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Autophagy and EMT in cancer and metastasis: Who controls whom?

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ABSTRACT

Metastasis consists of hallmark events, including Epithelial-Mesenchymal Transition (EMT), angiogenesis, initiation of inflammatory tumor microenvironment, and malfunctions in apoptosis. Autophagy is known to play a pivotal role in the metastatic process. Autophagy has pulled researchers towards it in recent times because of its dual role in the maintenance of cancer cells. Evidence states that cells undergoing EMT need autophagy in order to survive during migration and dissemination. Additionally, it orchestrates EMT markers in certain cancers. On the other side of the coin, autophagy plays an oncosuppressive role in impeding early metastasis. This review aims to project the interrelationship between autophagy and EMT. Targeting EMT via autophagy as a useful strategy is discussed in this review. Furthermore, for the first time, we have covered the possible reciprocating roles of EMT and autophagy and its consequences in cancer metastasis.

Summary: Metastatic malignancies are tumors that have spread to surrounding tissues and other parts of the body via a complex step-wise mechanism, including cell intravasation, transport through circulation, extravasation, and homing at a secondary tissue site. Metastatic cancers are difficult to treat and are the leading cause of cancer-related mortality [1]. Considering its clinical importance, the basic molecular and genetic underpinnings are poorly understood. Among the biological processes, autophagy, which is a self-degradative process, has been recently reported to play an important role in cancer cell metastasis [2]. Among other cellular processes, Epithelial-Mesenchymal Transition (EMT) is a switch that allows cells to transition between epithelial and mesenchymal states and is key to the metastatic process [3]. Recent observations have shown that these two processes are intertwined in a complicated manner in relation to metastasis [4]. In this review, we attempt to dissect the molecular and functional interaction that regulates the interplay of autophagy and EMT in regard to metastasis

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signalling.

1. Role of autophagy in cancer metastasis

In order to degrade long-standing cellular proteins and organelles, autophagy is triggered, which is not only important in normal development and response to changing environmental stimuli but also a chief component in diseases like cancer [5]. At the basal levels, autophagy maintains cellular homeostasis through the regular turnover of dysfunctional proteins and organelles. Cellular stress and nutritional deficiency, on the other hand, substantially enhance autophagy. Autophagy improves nutrient recycling, avoids misfolded protein accumulation, prevents damage-mediated by reactive oxygen species (ROS), protects organelle function, and modulates intracellular signalling cascades, all of which are critical cell survival strategies [6–8]. In cancer, autophagy can play neutral, tumor-suppressive, or tumor-promoting roles in different contexts and stages of cancer development, determined by nutrient availability, microenvironment stress, and pathogenic conditions [9].

Autophagy is principal for the quality control of the cell, such as removing damaged mitochondria and endorsing tumors and malignancies [10–12]. When tumors reach an advanced stage, autophagy aids in protection, survival, maintaining mitochondrial integrity, declining DNA damage, protecting cancer cells against stress, helping withstand tumor metabolism, articulate tumor promotion, and development, finally induces tumorigenesis and causes resistance to chemotherapeutic agents [9,13,14]. While it is reported that autophagy can enhance the aggressiveness of cancers by supporting metastasis, the effect of autophagy is dependent on factors such as tissue type, cancer microenvironment, and genetic disparities [15–17].

The several means of autophagy articulating cancer occur with the help of various underlying signalling pathways (Fig. 1). Autophagy exhibits a distinct pro-survival role by modulating proteins and associated pathways such as p53, Bax-interacting factor-1 (Bif-1), Beclin 1 (BECN1), ultraviolet irradiation resistance-associated gene (UVRAG), mTOR, protein kinase B (Akt), B-cell lymphoma 2 (Bcl-2), Ras, and Class I PI3K (PI3KI) [18]. mTORC1 is found to possess a critical role in adjusting and coordinating cells in response to stress and adapting to it. The PI3K signalling triggers mTORC2, which in turn phosphorylates AKT at two different sites, leading to AKT/mTORC1 signalling axis activation [19]. Intriguingly, mTORC1 orchestrates ULK1, ATG13, and FIP200 (which will be discussed in the subsequent section of this review).

5′-AMP-activated protein kinase (AMPK) is another crucial player in the regulation of ULK1 and mTORC1 autophagy pathway, which is switched on upon energy deprivation, especially during conditions of glucose starvation where the ratio of AMP to ATP in eukaryotic cells increases [20,21]. On the contrary, when the environment is devoid of nutrition, mTOR phosphorylates ATG14 in the VPS34 complex and inhibits its lipid kinase activity, providing mTORC1-mediated autophagy inhibition [22]. mTORC1 restrictive phosphorylation of ULK1 disturbs its interaction with AMPK, thereby impeding the autophagosome formation and autophagy. In congruence with this, triggered ULK1 was known to directly phosphorylate AMPK and inhibit its activation, thus providing a negative feedback loop on autophagy induction [23]. In addition, mTORC1 might influence autophagy through several other mechanisms, including the regulation of the death-associated protein 1 (DAP1), a suppressor of autophagy, and through WD repeat domain phosphoinositide-interacting protein 2 (WIPI2), a mammalian ortholog of Atg18 (a regulator of early autophagosome formation in yeast), which was identified as potential mTOR effector and by ULK1-dependent p62 phosphorylation, thereby facilitating the degradation of selective substrates [24–26]. In order to metastasize, tumor cells must overcome challenges related to the intrinsic properties of the cancer cell that influence metastasis. These factors include the propensity to migrate, invade, and survive using intracellular signalling pathways, as well as extrinsic microenvironmental properties such as extracellular matrix composition, interactions with other cell types, and access to the vasculature, which determines nutrient and oxygen availability. Thus, a complex network connects autophagy and consolidates both the intrinsic and extrinsic factors regulating metastasis [2].

2. Is autophagy a friend or foe for metastasis?

On one side, autophagy promotes tumor growth and survival by eradicating oxygen radicals, maintaining mitochondrial integrity, and helping survive under stress conditions [13]. Autophagy's role in cancer metastasis is quite tricky and intriguing. In the early stages, autophagy inhibits metastasis by impeding tumor necrosis and cell infiltration, whereas in the advanced metastatic disease or condition, autophagy aids

