constituting a heterogeneous and plastic population[66].

Given that TAMs are the most prevalent leukocytes in the TME[67], significant efforts have been directed toward understanding their role in tumor progression. Research has consistently shown that TAMs are associated with a poor prognosis in various cancer types, including colorectal[68], bladder[69], prostate[70], pancreas[71], and breast cancer[72]. This is primarily due to their ability to induce epithelial-mesenchymal transition (EMT)[73], angiogenesis[71], invasion[68], and, most importantly, alter the metabolism of tumor cells[74].

Recent studies have reported that metabolic changes in tumor cells promoted by macrophages are EVs-mediated. Chen *et al*. demonstrated that EVs derived from TAMs increase the aerobic glycolysis of breast cancer cells. Peripheral blood monocytes (PBDMs) were isolated from breast cancer patients or healthy donors and treated with a human breast adenocarcinoma cell line (MDA-MB-231) conditioned medium (CM) to obtain TAMs. Then, EVs derived from TAMs were isolated and used to treat MDA-MB-231 cells. TAM EVs enhanced glucose consumption, lactate production, and apoptosis resistance of tumor cells. These effects occurred due to the delivery of HISLA, a long non-coding RNA (lncRNA), which, upon binding to prolyl hydroxylase domain protein 2 (PDH2), decreases the hydroxylation and degradation of HIF-1α, stabilizing it. Furthermore, MDA-MB-231 cells were inoculated into the mammary fat of NOD/SCID mice. This model observed that the intratumoral injection of TAM EVs reduced the response to chemotherapy, enhanced ^{18}F-fluorodeoxyglucose (^{18}FDG) accumulation, and increased lung metastasis. Besides that, GLUT1, GLUT3, HK2, and HIF-1α expression were increased in the xenografts, indicating that TAM-EVs play an essential role in the metabolic reprogramming of breast tumor cells, *in vitro* and *in vivo* [Figure 1 and Table 1][75].

Similarly, TAM-derived exosomes increase aerobic glycolysis in hepatocellular carcinoma (HCC) cells. A human HCC cell line (Hep3b) was treated with exosomes obtained by the CM released by macrophages isolated from HCC tumor samples or PBDMs obtained from healthy donors polarized into M2 phenotype, with phorbol 12-myristate 13-acetate (PMA) and interleukin 4 (IL-4). It was observed that both exosomes induced an increase in glucose consumption, lactate production, extracellular acidification rate, and proliferation in Hep3b cells. Furthermore, it also increased GLUT 1, HK2, and LDHA expression. These changes were attributable to the delivery, through exosomes, of RP-11-1100L38 - an M2 macrophage polarization-associated lncRNA (lncMMPA). This acts as a competing endogenous RNA for miR-548, which targets aldehyde dehydrogenase 1 family member A3 (ALDH1A3). Reducing ALDH1A3 expression, in turn, promotes lactate production and cell proliferation. Concurrently, it was observed that exosomes obtained from PBDMs polarized into M2 phenotype increased tumor growth in BALB/c nude mice

Table 1. Overview of EVs derived from macrophages, fibroblasts, adipocytes, and AT cargoes and effects in cancer cell biology and metabolism

Study type	Donor cell	EVs content	Recipient cell	Animal model	Effects	Ref.
Macrophages						
In vitro and *in vivo*	PBDMs from breast cancer patients or healthy donors treated with MDA-MB-231 cells conditioned medium	HISLA	MDA-MB-231 (Breast cancer cell line)	NOD/SCID mice inoculated with MDA-MB-231	Increased glucose consumption, lactate production, and apoptosis resistancethrough HIF-1α stabilization *in vitro*. ^{18}FDG accumulation, lung metastasis, chemioresistance, increased GLUT1, GLUT3, HK2, and HIF-1 α, *in vivo*.	[75]
In vitro and *in vivo*	Macrophages isolated from hepatocellular carcinoma samples and PBDMs from healthy donors treated with PMA and IL-4	lncMMPA	Hep3b (Hepatocellular carcinoma cel line)	BALB/c nude mice inoculated with Hep3B cells	Increased glucose consumption, lactate production, extracellular acidification rate, proliferation, GLUT 1, HK2, LDHA expression *in vitro*, and tumor growth *in vivo*.	[76]
In vitro and *in vivo*	THP-1 (Leukemia monocytic cell line) treated with PMA and IL-4	miR- 193b-3p	SW1990 (Pancreatic cancer cell line)	Lung metastasis model inoculated with SW1990 cells	Increased glutamine uptake, proliferation, migration, and invasion *in vitro* and lung metastasis ***in vivo*** through TRIM62/cMyc signaling.	[77]
In vitro and *in vivo*	Bone marrow-derived macrophages from C57CL/7 mice and RAW264.7 (mice macrophage cell line) treated with MC-38 conditioned medium	DOCK 7	MC-38 and CT26 (colorectal cancer cell lines)	C57BL/6 and BALB-C mice inoculated with MC-38 and CT-26, pretreated with TAM-EVs	Increased migration and invasion, altered EMT markers, decreased membrane and intracellular cholesterol content, and enhanced membrane fluidity *in vitro* through the RAC1/ABCA1/AKT/FOXO1 pathway. It also increases metastatic burden *in vivo*.	[81]
Fibroblasts						
In vitro and *in vivo*	Fibroblasts from breast cancer patients	SNHG3	MCF7 and MDA-MB-453 (Breast cancer cell lines)	BALB/c nude mice inoculated with MDA-MB-453 cells	SNHG3 functions as a miR-330-5p sponge to positively regulate PKM expression, inhibit mitochondrial oxidative phosphorylation, and increase glycolysis carboxylation *in vitro*. SNHG3 knockout in CAF-derived exosomes inhibits breast tumor growth *in vivo*.	[91]
In vitro	Fibroblasts from prostate cancer patients	possible miR-22, let7a, miR-125b	PC3 (Prostate cancer cell line)	No longer detected	Reduced OXPHOS; glycolysis increase; increased glucose uptake and lactate secretion; upregulated reductive carboxylation of glutamine.	[51]
In vitro	Fibroblasts from pancreatic cancer patients	Amino acids, lactate, acetate, TCA intermediates and lipids	BxPC3 (WildType Kras) and MiaPaCa-2 (Homozygous Kras) (Pancreatic cancer cell lines)	No longer detected	Facilitate cancer cell proliferation under nutrient deprivation conditions.	[51]
In vitro and *in vivo*	Fibroblasts from lung adenocarcinoma patients	lncRNA-LINC01614	A549 (Lung cancer cell line)	BALB/c nude and NCG mice, and zebrafish inoculated with A549	Upregulation of glutamine transporters *in vitro and in vivo*. Higher mitochondrial oxidative phosphorylation and ATP synthesis *in vitro*. Increase in proliferation, migration, and invasion, *in vitro and in vivo*.	[92]
In vitro and *in vivo*	Fibroblasts from breast cancer patients	miRNA-7641 (Lower concentrations)	MDA-MB-231 and SKBR3 (Breast cancer cell lines)	BALB/c nude mice inoculated with MDA-MB-231	Higher glycolysis rate and proliferation in breast cancer cells by targeting HIF-1α regulation and upregulating HK2, GLUT1, and LDHA *in vitro*. Promotion of breast cancer growth, *in vivo*.	[90]
Adipocytes and the AT						
In vitro and *in vivo*	Breast AT(obese and overweight)	miR-155-5p, miR-30a-3p, and miR-10a-3p	MCF7 (Breast cancer cell line)	C57BL/6 mice treated with EO771 cells previously educated with O-EV	Increased cell proliferation, mitochondrial density, oxygen consumption rate, and ATP production *in vitro* through miR-155-5p, miR-10a-3p e miR-30a-3p transfer, and Akt/mTOR/P70S6K activation. Promotion of breast cancer growth, *in vivo*.	[82]

