The obesity-autophagy-cancer axis: Mechanistic insights and therapeutic perspectives

Amir Barzegar Behrooz [a,b,1], Marco Cordani [c,d,1], Alessandra Fiore [e], Massimo Donadelli [e], Joseph W. Gordon [a,i], Daniel J. Klionsky [f], Saeid Ghavami [f,g,h,i,*]

[a] *Department of Human Anatomy and Cell Science, University of Manitoba, College of Medicine, Winnipeg, Manitoba, Canada*
[b] *Electrophysiology Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran*
[c] *Department of Biochemistry and Molecular Biology, School of Biology, Complutense University, Madrid, Spain*
[d] *Instituto de Investigaciones Sanitarias San Carlos (IdISSC), Madrid, Spain*
[e] *Department of Neurosciences, Biomedicine and Movement Sciences, Section of Biochemistry, University of Verona, Verona, Italy*
[f] *Life Sciences Institute and Department of Molecular, Cellular and Developmental Biology, University of Michigan, Ann Arbor, MI, USA*
[g] *Faculty of Medicine in Zabrze, University of Technology in Katowice, 41–800 Zabrze, Poland*
[h] *Research Institute of Oncology and Hematology, Cancer Care Manitoba-University of Manitoba, Winnipeg, Manitoba, Canada*
[i] *Children Hospital Research Institute of Manitoba, University of Manitoba, Winnipeg, MB, Canada*

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ABSTRACT

Autophagy, a self-degradative process vital for cellular homeostasis, plays a significant role in adipose tissue metabolism and tumorigenesis. This review aims to elucidate the complex interplay between autophagy, obesity, and cancer development, with a specific emphasis on how obesity-driven changes affect the regulation of autophagy and subsequent implications for cancer risk. The burgeoning epidemic of obesity underscores the relevance of this research, particularly given the established links between obesity, autophagy, and various cancers. Our exploration delves into hormonal influence, notably INS (insulin) and LEP (leptin), on obesity and autophagy interactions. Further, we draw attention to the latest findings on molecular factors linking obesity to cancer, including hormonal changes, altered metabolism, and secretory autophagy. We posit that targeting autophagy modulation may offer a potent therapeutic approach for obesity-associated cancer, pointing to promising advancements in nanocarrier-based targeted therapies for autophagy modulation. However, we also recognize the challenges inherent to these approaches, particularly concerning their precision, control, and the dual roles autophagy can play in cancer. Future research directions include identifying novel biomarkers, refining targeted therapies, and harmonizing these approaches with precision medicine principles, thereby contributing to a more personalized, effective treatment paradigm for obesity-mediated cancer.

1. Introduction

1.1. Background on obesity and cancer

Globally, approximately one billion people are estimated to be obese by 2030, including 1 in 5 females and 1 in 7 males [77]. The prevalence of obesity, defined as a body mass index (BMI) greater than 30 kg/m^2, is continuously increasing. Research supports the connection between obesity and cancer [59]. Several cancers have been associated with obesity, including cancer of the esophagus, breast, colon, rectum,

gallbladder, kidneys, liver, ovaries, pancreas, thyroid, upper stomach, and uterus, as well as meningioma and multiple myeloma [195]. Obesity has also been associated with poor prognoses for cancer patients and increased mortality rates [204]. Therefore, it is crucial to discuss obesity's role in cancer risk. The pathophysiological processes underlying the link between obesity and cancer are still not completely understood. Elevated lipid levels and attenuated lipid signaling, inflammatory reactions, insulin resistance, and adipokines are a few postulated pathways to explain the link between obesity and cancer [179]. Recent literature, however, points to macroautophagy (hereafter autophagy) as a potential link between cancer and obesity [82].

1.2. An overview of autophagy

Autophagy is a conserved catabolic process that is implicated in various diseases [293]. Although autophagy is generally considered a cytoprotective mechanism, it is unclear whether it serves a protective or detrimental role in certain diseases [206,228]. Macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) are the three main subtypes of autophagy.

There are several markers for various types of autophagy. BECN1 (beclin 1), ATG5 (autophagy related 5), and ATG12 (autophagy related 12) are regarded as early indicators of macroautophagy and are crucial in the context of cancer, where they can either suppress tumor growth or facilitate survival of cancer cells, particularly in the unique metabolic environment created by obesity [18,95,124,167]. Rapamycin, an inhibitor of MTOR (mechanistic target of rapamycin kinase), is a well-known macroautophagy activator and its role becomes even more significant considering the complex metabolic reprogramming in obesity-related cancer [252]. Macroautophagy can lead to cell death or cell survival (under stress and hypoxia) in diseases such as cancer [5,72, 118]. This dichotomy is represented in Fig. 1 depicting how the cellular milieu in obesity may influence autophagic responses and subsequent cancer cell fate.

By generating a phagophore, a compartment that sequesters cytoplasmic components and then matures into a double-membrane autophagosome, macroautophagy is the most conserved, prevalent method for eliminating damaged organelles or unneeded proteins [7,6,92]. The second major type of autophagy is known as microautophagy, and it is a non-selective lysosomal breakdown mechanism in which the vacuole invaginates and internalizes the cytoplasmic components. The resulting lumenal vesicle will be degraded after budding into the lysosome lumen [172]. Microautophagy is divided into various subtypes, including micromitophagy, micronucleophagy, and micropexophagy. The lysosomal destruction of individual proteins is the focus of the third primary form of autophagy, chaperone-mediated autophagy (CMA). This autophagy differs from the other two types because it degrades individual cytosolic proteins and does not form an intermediate sequestering vesicle; unfolded substrate proteins are translocated directly across the lysosomal membrane into the lumen [85,118] (Fig. 1).

Overall, autophagy is a fundamental physiological pathway; however, in some cases, it is still unclear whether it is essential for cell survival or death, which appears to depend on cellular and environmental factors that dictate the response to different stressors.

1.3. Rationale for linking obesity, autophagy, and cancer

1.3.1. Autophagy and obesity

Obesity among humans is an imminent threat to health because it raises the risk of several pathological conditions, including sleep apnea, cancer, insulin resistance, diabetes mellitus, hypertension, and inflammation. The essential role of autophagy in preserving cellular homeostasis and organ function is being increasingly recognized. Metabolic illnesses, including obesity, insulin resistance, type 2 diabetes, and atherosclerosis, are thought to be linked to the dysregulation of autophagy homeostasis [300].

Oxidative stress, a common feature in obesity, is influenced by the balance of reactive oxygen species (ROS) within cells. Under normal
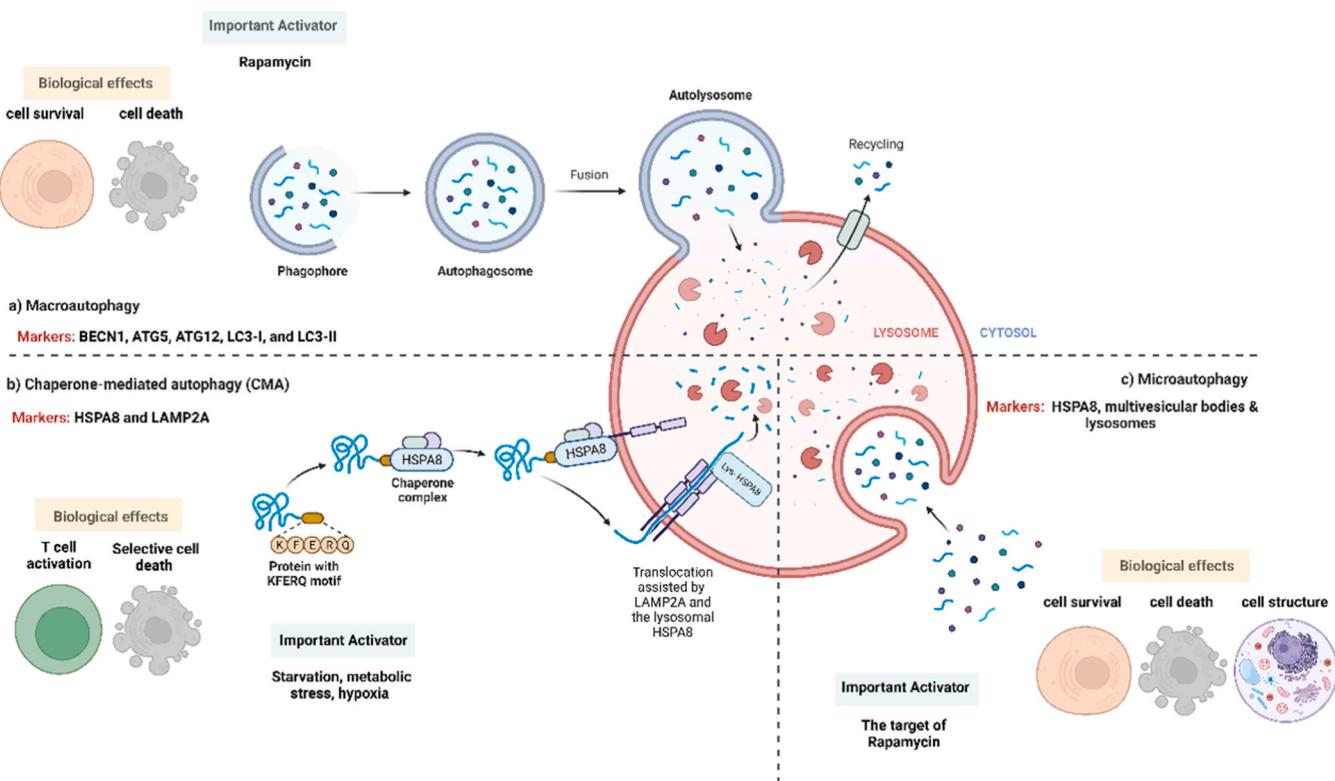

Fig. 1. Schematic representation of macroauotphagy, microautophagy, and chaperone-mediated autophagy. The components and compartments depicted here are not drawn to scale.

physiological conditions, moderate ROS levels are critical in maintaining cellular homeostasis [103]. However, in the context of obesity, the equilibrium is often disrupted, leading to elevated oxidative stress with detrimental effects [51,169]. This imbalance is primarily due to excess nutrient intake, increased adipose tissue mass, and the resultant metabolic disturbances, all characteristic of obesity [2,232]. Elevated ROS levels in obesity can induce oxidative damage to proteins, lipids, and DNA, contributing to cellular dysfunction [169]. Chronic oxidative stress, driven by persistent high ROS levels, is a key factor in the development of obesity-related complications. These include insulin resistance, systemic inflammation, endothelial dysfunction, and the progression of metabolic syndrome [79,171]. In essence, while ROS are essential for normal cellular functions, their excessive accumulation in obesity becomes a pathogenic factor, contributing to various complications. This crucial role of ROS in obesity-associated pathologies is supported by evidence linking oxidative stress with various obesity-related diseases [205]. It appears reasonable to hypothesize that the cell's overall response, which is designed to combat excessive ROS generation, is influenced by the activation of autophagy. In situations of nutritional excess, autophagy is crucial for eliminating damaged mitochondria and reducing ROS generation. A temporary increase in ROS

production appears necessary to trigger autophagy under conditions of food deficiency or during exercise [40,145,215,231]. ROS influence autophagy at different levels, including initiation (through direct or indirect ROS-mediated modulation of 5'-adenosine monophosphate [AMP]-activated protein kinase, AMPK, and MTOR complex 1 [MTORC1]), nucleation (through CAV1 [caveolin 1] or PRKD [protein kinase D]-dependent activation of the PIK3C3/VPS34 [phosphatidylinositol 3-kinase catalytic subunit type 3]-BECN1 complex), and expansion (through ROS-dependent activation of ATG4 [autophagy related 4 cysteine peptidase]) [205].

In adipose tissue (AT) from obese people, autophagy is increased. It has been demonstrated that triggering CASR (calcium sensing receptor) causes an increase in proinflammatory cytokines in preadipocytes. In addition, the expression of TNF/TNF-α (tumor necrosis factor), AT CASR expression, and AT autophagy are all connected. The level of body fat is closely correlated with CASR expression in visceral AT, and CASR activation may be a factor in the disruption of AT autophagy associated with obesity [175].