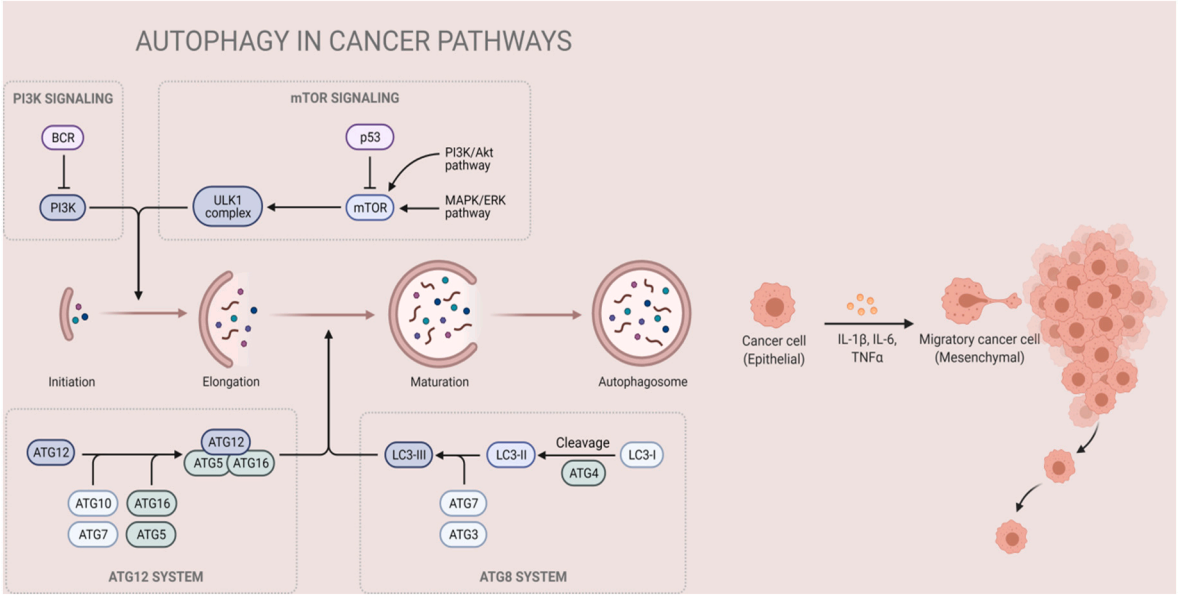

Fig. 1. Role of autophagy in cancer. PI3K signalling, mTOR signalling, ATG12 and ATG8 system leading to key processes like initiation, elongation, maturation, formation of autophagosome, and eventually bolstering in gaining a mesenchymal ability to the epithelial cells resulting in metastasis.

in the cancer cell migration, escalating cell colonization of detached cells and inducing the metastatic cells to reach dormancy and endorse to survive in the new environment [27–29]. An autophagic flux is induced after the cells have reached the stage of colonizing the target organs to fight hypoxia and nutritional limitation [30,31]. Several studies have established a link between autophagy and metastasis in diverse cancers, including breast, melanoma, hepatocellular carcinoma, and glioblastoma, demonstrating the active involvement of autophagy in cancer aggressiveness [32–35].

Autophagy is instrumental in metastasis. It is multifactorial and varies with cell type and the composition of the tumor microenvironment. Categorically, autophagy alters mechanisms that contribute to metastasis, including focal adhesion dynamics, integrin signalling, trafficking, and Rho GTPase-mediated cytoskeleton reorganization [2]. Regarding the regulation of focal adhesion dynamics and focal adhesion kinases by autophagy, the primary step is the formation of lamellipodia and filopodia. Secondly, integrins attach to the extracellular matrix and mature into focal adhesion complexes and trigger intercellular signalling mechanisms, and finally, these integrin adhesion complexes are facilitated for forward movement [36,37]. Adapter proteins are recruited during the binding of ECM ligands to integrin heterodimers. Subsequently, kinases such as PTK2 and SRC are recruited, which induce downstream signalling mechanisms such as Rho GTPase, mitogenic signalling, etc. [37]. Hence, several mechanisms like integrin focal adhesion formation and disassembly are actively involved in migration and metastasis. Collectively, targeting of SRC p-Y416 and RET from focal adhesion sites to phagophores highlights an essential link between autophagy and focal adhesion signalling, and autophagic assisted degradation of SRC may aid in focal adhesion disassembly to promote migration [2]. Targeting autophagic degradation might be a therapeutic avenue. Focal adhesion disassembly, turnover and impeding of autophagy by autophagic degradation of focal adhesion protein results in cell migration and metastasis mitigation. Knockdown of ATG7, ATG12, or ATG5 reduced migration and invasion in several cells [38,39]. Another tissue-specific autophagic receptor is NBRI. NBRI inhibition results in focal adhesion turnover and migration ability in specific tissues and cells, unlike breast cancer [39]. In both in vitro experiments and in syngeneic 4 T1 tumors, the loss of ATG7 and ATG12 causes PXN accumulation. Thus, autophagy targets and disintegrates focal adhesion complex proteins such as PXN and SRC p-Y416. Apart from focal adhesion degradation, autophagy also targets ULK1-RB1CC1-PTK2 signalling [2].

Mounting evidence suggests that RB1CC1 mediates an inverse relationship between autophagy and PTK2-induced migration, where the ULK1-RB1CC1 complex sequesters and reduces PTK2 in energy-deprived conditions to escalate autophagy and decline migration which denotes that inhibition of ULK1 or RB1CC1 will increase metastasis [40]. This study lays a foundation to support the theory of suppression of migration and invasion by starvation-induced autophagy utilizing ULK1-RB1CC1 mediated alleviation of PTK2 [2].

3. Autophagy tuning Epithelial-Mesenchymal Transition

EMT is a process where the cells gain invasive mesenchymal ability through a series of events such as loss of cell junctions, rearrangement of cytoskeleton, and remodeling of the extracellular matrix [41]. Among the many mechanisms known to govern EMT, autophagy stands as one of the prime mechanisms [42]. The role of autophagy in tumor development remains debatable. For instance, in the EMT of hepatocytes, Atg7 knockout escalates mesenchymal markers, especially Vimentin (VIM) and SNAI1 [43]. In addition, the repression of BEC1 and ATG7 in mouse hepatocytes declines the epithelial markers such as e-Cadherin, OCLN and inclines the mesenchymal marker levels like FN1, VIM, ACTA2, MMP9, and SNAI1 [43]. Surprisingly, starvation mediates autophagy TGF-β1-regulated EMT. Concurrently, SNAI1 is also degraded via SQSTM1-dependent autophagy, thereby directly linking autophagy and EMT. In contrast, starvation-induced autophagy triggers EMT, which is vital for hepatocarcinoma cell lines in vitro [44]. Furthermore, knockdown of ATG7 or ATG3 inhibits EMT and suppresses the expression of FN1, TGF-β1 and SMAD3. The bonding of SQSTM1 with TWIST was recently established. SQSTM1 stabilizes TWIST in order to induce EMT, and loss of autophagy escalates TWIST in SQSTM1 dependent fashion, which drastically increases EMT in vivo [45]. SQSTM1 also has the ability to sustain TWIST and trigger TGF-β1-SMAD signalling, which induces EMT-associated junction remodeling, enumerating a strong link between autophagy loss and EMT [46]. In glioblastoma, starvation-induced autophagy reduces cell migration and invasion, downregulating SNAI1 and SNAI2 [47]. Additionally, silencing BECN1 or ATG7 in the same cells escalated migration and invasion, suggesting that autophagy may impede EMT in glioblastoma under starvation conditions [47]. A similar phenomenon is observed in thyroid carcinoma, where CDH6 suppression results in increased EMT by autophagy proteins [48]. Strategic reduction of autophagy by starvation aids in decreased expression of mesenchymal markers [49]. ROS also plays an active role in regulating EMT in these cells. HMOX1 and ROS levels alter EMT conditions, thereby elucidating the active role of autophagy in the ROS-HMOX1-EMT axis [49]. This evidence clears up the double-edged role of autophagy in cancer, highlighting the prime role of starvation in autophagy-mediated anti-cancer therapy.

