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Virus, Exosome, and MicroRNA: New Insights into Autophagy

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Abstract

Autophagy is known as a conserved self-eating mechanism that contributes to cells to degrade different intracellular components (i.e., macromolecular complexes, aggregated proteins, soluble proteins, organelles, and foreign bodies). Autophagy needs formation of a double-membrane structure, which is composed of the sequestered cytoplasmic contents, called autophagosome. There are a variety of internal and external factors involved in initiation and progression of

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autophagy process. Viruses as external factors are one of the particles that could be associated with different stages of this process. Viruses exert their functions via activation and/or inhibition of a wide range of cellular and molecular targets, which are involved in autophagy process. Besides viruses, a variety of cellular and molecular pathways that are activated and inhibited by several factors (e.g., genetics, epigenetics, and environment factors) are related to beginning and developing of autophagy mechanism. Exosomes and microRNAs have been emerged as novel and effective players anticipated in various stages of autophagy. More knowledge in these pathways and identification of accurate roles of them could help to provide better therapeutic approaches in several diseases such as cancer. We highlighted the roles of viruses, exosomes, and microRNAs in the autophagy processes.

Keywords

Autophagy · Cancer · Chemoresistance · Exosome · MicroRNA · Viral infection

1 Autophagy

Although autophagy was recognized around 50 years ago in mammalian cells, its molecular function was revealed vastly in the past decade. Autophagy usually occurs as an evolutionary conserved mechanism in all eukaryotic cells for sustaining cell homeostasis. Recent studies have revealed that autophagy is one of the vital biological mechanisms, which is related to health, longevity, differentiation, starvation, homeostasis, cell survival, adaptation, elimination of microorganisms, and cell death (Shafabakhsh et al. 2021). This process begins with the formation of double-membrane vesicles (DMVs), which is generally termed autophagosome, as well as by various processes, such as fusing with lysosomes. This event leads to degradation/recycling of components which exist in cytoplasmic lysosomes (Cuervo 2004). Critical roles of autophagy process in longevity, homeostasis, and cell death have been recently demonstrated (Mizushima 2007). In eukaryotic cells, autophagy includes microautophagy, macroautophagy, and chaperone-mediated autophagy (CMA), three key intracellular pathways. Core molecular machinery of autophagy referred to subset of autophagy-related (ATG) proteins is essential for autophagosome formation (Fig. 1) (Mizushima 2007). P53 and Bcl-2 protein\families with dual regulatory properties play significant roles in autophagy induction (Yoon et al. 2012; Singletary and Milner 2008). Autophagy is involved in various pathologies, such as neurodegenerative and age-related disorders, infections, and inflammatory/immunity diseases, and especially in invasion and cancer progression (Yang and Klionsky 2010). Increasing evidences show the importance of autophagy in cancer and support the concept when it gets disturbed, it can lead to an accelerated tumorigenesis. Also, comparative evidences have shown that degradation of autophagy or proteolysis in tumors is less than normal cells (Yang et al. 2011). Anticancer role of autophagy is due to elimination of damaged cell component and inhibition of tumor growth. However, autophagy can cause tumor cells withstand stress in undesirable conditions leading to survival. Stress-induced autophagy may result in resistance to treatment and result in the progression of tumor cells (Yang et al. 2011; Kondo et al. 2005). Additionally, the efficacy of autophagy inhibitors, along with chemotherapy, in preventing tumor growth and inducing cell death is far better than the chemotherapy alone. Recent investigations have shown that autophagy may play an important role in drug resistance. It means that autophagy may contribute to increase tumor cells resistance to chemotherapeutic