Obesity is linked to impaired autophagy in recent research. Lipid droplets in the liver and other organs contribute to obesity-related autophagy dysfunction. Lipid droplets may disrupt autophagic
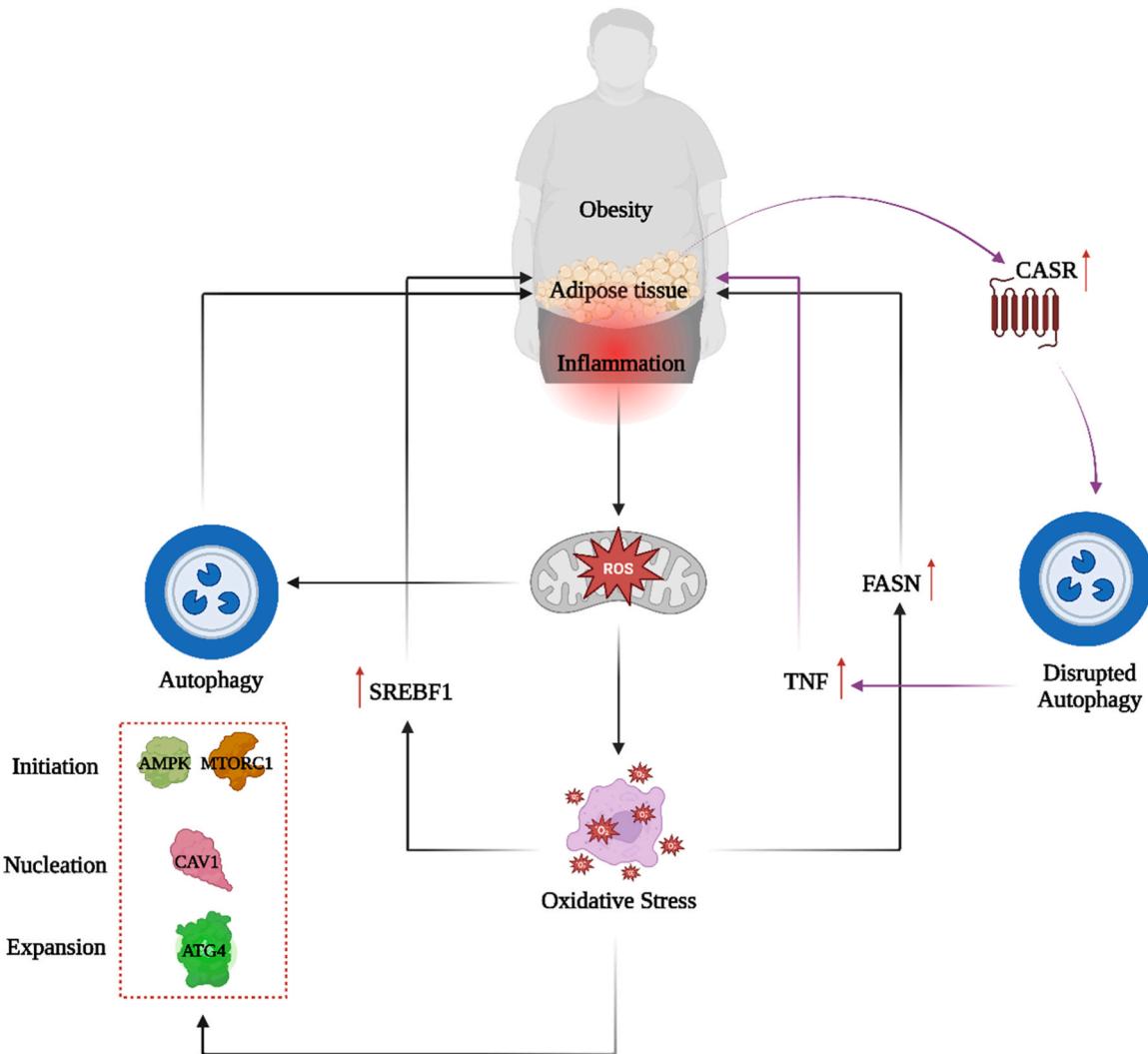
Fig. 2. Obesity and autophagy interaction. Obesity and autophagy are mutually dependent. Obesity enhances autophagy by increasing ER stress, inflammation, and ROS. Moreover, in high-nutrition conditions, obesity inhibits autophagy, and, in malnutrition, autophagy inhibits obesity. Furthermore, it has been observed that increasing ROS levels can modulate autophagy genes. ROS accounts for the induction of a detrimental lipogenic response (dependent on SREBF1/SREBP1 and FASN), contributing to or worsening the obese phenotype [187,207]. Abbreviations: BMI: body mass index; CASR: calcium sensing receptor; FASN: fatty acid synthase; ROS: reactive oxygen species; SREBF1/SREBP1: sterol regulatory element binding transcription factor 1; TNF: tumor necrosis factor.

machinery, impeding cellular component breakdown and recycling. Autophagy may be hindered by obesity-induced inflammation. Obesity-related autophagy malfunction may cause protein and organelle degradation, cellular dysfunction, and death. This may cause insulin resistance, type 2 diabetes, and other obesity-related issues. Thus, knowing the relationship between obesity and autophagy is crucial to creating therapies to enhance autophagy and prevent or cure obesity-related diseases. [187,300]. (Fig. 2).

1.3.2. Autophagy and cancer

Autophagy plays a pivotal role in the biology of cancer. This process is regarded as a tumor-suppressive mechanism during tumor initiation and malignant transformation. Eliminating damaged cells and organelles limits the spread of the tumor and reduces genetic instability. Nevertheless, autophagy is also considered to offer protection to cancer cells. Cancer cells require cellular building blocks throughout their development to support their metabolism and generate energy. As a tumor grows, autophagy supplies all the required metabolic intermediates to meet the needs of the expanding tumor cells [16,19,132,182,228,240].

As previously documented, the AKT (AKT serine/threonine kinase)-MTOR pathway is used by oncogenes such as mutant TP53/p53 (tumor protein p53) to inhibit autophagy. As a result, autophagy and TP53 have antagonistic roles, which control cancer development [47]. *BECN1* is one of the autophagy genes that function as a tumor suppressor, and it is reported to be deleted in 50–70% of breast tumors and up to 75% of ovarian malignancies [88,151]. It has also been established that EGFR (epidermal growth factor receptor) inhibits autophagy by binding to BECN1, which is involved in autophagic induction, allowing cancer cells to survive stressful situations. Cetuximab also blocks the translation of BECN1 by reducing *MIR216B* (microRNA 216b), suppressing EGFR. Deactivating EGFR causes cancer cells to produce more BECN1, which promotes autophagy [105]. Given these lines of evidence, autophagy may be associated with tumor suppression.

By contrast, in support of the protective function of autophagy in the outcome of cancer cell treatments, it has been shown that tongue squamous cell carcinoma (TSCC) exhibits cisplatin resistance via activating autophagy. Chloroquine/CQ and *BECN1* siRNA therapy of TSCC improve cisplatin sensitivity, demonstrating that autophagy suppression is a viable therapeutic target for TSCC [153]. Yet, it has also been shown that enhanced autophagic flux controls the ability of oral squamous cell carcinoma/OSCC to withstand cisplatin. The autophagic markers BECN1, ULK1 (unc-51 like autophagy activating kinase 1), ATG5, ATG7 (autophagy related 7), and ATG14 (autophagy related 14) are elevated in FaDu-CDDP-R (FaDu cisplatin-resistant) cells. In the same context, it was discovered that ATG14-deficient Fadu cells have lower levels of the surface resistance marker CD44 (CD44 molecule (Indian blood group)) [185]. These findings suggest that autophagy could be linked to mechanisms of cell survival and chemoresistance of cancer cells.

1.3.3. Obesity, autophagy, and cancer

Obesity is a rapidly spreading epidemic that can cause severe pathological disorders and has recently been identified as a preventable risk factor for cancer. By modifying IGF (insulin like growth factor), LEP (leptin), and ADIPOQ (adiponectin, C1Q and collagen domain containing) signaling, obesity modulates the activation of AMPK and phosphoinositide 3-kinase (PI3K)-AKT/protein kinase B pathways to promote cancer cell survival, proliferation, metabolism, and genome stability. Inflammation, lipotoxicity, oxidative stress, and proteotoxicity brought on by obesity are all decreased by autophagy. Autophagy controls various cellular metabolic processes and is impaired in obesity-related pathophysiology, which can lead to cancer [135].

Through various mechanisms, obesity-mediated cellular metabolic dysregulation reduces autophagy. Obesity may raise cancer risk by promoting systemic inflammation, changing the tumor microenvironment (TME), and promoting angiogenesis, cell proliferation, invasion,

and migration. LEP, ADIPOQ, IGF, and IL6 (interleukin 6) signaling are all modulated by obesity, which speeds up and maintains tumor growth [142,173,214].

Nutritional variables such as amino acids and growth factors can influence autophagy, as can negative and positive signaling from MTOR and AMPK, respectively. As MTOR is a regulator of ULK kinase, AMPK suppresses the MTOR pathway to upregulate autophagy by activating the ULK pathway. AMPK also activates BECN1 to increase autophagy. Autophagy is negatively regulated by PI3K-AKT signaling, which stimulates the MTOR pathway. Additionally, MTOR is activated by the MAPK (mitogen-activated protein kinase) pathway to suppress autophagy [102,114].

By activating MTOR and blocking the downstream ULK pathway (ULK1-ATG13-RB1CC1-ATG101), excess nutrition (glucose and amino acids) suppresses autophagy. High-nutrition conditions in obese people cause the PI3K-AKT pathway, an upstream MTOR activator that inhibits autophagy, to become activated. Autophagy is decreased by insulin resistance and hyperinsulinemia [135,157]. According to Zhang et al. [300], high blood sugar causes the activation of the INS-IGF-PI3K-AKT pathway, which in turn inhibits FOXO (forkhead box O) transcription factor-dependent autophagy [300]. IL1B (interleukin 1 beta) and IL18 (interleukin 18) levels are raised in association with impaired autophagy, which contributes to altered adipokines and inflammation of the adipose tissue [13,49,52,289].

Insulin is a potent growth factor that promotes tumorigenesis in both in vitro and in vivo models by inducing proliferation and inhibiting apoptosis in various benign and malignant cells [199]. Increased insulin levels have been independently linked to multiple malignancies in humans, including those most closely related to obesity, such as breast, colon, endometrial, and pancreatic cancers [29,122,164,235]. Breast, prostate, hepatic, and leukemic malignancies are only a few of the tumors with elevated insulin receptor expression [50,76]. *In vitro* and in vivo cancer growth-stimulating hormone IGF1 (insulin like growth factor 1), primarily released by the liver, is also promoted by insulin [127,144]. IGF1 exerts its tropic effects by attaching to its receptor, IGF1R (insulin like growth factor 1 receptor), and INSR (insulin receptor), both of which are overexpressed in many cancers and present in most normal cells [76]. Additionally, IGF1 stimulates angiogenesis, associated with cancer development [278].