4. Effects of starvation on autophagy-mediated anti-cancer ability

Decrease in blood glucose levels in nutrition starvation activates autophagy in organs as an adaptive switch to withstand stressful conditions [31,50]. This theory gained popularity, especially in chemotherapy, as it could potentiate effectiveness [51]. Among the different diet regimens, intermittent fasting was the best chosen one. Intermittent fasting eases DNA repair triggering mechanisms and preserves small intestinal (SI) stem cell viability as well SI architecture and barrier function after exposure to high-dose etoposide, indicating that intermittent fasting may be beneficial in reducing side effects and toxicity in chemotherapy patients [52]. It was shown in a breast cancer murine model that intermittent fasting reduced glucose and IGF-1 levels [53]. In a later study on colon cancer, intermittent fasting impeded tumor growth without adverse effects such as weight loss and reduced M2 polarization in the tumor-associated macrophages (TAM) in mice. Macrophages of the M2 phenotype (TAM) are abundant in tumors and play a critical role in tumor formation, invasion, and metastasis, among other functions. Further, autophagy-mediated inhibition of M2 polarization was noted in cell line models in the same study by the downregulation of the JAK1/STAT3 axis [54]. The utilization of nutrient starvation in vitro was successfully proved in a recent experimental model for glioblastoma [55]. The flowcytometric analysis revealed that nutrition starvation after 5 days resulted in 64% of cells undergoing apoptosis in glioblastoma-like stem cells. Autophagy was detected in 99.7% of the cells. There was a clear difference in expressions of phospo-Beclin 1, LC3B-1, and LC3B-2 [55]. 2-deoxy-D-glucose, an inhibitor of metabolism, was employed in multiple cellular models, including a transfected pEGFP-LC3 autophagy reporter construct in PC-3 and LNCaP cells to study the effects of autophagy and starvation on cancer therapeutics. There was an increase in LC3-II expression recorded in the cells. Further, the functional correlation of Beclin 1 was studied where; knockdown of Beclin-1 overturned the 2-deoxy-D-glucose induced autophagy [56]. A similar scenario regarding Beclin-1 was observed in hepatocellular carcinoma cell line study. Inhibition of autophagy by 3-methyladenine or siRNA-targeted Beclin 1 increased the nutrient deprivation-induced apoptosis and chemosensitivity [57]. Autophagosomes are actively produced and promptly consumed in colorectal cancer cells under nutrient deprivation. Autolysosome inhibitors and 3-methyl adenine, which suppresses autophagosome formation, remarkably induce apoptosis under amino acid-deprived and glucose-deprived

conditions [58].

Employment of mediums like Earle's balanced salt solution is a way of inducing canonical autophagy in thyroid cancer cells. Alteration of BAG3 expression in this study resulted in a marked reduction of autophagy and enhanced apoptosis of the thyroid cancer cells evoked by starvation [59]. A recent quantitative proteomic study investigated the effect of time-based starvation, where the early or acute starvation brought more significant changes in the cells. In the early starvation condition, autophagic receptors were degraded. Overall, amino acid deprivation obtains endocytosis of specific membrane receptors, triggering macroautophagy and degradation of autophagic receptors [60]. Prolonged or chronic starvation is once again a tricky phenomenon. A study correlating p53 and autophagy in colorectal cancer cell lines exhibited that p53 loss leads to the accumulation of autophagosomes in the absence of p52 in HTC116 cells. However, long-standing starvation wasn't beneficial as autophagosome recycling became ineffective under prolonged starvation, and the increased LC3 staining was actually because of the stalling of autophagy, causing aberrant accumulation of static autophagosomes. Furthermore, p53 aids in escalating HTC116 survival under long-term starvation [61]. This clearly shows that some cancer cells utilize p53 to survive under nutrient-deficit conditions.

Another relatively newer pharmacological interventional therapy is calorie restriction mimetics alongside cytotoxic agents. These agents aid in the activation of AMPK and repression of signalling such as mTOR resulting in autophagy induction (Fig. 2), depletion of energy sources such as ATP, and reduced employment of glucose [62]. This might yield successful therapeutic outcomes as autophagy dependent on the AMPK pathway is pivotal for survival to adapt to hypoxic stress, and suppression of autophagy under hypoxic conditions results in startling cytotoxicity and heightened apoptosis [63].

5. Autophagy scores epithelial markers in EMT

Cell adhesion molecules play a salient role in the interaction between cells and extracellular matrix proteins. Possible defects in these interactions lead to the initiation of metastasis [64]. Cadherins are transmembrane glycoproteins that act as cell-to-cell adhesion molecules in the presence of calcium. Cadherins are connected to the cytoskeleton via intermediary proteins, the catenins, which bridge the two. Under the circumstances of human malignancies, reduced expression of E-Cadherin was linked with lymphogenesis spread [65–67]. E-Cadherin expression negatively correlated with less mean survival time, and reduced expression resulted in tumor differentiation and lymphogenesis metastasis, making it a prime prognostic factor in non-small cell lung cancer [64]. E-Cadherin is a key component of autophagic machinery. E-Cadherin interacts with SQSTM1/p62, and silencing of SQSTM1/p62 downregulated E-Cadherin, which paves the direction for understanding that SQSTM1/p62 aids in E-Cadherin delivery to autophagosomes, thereby correlating with poor prognosis via autophagy activation [68]. Autophagy may downregulate the expression of Claudin-2 (CL-2) in intestinal epithelial cells induced by LPS correlating autophagy with inflammation. Claudins, alongside protein components, form tight junctions in the epithelium and endothelium. The alterations in the levels of Claudins may lead to severe disturbances in the barrier functions such as water regulation, ion and solute channeling and macromolecule uptake in affected areas, resulting in the specific clinical phenotype and inflammatory conditions such as IBD (Inflammatory Bowel Disease) [69]. Autophagy modulates tight junctions functioning, which has a major role in cancer metastasis (Fig. 3). CL-2 predominantly controls and influences inflammatory diseases and its levels can be tuned by autophagy. However, inflammation, autophagy and Cl-2 have a reciprocating role and may be modulated by inhibitors and inducers [69].