In vitro and *in vivo*	Adipocytes differentiated from 3T3-L1	MTTP	HCT116 and SW480 (Colorectal cancer cell lines)	Ob/ob mice previously treated with or without KD-MTTP lentivirus and MC-38 cells.	Promotes ferroptosis resistance through MTTP transfers, which increases GPX4 and xCT levels and worsens response to oxaliplatin.	[83]
In vitro and *in vivo*	Adipocytes differentiated from 3T3-F442A and Adipocytes isolated from HFD and LFD C57BL/6J mice	FAO Enzymes (ECHA, HCDH) and fatty acids (FA)	SKMEL28 and 1205L (Melanoma cancer cell lines)	Nude athymic mice treated with GFP-SKMEL28 and HFD AD-EXO	Increased FAO, mitochondrial dynamics rearrangement, and melanoma cell migration support through FAO enzymes and FA transport.Increased metastatic colonization in mice lungs.	[84] [85]
In vitro	Adipocytes differentiated from 3T3-L1	No longer detected	PC3 and DU145 (Prostate cancer cell lines)	No longer detected	Increased glucose uptake, lactate production, and ATP generation.	[86]

EVs: Extracellular vesicles; AT: adipose tissue; ATP: adenosine triphosphate; ABCA1: ATP-binding cassette subfamily A member 1; CAFs: cancer-associated fibroblasts; DOCK 7: dedicator Of cytokinesis 7; ECHA: trifunctional enzyme subunit alpha; EMT: epithelial-mesenchymal transition; FAO: fatty acid oxidation; ^{18}FDG: ^{18}F-fluorodeoxyglucose; GLUT: glucose transporter; GPX4: glutathione peroxidase 4; HCDH: 3-hydroxy acyl-CoA dehydrogenase; HFD: high-fat diet; HIF-1α: hypoxia-inducible factor 1-alpha; HK2: hexokinase 2; IL-4: interleukin 4; LDHA: Lactate dehydrogenase A; LFD: low-fat diet; LINC01614: long intergenic non-protein coding RNA 1614; lncRNA: long non-coding RNA; lncMMPA: RP-11-1100L38 - M2 macrophage polarization associated lncRNA; MTTP: microsomal triglyceride transfer protein; PKM: pyruvate kinase M; PMA: phorbol 12-myristate 13-acetate; OXPHOS: oxidative phosphorylation; RAC1: ras-related C3 botulinum toxin substrate 1; SNHG3: small nucleolar RNA host gene 3; TRIM62: tripartite motif containing 62; xCT: cystine transporter; 3T3-L1: murine preadipocyte cell line; 3T3-F442A: clonal sublines isolated from 3T3 mouse embryonic fibroblasts; TCA: tricarboxylic acid cycle; PBDMs: peripheral blood monocytes.

inoculated with Hep3B [Figure 1 and Table 1][76].

Concerning the role of EVs in promoting metabolic shifts within the TME, Zhang *et al.* have demonstrated an increase in glutamine uptake in a human pancreatic adenocarcinoma cell line (SW1990 cells) when co-cultured with M2 macrophages (differentiated *in vitro* from THP-1, a human leukemia monocytic cell line). Interestingly, this effect was prevented in the presence of GW4869, an inhibitor of exosome biogenesis. This metabolic alteration occurs due to miR-193-3b-3p delivery through exosomes, which targets tripartite Motif Containing 62 (TRIM62), thus reducing c-Myc degradation. The exact mechanism also promoted increased proliferation, migration, and invasion of SW1990 cells and lung metastasis in mice inoculated with SW1990 cells previously treated with M2 exosomes [Figure 1 and Table 1][77]. Those effects may be due to the increased glutamine uptake, which, as a carbon and nitrogen source, has a role in amino acid, nucleotide, and lipid biosynthesis and performs anaplerotic replenishment of the TCA[78], essential elements sustaining cancer cell proliferation[79], migration, and invasion[80].

It has already been demonstrated that TAM-EVs also alter cholesterol metabolism in CRC cells. A study conducted by Chen *et al.* showed that EVs obtained from C57CL/7 mice bone marrow-derived macrophages and a mice macrophage cell line (RAW264.7) previously educated with the CM from a mice CRC cell line (MC-38) promoted migration and invasion in mice CRC cell lines (MC-38 and CT26). Besides that, it also altered EMT markers and deregulated cholesterol metabolism by decreasing membrane and intracellular cholesterol content in a dedicator Of Cytokinesis 7 (DOCK 7)-dependent manner. Their results demonstrated that DOCK 7 was anchored on the TAM-EVs surface and delivered to the tumor cells. This promoted the upregulation of RAC1, a classic small GTPase, triggering the ATP-binding cassette transporter (ABCA1) increase via AKT/FOXO1. These alterations increased membrane fluidity, resulting in cell motility and invasiveness. Those results were corroborated *in vivo*; the injection of C57BL/6 and BALB-C mice with MC-38 and CT-26 cells previously