A complex interaction exists between AMPK, MTOR, and autophagy levels. The expression of AMPK rises, and MTOR is inhibited under conditions of low dietary status. Additionally, autophagy can be directly triggered by AMPK. Autophagy increases and functions as a tumor suppressor due to the inactivation of MTOR. To prevent VEGFA (vascular endothelial growth factor A) from increasing tumor vascularization, ADIPOQ stimulates the AMPK pathway. ADIPOQ levels decrease with obesity, increasing cancer development risk [139]. However, the MTOR-negative regulator AMPK is suppressed under conditions of excess nutrition. As a result, active MTOR may inhibit ULK kinase and cause a reduction in autophagy. MAPK, PI3K-AKT, and MTOR can all function as autophagy inhibitors. Additionally, the obesity-autophagy-cancer axis may enter into play through elevated LEP and insulin levels. Insulin resistance develops when the circulating blood contains higher insulin levels. The PI3K-AKT pathway is activated by insulin-IGFR signaling to mediate the anti-apoptotic pathway and advance tumor growth. Autophagy is prevented by PI3K-AKT pathway activation [60]. The activation of the insulin signaling pathways via the insulin receptor substrates IRS1 (insulin receptor substrate 1) and/or IRS2 and the PI3K-AKT pathway, as well as the nutrient sensors MTOR or the EIF2 (eukaryotic translation initiation factor 2) kinase EIF2AK4/GCN2 (eukaryotic translation initiation factor 2 alpha kinase 4), may suppress autophagy in response to overnutrition (excess glucose or amino acids). FOXO transcription factors are either inhibited or inactivated by PI3K-AKT signaling, suppressing autophagy [300]. As autophagy is downregulated tumor growth is induced by LEP-mediated PI3K overexpression. Promoting angiogenesis, LEP causes the

production of the inflammatory cytokines TNF, IL6, and VEGF (vascular endothelial growth factor) [210]. LEP has an impact on the insulin-glucose axis and appetite. LEP induces anorexia in the hypothalamus by inhibiting NPY (neuropeptide Y)-AGRP (agouti-related neuropeptide) neurons and activating POMC (proopiomelanocortin)-CARTPT (CART prepropeptide) neurons. LEP suppresses insulin synthesis and secretion from pancreatic beta cells in LEP-sensitive people (normal people), whereas insulin increases LEP release from adipose tissue. Through the sympathetic nervous system/SNS, LEP enhances insulin sensitivity in the liver and increases glucose absorption in

skeletal muscle tissue. Nevertheless, despite the rise in plasma LEP levels, LEP-resistant overweight people are resistant to LEP's anorectic and weight-reducing effects. Hyperinsulinemia caused by LEP resistance raises plasma LEP levels [8,225]. The overview of autophagy and its impact on cancer development in the context of obesity is presented in Fig. 3.
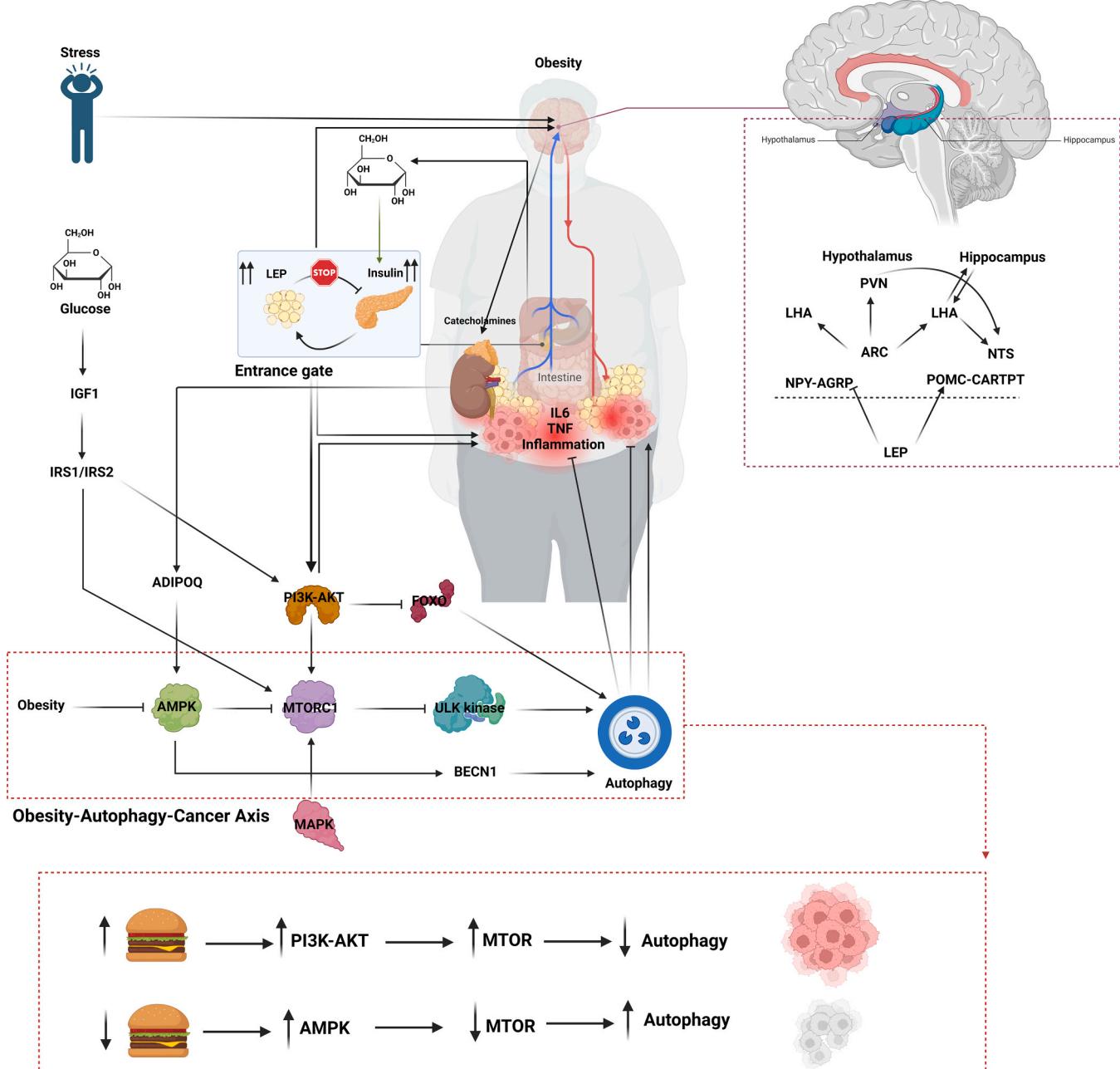

Fig. 3. Obesity increases the risk of developing cancer through impairing functioning autophagy. Autophagy rises and suppresses tumors when MTOR is inactivated. ADIPOQ/adiponectin activates AMPK to inhibit tumor vascularization by VEGFA. Obesity lowers ADIPOQ, increasing cancer risk. Overnutrition suppresses the MTOR-negative regulator AMPK. Thus, active MTOR may inhibit ULK kinase and reduce autophagy. MAPK, PI3K-AKT, and MTOR suppress autophagy. The obesity-autophagy-cancer axis may also enter into play via increased LEP and insulin. High blood insulin levels cause insulin resistance. Insulin-IGFR signaling activates the anti-apoptotic PI3K-AKT pathway to promote tumor development. PI3K-AKT pathway activation inhibits autophagy. In response to overnutrition, the insulin receptor substrates IRS1 and/or IRS2, the PI3K-AKT pathway, and the nutrient sensors MTOR and the EIF2 kinase EIF2AK4/GCN2 may suppress autophagy. FOXO transcription factors are repressed or inactivated by PI3K-AKT signaling, inhibiting autophagy. Autophagy is downregulated, and tumor development is promoted by LEP-mediated PI3K overexpression. LEP generates TNF, IL6, and VEGF to stimulate angiogenesis. LEP also affects appetite and insulin-glucose.

2. Obesity and cancer

2.1. General overview

Several extensive epidemiological studies have evaluated the association between obesity and mortality; a meta-analysis of 230 cohort studies, including > 3.74 million deaths among > 30.3 million participants, provided evidence that adiposity, measured by BMI, increases the risk of premature all-causes mortality [10]. Obesity is a risk factor for an expanding set of chronic diseases, such as cardiovascular disease, diabetes mellitus, chronic kidney disease, musculoskeletal disorders, and many types of cancer [250]. Primary prevention of overweight and obesity is, therefore, the most feasible and cost-effective alternative for disease prevention and all the associated complications, in particular in areas where healthcare resources are limited.

The link between obesity and cancer is rather complex; several studies reported that obesity is associated with an augmented risk and an increase in mortality [30,204]. In addition, people with a higher BMI during their cancer diagnosis or who have survived cancer have higher risks of developing a second, unrelated malignancy [74,86,249].

2.2. Obesity-associated mechanisms contributing to tumorigenesis

The higher cancer incidence and mortality associated with obesity have been explained by several mechanisms, including insulin resistance and hyperinsulinemia, alterations in the adipokine pathways and lipid signaling, and the general inflammatory status of the tissues.

2.2.1. Insulin resistance and hyperinsulinemia

The obesity epidemic goes in parallel with an augmented incidence of other disorders, such as metabolic syndrome, non-alcoholic fatty liver disease, and type 2 diabetes mellitus. All those metabolic abnormalities are linked to insulin resistance, a condition in which target tissues have decreased sensitivity to insulin, leading to elevated blood insulin and glucose levels. Insulin resistance triggers are genetic and environmental; several mutations in the insulin receptors and other mediators of the insulin pathway, even if rare, have been recognized as significant causes of insulin resistance, metabolic syndrome, and diabetes [22]. At the same time, excess visceral adipose tissue caused by sedentary life and food imbalances in genetically susceptible people is considered the main driver of insulin resistance worldwide. As a matter of fact, most obese subjects have insulin resistance that can be fully recovered after weight loss [89,217,233,247]. The main consequence of insulin resistance in patients is the development of hyperinsulinemia, the increased secretion of insulin by pancreatic β-cells to control blood glucose levels [194,201, 254,256,295].

The human insulin prohormone consists of a precursor protein, a signal peptide, the A and B chains of insulin, and a connecting peptide called C-peptide. C-peptide and insulin are secreted in equimolar amounts from the pancreatic β-cells but in the plasma, insulin, and C-peptide exhibit remarkably different kinetics: insulin has a half-life of ~2–3 min, while C-peptide has a half-life of ~30 min. Therefore, in clinical practice, C-peptide often replaces insulin as a marker for hyperinsulinemia [130,290] and has been extensively used to examine the risk of several cancers. Indeed, several reports demonstrated that individuals with high C-peptide or insulin levels have a higher risk of obesity-related and diabetes-related cancers, such as colorectal [121, 166], breast [115], endometrial [65,66], liver [161,287], pancreatic [178,193], ovarian [200] and gastric [106] cancer, when compared with the control individuals with low levels of the same factor. Interestingly, the Hoorn Study, a population-based study of glucose metabolism in individuals aged 50–75 years, showed that individuals with increased proinsulin levels have a twofold risk of cancer mortality over 20 years, suggesting that proinsulin levels may also have direct tumor-promoting effects [264]. Mechanistically, after ligand binding, INSR activates its tyrosine kinase and initiates downstream signaling,

including the PI3K-AKT, MTOR, and RAS-MAPK pathways [143]. Insulin can also bind to IGF1R, activating the mitogenic signaling pathways that promote cellular growth and proliferation [183].

2.2.2. The adipokine pathways

Adipose tissue belongs to the class of connective tissues whose bodily functions include energy storage, thermal insulation, and immune and endocrine functions. In particular, the AT is the largest endocrine organ responsible for the secretion of several adipocyte-derived hormones, called adipokines, that are crucial in maintaining energy homeostasis [45,141]. Traditionally, LEP and ADIPOQ/adiponectin are the two most important adipokines associated with developing obesity-related cancer.

LEP/OB, a 16-kDa adipocyte-derived adipokine, is currently considered a "satiety hormone." Synthesis and secretion of LEP depend on the adipocyte's mass and reflect the status of energy stores. Obesity significantly alters LEP regulation [279]. Like insulin, chronic overexpression of LEP induces LEP resistance, resulting in increased circulating LEP, called hyperleptinemia [208,218]. Augmented circulating LEP levels have been associated with increasing risk and incidence of several types of cancer, including prostate [108], breast [93,277], colon [67,68], thyroid [1,42], endometrial [32] and ovarian [211] cancer. Several pro-tumorigenic effects explain this association; LEP increases cancer cell proliferation, anti-apoptosis, cell migration and angiogenesis, self-renewal, and possibly resistance to chemotherapeutic treatment [26,27,42,67,93].