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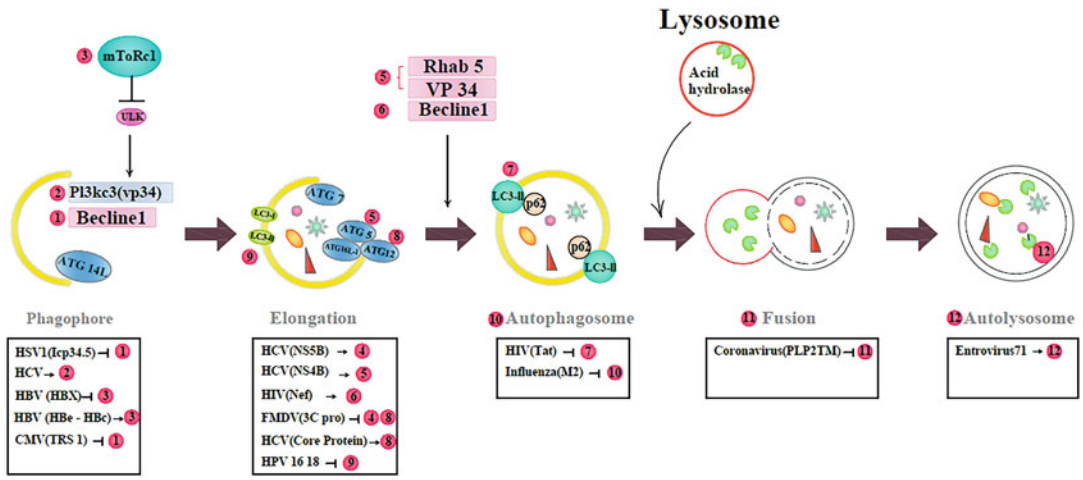

Fig. 1 A schema various stages of autophagy. Viruses, through the production of different proteins, can affect different stages of autophagy, such as the early stages of autophagy (phagophore and elongation), and the ending stages (Autophagosome and autolysosome), in order to survive in the host cell longer. Some of the viruses that can affect the autophagy process are hepatitis C and B viruses and HIV. For example, the hepatitis C virus by producing NS5B protein influences the ATG5 autophagy regulatory protein, which proceeds autophagy in the elongation phase, or, by producing the NS4B protein, affects the Rhab5 factor and drives autophagy from the elongation phase to autophagosome formation. Hepatitis B virus targets and impedes mToR protein kinase through the production of HBX protein, increases the efficiency of the ULK protein, and leads to the initial phase of autophagy, the formation of phagophore. It has also been observed that some of the proteins of the virus (HBe and HBc) inhibit the early stage of autophagy by increasing the efficiency of the mToR protein kinase. HIV produces nef and thus affects one of the major proteins in autophagy called BECN1, which causes the autophagy to progress from the elongation stage to the formation of autophagosome, or by producing TAT stops a factor necessary for the formation of autophagosome (LC3-II-PE complex), losing the autophagosome form. There are other viruses that can apply their effects on the autophagy process. For example, coronaviruses prevent lysosomal incorporation with the PLP2TM protein and impede the formation of autolysosomes. Enterovirus 71 affects and disables autolysosomes. Influenza virus via M2 protein destroys autophagosome. HSV prevents the formation of phagophore by producing Icp34.5 and inhibiting BECN1

and anticancer agents. Therefore, autophagy regulation can be considered as an appropriate therapeutic target in the therapy of cancer. Thus, various autophagy-modulating approaches may be assumed to circumvent chemoresistance (Huang et al. 2016; YiRen et al. 2017). Mounting evidences have revealed that autophagy along with chemotherapy and its association with chemoresistance can be a new therapeutic goal to succeed in cancer treatment.

2 MicroRNA and Autophagy

2.1 Regulation of Autophagy by MicroRNAs

MicroRNAs (miRNAs) are a group of noncoding small RNA molecules (~19–22 nucleotides long) which regulate protein-coding genes (Mollazadeh et al. 2019; Neshati et al. 2018; Letafati et al. 2022; Mousavi et al. 2022; Balandeh et al. 2021; Razavi et al. 2021; Mirzaei and Hamblin 2020). The main miRNA mechanisms are translational repression and mRNA degradation. In the nucleus, RNA polymerase II (RNAPII) produces long primary transcripts (pri-miRNAs), which acts as a substrate for RNase III enzymes and Drosha-DGCR8 complex (a microprocessor that is essential for miRNA maturation) to produce precursor miRNAs (pre-miRNAs). Then, pre-miRNA is exported from the nucleus into the cytoplasm by exportin-5 and Ran-GTP. In the cytoplasm, pre-miRNA is cleaved by another RNase III enzyme, Dicer, into miRNA duplexes approximately 19–22 nucleotides long. Mature miRNA is incorporated into RNA-induced

silencing complex (RISC) where it remains stable and binds to its complementary target mRNA. miRNAs are involved in many major biological functions such as intracellular signaling, cellular metabolism, differentiation, pathological processes, and regulation of gene expression (Su et al. 2015). Some miRNAs are only expressed in specific cell types. Expression patterns of miRNAs are unique to individual tissues and differ between cancer and normal tissues (Jafari et al. 2018). Aberrant expression of miRNAs is associated with multiple human diseases, such as metabolic disease, neurological disorders (Tavakolizadeh et al. 2018), cardiovascular complications, viral diseases (Keshavarz et al. 2018), immune-related diseases, and especially malignancies (Bartels and Tsongalis 2010).