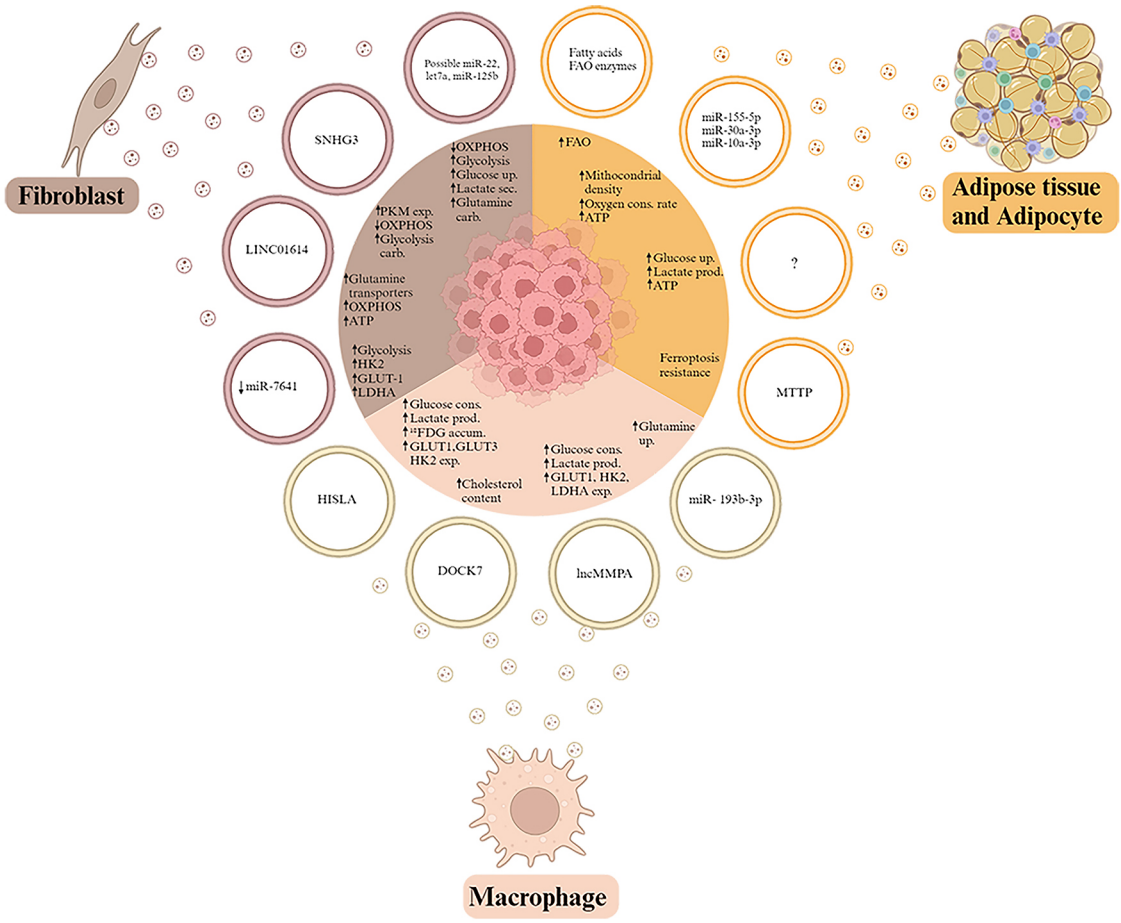

Figure 1. Overview of the metabolic alterations on cancer cell lines and tumors promoted by EVs derived from macrophages, fibroblasts, adipocytes, and AT. Fibroblasts liberate exosomes-containing lncRNA SNHG3, leading to positive regulation of PKM, resulting in the augmentation of glycolysis carboxylation and reduction of mitochondrial OXPHOS in breast cancer cell lines. Prostate cancer cells stimulated with CDEs demonstrated increased glucose uptake, glycolysis, lactate secretion, reductive carboxylation of glutamine, and reduced OXPHOS. These effects were possibly achieved by miR-22, miR-let7a, and miR-125b interaction through CDE delivery. CDEs transport LINC01614 to lung cancer cell lines, upregulating OXPHOS, glutamine transporters, and ATP synthesis. CDEs carrying lower concentrations of miR-7641 promote HIF-1α stabilization, resulting in an upregulation of HK2, GLUT1, LDHA, and increased glycolysis rate and cell proliferation in breast cancer cell lines. TAM-EVs deliver HISLA to breast cancer cells, generating enhanced glucose consumption, lactate production, ^{18}FDG accumulation, and elevated GLUT1, GLUT3, HK2, and HIF-1α expression. DOCK 7 was found to be carried on the surface of TAM-EVs, leading to increased cholesterol content and altered cholesterol metabolism in CRC cells. TAM-derived exosomes demonstrated a positive regulation of glucose consumption, lactate production, and GLUT1, LDHA, and HK2 expression in HCC. This effect was due to the transport of lncMMPA by TAM-derived exosomes. Moreover, TAM-derived exosomes were observed to carry miR-193-3b-3p, culminating in enhanced glutamine uptake in the human pancreatic adenocarcinoma cell line. AD-EXOs promote ferroptosis resistance mediated by the transference of MTTP to colorectal cancer cell lines, affecting the response to chemotherapy. The miRNAs miR-155-5p, miR-10a-3p, and miR-30a-3p were proposed to be enriched in O-EVs and delivered to human breast cancer cell lines, stimulating increased mitochondrial density, oxygen consumption rate, and ATP production. AD EVs carry enzymes responsible for FAO, upregulating this pathway, leading to an increased invasion and migration of the human melanoma cell line. AD EVs increase glucose uptake, lactate production, and ATP generation in prostate cancer cell lines, although the EVs cargo is unknown. EVs: Extracellular vesicles; AT: adipose tissue; SNHG3: small nucleolar RNA host gene 3; HIF-1α: hypoxia-inducible factor 1-alpha; DOCK 7: dedicator of cytokinesis 7; TAMs:tumor-associated macrophages; CRC:colorectal cancer; HCC:hepatocellular carcinoma; lncRNA: long non-coding RNA; lncMMPA: lncMMPA: RP-11-1100L38; ATP: adenosine triphosphate; FAO: fatty acid oxidation; ^{18}FDG accum.: ^{18}F-fluorodeoxyglucose accumulation; Glutamine carb.: Glutamine carboxylation; Glucose cons.: Glucose consumption; GLUT: glucose transporter; Glucose up.: Glucose uptake; HK2: hexokinase 2; LDHA exp.: lactate dehydrogenase expression; Lactate prod.: Lactate production; Lactate sec.: Lactate secretion; lnc-RNA: long non-coding ribonucleic acid; miR: micro-RNA; MTTP: microsomal triglyceride transfer protein; OXPHOS: oxidative phosphorylation; Oxygen cons. rate: Oxygen consumption rate; PKM exp.: pyruvate kinase M expression (Created with BioRender).

treated with TAM-EVs increased metastatic burden. Concurrently, simvastatin, an ABCA1 inhibitor,

decreased hepatic metastatic nodules. These results demonstrate the relevance of cholesterol metabolism in CRC, both *in vitro* and *in vivo* [Figure 1 and Table 1][81].

Adipocyte and adipose tissue-derived EVs

While the role of adipose tissue (AT) and cancer-associated adipocytes (CAAs) in cancer is well-established, with their secretion of adipokines, growth factors, and EVs stimulating tumor cell proliferation, invasion, and chemoresistance, the mechanisms by which EVs released by adipocytes and AT modulate tumor metabolism remain largely unexplored.

In a study by Liu *et al.*, the influence of EVs derived from obese breast AT on the metabolism of breast tumor cells was investigated. The results demonstrated that a human breast adenocarcinoma cell line (MCF-7 cells) educated with EVs derived from obese and overweight women AT (O-EVs) displayed increased proliferation, mitochondrial density, oxygen consumption rate, and ATP production. The increase in proliferation by O-EVs was shown to be OXPHOS-dependent as metformin, an inhibitor of mitochondrial complex I, reversed the proliferative effects. Concurrently, the previously educated MCF-7 cells had increased their proliferative capacity. This was abolished when the stimuli with O-EV occurred in the presence of metformin - an inhibitor of complex I and ATP synthesis. One proposed mechanism was the transfer of specific miRNAs, such as miR-155-5p, miR-10a-3p, and miR-30a-3p, which are enriched in O-EVs compared to EVs from lean women [Figure 1 and Table 1]. Silencing these miRNAs partially reduced the increase in proliferation and OXPHOS induced by O-EVs. Furthermore, activation of the AKT/mTOR/P70S6K pathway has also been shown to be a crucial mechanism for the metabolic and functional effects mediated by O-EVs. *In vivo* assays with female C57BL6 mice fed low-fat (LFD) or high-fat diets (HFD) showed that murine mammary cancer cells (EO771) previously educated with EVs isolated from HFD mammary AT increased tumor growth compared to EO771 educated with EVs from LFD-fed mice[82].

Zhang *et al.* demonstrated that exosomes derived from adipocytes (AD-EXOs) 3T3-L1 could reduce susceptibility to ferroptosis in human CRC cell lines (HCT116 and SW480), thus promoting chemoresistance to oxaliplatin. One proposed mechanism was the transfer of microsomal triglyceride transfer protein (MTTP), which increases AD-EXOs [Figure 1 and Table 1]. They showed that the MTTP/PRAP1 complex inhibits the expression of ZEB1 and increases the levels of glutathione peroxidase 4 (GPX4) and the cystine transporter (xCT). Together, these alterations triggered lower lipid peroxidation and a reduced proportion of polyunsaturated fatty acids (PUFA), decreasing the ferroptosis induced by oxaliplatin. The *in vivo* assays involved genetically obese mice (ob/ob), local adipose KD-MTTP using lentivirus transfection, and tumor implantation (MC-38 cells). The obese mice treated with KD-MTTP showed a more significant response to oxaliplatin, confirming that MTTP activity inversely regulates sensitivity to chemotherapy[83].