Desmosomes are integral like other epithelial members. They maintain integrity, tissue remodeling, adhesion, and development [70]. Downregulation of desmosomal adhesion is ideal for cell migration and cancer invasion [70]. Macromolecular assemblies of junctions and desmosomes are degraded by autophagy machinery. A mechanism that

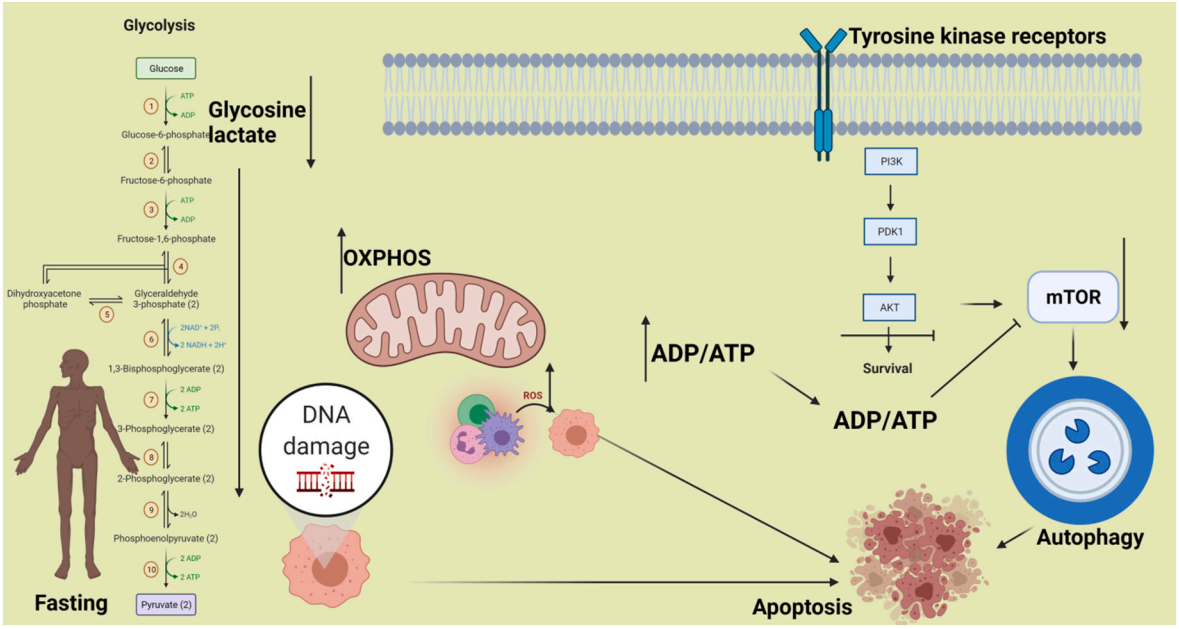

Fig. 2. Starvation mediated effects on autophagy.
Fasting may counteract the Warburg effect, facilitating oxidative phosphorylation in tumor cells and escalating ROS production, and reduced levels of lactate and ATP. The increase in the ADP/ATP can induce the AMPK pathway, leading to autophagy induction. Furthermore, the long-standing stressful environment can result in cell death induction. Several tumors harbor mutations that endorse MAPK pathway activation, which empowers tumor cell growth, survival, and proliferation. Chemotherapies targeting this pathway and fasting may result in the downregulation of this pathway along with a reduction in AKT and mTOR activation, resulting in autophagy induction and apoptosis eventually. Additionally, fasting potentiates the detrimental effects of chemotherapy, such as DNA damage, thus activating the apoptosis axis, decontrolling pro-apoptotic, anti-apoptotic proteins, and inducing mitochondrial modulations and caspase activation, which in turn concludes in programmed cell death.

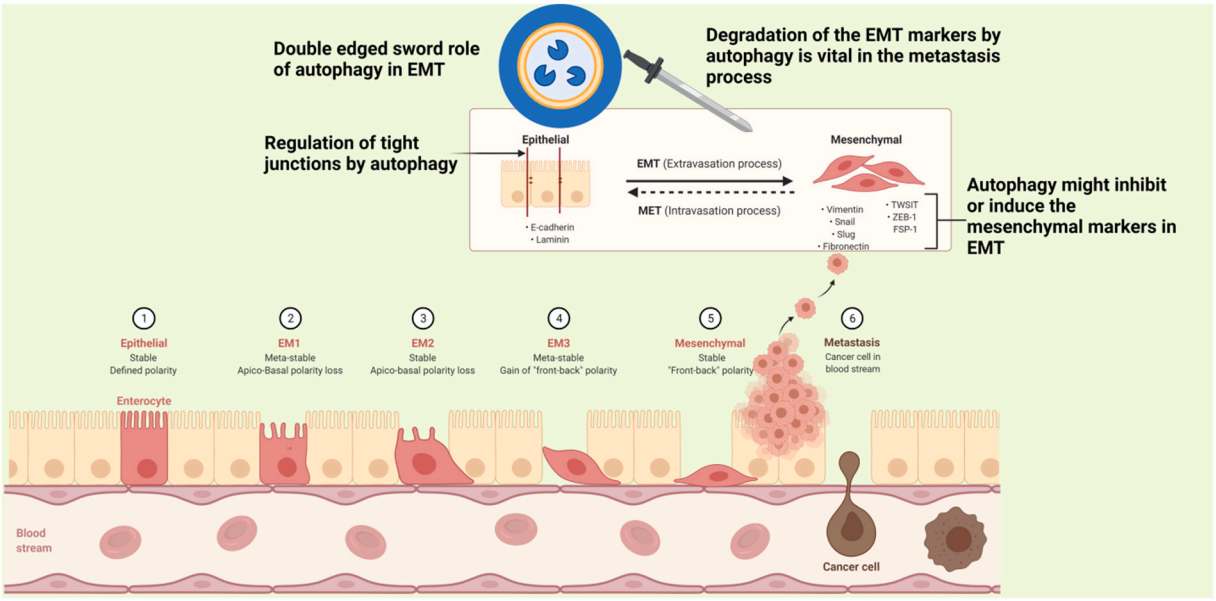

Fig. 3. Multifunctional role of autophagy over EMT markers.

inhibits autophagy shows the hijacking of components of autophagy initiation, for example, Atg16, by the connexins themselves. Upon nutrient starvation, connexins release Atg16, the blockade is lost, and autophagy proceeds. This axis shows that autophagy controls desmosomes in disease. Ideally, desmosomes are degraded by non-selective autophagy. Autophagy is also relatable to anoikis, the apoptosis initiation process leading to the detachment of the cell from the substrate. Integrin-mediated adhesion loss results in autophagy, impedes anoikis, and down-regulates programmed cell death signalling. In cancer cells, enhanced autophagy activity succeeding detachment aids in resistance and promotes malignancy, making the cells adapt to stress conditions and increasing motility [71–73].