Autophagy-related protein 7 (ATG7) was recently considered as a potential target of miR-96-5p. The aberrant expression of this miRNA reduces autophagy activity (Yu et al. 2018a). Based on the current data, miR-20a-5p inhibits cell proliferation and autophagy and promotes apoptosis through negative regulation of ATG7 (Yu et al. 2018b). Moreover, the overexpression of miR-140-5p/miR-149 inhibits apoptosis and promotes autophagy by downregulating fucosyltransferase1 (FUT*1*) (Wang et al. 2018a). According to the investigation conducted by Liu et al. (2017a) miR-20a negatively relates to autophagy/lysosome pathway. They reported that miR-20a inhibited autophagy and lysosomal proteolytic activity through targeting several key regulators of autophagy, including BECN1, ATG16L1, and sequestosome 1 (SQSTM1) (Liu et al. 2017a). Various molecular components involve in autophagy cascade, including Atg1/unc-51-like kinase (ULK) complex, Beclin-1/class III phosphatidylinositol 3-kinase (PI3K) complex, Atg9 and vacuole membrane protein 1(VMP1), two ubiquitin-like protein (Atg12 and Atg8/LC3) conjugation systems, and proteins which mediate fusion between autophagosomes and lysosomes (Kroemer et al. 2010). Some of these core components of autophagy pathway are direct targets of miRNAs (such as miR-30a, miR-23a, and miR-129-5p) and have key roles in the inhibition/induction of autophagy process (Fig. 2) (Xiao et al. 2015; Guo et al. 2017a; Zhu et al. 2009; Sadri Nahand et al. 2021; Pourhanifeh et al. 2020a, b; Rezaei et al. 2020; Jamali et al. 2020). In the following, the role of miRNAs in the regulation of autophagy and their potential molecular mechanisms has been reported in some disorders.

Meng and colleagues revealed the clinical significance of miR-138 in patients with malignant melanoma, which inhibits cell proliferation and induces apoptosis. Overexpression of miR-138 increases cell autophagy by LC3 protein induction as well as the suppression of PI3K/AKT/mTOR and PDK1 (Meng et al. 2017). It was exhibited that the upregulation of miR-18a-5p in melanoma cell lines and tissues had promising role in melanoma pathogenesis mediated by EPHA7 silence leading to tumor development as well as apoptosis and autophagy blockage (Guo et al. 2021).

Long et al. reviewed the association between miRNAs and autophagy in colorectal cancer (CRC) and concluded that miRNA-regulated autophagy could be up- or downregulated in various CRC conditions associated with the tumor microenvironment. In this context, it can referrer to the roles of miR-140-5p and miR-502 in inhibition of autophagy in chemotherapy of CRC stem cells; miR-214, miR-183-5p, and miR-31 in inhibition of autophagy in radiotherapy of CRC; and miR-124, miR-18a, and miR-210 in promotion of autophagy in metabolism and hypoxia of CRC. Also, blockage of autophagy in inflammatory bowel disease could be mediated via miR-142-3p, miR-143, miR-130a, etc. (Long et al. 2020).

In hepatocellular carcinoma (HCC), autophagy could be reduced via miR-490-3p/ATG7 (Ou et al. 2018) or microRNA-181a/Atg5 axis, suggestive of the profounding value of autophagy deficiency in HCC (Yang et al. 2018). Jin et al. showed that miR-513b-5p attenuated tumorigenesis of liver cancer cells in HCC via inactivation of PIK3R3-mediated autophagy (Jin et al. 2021). Zhang et al. demonstrated that downregulation of miR-638 in human liver cancer led to a noticeable reduction in malignancy of liver cancer cell accompanied by increase of autophagosomes and