Concurrently, AD-EXOs from 3T3-F442A were reported to increase both the migratory and invasive capacity of two lineages of human melanoma (SKMEL28 and 1205L) in an FAO-dependent manner [Figure 1 and Table 1]. The functional effect of these EVs was confirmed in an *in vivo* model, in which the injection of GFP-SKMEL28 treated with AD-EXOs increased the metastatic colonization in the lungs of female nude athymic mice[84]. Proteomic and western blotting analysis of these EVs revealed the presence of enzymes committed to FAO, such as ECHA (a subunit of the trifunctional protein) and HCDH (hydroxy acyl-coenzyme A dehydrogenase). Those findings aligned with the increased rate of FAO in the cells treated with AD-EXOs, sustaining the rise in migration and invasion once reverted in etomoxir's presence[84]. As expected, those effects were even more pronounced within the obesity context; in an HFD model using C57BL/6J mice, the results showed an increase in exosomes released from adipocytes derived from obese

AT, which further promoted the invasive capacity of SKMEL28 and 1205L cells[84].

To further comprehend the mechanisms by which obesity increased the invasive capacity of Mel 1 in an FAO-dependent manner, Clement *et al.* monitored the transference of proteins from exosomes derived from 3T3-F442A adipocytes to SKMEL28 cells using SILAC (Stable Isotope Labeling of Amino Acids in Cell Culture) followed by mass spectrometry, and identified that transferred proteins from exosome to SKMEL28 cells were selectively sorted. Even though obesity was not related to an increment in transferred proteins, it was related to the increased transfer of fatty acids to the Mel 1. Such fatty acids were then mobilized by lipophagy, in conjunction with OXPHOS-transferred enzymes, thus increasing FAO. The increase in FAO, in turn, was related to a modulation in mitochondrial dynamics changes, which were co-localized with the cytoskeleton protrusions to support the migration of Mel 1 [Figure 1 and Table 1][85].

In addition to the effects of EVs derived from adipocytes upon changes in FAO, it was observed that EVs originating from differentiated 3T3-L1 adipocytes (AD-EVs) promoted a metabolic switch toward a glycolytic state in two human prostate cancer tumor lines (PC3 and DU145). Upon treatment with AD-EVs, both cell lineages displayed increased glucose uptake and lactate production, along with ATP generation sustained by HIF-1α stabilization in an AKT-dependent manner [Figure 1 and Table 1]. Such metabolic reprogramming promoted by AD EVs sustained the aggressiveness by increasing the rates of proliferation, migration, and invasion, other than resistance to the chemotherapy drug docetaxel[86].

Although the importance of EVs released by adipocytes and AT is recognized in cancer, few studies thoroughly explore their role as a metabolic modulator of tumor cells. In addition to the scarcity in the literature, another limitation concerns the model for obtaining adipocyte EVs; most studies isolate these vesicles from differentiated immortalized murine lines such as 3T3-L1 preadipocytes, which may not reliably reflect the conditions of human preadipocytes. Finally, many articles associate the findings of EVs derived from adipocytes and extrapolate their interpretation to obesity. The interest in this condition can be understood by the fact that an increase in AT characterizes obesity and is directly associated with several types of cancer. However, few studies detail the metabolic mechanisms induced by EVs released by adipocytes or AT in this condition.

Fibroblast-derived EVs

Fibroblasts, integral to the stroma, are key players in maintaining the extracellular matrix (ECM) and engaging in signal exchange with the microenvironment, particularly in wound healing. In the context of cancer, the TME is densely populated by fibroblasts, which undergo an activation process mediated by neoplastic cells, transforming them into CAFs. These CAFs, as subverted cells, overexpress different types of molecules, such as transforming growth factor beta (TGF-β), stromal cell-derived factor 1 (SDF-1), matrix metalloproteinase-2 (MMP-2), and so on[87], thus significantly contributing to tumor initiation, progression, and metastasis through a variety of interactions[88]. Therefore, the role of CAFs in the TME is paramount, and understanding their mechanisms is crucial in cancer biology and TME.

EVs released from neoplastic cells also contribute to converting fibroblasts to CAFs. These EVs trigger the metabolic reprogramming of CAFs toward glycolysis, producing lactate, pyruvate, and other metabolites that cancer cells absorb to fuel their metabolic pathway and survive. Conversely, these "educated" fibroblasts can also secrete EVs that may interact with cancer cells, inducing metabolic reprogramming and potentially leading to cancer cell progression[89].

A study performed by Zhao *et al.* provided compelling evidence of the role of exosomes released by CAFs (CDEs) derived from prostate cancer biopsies. These CDEs drive the oxygen consumption rate (OCR) inhibition in PC3 cells. The effects of CDEs were partly due to miRNAs, including miR-22, let7a, and miR-125b. In addition to the dysregulation in OXPHOS, CDEs also upregulated glucose uptake and glycolysis [Figure 1 and Table 1]. Oppositely, CDEs increased the reductive carboxylation of glutamine-driven glutamine's contribution to lipogenic acetyl-CoA for enabling membrane synthesis, which probably sustained the enhanced proliferative state of the prostate cancer cells[51].

Corroborating the role of EVs in the metabolic reprogramming of cancer cells, CDEs from biopsies of pancreatic cancers, enriched in amino acids (glutamine, threonine, phenylalanine, valine, isoleucine, glycine, arginine, and serine), lactate, acetate, lipids, and TCA intermediates, displayed a role on supplying amino acids to oncogenic pancreatic cancer cells. The results demonstrated that this supply was independent of Kras since CDEs could rescue the loss of proliferation in the two human pancreatic cancer cell lines studied: BxPC3 (wild-type Kras) and MiaPaCa-2 (homozygous Kras) under nutrient deprivation [Figure 1 and Table 1][51].

In line with those findings, CAFs-derived exosomes obtained from breast cancer biopsies containing lower levels of miR-7641 drove glycolytic profiles in human breast cancer cell lines (MDA-MB-231 and SKBR3) and increased proliferative rates compared to exosomes derived from normal fibroblasts. This mechanism was attributable to the tumor suppressive properties of miR-7641 in targeting the transcription factor HIF-1α; when in low concentrations of miR-7641, upregulation of HIF-1α was reported, thus triggering increased expression of HK2, GLUT1, and LDHA [Figure 1 and Table 1][90].

Exosomes from CAFs derived from breast cancer biopsies were reported to be enriched in SNH3G, a lncRNA that acts as a molecular sponge for miRNA-330-5p. Theoretically, miR-330-5p decreases pyruvate kinase M (PKM) expression, suppressing glycolysis metabolism and proliferation in tumor cells. However, the uptake of those exosomes induced a PKM-positive regulation in a human breast cancer cell line (MDA-MB-453), inhibiting the OXPHOS [Figure 1 and Table 1]. This effect was due to the suppressive SNHG3/miR-330 signaling axis regulating the proliferation and metabolism of breast tumor cells by modulating PKM at the post-transcription level[91].

Liu *et al.* identified that exosomes derived from CAFs from lung adenocarcinoma (LUAD) biopsies were enriched in the long intergenic non-protein coding RNA 1614 (LINC01614). LINC01614, in turn, enhanced the glutamine metabolism of a human LUAD cell lineage (A549), thus promoting glutamine "cell addiction." The results demonstrated that LINC01614 was transported via exosomes from CAFs and subsequently absorbed by LUAD cells, modulating the tumor metabolism by upregulating the expression of glutamine transporters and consequently inducing a preferential uptake of glutamine, driving higher proliferation, migration, and invasion abilities. Both glycolysis and OXPHOS rates did not differ by the treatment with the exosomes from CAFs, although a higher OXPHOS and ATP synthesis were observed. Interestingly, it was shown that LINC01614 transported within CAF exosomes enhanced Annexin A2 and p65 (Rela) interactions, promoting NF-κB activation and the release of interleukin-6 (IL-6) and CXCL10 by A549 cells, thus upregulating LINC01614 by CAFs when in co-culture, revealing a feedforward loop [Figure 1 and Table 1][92].