ADIPOQ/adiponectin is a 30-kDa adipocyte complement-related protein, structurally similar to complement factor C1Q, and is the most abundant peptide secreted by adipocytes. ADIPOQ/adiponectin has several functions in human physiology, balancing glucose and lipid metabolism, insulin-sensitizing, anti-apoptotic, and immune regulatory effects [14]. Consistently, hypoadiponectinemia has been associated with obesity-related insulin resistance, type 2 diabetes, atherosclerosis, and coronary heart disease, as well as with a higher risk of various cancer types, thus being generally considered a beneficial adipokine [54, 55,56,104,107,117,203,273].

2.2.3. Bioactive lipid signaling

Signaling molecules and metabolites secreted by adipose and cancer tissues, especially in the obese state, are now recognized as important factors for cancer progression as they can stimulate anti-apoptotic effects, cell proliferation, angiogenesis, and migration through paracrine or autocrine interactions [191,202]. As a matter of fact, the enzymes responsible for the biosynthesis and breakdown of these signaling lipids are often dysregulated in cancer, thus acquiring oncogenic functions [78].

Sphingolipids comprise a wide range of complex lipids essential to all eukaryotic membranes [7,90]. The significant contributors to sphingolipid signaling are ceramide and sphingosine-1-phosphate (S1P), which have divergent roles in regulating cell survival and growth [7,99,291]. Ceramide promotes growth arrest and apoptosis by activating mitochondrial permeabilization, releasing caspases into the cytosol, and activating apoptotic pathways [53,100]. By contrast, S1P promotes cell proliferation and survival by binding its receptor and suppressing CASP3 (caspase 3) activity, thus preventing apoptosis [226]. Altered levels of ceramide and S1P and the modulation of several enzymes involved in sphingolipid metabolism have been detected in cancer, indicating the contribution of these pathways in cancer pathogenesis and progression [197].

Adipocyte-originated prostaglandins have been reported to regulate almost all the hallmarks of cancer. PTGS2/COX2/cyclooxygenase 2 (prostaglandin-endoperoxide synthase 2) is a key enzyme responsible for the biosynthesis of prostaglandins from arachidonic acid and, in particular, prostaglandin E2/PGE2, which is one of the most abundant lipid mediators in the human body endowed with proinflammatory activity. PTGS2/COX2 enzyme is frequently upregulated in cancer, and prostaglandin E2 is produced by many human solid tumors, including

colon, stomach, and breast cancers [25,111,133,180,184,245,246].

Lysophosphatidic acid (1- or 2-acyl-sn-glycerol 3-phosphate/radial-glycerol-phosphate [LPA]) is the smallest bioactive lipid produced during the synthesis of cell membranes. LPA induces several cellular responses by interacting with its six specific G protein-coupled LPAR (lysophosphatidic acid receptor) proteins [84]. The range of cellular effects caused by LPA and its receptors is hugely vast and varied and includes immediate morphological modifications, motility, chemotaxis, invasion, gap-junction closure, and tight-junction opening, as well as promotion of cell-cycle progression, sustained cell viability, wound healing, production of EDN (endothelin) and pro-angiogenic factors (VEGF, IL6, IL8 and CXCL1/GRO1 [C-X-C motif chemokine ligand 1]). Because of this broad range of cellular responses, LPA has been implicated in the pathophysiology of several types of malignancies, such as ovarian, prostate, breast, melanoma, head and neck, bowel, and thyroid cancers [70,112,186,236,241,251,253,265,280,281].

2.2.4. Chronic Inflammation in Obesity and Cancer

Obesity is accompanied by chronic subclinical inflammation, which mediates most of the associated systemic complications. Numerous factors originating from the inflamed adipose tissue have been implicated in the increased obesity-associated cancer risk; indeed, inflammation is a central component of tumor development and progression, as demonstrated by the presence of multiple inflammatory cells and mediators within the TME that sustain proliferative signaling, activate migration and metastasis, and promote angiogenesis [61,97]. Adipocytes and macrophages, which typically accumulate in tissues with increased adiposity, are the primary obesity-associated pro-inflammatory mediators producing TNF and IL6 pro-inflammatory cytokines that favor tumor initiation and progression [125,170,192,219, 270]. This activity is also exacerbated by the shift in the macrophage's polarization from an anti-inflammatory "M2-like" phenotype to a more pro-inflammatory "M1-like" phenotype in obese AT, which can be explained by the imbalance in the LEP: ADIPOQ/adiponectin ratio [35, 165,227]. However, the contribution to the obesity-associated inflammatory status is not restricted to macrophages. Still, alterations in many immune populations, responsible for both adaptive and innate immunity, have been associated with obesity, such as an augmented Th1 cell response [275], CD8^{+} cytotoxic T cell response [192], natural killer (NK) cells [220] and a decreased number of regulatory T cells [75]. CD8^{+} T cells accumulate in the AT in the early phase of the development of obesity and promote M1 macrophage infiltration via CXCR3 signaling
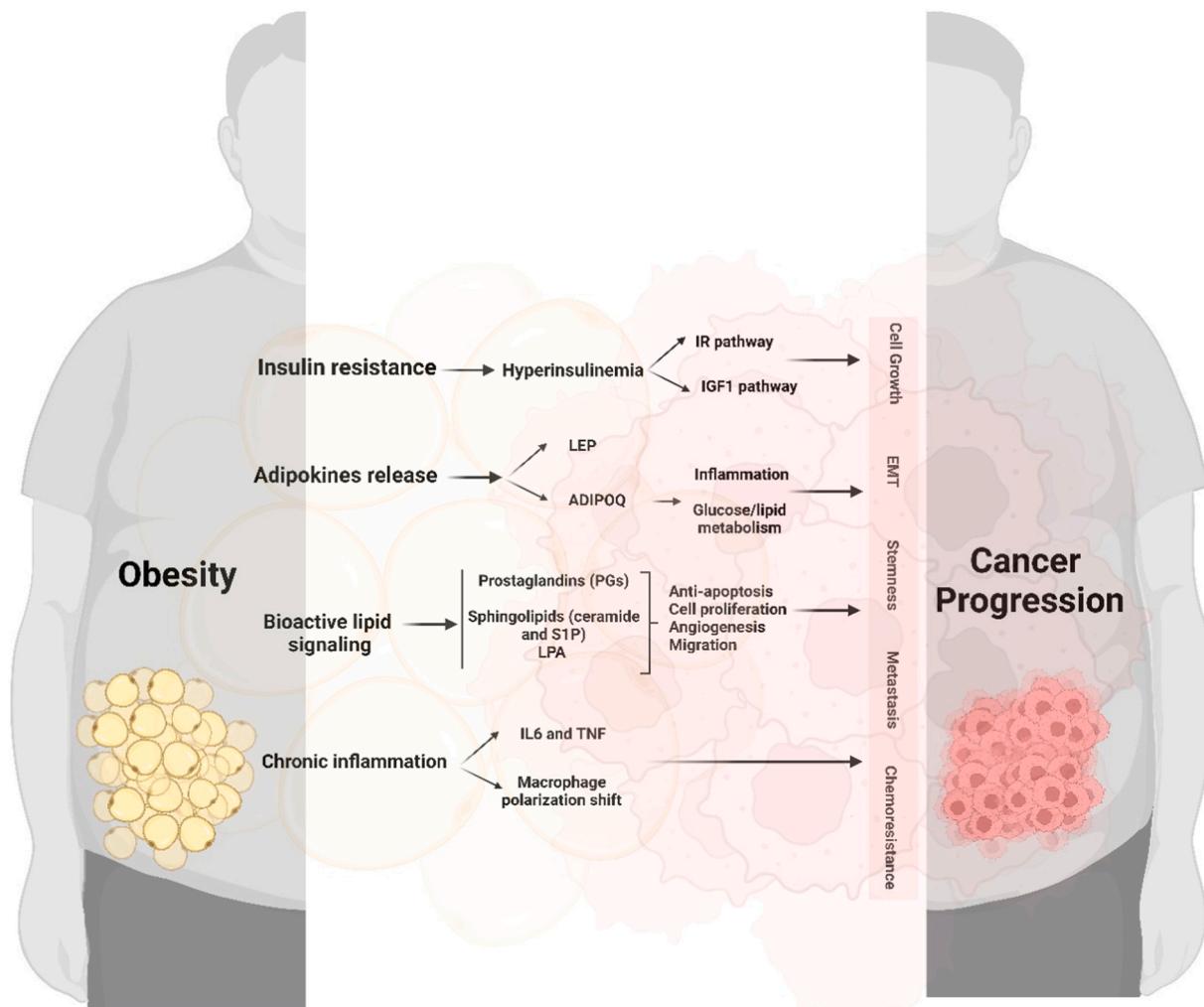
Fig. 4. Obesity-mediated cancer progression. It is possible to consider obesity and cancer progression as intimate friends because of their close interplay. Five factors facilitate cancer progression: cancer cell growth, EMT (epithelial-mesenchymal transition), stemness, metastasis, and chemoresistance. As a result of obesity, these factors can change. One of the important characteristics of obesity is hyperinsulinemia. Cancer cells can progress by activating insulin resistance (IR) and IGF1 (insulin like growth factor 1) pathways. Moreover, adipokines released by adipocytes modulate inflammation and glucose/lipid metabolism. A bioactive lipid signaling pathway, such as that involving prostaglandins and sphingolipids, can also regulate cancer progression. Chronic inflammation is common to both cancer cells and obesity. Inflammatory factors influence cancer progression, including TNF (tumor necrosis factor), and IL6, and macrophage polarization.

[69,129].

Chronic inflammation significantly contributes to the development of other chronic illnesses, such as obesity and cancer. Obesity leads to chronic inflammation due to the excessive build-up of adipose tissue, which generates pro-inflammatory cytokines. Cytokines can harm cells and tissues, resulting in insulin resistance. Chronic inflammation may facilitate the proliferation and metastasis of cancer cells. For example, inflammatory cells can generate growth factors that promote the proliferation of cancer cells. Additionally, they may provide a conducive environment for cancer cells to infiltrate and spread to other parts of the body [248] (Fig. 4).

3. The role of autophagy in obesity-mediated cancer progression

3.1. Autophagy and metabolic reprogramming in obese tissues

In obese tissues, metabolic reprogramming is a fundamental adaptive response that aims to cope with altered nutrient availability and energy demands [271]. Autophagy plays an essential role in this reprogramming by maintaining cellular homeostasis through the degradation and recycling of damaged organelles and misfolded proteins, which is especially critical in the context of energy excess and oxidative stress common in obesity [224].

One of the most significant adaptations in energy metabolism in obesity is the shift toward utilizing fatty acids as a primary energy source [6,239,272]. This is partly due to the excessive storage of lipids in adipose tissue, leading to increased lipid availability. Autophagy is instrumental here, as it helps in the turnover of lipid droplets through a specific process called lipophagy, a form of selective autophagy that facilitates the mobilization of stored lipids for fatty acid oxidation [243]. In this context, a relevant study by Agostinis and colleagues [177] has shown that autophagy is vital for lymphatic endothelial cells/LECs in managing lipid accumulation and preserving mitochondrial function, which is essential for lymphangiogenesis; this process is also crucial in obesity [159].

3.1.1. The role of PPARGC1A/PGC-1α

PPARGC1A (PPARG coactivator 1 alpha) is a master regulator of mitochondrial biogenesis and is critical in enhancing mitochondrial oxidative metabolism [305]. PPARGC1A is upregulated in response to energy stress conditions, such as during high-fat feeding [268,98]. In this regard, PPARGC1A expression increases in white adipose tissue/WAT of *nfe2l2/nrf2$^{-/-}$* (NFE2 like bZIP transcription factor 2) mice fed with a high-fat diet [234], which exacerbates oxidative stress in fat cells [174]. In addition, PPARGC1A can enhance mitochondrial fatty acid oxidation, which is crucial for dealing with lipid excess in obesity [41,113].