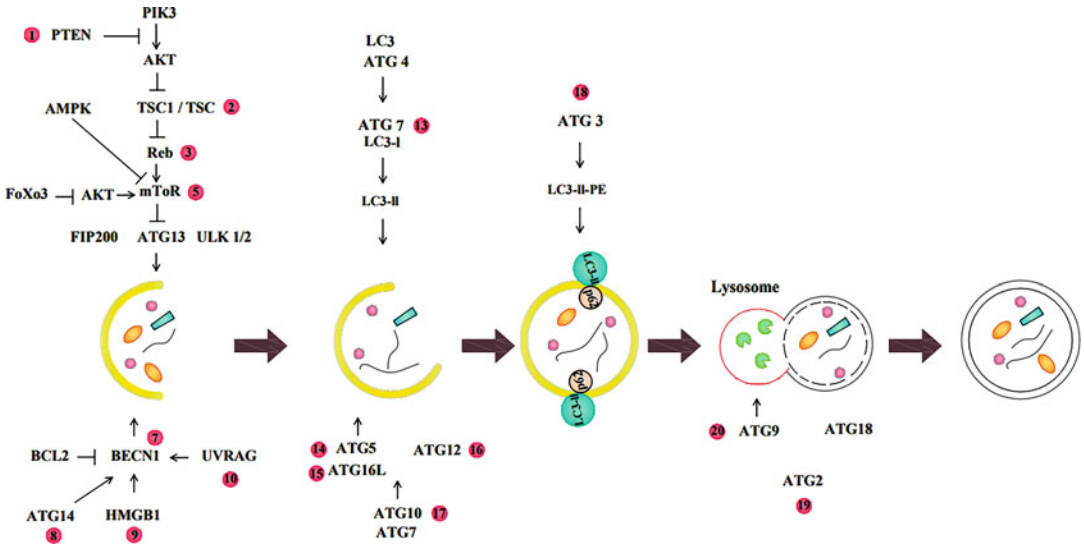

Fig. 2 Various factors involved in the formation of the autophagy mechanism, each of which is affected by different microRNAs that somehow regulate the autophagy steps. The PTEN protein by inhibiting the PIK3-akt pathway paves the way for autophagy to start, increasing the expression of mir-21 that inhibits this protein, thus activating the pik3-akt pathway, and preventing the onset of autophagy (1). Autophagy starts/miR-193b-3p declines, and this protein is most produced and autophagy occurs more (2). Reb has an incremental effect on the mTOR protein that activates this pathway and prevents the formation of the initial autophagy phase. The expression of miR-199a-5p decreases, the inhibitory effect on Reb is inactivated, and autophagy is inhibited (3). Foxo3 disables Akt and causes the MPT pathway to be deactivated/miR-27a decreases its expression, and the foxo3 protein is further produced and autophagy continues to function (4). mTOR, one of the important pathways involved in the autophagy mechanism, has an inhibitory effect on this process and does not allow autophagy to begin and applies its effect on the ULK1/2 factor/miR-7 declines, and its inhibitory effect on this pathway is removed, and the autophagy does not start (5). ULK1/2 is one of the important factors for the onset of autophagy and phagophore formation, declining miR-26b and its inhibitory effect on ULK2, and autophagy begins its pathway, but the expression of miR-290-295 cluster is increased, and the ULK1 protein level is reduced, and the phagophore is not formed, so autophagy does not occur (6). Beclin-1 is somehow one of the important proteins in the development of phagophore and the onset of autophagy. The expression of mir-20a increases, and its inhibitory effect on the gene does not allow the formation of proteins and, accordingly, autophagy does not begin, but miR-30a expression reduces, the Beclin-1 gene is more expressed, and autophagy starts (7). ATG14 has an increased effect on Beclin-1 and makes phagophore more likely to form miR-135a expression increases, thereby inhibiting ATG14 gene and autophagy formation (8). HMGB1 stimulates the Beclin-1 gene and causes the autophagy to start its first phase/miR-34a expression decreases, and its inhibitory effect on the HMGB1 gene is removed, and Beclin-1expression increases (9). UVRAG interferes somehow behind the initial pathway of autophagy and reaches the formation of autophagosome/the miR-183 which disrupts the process by targeting and inhibiting the gene (10). FIP200, present in ULK complex and is effective in the formation of phagophore/miR-224-3p expression, is increased, and an inhibitory effect on this gene is increased, and the initial phase of autophagy does not occur, but miR-20b, which declines, causes an increase in the expression level of FIP200, and phagophore is formed (11). AMK with inhibitory effect on MTOR pathway and TSC1/TSC2 stimulation inhibits autophagy. The expression of miR-185 is reduced, AMK is more expressed, and autophagy is more active (12). ATG7 is a factor accelerating the conversion of lc3-I to Lc3-II, which is an important process for the onset of autophagosome formation. miR-490-3p expression declines and further stimulates its target and ATG7, and autophagy continues (13). ATG5 is a protein that causes autophagy to evolve from the phagophore formation phase to the next formation of the process. miR-181a is increased, and most of the ATG5 gene is inhibited, and this functional trend is disrupted (14). ATG16L is a factor that accelerates the formation of autophagosomes. The expression of miR-130a is increased, the level of the ATG16L protein decreases, and the autophagy is inhibited/expression of the miR-410 decreases, and this process continues (15). The activity of ATG12 is similar to that of ATG16L. The expression of MIR-23a is reduced, its inhibitory effect on this gene is reduced, and autophagy continues its process. miR-378 inhibits the autophagy process by inhibiting the gene (16). ATG10 is a protein that stimulates the activity of ATG5, ATG16L, and ATG12 proteins and accelerates the process of autophagosome formation. miR-20 has an inhibitory effect on this protein, which can disrupt this activity (17). ATG3 is a factor to stimulate the formation