Apart from coating, lubricating, and protecting the epithelial surfaces, Mucins are devoted to maintaining the epithelial cell integrity [74]. Mucins are over-expressed in various cancers [75], and their aberrant expression and large size of mucins might possess a survival advantage under nutrient deficit conditions by undergoing autophagy. MUC1 has been investigated and proved to inhibit necrosis induction in response to the deprivation of glucose with the induction of autophagy [76]. MUC4 deregulates apoptosis in response to nutrient deprivation. Additionally, MUC4 also represses starvation-induced increase in ROS generation.

Further, the expression of ATG7, a protein essential for the formation of autophagic vacuoles, has a vital role in MUC4-overexpression. A significant time-dependent increase in ATG7 expression is observed upon starvation of MUC4-expressing cells compared to the respective control cell lines. These results suggest that overexpression of MUC4 in human malignancies enhances autophagy and may offer a survival benefit during nutritional deprivation [77]. To support this, a study by Patel et al. stated that autophagic proteins and endosomal formation are vital for ROS formation. Production of ROS is crucial to orchestrate mucin granule accumulation in colonic goblet cells. Thus, autophagy proteins can alter secretory function through ROS, which is in part generated by LC3-positive vacuole-associated NADPH oxidases [78]. Zonula occludens (ZO) which act as scaffold proteins have been identified in the regulation of cell migration via modulation of ZO-1 [79]. On the other hand, ZO-2 suppression leads to increased migration. Claudin-1 is reported as a primer of migration and is controlled by ZO-1 and ZO-2 [80]. Autophagic inhibition was the mechanism employed in ZO-1 modulation by lycopene in COLO-16 cells [81]. Keratins under the class of cytokeratins are epithelial markers in EMT. Keratin-19 is elevated in aggressive breast cancer [82]. Autophagy dysfunction dysregulates keratins in mammary glands, and elevated levels of p62, keratins, and ER chaperones were observed in autophagy-deficient mammary tissues and beclin *1*+/− immortalized mouse mammary epithelial cell (iMMEC)–generated tumors [83]. This evidences that autophagy is a key aspect of Keratin homeostasis. In the course of TGF-β2–induced EMT process, it was evaluated that p-KRT8 was enhanced in RPE cells, which was followed by an increase in autophagic flux. Besides, disruption of autophagy with the aid of pharmacological inhibitors or specific siRNAs resulted in a reduction in cell migration and further synthesis of several EMT markers [84].

6. How far can autophagy alter mesenchymal markers?

Vimentin, a subtype of intermediate filament, aids in the formation of a cytoskeletal network and a superiorly conserved protein. Vimentin is fundamental in processes such as cell migration, invasion, motility and promoting resistance to stress conditions [85]. Vimentin is phosphorylated by Akt1 and protects from caspase-mediated cell death [85]. Vimentin has been relatively active in the prostate, gastrointestinal tract, breast, etc. [86–88]. Vimentin further participates in metastatic progression via cytoskeletal reorganization and focal adhesion maturation that occurs during EMT [89]. What makes Vimentin a true class of mesenchymal marker is its ability to increase β1-integrin and the decline expression of junction protein E-cadherin. Furthermore, slug expression is also mediated by Vimentin [89]. Vimentin has been markedly identified as a pre-metastatic marker and is related to poor prognosis and outcomes in solid tumors [85]. The interrelationship between autophagy and Vimentin has been investigated using D-limonene, where D-limonene reduces the expression of Vimentin via autophagy modulation [90]. This is particularly helpful since LC3 lipidation by D-limonene is independent of mTOR inhibition, which plays a crucial role in autophagy induction. Further, D-limonene stimulates ERK and ROS generation [90]. These characteristics are considered important in cancer therapeutics. Mesenchymal cell motility and mortality are of paramount importance in the EMT process. The Fsp-1 family has been indicated in microtubule dynamics, signal transduction processes, and cell cycle regulation [91]. Tubular epithelium transfected with cDNA encoding Fsp1 displays several properties of EMT, including a reduction in cell adhesion, cytokeratin, and expression of Vimentin. ATG7 modulates fibrosis by altering EMT in vitro [92]. In endothelial cells, loss of

endothelial autophagy induced by silencing of *ATG7* promoted endothelial mesenchymal transition. Silencing of ATG7 was further assisted by marked morphological and ultra-structural changes changing cells. These morphological changes were also linked with the rearrangement of cytoskeletal proteins, a feature specific to the increased expression of mesenchymal markers. EMT was associated with decreased levels of endothelial markers, such as CD31, VE-cadherin, and Tie2, and increased levels of mesenchymal markers, such as FSP-1, suggesting that endothelial autophagy is active during the transition from one state to another [92]. The FSP-1 expression was clear in inflammatory mediated conditions such as ductular reactions, which are ideally the preliminary steps in most cancers [93]. The ductular cells from fibrotic livers showed an increased autophagy and underwent a mesenchymal transition, which demanded the initiation of the TGF-β/Smad2/3 signalling axis in an autophagy-dependent manner. Essentially, ductular cells were not only positive for LC3-II but also showed increased expression of TGF-β and fibroblast-specific protein-1 (FSP1) in cirrhotic human livers [94]. Autophagy orchestrates cancer cell proliferation, invasion and EMT, and in cancers, dysregulated circuits such as NFκB/SNAIL/YY1/RKIP/PTEN—define the fate and regulation of tumor cell characteristics [95]. The relationship between SNAIL-induced EMT and autophagy was investigated where it was evaluated that the level of SNAIL increases post-transcriptionally and autophagy degrades SNAIL, but its inhibition increases SNAIL. Therefore, stimulation of autophagy inhibits EMT progression in this context [43]. Autophagy acts as a double-edged sword in the context of induction and inhibition of EMT through SNAIL degradation. MiR57c, for instance, impedes autophagy, cell infiltration, and cell migration. MiR57c is involved in the upregulation of the expression of the epithelial markers E-cadherin and Claudins in contrast, decreases the mesenchymal marker expression such as SNAIL and Vimentin, elucidating the blocking ability of miR517c against autophagy and its reflective effect on mesenchymal markers [96]. A clear description of SNAIL and autophagy in EMT has been reported, where the autophagy strives in the degradation of SNAIL and initiates a switch from the mesenchymal to the epithelial type, which is the prime characteristic in cancer metastasis [95]. The SNAIL axis and mechanisms basing autophagy can be extremely useful in designing therapeutics because starvation-mediated autophagy triggers SNAIL(SNAI1) degradation and inhibits EMT and metastasis in cancer cells. Surprisingly, SNAI1 proteins are associated and colocalized with LC3 and SQSTM1 in cancer cells. In a study, *ATG7* knockdown inhibited autophagy-induced SNAI1 degradation in the cytoplasm, which was associated with a decrease in SNAI1 nuclear translocation resulting in suppressed cancer cell invasion and migration by starvation-instigated autophagy [97].