Interestingly, PPARGC1A has also been linked to the regulation of autophagy. In particular, PPARGC1A can promote the expression of autophagy-related genes, indicating a potential role in facilitating selective mitochondrial turnover and quality control through a process known as mitophagy, especially under conditions of metabolic stress in obesity [261]. In a study by Salazar et al., it was found that PPARGC1A upregulates autophagy and reduces senescence in vascular smooth muscle cells through an SQSTM1 (sequestosome 1)-dependent mechanism, highlighting the critical interplay between mitochondrial regulation and autophagy in cellular aging [229]. Along these lines, Zhang et al. demonstrated that PPARGC1A, which is upregulated in dermal fibroblasts in systemic sclerosis, promotes autophagy and facilitates fibroblast activation and collagen production, suggesting a potential therapeutic target for fibrotic diseases through modulation of the PPARGC1A and autophagy pathways [301].

However, although PPARGC1A is typically upregulated in response to a high-fat diet, it is interesting that its expression can be differentially modulated depending on the tissue and context. For instance, a study by Barroso et al. found that a high-fat diet reduces hepatic PPARGC1A

expression in mice and induces liver inflammation through suppression of the regulation effects of PPARGC1A on the NFKB/NF-κB (nuclear factor kappa B) pathway, which is integral to inflammation [15]. In addition, Zhang et al. revealed that repression of PPARGC1A in retinal pigment epithelium (RPE), especially under conditions of a high-fat diet, is associated with abnormalities resembling age-related macular degeneration/AMD, implicating the importance of PPARGC1A in maintaining mitochondrial function and autophagic dynamics in the retina [298]. These findings suggest that regulating PPARGC1A expression in response to a high-fat diet can be tissue-specific and have diverse implications for metabolic reprogramming and cellular functions across different tissues. It is worth noting that the differential modulation of PPARGC1A expression in other tissues under conditions of a high-fat diet, as observed by Barroso et al. in the liver and by Zhang et al. in the RPE, suggests that the role of PPARGC1A in autophagy regulation may also be tissue specific. In the liver, reduced PPARGC1A expression might impede the autophagy process. In contrast, in the RPE, repression of PPARGC1A can hinder mitochondrial turnover through mitophagy, leading to compromised mitochondrial function and the onset of age-related macular degeneration. These observations highlight the complex interplay between PPARGC1A, autophagy, and metabolic programming in different tissues, emphasizing the need for targeted approaches in therapeutic interventions.

3.1.2. The role of AMPK

AMPK is the cellular energy sensor activated in response to a depletion in cellular energy levels [81,299]. In the context of obesity, where there is an energy surplus but often a functional energy deficiency at the cellular level, AMPK helps restore energy homeostasis [181]. Many studies highlight the central role of AMPK in regulating fatty acid metabolism, which is crucial for addressing obesity and insulin resistance. In this regard, the compound Yhhu981 activates AMPK, thus significantly enhancing fatty acid oxidation while inhibiting fatty acid synthesis, which could have implications for managing insulin resistance and obesity by modulating lipid metabolism [294].

Similarly, another compound, glabridin, activates AMPK and reduces adiposity and hyperlipidemia in obese rodents by suppressing lipogenic gene expression and promoting fatty acid oxidation and mitochondrial activity, suggesting a model where AMPK activation is central to improving fatty acid metabolism [140].

However, AMPK stimulates fatty acid oxidation and inhibits pathways consuming energy, making it a key player in cellular energy homeostasis [58]. Its activation in adipose tissue is particularly interesting because it reduces fatty acid efflux and promotes local fatty acid oxidation, which may have therapeutic potential in treating insulin resistance and obesity. A study by Boyle et al. reveals that metformin, a common drug for type 2 diabetes, activates AMPK in human AT, leading to the reduction in ACAC/ACC (acetyl-CoA carboxylase) protein levels, which is critical in fatty acid synthesis [23]. Interestingly, Gallic et al. found the ACAC regulation by AMPK has implications for appetite control. Indeed, mice with mutations that prevent AMPK from inhibiting ACAC show reduced appetite in response to metabolic stress [80].

Notably, AMPK is also a master regulator of autophagy. By phosphorylating several autophagy-related proteins, AMPK links energy sensing to the autophagic process [94,128,296]. In obese tissues, this regulation of autophagy by AMPK can be speculated to work in tandem with its roles in fatty acid oxidation and synthesis.

AMPK could optimize the mitochondrial capacity for oxidizing fatty acids by facilitating the removal of damaged mitochondria through mitophagy activation and possibly promoting the biogenesis of new mitochondria [237,306]. In obesity, where excessive nutrient intake can lead to mitochondrial stress and dysfunction [213], AMPK-mediated mitophagy could be crucial for maintaining mitochondrial quality control, as an efficient mitochondrial network is fundamental for fatty acid oxidation [147]. This might be particularly relevant in counteracting the lipid overload observed in obese tissues by enhancing the ability to

convert stored fats into usable energy. Conversely, by inhibiting anabolic pathways like fatty acid synthesis, AMPK ensures that the energy and resources are directed towards catabolic processes, including autophagy and fatty acid oxidation.

It is tempting to speculate that AMPK might be a metabolic sensor orchestrating a coordinated response to obesity-induced stress. By stimulating autophagy and mitophagy, AMPK could promote the removal of damaged organelles and supports a metabolic shift towards energy conservation. This, coupled with suppressing fatty acid synthesis, could represent a concerted effort to realign metabolic pathways toward homeostasis in obese patients. The regulatory activities of AMPK, from the enhancement of fatty acid oxidation to the modulation of systemic energy expenditure are illustrated in Fig. 5. In summary, AMPK forms a comprehensive network that combats the metabolic challenges presented by obesity. By inhibiting fatty acid synthesis, AMPK may modulate the cell's metabolic response towards equilibrium, mitigating the adverse effects of nutrient excess.

3.1.3. AMPK-PPARGC1A-UCP2 axis

Based on what was discussed above, the tightly coordinated axis of AMPK-PPARGC1A-UCP2 (uncoupling protein 2) emerges as a critical regulator of metabolic reprogramming and autophagy in obese tissues, influencing energy homeostasis, inflammation, and protection against cellular stress. UCP2 is an inner mitochondrial membrane protein belonging to the uncoupling protein family responsible for lowering mitochondrial membrane potential and dissipating metabolic energy to prevent oxidative stress accumulation. The role of UCP2 in metabolic reprogramming in obesity is carried out mainly through its ability to uncouple mitochondrial respiration from ATP synthesis, essentially dissipating energy as heat [64]. This can be protective in obesity as it reduces ROS production, which is often elevated due to excess nutrient availability. UCP2 is also intimately involved in regulating energy metabolism by modulating ATP production and proton leak in the inner mitochondrial membrane. In adipose tissue, UCP2 expression is influenced by adipokines such as LEP and ADIPOQ/adiponectin, which are involved in energy homeostasis and inflammation [168]. UCP2 also plays a role in thermogenesis, which leads to increased energy utilization and decreased fat accumulation [33].

AMPK has been described to activate PPARGC1A through phosphorylation at threonine 177 and serine 538 in skeletal muscle [119]. Irrcher et al. showed that the activation of AMPK through 5-aminoimidazole-4-carboxamide ribonucleotide/AICAR increases *PPARGC1A* promoter activity and mRNA expression in skeletal muscle, with the effect mediated by an overlapping GATA/EBox (GATA binding protein) binding site in the *PPARGC1A* promoter, involving USF1 (upstream transcription factor 1) as a key transcription factor [116]. This activation of PPARGC1A through multiple mechanisms is essential as it leads to mitochondrial biogenesis and the orchestration of antioxidant responses, which are of notable importance in the metabolically stressed environment of obesity [11].

UCP2 is yet another player that takes part in this axis. PPARGC1A, being a potent coactivator, stimulates the transcription of *UCP2*. In this regard, a study by Oberkofler et al. reveals that PPARGC1A enhances the activation of the human *UCP2* gene by thyroid hormone in insulinoma
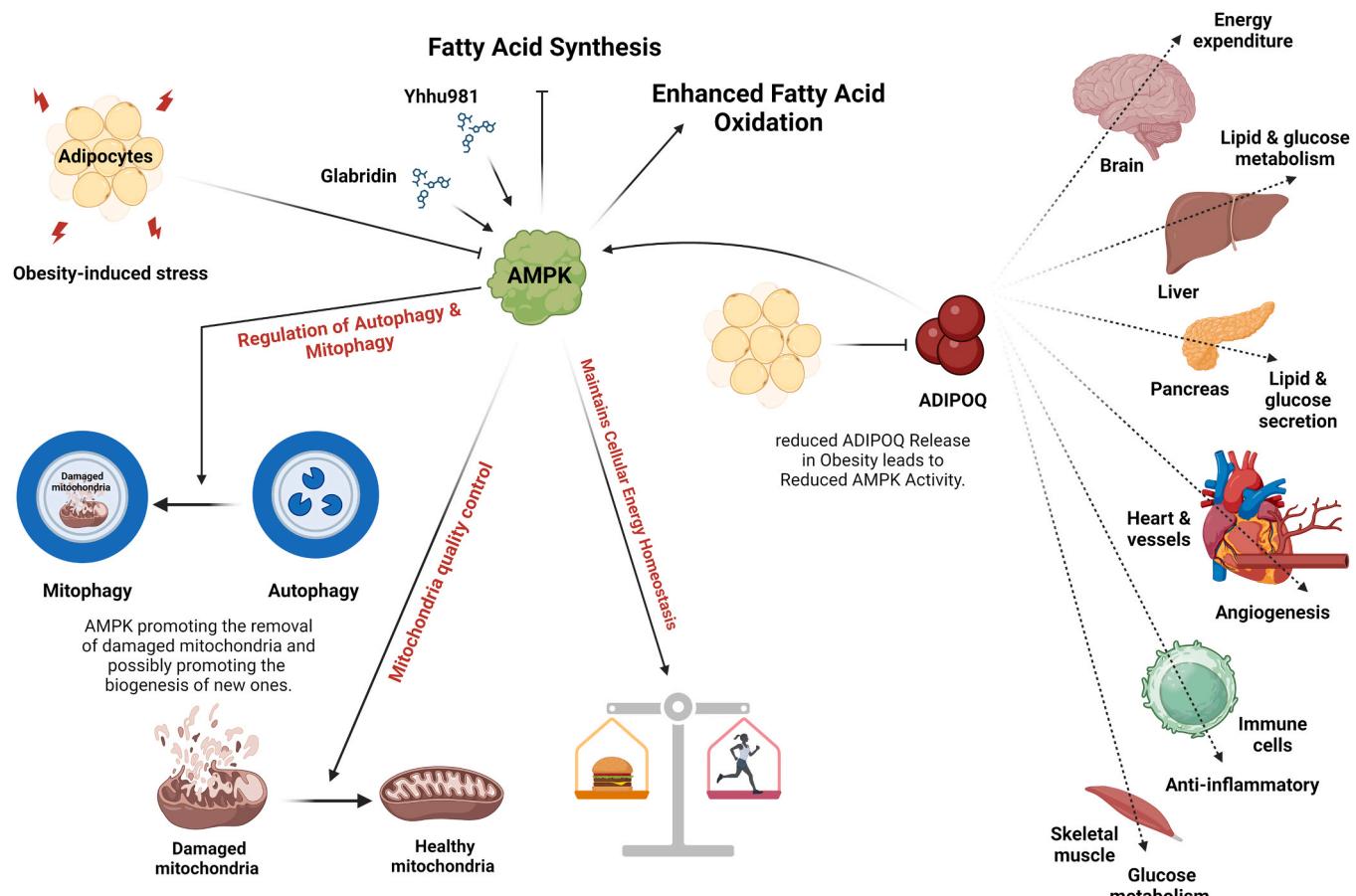

Fig. 5. The Central Role of AMPK in Cellular Energy Homeostasis and Response to Obesity. 5' AMP-activated protein kinase (AMPK) regulates cellular energy metabolism. When energy levels are low, AMPK is activated. The activated AMPK initiates a series of reactions that increase energy production and decrease energy consumption. AMPK plays various roles, including regulating glucose and lipid metabolism, promoting fatty acid oxidation, inhibiting protein synthesis, promoting autophagy, and regulating mitochondrial biogenesis. However, obesity can inhibit AMPK and reduce ADIPOQ/adiponectin released in obesity, which leads to reduced AMPK activity. Overall, AMPK contributes to the maintenance of cellular energy balance and the overall health of the metabolic system.