A growing landscape of studies corroborates the idea that noncancerous cells associated with tumors secrete a variety of cargo delivered by EVs that can modulate some of the well-known hallmarks of cancer. Regarding cancer cell metabolism, we have compiled evidence highlighting the role of CAF-derived EVs in

metabolic reprogramming. In this scenario, CAFs-derived EVs fuel tumor cells with amino acids and ready-to-use metabolic intermediates, modifying the target cells' balance between glycolysis and OXPHOS. In addition, miRNAs and lncRNA carried by CAF EVs induce metabolic reprogramming, ultimately sustaining enhanced cancer cell proliferation, migration, and invasiveness.

Figure 1 and Table 1 show the recognized modulatory roles of macrophage, fibroblast, adipocyte, preadipocyte, and AT-derived EVs within the TME upon cancer cell metabolism.

POSSIBLE ROLES OF EVS FROM SURROUNDING TME IN MODULATING CANCER CELL METABOLISM: A PERSPECTIVE VIEW

Tumor-infiltrating lymphocytes-derived EVs

Tumor-infiltrating lymphocytes (TILs) are a crucial component of the TME. They are lymphoid cells comprising T cells, natural killers (NKs), and, more recently, B cells, and are easily found within TME. Initially committed to antitumor defense, TILs can lose their tumor-killing ability in response to immunosuppressive factors secreted in TME, thereby leading to disease progression[93].

NK cells act in the initial defense against the tumor because they do not need prior stimulation and have a non-specific killing ability[94]. It has been demonstrated by several studies that NK-derived EVs (NK-EVs) contain miRNAs that are known to regulate the glycolytic metabolism of tumor cells. Among them, miR-186[95] reduces aerobic glycolysis through the downregulation of HIF-1α in the human osteosarcoma (OS) (U2 and HOS) [111] and in the human gastric[96] cell lines (MKN45 and SGC7901) [Figure 2A], thus functioning as a tumor suppressor. Concurrently, miR-125b-5p and miR-199a-5p, whose levels are increased in NK-EVs[97], also downregulate HK2 activity [Figure 2A], decreasing glycolysis in human laryngeal squamous cell carcinoma cell lines (AMC-HN-8 and Tu-177)[98], and human hepatocarcinoma cell lines (Huh-7, HepG2, and Hep3b)[99] [Figure 2A].

The infiltration of $CD8^+$ cells, also known as cytotoxic T lymphocytes, into the TME indicates a better prognosis for several types of cancer; hence, $CD8^+$ T cells are recognized as critical drivers of antitumor activity[100]. In this context, emerging evidence suggests that one of the primary mechanisms by which $CD8^+$ cells exert tumor-killing mechanisms involves the delivery of cargo such as mRNA, miRNA, proteins, and lipids to tumoral cells within EVs[101,102]. It has already been reported that miR-765 exists within exosomes from healthy $CD45RO^-CD8^+$ T cells[102]. Interestingly, miR-765 has been recognized as a tumor suppressor, once promoting decreased lipid content in two human lineages of clear cell renal cell carcinoma (ccRCC) cell lines (A498 and Caki-1). This effect was mediated by the downregulation of proteolipid protein 2 (PLP2), a direct target gene of miR-765[103]. Thus, such evidence can highlight a possible mechanism by which EVs derived from $CD8^+$ T cells affect lipid metabolism in ccRCC [Figure 2B].

$CD4^+$ T cells, also known as helper T lymphocytes, assist the $CD8^+$ T and B cell response[104]. They can also produce pro-inflammatory cytokines and directly kill tumor cells[105]. In the presence of interleukin-2 (IL-2), which promotes its activation, $CD4^+$ T cells release exosomes enriched in miRNAs, such as miR-155-5p, among others[106]. The role of miR-155-5p in mediating the metabolic reprogramming in renal cancer has been highlighted by Bogusławska *et al.*, which demonstrated the commitment of this miRNA under the downregulation of glycine amidinotransferase (GATM) gene expression in human ccRCC cell lines (Caki-2 and KIJ265T). GATM encodes glycine amidinotransferase, an enzyme committed to creatine synthesis[107] [Figure 2C]. It is worth mentioning that creatine is predicted to inhibit the growth of tumor cells by inhibiting glycolysis and attenuation of acidosis. However, the exact mechanism remains unknown[107,108].

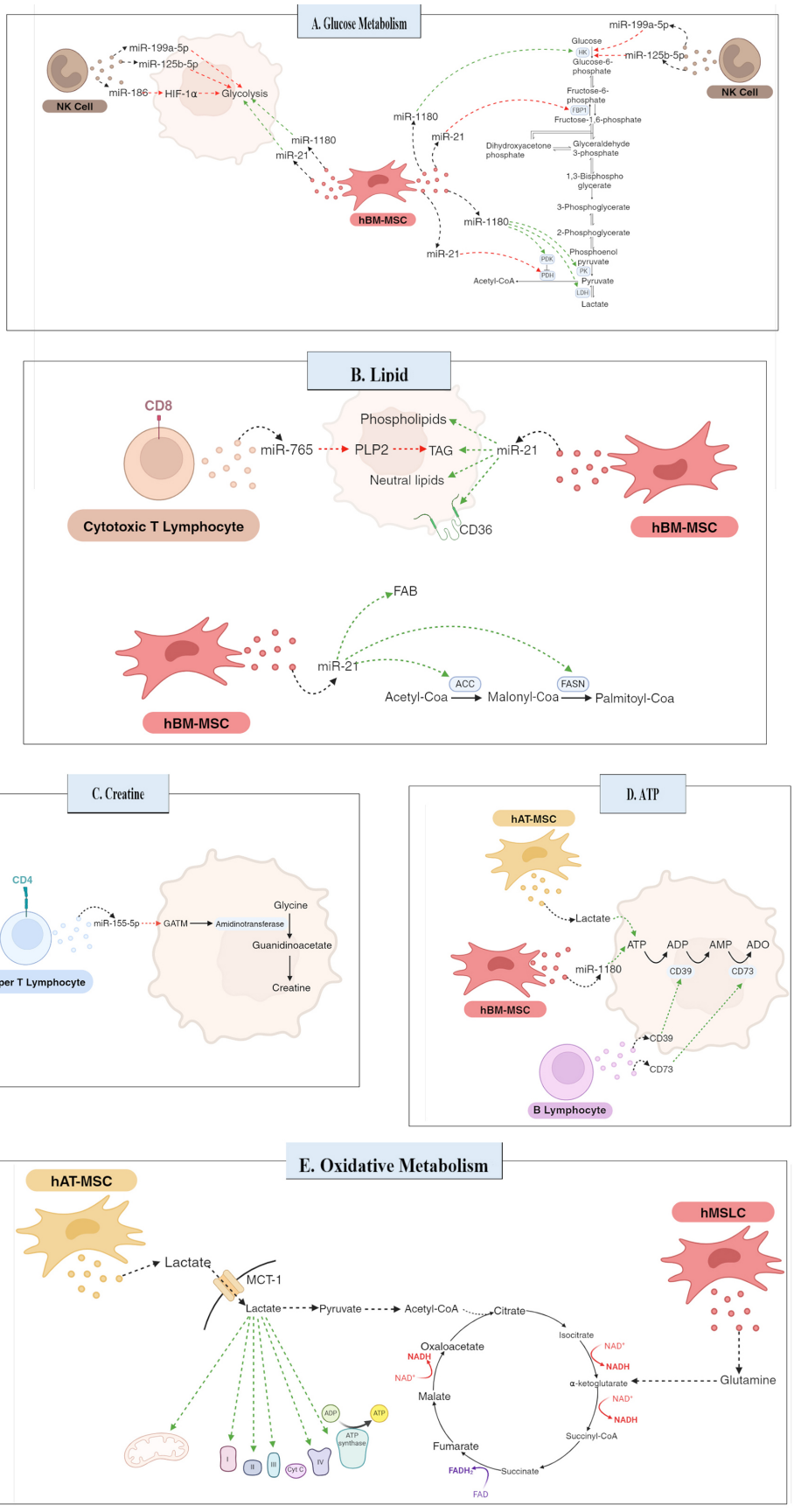
A. Glucose Metabolism
NK Cell
miR-199a-5p
miR-125b-5p
miR-186
HIF-1α
Glycolysis
miR-1180
miR-21
hBM-MSC
Glucose
HK
Glucose-6-phosphate
Fructose-6-phosphate
FBP1
Fructose-1,6-phosphate
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate
1,3-Bisphospho glycerate
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenol pyruvate
PK
Pyruvate
LDH
Lactate
PDK
PDH
Acetyl-CoA
B. Lipid
CD8
Cytotoxic T Lymphocyte
miR-765
PLP2
Phospholipids
TAG
Neutral lipids
CD36
FAB
ACC
FASN
Acetyl-Coa
Malonyl-Coa
Palmitoyl-Coa
C. Creatine
CD4
Helper T Lymphocyte
miR-155-5p
GATM
Amidinotransferase
Glycine
Guanidinoacetate
Creatine
D. ATP
hAT-MSC
Lactate
ATP
ADP
AMP
ADO
CD39
CD73
B Lymphocyte
E. Oxidative Metabolism
hMSLC
MCT-1
Pyruvate
Acetyl-CoA
Citrate
Isocitrate
Oxaloacetate
NADH
NAD+
α-ketoglutarate
Glutamine
Malate
Fumarate
Succinyl-CoA
Succinate
FADH2
FAD
ATP synthase
Cyt C