The transcription factor TWIST actively regulates EMT in both the embryonic stage and in cancer [98]. Autophagy insufficiency stabilizes TWIST1 protein through SQSTM1/p62 accumulation. SQSTM1 binds with TWIST1 to inhibit TWIST1 degradation in both autophagosomes and proteasomes. This supports SQSTM1-mediated TWIST1 stabilization to promote EMT in vitro, tumor growth, and metastasis in mice. This suggests autophagy as a novel pathway to control the TWIST1 protein levels [98]. P62 acts as a bridge between autophagy and cancer. Autophagy repression leads to p62 accumulation and the promotion of tumorigenesis. p62 inhibits degradation of Twist1. In murine models, p62 elevation escalates tumor cell growth and metastasis in a Twist1-dependent manner, thereby projecting Twist1 as a key downstream effector of p62 in the regulation of cell proliferation and migration [45]. Twist1 and Twist2 may also tag in conjunction with H-RASV12 to prevent premature senescence of mouse embryonic fibroblasts by inhibiting the p53 pathway and promoting EMT by inhibiting E-cadherin expression and increasing vimentin expression [99]. In human skin squamous cell carcinoma and melanoma, autophagy deficiency supports EMT by stabilizing TWIST1 [98]. Research on breast and colon cancers affirmed that the death effector domain-containing DNA-binding protein (DEDD) negatively regulated EMT by triggering autophagy and subsequently inducing the autophagy-mediated lysosomal degradation of Snail and Twist [100]. SNAIL or SNAIL-1 is a vital player in EMT, especially in offering resistance to therapies in multiple cancers [101]. SLUG also carries a role in human oral squamous carcinoma, and silencing SLUG results in repression of anti-tumor drug resistance and invasion ability. TGF-β upregulates the expression of SNAIL and SLUG and promotes aggressiveness in cancers [101]. Either Slug or Snail silencing alone can partially mitigate malignancy potential in the presence of TGF-β, whereas both Slug and Snail siRNAs together can significantly suppress them.

Inhibition of autophagy can be a therapeutic target in cancer. Autophagy inhibition in RAS-mutated cells induces EMT, which is related to enhanced tumor invasion. ZEB1 is a principal determinant of cell plasticity, furnishing cells with the ability to cope with an aberrant mitogenic activity, and has a profound effect on the genetic history of tumorigenesis, and the various limitations faced throughout tumor growth [102]. Suppression of ATG3 or ATG5 enhances oncogenic RAS-induced expression of ZEB1 [103]. In a very recent study on cancer stem cells (CSC), it was confirmed that autophagy supplements the stemness of lung CSCs by degrading ubiquitinated p53. Furthermore, Zeb1 is essential for TP53 regulation of CSC self-renewal. CSC utilizes the autophagy-p53-Zeb1 arm for renewal and oncogenesis [104]. This study strengthens the evidence of Zeb1 role in p53 regulation of CSC renewal.

Autophagy modulation might act as a molecular switch from a mesenchymal phenotype to an epithelial-like one and vice versa in the GBM cellular model [47]. During the process of autophagy induced by nutrient deprivation or by pharmacological inhibition of the mTOR complexes, GBM migration and chemokine-mediated invasion are impaired. SNAIL and SLUG are down-regulated upon autophagy stimulation and, a transcriptional and translational up-regulation of N and R-cadherins is further noted. Conversely, in BECLIN 1 silenced GBM cells, an increased migration capability and an up-regulation of SNAIL and SLUG are observed, with a resulting decrease in N- and R-cadherin mRNAs [47].

7. EMT modulates autophagy

EMT plays a role in the genesis and progression of malignancies, as well as the chemoresistance of metastatic tumors. EMT and autophagy connection is complicated but critical in malignant cell invasion, metastasis, and generation of stem cell-like state and is an exciting topic in oncology research. The connection between EMT and autophagy is complex because recent findings suggest that autophagy may be activated or inhibited by EMT-related signalling pathways, while autophagy may also play an important role in the initiation and suppression of EMT. Understanding the molecular intricacies at the crossroads of autophagy and EMT, and this section intends to present the current know-how EMT modulates autophagy. Early in tumor development, adherent epithelial cells transform into highly motile mesenchymal cells by the process of EMT, followed by a metastatic transition. Cellular stresses like oxidative stress, ER-stress, are known to induce EMT, and EMT-inducing stimuli may activate autophagy to maintain the viability of the migratory cancer cells that mediate metastatic spread. Several signalling pathways related to EMT, including Ras, WNTs, and NF-kβ signalling cascades, also play a critical role in autophagy. Oncogenic activation of Ras mutation stimulates not only the Rac-MEK-ERK-Snail mediated EMT induction, but also Rac-JNK-Atg pathway mediated autophagy [105]. Similarly, NF-kβ modulates both EMT via SNAIL1/SLUG/TWIST1/SIP1 [106] and autophagy by the suppression of Beclin-1 (an autophagy initiator) [105]. These associations between oncogenic signalling, EMT and autophagy are genetics dependent as well as tissue-dependent, hence intriguing.

Several EMT-inducing signalling triggers, such as hypoxia and TGF-β, have been shown to potently induce autophagy in different disease contexts and cell types [107–109]. Kiyono et al. showed that TGF-β induced autophagosome formation and enhanced expression of many autophagy-related genes, via the Smad-JNK-dependent pathway in

human hepatocellular carcinoma cell lines and MDA-MB-231 mammary carcinoma cells [109]. Though these studies showed that EMT-inducers like TGF-β activate autophagy but whether EMT is upstream or downstream was not clear. He et al., demonstrated that TGF-β promoted transcription factor EB (TFEB)-driven autophagy in pancreatic cancer cells via the Smad pathway [110]. Liang et al., showed differential role of TGF-β-induced autophagy in pancreatic ductal adenocarcinoma and its association with specific genetic backgrounds. TGF-β-induced autophagy was associated with enhanced proliferation and reduced migration in Smad4-positive cells. Whereas in Smad4 deficient cells, TGF-β-induced autophagy leads to increased migration and reduced proliferation along with the activation of MAPK/ERK activation and EMT phenotype [111]. This study elucidates the role of EMT-inducers, the molecular underpinning with autophagic flux generation in the context of genetic background, and its significance in understanding the cancer heterogeneity. These studies though show TGF-β-promoted EMT inhibition by autophagy suppression. Recent data suggest that EMT is a non-binary phenomenon and encompasses dynamic intermediate cell states and also establishment of EMT memory are interesting aspects that are not phenotypically demarcated [112–114].Hence, additional research is required to better understand the divergence and convergence of EMT-inducing signalling on EMT and autophagy. Though converse relations where autophagy regulates EMT are also reported and discussed in the earlier section.