autolysosomes, suggestive of tumor-suppressive role of miR-638 via silence of EZH2 (Zhang et al. 2021a).

In osteosarcoma (OS), miR-210-5p induced epithelial-mesenchymal transition (EMT) and oncogenic autophagy via PIK3R5/AKT/mTOR axis (Liu et al. 2020a). Also, upregulation of miR-22 in OS suppressed autophagy and induced apoptosis resulted in increased sensitivity to cisplatin (Meng et al. 2020). In prostate cancer (PC) cells, overexpression of miR-381 increased cellular autophagy and apoptosis, while decreased cell proliferation mediated by reelin (RELN) suppression (Liao and Zhang 2020). Deng et al. recognized that miR-493 respectively activated cytotoxic autophagy and reduced invasion of PC cells via up-modulation of BECN1 and ATG7 (Deng et al. 2020).

In cervical cancer cells, miR-211 overexpression targeted autophagy and apoptosis through Bcl-2 regulation (Liu et al. 2020b). Besides, aberrant expression of miR-106a in cervical squamous cell carcinoma (CSCC) was related to malignancy parameters of CSCC tissues. Based, overexpression of miR-106a elevated CSCC growth and suppressed autophagy via binding to 3UTR of LKB1 in human papilloma virus (HPV) 16-positive CSCC (Cui et al. 2020). Consistently, miR-378 has a potential impact on cervical cancer progression via binding to ATG12-regulated autophagy (Tan et al. 2018). In the ovarian cancer (OC), increased expression of miR-34 activates apoptosis and autophagy followed by significant reduction in the proliferation of cancerous cells (OVACAR-3 cells) via silencing Notch 1 (Jia et al. 2019). Shao et al. identified that miR-1251-5p upregulation had oncogenic effects on human ovarian cancer via preventing TBCs (negative modulator of autophagy) (Shao et al. 2019).

In bladder cancer, reduced expression of miR-221 facilitated autophagy through increasing TP53INP1 levels, indicative of the valuable importance of miR-221 as therapeutic targets in this malignancy (Liu et al. 2020c). Dai et al. represented the *tumorigenic* capacity of miR-130 in bladder cancer cells as it was proved by autophagy induction through blocking CYLD (Dai et al. 2020). Also, Zhang et al. displayed that upregulation of miR-21 in bladder tumor cells (T24 cells) promoted T24 cells progression alongside with apoptosis and autophagy obstruction via downregulation of, Beclin-1, PTEN, caspase-3, LC3-II, and E-cadherin (Zhang et al. 2020a). Similarly, Rezaei et al. focused on the impacts of up-/downregulation of miRNAs in the different lung diseases including lung cancer either in in vitro and in vivo conditions or human. In this regard, up- and downregulation of respectively miR-210 and miR-181 inactivated autophagy, while down- and upregulation of respectively miR-3127-5p and miR-21 activated autophagy (Rezaei et al. 2020).