INS-1E beta-cells, a process involving specific regulatory elements, suggesting that UCP2, similarly regulated in rats and humans, plays a role in modulating insulin secretion [196]. The role of UCP2 in uncoupling mitochondrial respiration is especially relevant in obesity, where the tissue faces an abundance of nutrients and increased ROS. Through UCP2, energy is dissipated as heat, which tackles excessive ROS production, mitigates metabolic stress, and promotes anti-inflammatory pathways.

The AMPK-PPARGC1A-UCP2 axis also plays a significant role in the regulation of autophagy. The redox-sensitive nature of autophagy [48] implies that the antioxidant responses facilitated by this axis can modulate autophagic processes. Given that autophagy is essential for recycling cellular components and maintaining cellular homeostasis, its regulation through this axis can be crucial for coping with the metabolic challenges presented by obesity.

In conclusion, the coordinated interplay between AMPK, PPARGC1A, and UCP2 forms a robust regulatory axis for metabolic reprogramming, autophagy, and inflammation control in obesity. Understanding the intricacies of this axis may open avenues for targeted therapies not only for obesity and its associated complications but also for metabolic disorders and cancer, where this axis may play a pivotal role. Future sections will delve specifically into the implications of autophagy in obesity-related metabolic regulation and cancer.

3.2. Autophagy in obesity-associated tumorigenesis

3.2.1. Focus on nutrient sensing and MTOR

In obesity, the nutrient-rich environment poses an important challenge for cellular regulatory mechanisms. As a critical nutrient sensor, MTOR becomes hyperactive in response to the overabundance of glucose and amino acids. In this regard, several studies revealed the molecular mechanisms by which nutrient availability—in the context of obesity—fosters MTOR activation and the subsequent suppression of autophagy, setting the stage for cellular damage and tumorigenesis. For instance, Gulati et al. [91] showed that excess levels of circulating amino acids, common in obesity, lead to MTORC1 activation through an increase in intracellular calcium, which subsequently enhances the binding of calcium-CALM (calmodulin) to an evolutionarily conserved motif in PIK3C3/VPS34, a class III phosphatidylinositol 3-kinase, critical for lipid kinase activity [91]. In another study, Um et al. revealed that RPS6KB1/S6K1 (ribosomal protein S6 kinase B1), an effector of MTOR, is sensitive to amino acids, and its activation through amino acid influx can lead to insulin resistance by negatively affecting insulin signaling through MTOR-RPS6KB1 phosphorylation of IRS1 [259]. In the same vein of investigation, Cho et al. demonstrated that synergistic activation of MTORC1 through growth factor and nutrient signaling results in pronounced hepatocyte damage, indicative of oxidative stress and DNA damage, aligning with features of obesity-associated liver failure [43]. This hyperactivation of MTOR has been directly associated with the suppression of autophagy in different models [149,269,284], which may be protective against tumorigenesis by maintaining cellular homeostasis and preventing the accumulation of damaged organelles and proteins.

Several studies shed light on how MTOR activation may alter inflammatory responses, thereby facilitating the establishment of a pro-tumoral environment. In a survey by Sedda et al., it was observed that in celiac disease, which is characterized by chronic inflammation, there is an increased expression of active MTOR in the epithelial compartment of the duodenum, and this upregulation is correlated with enhanced production of inflammatory cytokines [238]. Extending this concept, Liu et al. elucidated the link between MTOR activation and immunosuppression, showing that high MTORC1 activity in tumors leads to upregulation of the immune checkpoint CD276/B7-H3 (CD276 molecule), contributing to an immunosuppressive microenvironment that is favorable to tumor growth [156]. Furthermore, Laberge et al. demonstrated that rapamycin, an MTOR inhibitor, selectively reduces the proinflammatory phenotype of senescent cells, often associated with

age-related pathologies, including cancer [136]. This finding indicates that the inhibition of MTOR can suppress senescence-associated inflammation, which might have implications for ameliorating cancer.

Combining these insights, it is evident that the hyperactivation of MTOR due to excess nutrients in obesity suppresses autophagy and stimulates a proinflammatory environment. This inflammation, immunosuppression, and cellular senescence create a milieu that facilitates tumorigenesis. Targeting MTOR and its associated pathways could be pivotal in managing obesity-associated cancer by restoring autophagy and mitigating inflammation.

3.2.2. Focus on autophagy

In the context of obesity, an excess of nutrients inhibits autophagy via the MTOR pathway. This inhibition of autophagy in obese individuals has multifaceted consequences that contribute to establishing a pro-tumoral microenvironment. The adipose tissue in obese individuals undergoes functional alterations. It deregulates the secretion of bioactive factors such as hormones, cytokines, and adipokines, which foster an inflammatory microenvironment conducive to tumorigenesis. ADIPOQ/adiponectin and LEP play pivotal roles in modulating autophagy among the adipokines. For instance, Li et al. [148] demonstrated that ADIPOQ/adiponectin inhibits autophagy in retinal endothelial cells under high-glucose conditions by promoting the PI3K-AKT-MTOR pathway.

Conversely, LEP, as shown by Cassano et al. [34], inhibits autophagy in human CD4$^+$ IL2RA/CD25$^-$ conventional T cells through the activation of the MTOR pathway. Interestingly, another study [87] indicates that LEP can induce autophagy in adipocytes in a cell-type-specific manner. The altered secretion and modulation of adipokines such as LEP and ADIPOQ/adiponectin in obesity can foster chronic inflammation [260]. This chronic inflammation creates a tissue microenvironment rich in growth factors, cytokines, and chemokines, which not only supports inflammatory cell recruitment but contributes to the DNA damage and cell proliferation that underlie tumor development [302]. Notably, adipokines have been described to orchestrate the sophisticated vascular network, leading to angiogenesis [24,262]. In this regard, overexpression of the adipokine RARRES2/chemerin (retinoic acid receptor responder 2) is associated with tumor angiogenesis and poor clinical outcome in squamous cell carcinoma of the oral tongue [266]. Furthermore, the complex interplay between adipokines and autophagy contributes to the deregulation of cellular homeostasis; it may promote tumorigenesis by enabling the survival of damaged cells that would normally be removed via autophagy. This mechanism becomes particularly relevant as obesity alters adipokine levels and, thereby, influences the local microenvironment, which may, in turn, encourage the initiation and progression of tumors [82].

In obese tissue, autophagy plays a critical role in suppressing inflammation. Indeed, studies reported that autophagy could act as a negative feedback mechanism that attempts to limit inflammation by reducing the expression and secretion of proinflammatory cytokines, which, in the context of obesity, may lead to chronic low-grade inflammation referred to as "metabolic endotoxemia" [190]. In this regard, it was found that inducing autophagy in HUVEC cells with rapamycin decreases the expression of inflammatory cytokines and reduces inflammation-induced cell death, suggesting potential therapeutic benefits in psoriasis [304]. In another study focused on bone marrow mesenchymal stem cells [303], the activation of autophagy counteracts the inhibition of osteogenic differentiation induced by inflammation, indicating a protective role of autophagy against inflammation-induced bone loss.

Hence, in the context of obesity, autophagy is inhibited due to an excess of nutrients, and the anti-inflammatory effects of autophagy may be compromised. This may affect adipose tissue mass and homeostasis, potentially altering immune responses and leading to sustained inflammation within the AT. A pro-inflammatory state is maintained with altered secretion of adipokines, which modulate autophagy. This

chronic inflammation and the deregulated autophagy in the AT of obese individuals contribute to establishing a pro-tumoral microenvironment. Such an environment is conducive to DNA damage and uncontrolled cell proliferation, crucial factors in tumor development and progression. Therefore, the interplay among obesity, autophagy, adipokines, and inflammation is central to understanding the underlying mechanisms of obesity-associated cancer.

Interestingly, autophagy is also critical in regulating the innate immune system. Yang et al. delve into the interplay between autophagy and the TME, particularly emphasizing tumor-infiltrating immune cells. Within the TME, the intercommunication between immune mediators and autophagy orchestrates a complex network that is decisive for tumor immunity and the functioning of tumor-infiltrating immune cells [286]. Autophagy shapes the anti-cancer immune response by modulating the development and functionality of natural killer cells. NK cells are innate lymphoid cells crucial in the immune response against viral infections and cancer through their cytotoxic and secretory functions. Impaired NK cell physiology plays a role in obesity-associated diseases [12]. Activation of autophagy supports NK cell maturation and enhances their antiviral and anticancer activity [71,267]. In contrast, autophagy inhibition leads to mitochondrial damage, overproduction of ROS, and regulated cell death, interrupting NK cell development. These events could foster a pro-tumoral phenotype [163].

Macrophages play a key role in obesity, as adipose tissue expansion alters the balance between pro- and anti-inflammatory macrophages, fueling chronic low-grade inflammation [288]. Critically, Yang et al. shed light on the central role of autophagy in governing macrophage differentiation and polarization within the TME. Macrophages in the TME are dichotomized into the "M1-like" phenotype, which is geared towards anti-cancer immunity, and the "M2-like" phenotype, which, by contrast, propels tumor progression through immunosuppression [286]. It has been demonstrated that impaired macrophage autophagy due to excessive lipid accumulation in obesity significantly amplifies innate immune activation, setting the stage for the obesity-associated pro-inflammatory state [158]. In addition, macrophages with impaired autophagy shift towards pro-inflammatory M1 polarization while suppressing the anti-inflammatory M2 phenotype, which fuels systemic inflammation and has been linked to liver injury under high-fat diet conditions [158,187].

In the obese microenvironment, where autophagy is impaired due to MTOR activation, there is a clear trend towards differentiating macrophages into the pro-tumoral M2 phenotype. The diminished autophagy, coupled with changes in adipokines and the low-grade chronic inflammation characteristic of obesity, creates a setting that promotes the polarization of macrophages toward the M2 phenotype. This type of polarization is linked to poor prognosis in various cancers, including gastric and pancreatic [285,297]. In particular, M2 macrophages have been associated with promoting tumor proliferation and metastasis and altering the expression of critical immune-related genes.

This aligns with the observation that inhibited CMA orchestrates the recruitment of inflammatory T cells, a signature move in the proinflammatory playbook characteristic of obesity [297]. When intertwined with compromised autophagy and distorted adipokine profiles, such a proinflammatory milieu forges a hotbed for tumor transformation and progression within the obese microenvironment.

Autophagy has a multifaceted and stage-dependent relationship with the immune response in the context of cancer. While autophagy is essential for various functions of immune cells, its role in cancer is complex. Generally, autophagy inhibition can lead to a pro-tumoral immune system. However, in some contexts, counteracting autophagy can also facilitate antitumor responses, such as promoting immunogenic cell death [62,83].

The intricate relationships between autophagy, macrophage polarization, and the TME highlight the multifaceted nature of obesity-associated cancer development. Autophagy, known to have anti-inflammatory effects, can be inhibited in the context of obesity,

leading to immune reprogramming that favors tumor development. Understanding this complexity is vital for developing targeted therapies, especially for cancer patients who are obese. Integrating therapies that modulate autophagy with immunotherapies might be crucial in treating cancers that are associated with obesity.

Autophagy is critical for maintaining metabolic homeostasis and cellular integrity in adipocytes, as demonstrated by the observation that its impairment leads to inflammation, insulin resistance, and metabolic syndrome [28,131,221].

Inhibition of autophagy is increasingly recognized as a critical factor contributing to DNA damage and compromised DNA repair mechanisms, directly affecting cellular integrity and oncogenic transformation. In this regard, autophagy is intrinsically linked to DNA repair through the error-free process of homologous recombination. When autophagy is impaired, cells increasingly rely on the error-prone nonhomologous end joining for DNA double-strand break repair, accumulating genomic damage and senescence-like phenotypes [123,155]. Autophagy inhibitors hinder DNA damage repair, resulting in elevated levels of the DNA double-strand break marker γ-H2AX (H2A.X variant histone). This suggests that autophagy is protective in maintaining genomic integrity, especially in response to radiation-induced DNA damage [230].