Hypoxia-inducible factor-1 (HIF-1) is a key regulator of hypoxic stress and is a mediator of EMT in many cancer and associated metastasis [115]. HIF-1 is also reported to promote esophageal cancer cell growth in a xenograft model [109]. HIF-1 triggered autophagy via the p27-E2F1 signalling pathway in human esophageal cancer cells [116] and also mediates mitochondrial autophagy [117]. Once again, the transcription factor E2F1 is reported to induce EMT via upregulating ZEB2 [116]. Hence, more evidence is essential to uncover the HIF-1 mediated regulation of EMT and autophagy in the pathogenesis of cancer. EMT transcription factors, on the other hand, seem to have an impact on the PI3K/Akt pathway, according to research. Twist has the ability to disrupt the Akt signalling pathway, according to current studies. This transcription factor enhances cancer cell phosphorylation, invasion, and metastasis via increasing miR-10b production [118]. Twist also seems to activate the PI3K/Akt signalling pathway by binding to the *E*-box area of the Akt2 promoter, according to the findings [119]. As a consequence of the positive feedback loop between Twist and Akt, the EMT and metastatic spread processes are initiated. The PI3K-Akt-Ulk pathway is also important for autophagy. MT enhances tumor spread by increasing autophagy in cancer cells by enhancing the activity of transcription factors like Snail and Slug [120]. Slug is a Zinc finger transcriptional factor that promotes EMT and imparts cancer stem cell phenotype in breast cancer [121]. EMT-TF components regulate MITF activity during melanoma-genesis, which, as previously stated, promotes autophagy gene expression. This is an interesting finding [122].

Epithelial cells must utilize integrins to stay connected to the extracellular matrix (ECM) in order to survive. Anoikis, a kind of apoptotic cell death, is caused by prolonged detachment from the ECM [123]. Autophagy is triggered in cells when the epithelial cell-matrix is detached or blocked directly by integrins, and autophagy suppression increases the amount of epithelial cell death that happens when the matrix is removed. As a consequence, it is thought that autophagy is important for preventing anoikis and ensuring the survival of detaching tumor cells during metastatic dissemination [124]. The ER-stress sensitive kinase, protein kinase R-like ER kinase, was shown to be activated in mammary tumor models in response to matrix separation or integrin blocking, and this was related to ROS-dependent activation of the autophagy induction pathway (PERK1) [125]. Using either the inhibition of PERK or autophagy itself during matrix detachment or the blockage of integrin signalling during detachment, a similar trend was seen. These findings indicate that autophagy-mediated by PERK is critical for breast tumor cell survival during matrix detachment. It is noteworthy that EMT enhances tumor spread by increasing autophagy in cancer cells. It is also a matter of investigation as to how EMT in different cancers might correlate with the different forms of autophagy namely, microautophagy, chaperone-mediated autophagy, and macroautophagy.

8. Utilizing autophagy as therapeutic target

Inhibition of EMT in cancer by regulating autophagy has caught great attention from researchers. Autophagy and EMT cross regulate each other via diverse signalling pathways. The major signalling pathways of autophagy regulation are PI3K/AKT/mTOR, Beclin-1, and JAK/STAT pathways, which also significantly impact EMT [105]. On the other hand, the EMT process signalling pathways such as WNTs, TGF-β, and NF-κB involve in autophagy [105]. PI3K/AKT/mTOR signalling pathway is one of the most important pathways that regulate autophagy and EMT in cancer metastasis and as a therapeutic target. Pleckstrin homology like domain family A member 2 (PHLDA2) is one essential gene correlated with tumor progression by regulating PI3K/AKT/mTOR signalling pathway in osteosarcoma [126].Research has indicated that downregulation of PHLDA2 inhibited cellular proliferation, invasion, migration, and EMT and promoted autophagy apoptosis via PI3K/AKT/mTOR signalling pathway in colorectal cancer [127]. FAT tumor suppressor homolog 4 (FAT4) has been found to display an inhibitory effect on EMT in gastric cancer cells [128]. FAT4 regulates the PI3K activity to promote autophagy and inhibit EMT via PI3K/AKT/mTOR and PI3K/GSK-β signalling pathways in colorectal cancer [129]. In addition, some of the growth factors that activate the PI3K/Akt/mTOR signalling pathway induce EMT in cancer cells [130]. Blocking the growth factors can reverse the inductive effect therefore inhibiting the PI3K/Akt/mTOR signalling pathway and further inhibiting metastasis. TGF-β is one of the prime EMT inducers, and it is involved in the induction of EMT by direct and indirect activation of PI3K/Akt/mTOR signalling [131]. Additional signalling pathways are involved in the cancer cell metastasis via inhibiting EMT by regulating autophagy (Table 1).

Furthermore, the crosstalk between autophagy and EMT can be utilized for anticancer drug development. Autophagy is like a "double-edged sword" that can suppress and advance cancer progress. Some anticancer drugs are autophagy inhibitors or activators involved in different pathways to suppress the EMT process and reduce the anticancer therapeutic resistance [13](Table 2). Alisertib promotes autophagy and suppresses the EMT process by inhibiting the PI3K/AKT/mTOR pathway to impede the metastasis of cancer cells in pancreatic cancer [135] and ovarian cancer [136]. On the other hand, autophagy inhibitors, such as Chloroquine, 3-Methyladenine, are commonly used autophagy inhibitors in cancer treatment, which inhibit cancer cell

Table 1
Target signalling pathways for inhibiting EMT via regulation of autophagy.

Inhibitor target	Signalling pathways	Promotion	Inhibition	Cancer
PHLDA2	PI3K/AKT/mTOR	Apoptosis	Cellular proliferation, invasion, migration, EMT	Colorectal cancer [127]
FAT4	PI3K/AKT/mTOR PI3K/AKT/GSK-3β	Autophagy	EMT, invasion, migration	Colorectal cancer [129]
CDH6	TGF-β	Autophagy	EMT, metastasis	Thyroid cancer [48,132]
GSK-3β	LKB1/AMPK	Apoptosis	EMT, PI3K/AKT/mTOR	Prostate cancer [133]; Head and neck squamous cell carcinoma [134]

Table 2
Autophagy inhibitors and activators used for anticancer drugs development.