In esophageal squamous cell carcinoma (ESCC), autophagy is triggered by miR-503 via PKA/mTOR pathway followed by inhibition of ESCC invasiveness (Wu et al. 2018). In another study, Li et al. focused on the effect of miR-126 on apoptosis and autophagy of ESCC cells and found that miR-126 expression was increased in ESCC followed by enhancement of apoptosis and autophagy; however, miR-126 inhibition reversed current trend via suppression of STAT3 (Li et al. 2020a). Phatak et al. (2021) clarified that miR-141-3p could act as an oncogene in esophageal cancer cells via binding to TSC1 mRNA which led to tumor progression as well as autophagy reduction (Phatak et al. 2021).

In gastric cancer (GC) cells, miR-let-7a/Rictor/Akt-mTOR axis modulates autophagy activity

Fig. 2 (continued) of LC3-PE, which causes the LC3 protein binding to phosphatidylethanolamine and the formation of autophagosome and maintains its stability. The expression of miR-1 is reduced, this factor is further developed, and autophagosome is formed (18). ATG2 protein is effective in the formation of autolysosome. The expression of miR-143 is increased, the ats2 gene is suppressed, and this process is disrupted (19). ATG9 is an agent for stimulating the formation of autolysosome and accelerating the process of lysosome fusion with autophagosome/miR-29a expression which is decreased and the level of atg9 increased, and this trend continues (20). Akt is a stimulant factor for the mTOR pathway and prevents the formation of autophagy/miR-185 which targets this gene and inhibits autophagy (21)

(Fan et al. 2018). Among another regulators of autophagy in GC, it can mention miR-183 which its downregulation blocks apoptosis and autophagy via interacting with MALAT1 and SIRT1 through PI3K/AKT/mTOR pathway (Li et al. 2019a). Li et al. evidenced that miR-133a-3p could strengthen autophagy and proliferation of GC cells via downregulation of FOXP3 (Li et al. 2020b). In breast cancer cells, transfection of MCF-7 with miR-26b mimic reduced autophagy dependent to irradiation through silence of DRAM1 (Meng et al. 2018). Ai et al. (2019) clarified that overexpression of miR-107 in breast cancer cell lines (MDA-MB-231 and MDA-MB-453 cells) causes significant reduction in cellular autophagy, proliferation, and metastasis via silencing HMGB1. ULK1 and lysosomal protein transmembrane 4 beta (LAPTM4B), autophagy-related mediators, have also been identified as direct targets of miR-489 which is downregulated in the most of breast cancer cells and several drug resistant breast cancer cell lines (Soni et al. 2018a).

In the metabolic diseases such as osteoporosis, the condition can be exacerbated via miR-15 overexpression which modulates osteoblast genesis and autophagy alongside with downregulation of USP7 (Lu et al. 2021). Wang et al. provided evidences that in osteoarthritis (OA), joint disease, miR-140-5p/miR-149 could affect autophagy, apoptosis, and proliferation of chondrocytes via their potential target, FUT1 (Wang et al. 2018a). Also, miR-20 has a pivotal impact on OA evidenced by inhibition of autophagy and chondrocytes proliferation through ATG10/PI3K/AKT/mTOR axis (Vojtechova and Tachezy 2018). Besides, He et al. (2018) assigned that the inhibition of miR-20 promoted proliferation and autophagy machinery in articular chondrocytes by targeting ATG10 via PI3K/AKT/mTOR signaling pathway (He and Cheng 2018). Furthermore, pathogenesis of intervertebral disc degeneration (IDD) can be influenced by miRNA-regulated autophagy including decreased autophagy facilitated by upregulation of miR-210 and miR-202-5p via targeting ATG7 (Lan et al. 2020). Yun et al. (2020) highlighted the promising role of miR-185 in preventing IDD via improving cell survival and suppressing apoptosis and autophagy of nucleus pulposus cell via blockage of galectin-3/Wnt/β-catenin pathway (Yun et al. 2020). Similar results have been achieved by miR-142-3 overexpression in controlling and inhibiting IDD (Xue et al. 2021).