Figure 2. Proposed tumor metabolic modulation exerted by EVs derived from TILs and MSCs. Small circles represent EVs and exosomes from the origin cells. Suggested tumor metabolic targets of the microparticles cargo are depicted and represented by dotted arrows (red: negative regulation; green: positive regulation). A: Reduced tumor glycolysis could be achieved by miRs within NK-derived EVs by downregulating HIF-1α (miR-186) and HK (miR-125b-5p and miR-199a-5p, as detailed). Conversely, increased glycolysis may be epigenetically induced by miR-21 and miR-1180 within hBM-MSC exosomes at specific regulatory checkpoints. Expected glycolytic targets of miRs within NK and h-BM-MSC-derived EVs and exosomes. Depending on the EV-secreting cell and specific miR cargo, both glycolysis downregulation (at HK level, by miR-186, miR-125b-5p, and miR-199a-5p from NK-derived EV, and at FBP1 and PDH levels, by the action of miR-21 contained in h-BM-MSC EVs) and upregulation (at HK, PK, PDK, and LDH levels through a miR-1180 modulation mediated by h-BM-MSC EVs) can be observed; B: cytotoxic T lymphocytes ($CD8^+$) can release miR-765 within exosomes. This miRNA could decrease the lipid content of tumor cells through PLP2 downregulation. Inversely, the onco-miR-21 contained in the exosomes of h-BM-MSC may increase the expression of the fatty acid translocase (CD36) in tumor cells, leading to enhanced exogenous uptake and intracellular levels of the energetic supply of phospholipids, neutral lipids, and TAG. Additionally, increased intracellular levels of the enzymes ACC and FASN related to lipid synthesis and FABP5 related to tumor progression in many cancers (reviewed in 26) may also be observed due to the miR-21 within h-BM-MSC exosomes. C: helper T lymphocytes ($CD4^+$) release exosomes enriched in miR-155-5p, which could negatively regulate the expression of the GATM gene that encodes glycine amidinotransferase, an enzyme involved in creatine synthesis; D: EVs derived from B lymphocytes contain CD39 and CD73, which are proteins involved in the phosphohydrolysis of ATP and ADP to AMP, producing ADO. Inversely, pro-tumoral roles of lactate and miR-1180 within h-MSC microparticles could be induced by increased ATP production and migratory capacity as a result of a modulation of the oxidative (E) or glycolytic (A) metabolism, respectively; E: hMSLC-EVs may provide Glutamine and further converted in α-ketoglutarate, replenishing the citric acid cycle (TCA) and fueling the metabolism of cancer cells. Similarly, a possible conversion of the exosomal lactate from hAT-MSC exosome to pyruvate may also replenish the TCA and enhance the ATP production by the mitochondrial complexes, thus boosting the tumor cell migration in an uptake mediated by the MCT-1 transporter. EVs: Extracellular vesicles; TILs: tumor-infiltrating lymphocytes; ACC: acetyl-CoA carboxylase; ADO: adenosine; ADP: adenosine diphosphate; AMP: adenosine monophosphate; ATP: adenosine triphosphate; CD4: T-cell surface glycoprotein CD4; CD8: a cluster of differentiation 8; CD36: fatty acid translocase; CD39: ectonucleoside triphosphate diphosphohydrolase 1; CD73: ecto-5′-nucleotidase; FABP5: fatty acid binding protein 5; FASN: fatty acid synthase; FBP1: fructose-1,6-bisphosphatase; GATM: glycine amidinotransferase; hAT-MSC: human adipose tissue mesenchymal stem cell; hBM-MSC: human bone marrow mesenchymal stem cell; HIF-1: hypoxia-inducible factor 1-alpha; HK: hexokinase; hMSLC: human mesenchymal stem-like cell; LDH: lactate dehydrogenase; MCT-1: monocarboxylate transporter 1; miR: micro-RNA; NK: natural killer; PDH: pyruvate dehydrogenase; PDK: pyruvate dehydrogenase kinase; PK: pyruvate kinase; PLP2: proteolipid protein 2; TAG: triacylglycerol; TCA: tricarboxylic acid cycle; I-IV: mitochondrial respiratory complexes. (Created with BioRender).

B lymphocytes also play an essential role in tumor immunity due to their ability to produce antibodies[105]. An analysis performed by Zhang *et al.* revealed that EVs derived from B lymphocytes obtained from C57BL/6J mice contained CD39 and CD73[109]. These proteins are involved in the phosphohydrolysis of ATP and ADP to AMP[110], producing adenosine, a metabolite produced at high concentrations in TME, playing a role in tumor-mediated immune evasion[111] [Figure 2D]. Concurrently, it was already reported that CD39 and CD73 are committed to the EMT of cancer cells[112].

This compiled evidence shows that EVs derived from TILs probably play an essential role in modulating tumor metabolism, increasing malignancy, or providing antitumoral properties. Therefore, studies are necessary to elucidate the role of EVs derived from TILs upon metabolic reprogramming in cancer cells.

Stem cell and mesenchymal cell-derived EVs

Mesenchymal stromal cells (MSCs) consist of a heterogeneous group of multipotent progenitor cells found in distinct adult tissues, harboring the capacity for self-renewal and differentiation into different cell types, such as adipocytes, chondrocytes, and osteoblasts[113]. Due to metabolic plasticity, MSCs acquire specific phenotypes in response to changes in the microenvironment. Likewise, in hypoxic conditions, glycolysis and PPP maintain the MSC stemness profile[114,115]. CSCs, which can be raised from mutated MSCs, also present self-renewal ability and differentiate into multiple malignant cell types, strongly related to tumorigenesis, treatment resistance, tumor metastasis, and recurrence[116].

Exosomes (MSC-Exo) and EVs (MSC-EVs) released by MSCs can exert both pro- or antitumoral effects, depending on tumor type and the source of the MSCs[117-124]. However, details about the underlying molecular mechanisms by which these microparticles modulate cancer cell metabolism remain scarce. To

the best of our knowledge, very few studies captured their content[118,124-126] and, to a lesser extent, the EVs released by CSCs (CSC-EVs)[127,128]. Biological activities, both *in vitro*[117-121,123-126,128-130] and *in vivo*[117-119,124,125,129], including internalization or cargo transference to tumor cells[118,119,121,124,125,130] were also identified. Based on captured knowledge and considering the known effects of representative individual cargo[131-135], the proposed modulatory mechanisms for cancer cell metabolism are depicted in Figure 2.