Autophagy activator	Pathways/target	Inhibition	Cancer
Alisertib	PI3K/AKT/ mTOR	EMT, metastasis	Pancreatic cancer [136]; ovarian cancer [136]
Rapamycin	mTOR regulating TGF-β	EMT	Gallbladder cancer [137]; Colorectal cancer [138]
Brusatol	PI3K/AKT/ mTOR	EMT	Hepatocellular carcinoma [139]
Metformin	mTOR	EMT	Thyroid cancer [140]
FTY720	PI3K/AKT/ mTOR	Migration, invasion	Glioblastoma [141]
Autophagy inhibitor	*Pathways/target*	*Inhibition*	*Cancer*
Chloroquine Hydroxychloroquine	Autophagosome-lysosome fusion;	EMT, Beclin1	Colorectal cancer, Renal cell carcinoma [142]; Bladder cancer [143]; Breast cancer [144]
3-Methyladenine		PI3K	NSCLC [145]
Afatinib	AKT/mTOR, Erk	EGFR	NSCLC [146]
Vismodegib	ROS, GLI2	SMO	Lung adenocarcinoma [147]
Bevacizumab		VEGF	Colorectal cancer [148]

proliferation and metastasis.

9. Conclusion and future directions

Targeting both autophagy and EMT is an intriguing tumor-targeting strategy. Autophagy and EMT are intertwined processes that are critical in the onset and progression of cancer and pose significant challenges to anticancer therapy. Autophagy and EMT: Who controls whom? (Fig. 4) This is an interesting question. EMT and autophagy are modulated by both cell-intrinsic and extrinsic factors and are dynamically associated with tumor developmental stages. Therefore, new studies are required to generate a comprehensive idea about the complicated genetic and molecular network of regulatory signalling pathways and their control of EMT and autophagy. The EMT-autophagy interaction can play a crucial role in cancer development, metastasis, development of cancer stem cell phenotype, alteration of metabolic signature, and drug resistance, and much of this is an open question. The role of different oncogenic factors in differentially controlling EMT and autophagy in different cancers needs to be investigated. Paradoxically autophagy has been shown to impact EMT, depending on the environment of cancer cells during metastasis. Currently, autophagy inhibitors and activators, such as chloroquine and 3-methyladenine, have translational implications in anticancer treatment via modulating EMT. However, due to the unavoidable adverse effects, such as significant cytotoxicity and poor selectivity, there is a lack of clinical data regarding the therapeutic use of autophagy regulators.

Additional studies are needed to understand the different categories of autophagy and their induction concerning the distinct epithelial-mesenchymal cell transition stages. Another exciting aspect is to study the metabolic shift and its correlation with EMT–autophagy interaction. Considering the role of several membrane proteins, like integrins and Cadherin's in relation to autophagy, leads to the need to investigate these membrane proteins' non-canonical roles. An additional exciting aspect is that the role of the tumor microenvironment in the regulation of EMT-autophagy in different cancers needs to be investigated in vivo.

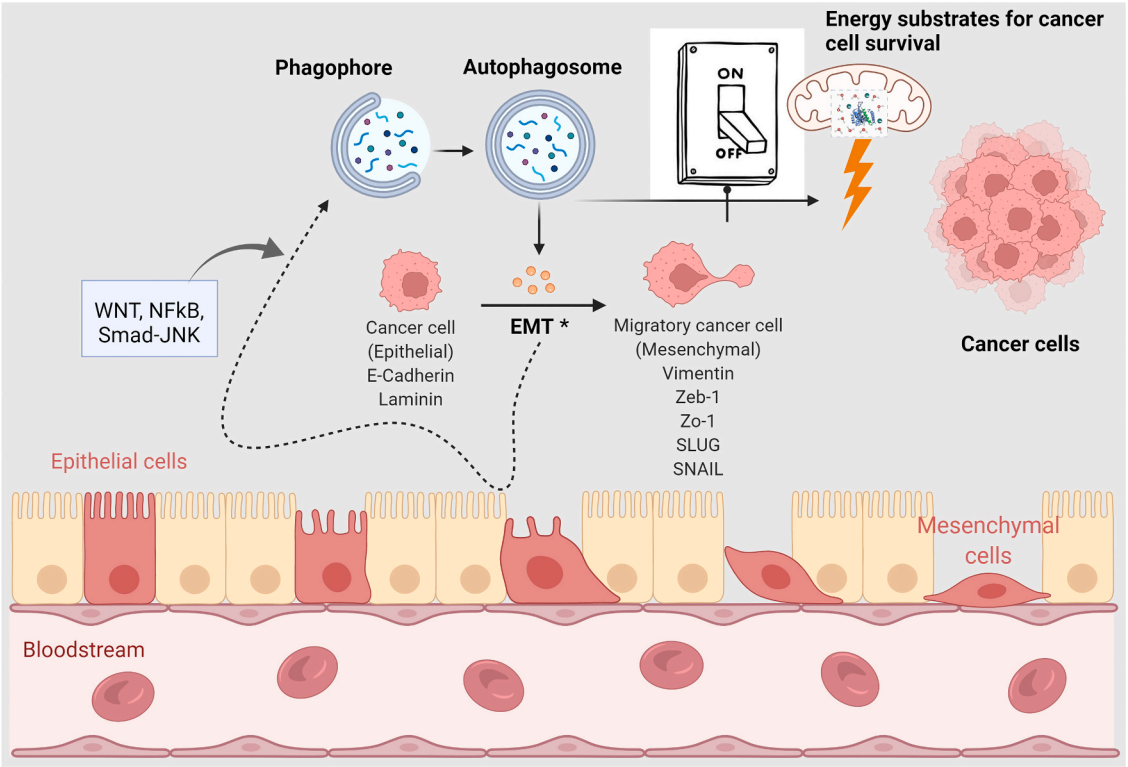

Fig. 4. Interrelationship between autophagy and EMT.
Autophagy allows cellular material to be delivered to lysosomes for degradation resulting in a basal or stress-induced turnover of cell components that provide energy vital to cancer cells, promoting tumor and key processes like EMT. Autophagy holds the ability to control the regulatory switch for cancer initiation and progression/ inhibition. As described in the review, autophagy can widely orchestrate and modulate the EMT process and individual markers via diverse pathways and serve as a therapeutic target. On the other hand, EMT can control autophagy via a few pathways such as WNT, NF-kB, Smad-JNK, etc. Therefore, the hallmark of events in EMT-autophagy crosstalk can be extremely beneficial in cancer therapy to combat therapeutic resistance and control metastasis.

It is interesting to think of a tumor-targeting strategy that targets both autophagy and EMT. Though preclinical data support targeting both EMT and autophagy processes, there is a dearth of clinical data. Further, there is a need for the development of suitable biomarkers defining different stages of EMT and different categories of autophagy. This can help in categorizing cancer genotypes for personalized medicine. It will be interesting to understand how EMT-autophagy interactions cause resistance to chemotherapy and immunotherapy. Recent advances in single-cell sequencing, single-cell proteomics, creation of data repositories, and machine learning algorithm-based big data analysis can help dissect out the interlink between autophagy, EMT, and metastasis. As a result, we should be able to search for more effective and precise ways to activate or inhibit autophagy, thus inhibiting EMT and regulating cancer growth. Combination therapies can be a more promising anticancer strategy when coupled with EMT-autophagy inhibitors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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