Moreover, evidences are in a favor of miR-145-3p in exerting autophagic flux in multiple myeloma (MM) via *HDAC4* inhibition (Wu et al. 2020). In the neurodegenerative disorders such as Parkinson's disease (PD) defined by dopaminergic neurons apoptosis, Wen et al. (2018a) confirmed that AMPK/mTOR-regulated autophagy and apoptosis could be a potential therapeutic platform as this axis can be inhibited by miR-185 overexpression leading to prevention of dopaminergic cells death in PD model (Wen et al. 2018a). Similarly, Li et al. (2018a) observed that autophagy in PD could be triggered by miR-181b/PTEN/Akt/mTOR axis in a way that overexpression of miR-181b is associated with increased cell viability. Also, Lu et al. (2020) conducted similar research on PD model and reached to the findings that upregulation of miR-133a in a PD cell model increased cell proliferation and inhibited autophagy and apoptosis by binding to 3 UTR of RAC1 (Lu et al. 2020). Wen and colleagues demonstrated that overexpression of miR-185 inhibited autophagy and apoptosis through regulating the AMPK/mTOR signaling pathway in PD (Wen et al. 2018b). In Alzheimer's disease (AD), the amounts of miRNA-101a was significantly decreased in patients as well as in vivo model and resulted in autophagy regulation through the MAPK pathway (see Table 1) (Li et al. 2019b). Another novel therapeutic option in AD could be proposed by upregulation of miR-16-5p or downregulation of BTG2, which inhibit neuronal damage and autophagy (Dong et al. 2021). Yang et al. (2020) pinpointed that melatonin could reduce neuronal death and autophagy in cerebral ischemia-reperfusion injury (CIRI) mechanistically through regulation of miR-26a-5p/NRSF as well as JAK2-STAT3