Although these studies broadly address the impact of autophagy inhibition on DNA repair mechanisms and genomic integrity in various cellular models, it is conceivable that similar mechanisms apply to adipocytes, especially in obesity. Indeed, in obesity, adipocytes are subject to metabolic stress, which might render them more susceptible to DNA damage, especially when autophagy is impaired. In these circumstances, the adipocytes can undergo oncogenic transformation.

As mentioned in the previous section, the defective autophagy in adipocytes during obesity can contribute to the perturbation of key metabolic regulators such as PPARGC1A, AMPK, and UCP2, which are involved in mitochondrial biogenesis, energy homeostasis, and ROS regulation. The loss of PPARGC1A-regulated mitochondrial function and AMPK activity due to impaired autophagy exacerbates oxidative stress; this situation favors a metabolic profile akin to the Warburg effect, characterized by enhanced glycolysis and is frequently observed in cancer cells [57,209].

The interplay between autophagy, ROS accumulation, insulin resistance, and adipocyte tumorigenesis forms a complex cascade of events. Autophagy is critical in clearing damaged organelles, such as mitochondria and long-lived proteins. Inhibition of autophagy in adipocytes leads to the accumulation of dysfunctional mitochondria, which, in turn, produce excessive ROS, contributing to oxidative stress [48,120,146].

In obesity, characterized by an excess energy delivery to adipose tissue, ROS have been implicated in the onset and progression of insulin resistance. Different sources of ROS, including mitochondria and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases such as NOX4 (NADPH oxidase 4) and CYBB/NOX2 (cytochrome b-245 beta chain), contribute to the increased oxidative stress in obesity [96]. NOX4 is predominant in the early stages, transitioning to CYBB/NOX2 and eventually to mitochondria-derived ROS in the later stages of obesity. Furthermore, obesity is coupled with augmented NADPH oxidase expression and decreased antioxidant enzyme expression [79]. This increased ROS affects the production of adipocytokines, which in turn sustain the inflammatory and pro-tumoral environment.

Hyperinsulinemia, a hallmark of insulin resistance, is linked to cancer through various mechanisms [9]. Elevated insulin and IGF1 levels contribute to cellular proliferation and inhibit apoptosis. Moreover, the increased oxidative stress in accumulated fat due to ROS overproduction is an early trigger of metabolic syndrome, which has a strong association with tumorigenesis. This is attributed to the role of ROS in linking high energy intake, increased cell proliferation, and suppression of apoptosis to cancer risks [63]. Finally, autophagy depletion has been directly connected with establishing insulin resistance in obese patients [134,282].

These studies provide insight into the intricate relationship between autophagy, ROS accumulation, insulin resistance, and adipocyte cancer. The inhibition of autophagy leads to the accumulation of dysfunctional mitochondria and ROS, which, in turn, contributes to oxidative stress. This oxidative stress is a significant factor in developing insulin resistance, linked to an increased risk of tumorigenesis. Understanding these interlinked pathways is crucial for identifying novel therapeutic targets for obesity-related metabolic disorders and cancer (Fig. 6).

4. Targeting autophagy as a therapeutic strategy for obesity-driven cancer

Given the elucidation of autophagy's multifaceted role in obesity and tumor transformation, it is imperative to explore the prospects of targeting autophagy for preventing obesity-driven cancer [46,205,300]. In this regard, there is a growing consensus that autophagy holds promise as a therapeutic target. In the obese microenvironment, autophagy is often compromised, thus leading to immune reprogramming, inflammation, ROS induction, and other critical aspects described above. Therefore, we hypothesize the possibility of counteracting obesity-mediated tumorigenesis by overstimulating autophagy.

To put this in context, a body of literature suggests that interventions with the propensity to induce autophagy have demonstrated efficacy against obesity [126]. These interventions span lifestyle changes, such as caloric restriction, low-calorie diets, physical exercise, and surgical and pharmacological options. For instance, rapamycin, an MTORC1 inhibitor, has been singled out as an autophagy activator with anti-obesity properties [31]. Treatment with rapamycin has demonstrated the potential to alleviate excessive body fat accumulation and rectify liver damage in preclinical models [37,138,222]. However, a low benefit:risk ratio curtails the implementation of pharmacological strategies, including the use of rapamycin, and raises concerns about exacerbating ROS production [20,276]. As summarized by Pietracola and Bravo-San-Pedro, a plethora of other agents, such as L-carnitine, polyamines, zinc, and phenolic compounds such as gallic acid and resveratrol, have emerged as pro-autophagic substances [205]. These compounds promise to mitigate obesity and related liver damage by promoting autophagy. For example, L-carnitine is a free-radical scavenger that stimulates autophagy and corrects high-fat-diet-induced mitochondrial dysfunction [44,212]. Moreover, compounds such as spermidine and zinc activate autophagy, and, when supplemented, they have resulted in body weight reduction and improved obesity-related parameters [109,152,154,160].

It is essential to address the complexities that emerge in targeting autophagy for obesity-driven cancer. MTOR inhibitors, such as rapamycin, have feedback mechanisms in the PI3K-AKT signaling pathway [198,223]. Whereas MTOR plays a role in diverse cancer processes, activating AKT by MTOR inhibitors can limit their clinical effectiveness. However, recent studies have indicated that combining MTOR inhibitors with other antitumor drugs can surmount this limitation. For example, combination therapy of the VEGF inhibitor lenvatinib and everolimus, an MTOR inhibitor, has shown promise in advanced or metastatic renal cell carcinoma/RCC [274]. This finding illustrates that combination therapies involving autophagy modulation may offer enhanced antitumor efficacy.

However, clinical applications of MTOR inhibitors are limited due to poor water solubility and biodistribution [4]. Nanocarriers can improve the delivery of rapamycin and other bioactive drugs, specifically to adipose tissue or adipocytes. Indeed, to prevent obesity-mediated tumorigenesis, targeting AT is critical as this is where many of the
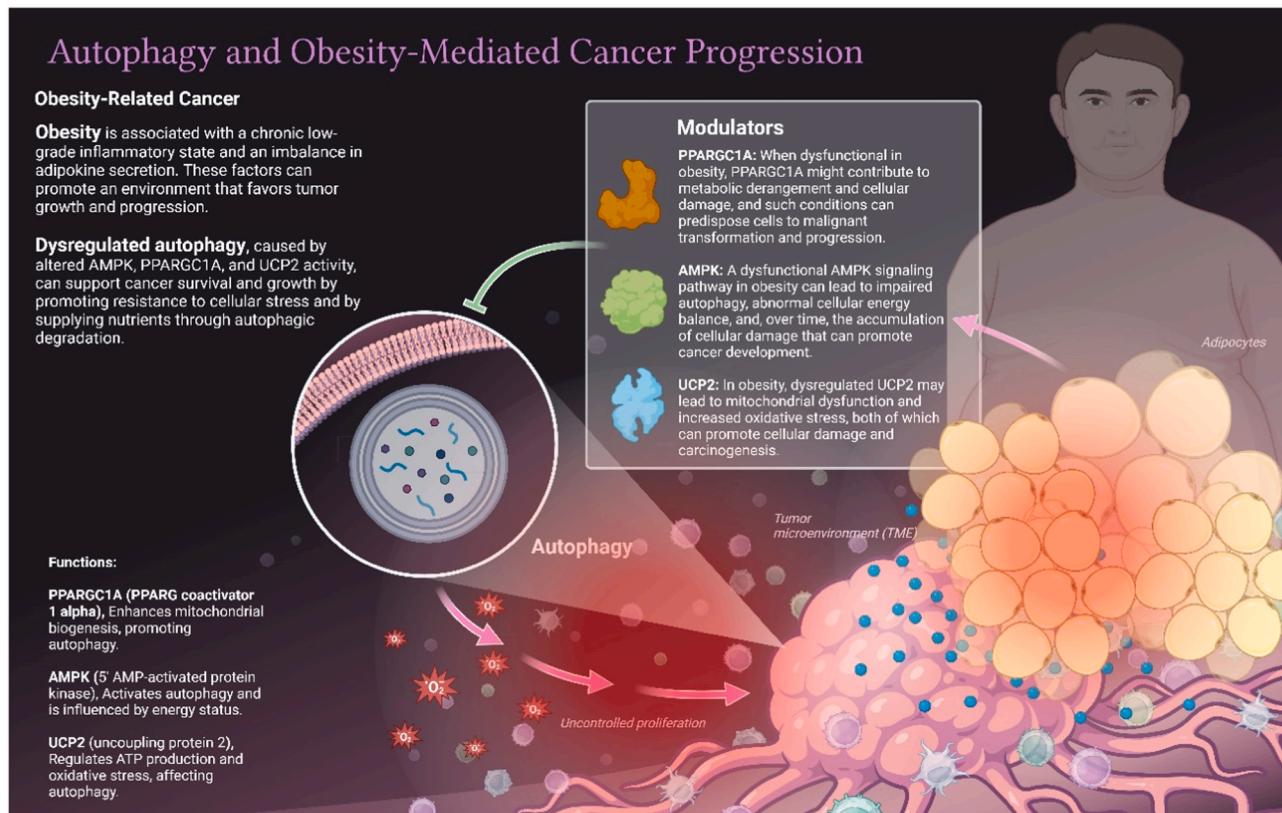

Fig. 6. Autophagy and obesity-mediated cancer progression. PPARGC1A, key for mitochondrial function and autophagy, when dysregulated in obesity, can lead to metabolic disorders and cellular damage, increasing cancer risk. Similarly, impaired AMPK function in obesity disrupts autophagy and energy regulation, contributing to cellular damage that fosters cancer development. Dysfunctional UCP2 in obesity further exacerbates mitochondrial dysfunction and oxidative stress, promoting cellular damage and the potential for cancer progression.

pro-tumorigenic signals may originate. Specifically, targeting the AT with autophagy modulators could help in altering the microenvironment that supports tumor growth.

Several strategies have been developed or are under investigation to achieve specific delivery of drugs or nanomedicines to fat tissues. These include:

i) Lipophilic carriers: Because AT mainly comprises lipid cells, using lipophilic carriers with an affinity for lipids can be an approach to accumulate the drug in fat tissues preferentially. For instance, liposomes and other lipid-based nanoparticles can be formulated to be more likely to be taken up by AT [38,73,137, 307].

ii) Peptide targeting: Certain peptides have been found to have a natural affinity for AT. Attaching these peptides to the surface of drug-loaded nanoparticles makes it possible to direct the nanoparticles to accumulate preferentially in AT. For example, the AP2 peptide has been identified as having a high affinity for AT and has been used to target drugs to fat deposits [255,257,283].

iii) Hormone receptor targeting: Adipose tissues have specific hormone receptors, such as those for insulin and LEP. Therapeutic agents or nanomedicines can be engineered to bind to these receptors, which ensures that adipocytes selectively take them up. For instance, insulin-mimetic agents have been developed that bind to insulin receptors on adipocytes, allowing for targeted drug delivery to AT [101,258].

iv) Fatty acid transporter targeting: Adipocytes express specific fatty acid transport proteins/FATPs. Therapeutics can be designed to be taken up by these transporters. For example, drug molecules can be conjugated to fatty acids recognized by these transporters, leading to enhanced uptake by AT [110].

v) Microbubble and ultrasound combination: This technique involves encapsulating the therapeutic agent within microbubbles, which are then injected into the bloodstream. Focused ultrasound is applied to the target area (where the AT is located), causing the microbubbles to vibrate and release the drug directly into the AT [17,39].

vi) Local administration: For subcutaneous AT, local administration methods such as subcutaneous injection or transdermal patches loaded with drug-containing nanoparticles can deliver therapeutics directly to the site of interest [150].