A large-scale study conducted in hypoxic and nutrient-deprived conditions to investigate the tumor-supporting role of human bone marrow MSC (hBM-MSC)-derived EVs (hBM-MSC-EVs) revealed the presence of critical components such as lactic and glutamic acids, lysosome-associated membrane glycoprotein 2 (LAMP2), tissue inhibitors of metalloproteinases-1 (TIMP-1) and -2 (TIMP-2), CD9 (tetraspanin-29), platelet-derived growth factor receptor (PDGFR), sphingomyelin, diacylglycerol, miR-21, and miR-34a. These hBM-MSC-EVs were then used as a stimulus in MCF-7 cells and human OS (KHOS) cells, leading to increased cell survival. Importantly, xenograft assays of MCF-7 cells injected with hBM-MSC-EVs provided *in vivo* evidence of their potential to support breast tumor growth, underscoring the practical implications of the study's findings[125].

Regarding the cargo present in MSC-Exo, studies have already demonstrated an enriched content of FDFT1 (farnesyl-diphosphate farnesyltransferase 1) involved in cholesterol metabolism, stearoyl CoA desaturase (SCD) involved in lipid metabolism, aldolase B and enolase 3 involved in glycolysis, apoptosis signal-regulating kinase 1 (ASK1, also known as mitogen-activated protein kinase 5 - MAP3K5), MKK3/6 (dual specificity mitogen-activated protein kinases 3 and 6), and ferritin heavy chain 1 (FTH1) involved in NRF2/glutathione pathway, as well as epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and proteins related to the canonical angiogenesis pathway[126]. Five miRs (miR-21, miR-92, miR-100, miR-143, miR-148) were identified as highly expressed within exosomes derived from human umbilical cord MSCs (hUC-MSC-Exo), of which miR-100-5p promoted both proliferation and migration of human pancreatic cancer (Panc-1) cells and tumor growth in a xenograft tumor model in which nude mice were injected with panc-1 cells in the presence of hUC-MSC-Exo[124]. Bioinformatic analysis revealed that ascorbic acid and aldehyde metabolism are the most significantly enriched pathways of the predicted targeted genes of these miRs. Besides that, (i) pentose and glucuronate interconversion; (ii) porphyrin metabolism; (iii) starch and sucrose metabolism; (iv) alanine, aspartate, and glutamate metabolism; and (v) regulation of lipid metabolism were also highlighted, among others[124]. A study by Vallabhaneni *et al.* demonstrated changes in the expression of twenty-nine miRs related to metastasis and cellular response to nutrients in KHOS cells treated with hBM-MSC-EVs. Through bioinformatic analysis, the results regarding the upregulated genes predicted interactions between the monocarboxylate transporter (MCT-1), ATPB5 (ATP-synthase), and oxidative stress players (Nrf2)[123]. Such findings highlight the hypothesis that MSC-EVs may affect oxidative metabolism in cancer cells.

In this context, an *in vitro* model demonstrated that treating the human OS cell line (Saos-2) with human MSCs derived from AT (hAT-MSC) revealed the influence of extracellular lactate in this tumor cell line. Indeed, the addition of known lactate concentrations to the culture of the OS cells triggered increased mitochondrial biogenesis, increased expression of I, II, IV, and V complexes of the respiratory chain, together with an increase in ATP production in an MCT-1 transporter-dependent manner, thus driving increased migratory capacity. Hence, lactate from hAT-MSC exosome to pyruvate may also replenish the TCA and enhance ATP production[129] [Figure 2D and E].

Another study demonstrated the influence of the glutamine released by human primary mesenchymal stem-like cells (hMSLC) on A549 and MCF-7 cell lines and primary cells isolated from malignant pleural effusion

and ascites samples from cancer subjects. The increased glutamine levels within the CM from hMSLC triggered tumor-repopulating cells' proliferation and colony formation in 3D soft fibrin gels. Such effects were blocked by the addition of l-γ-glutamyl-p-nitroanilide (GPNA), a glutamine transporter inhibitor, thus suggesting that glutamine may provide energy supply once glutamine can be converted in α-ketoglutarate, therefore replenishing the TCA[130] [Figure 2E].

miR-21 presents as a remarkable onco-miR in many human cancers[136], thus modulating the cancer cell metabolism at distinct targets. Additionally, the transference of miR-21 within hBM-MSC exosomes to MCF-7 and MDA-MB-231 cells was demonstrated, being related to chemoresistance and tumor progression, both from *in vitro* and *in vivo* tumor xenograft models, due to the miR-25-induced S100A6 protein expression[135]. Indeed, increased glycolysis is observed in the human gastric cell lines (MGC803 and SGC□7901) by the direct effect of the miR-21 upon the reduction of mRNA and protein levels of pyruvate dehydrogenase A1 (PDHA1)[132]. Similar findings were observed in an *in vitro* study performed in A549, evidencing the suppression of the expression of glycolytic enzyme fructose-1,6-bis phosphatase (FBP1) as a direct target of miR-21[133] [Figure 2A]. Additionally, miR-21 promoted the growth and migration of A549 and H1703 cells by increasing the expression of the CD36 (fatty acid translocase), intracellular levels of phospholipids, neutral lipids, and triacylglycerides, together with an increase in both fatty acid synthase (FASN), acetyl-CoA carboxylase 1 (ACC1), and fatty acid binding protein 5 (FABP5) levels[131] [Figure 2B]. Similarly, increased pro-tumoral activity and chemoresistance were features mediated by the miR-1180, the most abundant miRNA within CM from hBM-MSC. This was demonstrated by evaluation based on *in vitro* and *in silico* models with the human ovarian cancer cell lines (SKOV3 and COC1). The mechanism involved: *i*. the modulation of the secreted frizzled-related protein 1 (SFRP1); *ii*. activation of the Wnt signaling pathway; *iii*. increased glycolysis togheter with the increased expression of glycolitic enzymes [Figure 2A] and; *iv*. increased ATP production[134] [Figure 2D].

The metabolomic profile of hCSC-EVs obtained from human primary metastatic Mel 1 highlights the differentially expressed metabolites glycerophosphocholine (GPC), triacylglycerol (TAG), glycerophosphoglycerol (PG), glycerophosphoserine (PS)[127]. Such findings are compatible with lipid metabolism's role in the metastatic process[137]. A multi-omic study of the small EVs (sEVs) from distinct subpopulations of human glioblastoma stem-like cells (GSC) (proneural: NCH421k, NCH644, NCH441; mesenchymal: NCH705, NCH711d) has demonstrated their role as critical mediators of proteins and metabolites related to the metabolism of amino acids and fatty acids both related to glioblastoma progression. Furthermore, the role of such EVs in the phenotype modulation of GSC subpopulations highlights their relevance in supporting the metabolic heterogeneity in glioblastoma[128].

The findings captured by distinct experimental approaches support the modulatory role of microparticles shed by MSCs and CSCs upon the metabolism of different cancer cells. Despite the scarcity of studies in this field, the outcomes of biological relevance reinforce the need for additional investigations to highlight the underlying molecular mechanisms that may suggest possible targets for metabolic cancer control.

Therapeutic role of EVs in cancer metabolism

The applicability of EVs in cancer treatment has become an interesting strategy. Some studies investigate the role of non-tumor EVs in altering the tumor metabolism, leading to an antitumoral effect. Another interesting approach is to treat tumor cells with EVs that have had their content previously modified.

An interesting study showed that EVs from Lactobacillus plantarum can affect the metabolism of CRC. The study observed that the EVs can decrease glycolysis in 5-fluorouracil-resistant colorectal cells, and this

metabolic shift can inhibit cancer cell proliferation and lead to apoptosis. The authors also observed that these effects rely on tumoral PDK2 expression decrease in p53/p21-dependent metabolic signaling[138].