The utility of such nanocarriers for delivering autophagy modulators is highlighted by several preclinical studies explored in the last few years [162]. For instance, ABI-009 is an ALB (albumin)-bound nanoparticle formulation of rapamycin that holds promise in enhancing the delivery of autophagy modulators. In preclinical models, this nano-drug shows increased tumor accumulation and enhanced anti-tumor effects compared to free rapamycin [263]. Several clinical trials are underway investigating the efficacy of ABI-009 in combination with other agents for advanced sarcomas, metastatic colorectal cancer, and other malignancies [176,189,188]. The nanoparticle encapsulation helps achieve a more targeted delivery, potentially reducing side effects and increasing the drug's efficacy. This finding indicates that a focused approach towards the modulation of autophagy using combination therapies and advanced drug delivery systems such as nanoparticles could be instrumental in combating obesity-driven cancer.

AMPK is another target for activating autophagy. Metformin, an AMPK activator, is widely used in treating type 2 diabetes and has shown promise in reducing cancer risk [21]. However, like rapamycin, metformin's application can be limited due to its distribution and pharmacokinetics [292]. Nanoparticles loaded with metformin or other AMPK activators can improve drug delivery to specific tissues [3,36]. In the context of obesity, where there is often an altered metabolic state, targeting AMPK via nanocarriers might enhance the activation of autophagy in a more controlled manner, potentially reducing the

pro-tumorigenic environment [242].

However, it is important to consider that targeting autophagy is a double-edged sword, especially in cancer. In some cases, autophagy may protect against tumor development; in others, it may promote tumor survival and growth [244]. Hence, the nanocarriers must be designed precisely to target specific pathways and cellular processes without inducing unwanted effects [162].

For obesity-mediated tumorigenesis, using nanocarriers can provide several benefits [242]. They allow for targeted delivery, which means that drugs can be delivered specifically to the tumor cells or tissues affected by obesity, thus minimizing side effects. This is especially important as drugs that affect autophagy and cellular metabolism may have systemic effects. Additionally, encapsulation in nanocarriers can also provide better control over the release of the drug, allowing for sustained release over time, which might be beneficial in managing chronic conditions such as obesity and cancer [242].

Therefore, the innovative use of nanocarriers targets autophagy pathways, crucial within the obesity-cancer nexus. This precise delivery of therapeutic agents to tumor cells influenced by obesity can mitigate systemic side effects and enhance treatment efficacy (Fig. 7). The targeted strategy employed by nanocarriers addresses the complex interplay of cellular metabolism and autophagy in obesity-associated tumorigenesis. Furthermore, the controlled drug release potential of nanocarriers is critical for the sustained treatment of obesity-related cancers. Despite these advantages, nanocarriers also display some challenges, including off-target effects and drug stability, which are vital for clinical translation [162]. The integration of nanocarrier technology in treatment regimens is a promising avenue to improve drug delivery specificity and efficacy in obesity-mediated cancer progression, aligning with the therapeutic goal of modulating autophagy, a key factor in cancer's metabolic reprogramming.

It is important to note that while these nanocarrier-based approaches are promising, they also present challenges, including the potential for off-target effects, the stability of the therapeutic agents, and the need to control the release and dosage of the drug carefully. Research and development in this field are essential for optimizing these delivery methods for clinical applications.

In conclusion, nanocarriers offer an innovative and promising approach to delivering autophagy-modulating agents and combination therapies. This could be particularly beneficial in tackling obesity-mediated tumorigenesis by ensuring targeted, controlled, and efficient drug delivery. Further research and clinical trials are required to assess the safety, efficacy, and best strategies for implementing nanocarrier-based therapies in clinical practice. (Fig. 7).

5. Concluding remarks and future directions

The function of autophagy in cancer and obesity is addressed in this review as the intersection of pathways associated with obesity and autophagy regulation during tumor growth, maintenance, and progression. We argue that insulin and LEP levels influence the obesity-autophagy-cancer axis and the signaling mechanisms that control it. In addition, recent research on the molecular factors that relate obesity to cancer was discussed. These factors include changed hormone levels, altered metabolism, and secretory autophagy. In this review, we have emphasized some of the most important research results on the roles of autophagy in tumor microenvironments and obesity-mediated cancer development. Finally, we discussed the evidence in favor of targeting autophagy as a treatment approach for obesity-associated cancer, given the substantial correlations between autophagy and obesity-related cancer.

Future research should identify novel biomarkers to better predict obesity-associated cancers' onset and progression. With the known impact of autophagy on obesity and cancer, there is a need to unravel the underlying mechanisms and discover the unique markers that can be targeted therapeutically. Identifying such biomarkers will not only help

# Targeting Autophagy in Obesity-Driven Cancer Using Nanocarriers
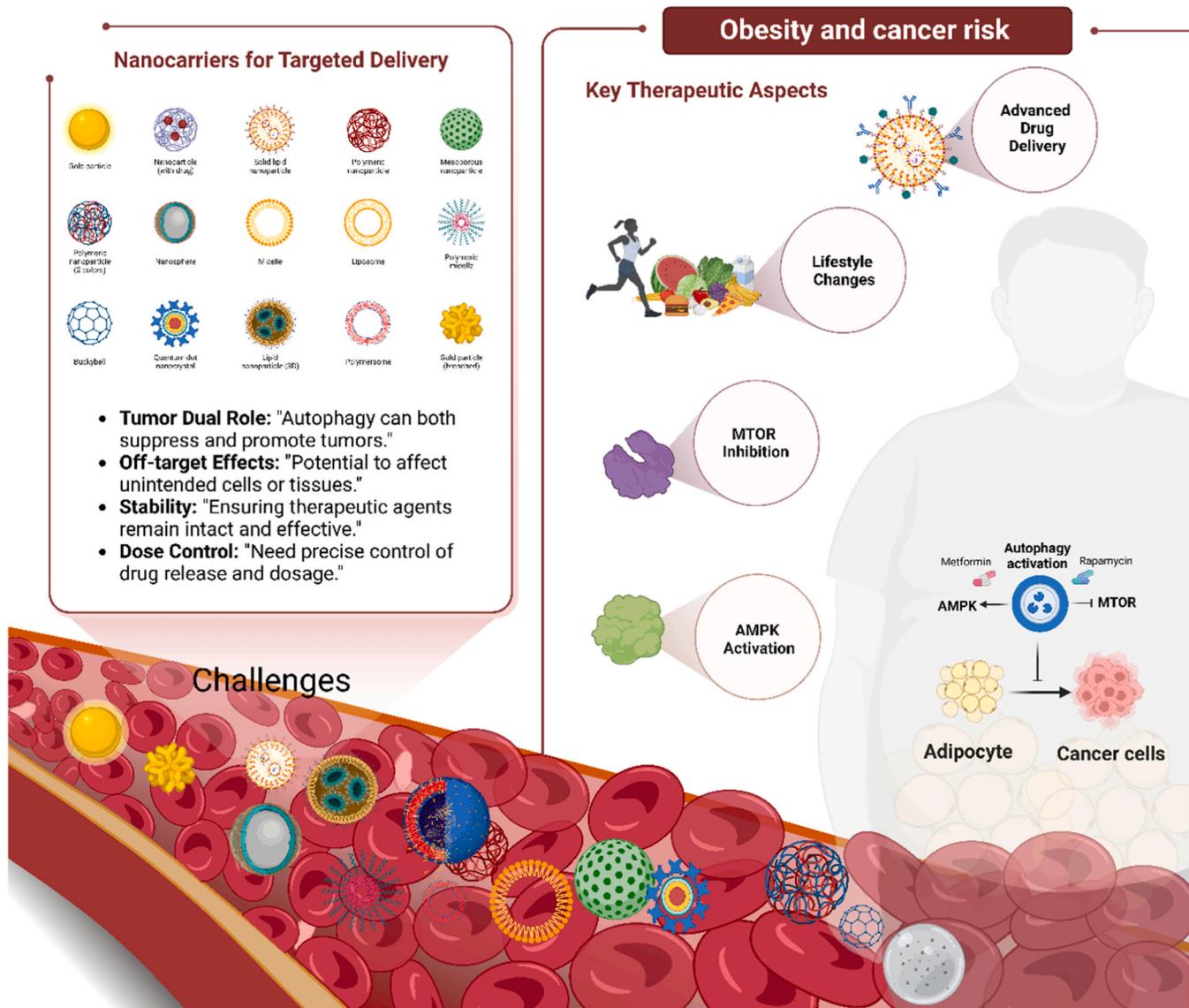
Fig. 7. Targeting Autophagy in Obesity-Driven Cancer Using Nanocarriers. Autophagy is disrupted in the obese microenvironment, causing immunological reprogramming, inflammation, ROS production, and other important factors. Overstimulating autophagy may prevent obesity-mediated carcinogenesis. AMPK activation or MTOR inactivation may cause overstimulation. Nanoparticle encapsulation targets medication delivery, possibly lowering adverse effects and improving effectiveness. This suggests that combination therapy and nanoparticle-based drug delivery methods might help treat obesity-driven cancer by modulating autophagy. Nanocarriers may help obesity-mediated carcinogenesis. They provide targeted delivery of medications to tumor cells or obesity-related organs, reducing adverse effects. Drugs that influence autophagy and cellular metabolism may have systemic consequences, making this crucial. Encapsulation in nanocarriers may also improve medication release control, allowing for continuous release over time, which may help treat chronic diseases like obesity and cancer. These nanocarrier-based techniques are intriguing but have drawbacks, such as off-target effects, therapeutic agent stability, and the need to carefully manage medication release and dose.

in the early detection of disease but also in monitoring treatment response and predicting prognosis [216]. In addition, studying the impact of well-known and emerging autophagy modulators on such biomarkers can also guide the development of targeted therapies.

In this sense, the field of nanomedicine offers promising avenues for developing targeted therapies. The ability to encapsulate autophagy modulators in nanocarriers and deliver them precisely to adipose tissues or tumors could significantly enhance their therapeutic efficacy while minimizing systemic side effects. Although initial preclinical studies are promising, more research is needed to optimize these delivery systems and thoroughly evaluate their safety and effectiveness in diverse models [242]. The challenge lies in achieving precise control over drug delivery

and release and ensuring the therapeutic agents' stability and activity.

In the era of precision medicine, the focus is shifting toward individualized treatments tailored to each patient's unique genetic and metabolic profiles. Given the heterogeneity of obesity and cancer, it is crucial to integrate our knowledge of autophagy, adipose tissue biology, and cancer biology into a precision medicine framework [28,205]. Understanding how individual variations in autophagy-related genes or metabolic pathways influence the response to autophagy modulators could allow for more personalized and effective treatment strategies. However, this integration is not without challenges; it requires comprehensive and high-resolution patient data, sophisticated computational models to predict treatment responses, and interdisciplinary

collaborations to translate these insights into clinical practice.

Finally, we should note that there remains controversy and complexity surrounding the role of autophagy in cancer and obesity. In some cases, autophagy may protect against tumor development; in others, it may promote tumor survival and growth [244]. The manipulation of autophagy for therapeutic purposes must be done carefully, considering these dual roles. The interplay between autophagy, obesity, and cancer is multifaceted and dependent on many factors, which requires a nuanced and highly individualized approach. Further research in this field is crucial to unravel the complexities and pave the way for innovative, effective, and safe therapeutic strategies for obesity-associated cancers.

CRediT authorship contribution statement

Amir Barzegar Behrooz (A.B.B.): Conceptualization, Writing-Original draft preparation, Writing – review & editing, Figure preparation. **Marco Cordani (M.C.)**: Conceptualization, Writing-Original draft preparation, Writing – review & editing. **Alessandra Fiore (A.F.)**: Writing-Original draft preparation, Writing – review & editing. **Massimo Donadelli (M.D.)**: Writing-Original draft preparation, Writing – review & editing. **Joseph W Gordon (J.W.G.)**: Writing – review & editing, Supervision. **Daniel J Klionsky (D.J.K.)**: Writing – review & editing, Supervision. **Saeid Ghavami (S.G.)**: Conceptualization, Writing-Review and Editing, Supervision. All authors read and approved the final manuscript.

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.

Data Availability

No data was used for the research described in the article.

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