Alcaya *et al.* investigated the role of EVs derived from menstrual stem cells affecting prostate tumor-induced angiogenesis once it became known that endometrial cells induce an angiostatic condition associated with the end of the menstrual cycle. So, the authors observed that the prostate tumor cells treated with the EVs had decreased VEGF levels, NF-κB activity, and tubulogenesis in a ROS-dependent manner. Furthermore, the authors showed that EVs derived only from endometrial mesenchymal cells had antitumoral properties, affecting cancer cell metabolism and inhibiting VEGF and HIF-1α expression. Finally, they observed in a xenograft model that the exosomes can inhibit angiogenesis *in vivo*[139]. It is important to note that HIF-1α is a pivotal modulator of the metabolic reprogramming that takes place in cancer cells, inducing glycolysis and glycogenesis, favoring PPP, and reducing oxidative metabolism through inhibition of pyruvate conversion to acetyl-CoA via PDK[140].

It is well described that miR-100 may act as a tumor suppressor in breast cancer since it has been found that this miRNA inhibits tumor growth and is downregulated in clinical breast cancers[141,142]. Thus, Pakravam *et al.* observed that EVs derived from human bone marrow mesenchymal cells are rich in miR-100 and investigated their role in breast cancer cells. They showed that the EVs can transfer miR-100 to MDA-MB-231, inhibiting the mTOR-HIF-1α axis. Finally, they observed that this effect could lead to decreased VEGF production by breast cancer cells, culminating in a decrease in tubulogenesis by endothelial cells[143].

Interestingly, Bruno *et al.* showed that EVs derived from human bone marrow mesenchymal cells inhibited cell cycle progression in all cell lines, induced apoptosis in HepG2 and Kaposi's cells, and necrosis in the ovarian tumor cells (Skov-3). The authors observed that the EVs' *in vitro* effects on cell metabolism rely on the activation of negative regulators of the cell cycle. Then, this antitumoral *in vitro* property was confirmed through *in vivo* analysis when EVs inhibited tumor growth of all cancer cells (HepG2, Kaposi´s, and Skov-3)[144].

Another interesting approach is to modify EVs *in vitro* and investigate their antitumor effects by overexpressing miR or adding a drug delivery system. Considering this, Lou *et al.* isolated human mesenchymal cells from subcutaneous AT and constructed cells expressing miR-199a. In this work, they isolated EVs enriched in miR-199a from these mesenchymal cells, and they observed its ability to deliver this miR to HCC cells, which were able to inhibit the mTOR pathway, reducing chemoresistance to doxorubicin in these cancer cells[145]. It is essential to the hallmark that mTOR plays a pivotal role in cell metabolism: 1) promoting the uptake of nutrients by tumor cells to allow rapid growth of tumors; 2) activating sterol regulatory element-binding protein (SREBP) pathway, which in turn promotes new lipid synthesis, inducing breast cancer proliferation[146]; 3) mTOR is implicated in chemotherapy resistance activating Fanconi anemia DNA repair pathway, and suppressing autophagy[147]. In the same way, Lin *et al.* suppressed oxaliplatin chemoresistance in colon cancer cells utilizing a drug-delivered approach. They generated EVs from modified HEK293T cells containing iRGD, which can bind to αvβ3, αvβ5, and NRP-1 in different tumor cells. Once the authors observed that CPT1A inhibition could reverse the chemoresistance of colon cancer cells to oxaliplatin, they loaded the iRGD EVs with siRNA CPT1A. They observed the ability of these EVs to reverse oxaliplatin resistance and inhibit tumor growth *in vivo*[148].

Figure 3 shows all the effects of EVs or previously modified EVs on different tumor types. It identifies the mechanisms of action and how the vesicles can affect tumor metabolism.

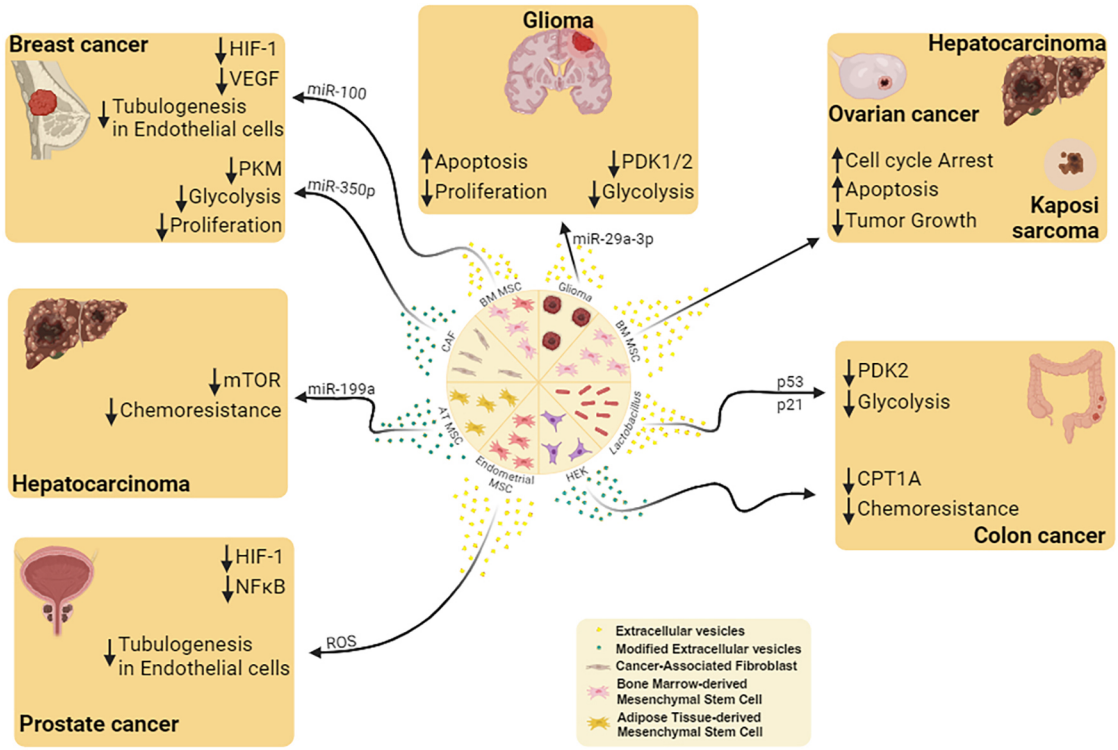

Figure 3. The therapeutic role of EVs in cancer metabolism. Different approaches involving modified or unmodified EVs point to their role in inhibiting tumorigenesis in various types of cancer. EVs: Extracellular vesicles; AT: adipose tissue; BM: bone marrow; CAF: cancer-associated fibroblast; MSC: mesenchymal stem cell.

CONCLUSION

The pivotal role of vesicles as metabolic modulators in the microenvironment cannot be overstated. Vesicles derived from non-cancer cells in the TME play a significant role in modulating metabolic pathways in various cancer cell types. Research has revealed that EVs induce an aggressive phenotype in tumor cells through metabolic reprogramming. However, the number of studies exploring this area is limited, particularly in understanding how EVs precisely alter metabolic pathways, the specific role of the cargo within vesicles, and their impact on tumor phenotype. Understanding EVs' communication mechanisms and systems is crucial in unraveling the intricacies of metabolic rearrangement in cancer cells. It can provide valuable insights for developing new therapeutic approaches.

DECLARATIONS

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Authors' contributions

Made substantial contributions to the design of the study, writing, and compiled evidence: Costa Encarnação C, Renovato-Martins M

Made substantial contributions to the conception of the study, writing, and critical review: Renovato-Martins M

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