Table 1 microRNAs and autophagy

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-26b	Down	ULK2	Induction	Prostate cancer	Downregulation of mTOR	Clotaire et al. (2016)
miR-21	Up	Rab11	Inhibition	Renal ischemia-reperfusion	Reduction of Beclin-1andLC3-II expression and upregulation of p62	Liu et al. (2015a)
miR-185	Down	mTOR AMPK	Induction	Parkinson	Increase of neuronal apoptosis through elevating AMPK/ mTOR signaling pathway activity, upregulation of Beclin-1, LC3-I/ LC-II	Wen et al. (2018a)
miR-96-5p	Up	FOXO1	Inhibition	Breast cancer	Increase of migration, invasiveness, and proliferation by decreasing apoptosis	Doan et al. (2017)
miR-502	Down	Rab1B DHODH	Induction	Colon cancer	Increase of cell proliferation and metastasis	Zhai et al. (2013)
miR-100	Down	mTOR IGF-1R	Inhibition	HCC	Decrease of LC3B-II and Akt proteins enhance tumor growth	Ge et al. (2014)
miR-30a	Down	Beclin-1	Induction	Breast cancer Lung cancer Glioma	–	Zhu et al. (2009)
miR-143	Down	ATG2B HK2	Induction	Non-small-cell lung cancer (NSCLC)	Promotion of cell proliferation, metastasis and Warburg effect	Wei et al. (2015)
miR-23a	Down	ATG12	Induction	Melanoma	Increase of the expression of RUNX2 reduces miR-23a Increase of metastasis and invasion via blocking AMPK-RhoA pathway	Guo et al. (2017a)
miR-130a	Up	ATG16L	Inhibition	COPD	Enhancement of apoptosis and increase of the development of COPD	Li et al. (2016a)
miR-193b-3p	Down	TSC1	Induction	Amyotrophic lateral sclerosis (ALS)	Increase of cell survival by increase of TSC1 expression, and decrease of mTORC1 activity, apoptosis	Dhital et al. (2017)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
let-7i	Up	IGF-1R	Induction	Ankylosing spondylitis (AS)	Protection of T cell from apoptosis through (PI3 K)/Akt and MAPK signaling pathways, LC3B-II increase in T cell and p62 decline, inhibition of mTOR	Hou et al. (2014a)
miR-20a-5p	Down	ATG16L1	Induction	Ischemic kidney injury	The hypoxia downregulated HIF-1α and miR-20a-5p expression, increase of LC3-II	Wang et al. (2015a)
miR-20a	Up	THBS2	Induction	Cervical cancer tissue	The miR-20a deficiency led to trigger the decrease of autophagic activity in cervical cancer cell lines	Zhao et al. (2015a)
miR-338-5p	Up	PIK3C3	Inhibition	Colorectal cancer	Promotion of metastasis and cell migration, decline of ATG14, LC3-II and Beclin-1 expression	Ju et al. (2013)
miR-301a	Up	NDRG2	Induction	Prostate cancer	Hypoxia-induced miR-301a expression, increase of cell viability and decrease of cell apoptosis, promotion of PTEN expression	Guo et al. (2016)
miR-301b	Up	NDRG2	Induction	Prostate cancer	Hypoxia-induced miR-301b expression, increase of cell viability and decrease of cell apoptosis, promotion of PTEN expression	Guo et al. (2016)
miR-290-295 cluster	UP	Atg7 ULK1	Inhibition	Melanoma	Promotion of cell Proliferation and migration Increase of melanoma cells resistance to glucose deficiency	Cheng et al. (2012)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-185	Down	AKT1 RICTOR RHEB	Inhibition	HCC	Increase of cell proliferation by overexpression of mTOR Decrease of apoptosis via Bcl-2, upregulation of cyclin D1	Zhou et al. (2017)
miR-96-5p	Up	ATG7	Inhibition	Liver fibrosis	TGF-β1 promotes miR-96-5p expression, inverse cell proliferation, inhibition of mRNA, and protein levels of α-SMA and Col1α1	Yu et al. (2018b)
miR-101	Down	EZH2	Induction	HCC	Increase of chemoresistance and decline of apoptosis	Xu et al. (2014)
miR-101	–	–	Inhibition	Liver ischemia/ reperfusion injury (LIRI)	miR-101 can inhibit autophagy and reduce LIRI by activating the mTOR pathway	Song et al. (2019)
miR-101a	Down	–	Inhibition	Alzheimer's disease (plasma)	miRNA-101a could regulate autophagy by targeting the MAPK pathway	Li et al. (2019b)
miR-129-5p	Up	Beclin-1	Inhibition	Prostate cancer	Increase of resistance to the Norcantharidin (NCTD)	Xiao et al. (2016)
miR-140-5p/ miR-149	Down	FUT1	Inhibition	Osteoarthritis	Decrease of chondrocyte proliferation, overexpression of IL-1β, and promotion of apoptosis	Wang et al. (2018a)
miR-124	Down	Bim	Inhibition	Parkinson	Increase of apoptosis and inhibition of autophagosome accumulation and lysosomal depletion	Wang et al. (2016)
miR-124	–	p62/p38	Induction	Parkinson	miR-124 can suppress neuroinflammation during the Parkinson's disease development via targeting autophagy, p62, and p38	Yao et al. (2019)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-224-3p	Up	FIP200	Inhibition	Cervical cancer	Promotion of cell proliferation	Fang et al. (2016)
miR-143	Down	GABARAPL1	Induction	Gastric cancer	Increase of resistance to the quercetin	Du et al. (2015)
miR-22	Up	PTEN	Inhibition	Diabetic nephropathy	Increase of renal tubulointerstitial fibrosis, increase of glucose inducing miR-22 and promoting AKT/mTOR pathway	Zhang et al. (2018a)
miR-130a	Down	ATG2B DICER1	Induction	Chronic lymphocytic leukemia	Promotion of cell proliferation	Kovaleva et al. (2012)
miR-181a	Up	MTMR3	Inhibition	Gastric cancer	Promotion of cell proliferation, metastasis and inhibition of apoptosis	Lin et al. (2017)
miR-21	Up	PTEN	Inhibition	HCC	Increase of resistance to sorafenib, promotion of AKT pathway	He et al. (2015a)
miR-409-3p	Down	Beclin-1	Induction	Colon cancer	Increase of resistance to oxaliplatin	Tan et al. (2016)
miR-30a	Down	Beclin-1	Induction	Renal carcinoma	Increase of resistance to sorafenib, upregulation of ATG5 and decrease of apoptosis	Zheng et al. (2015)
miR-503	Up	PRKACA	Inhibition	Esophageal carcinoma	Promotion of cell proliferation, metastasis, increase of PKA/mTOR signaling pathway activity	Wu et al. (2018)
miR-143	Up	ATG2B	Inhibition	Crohn's disease	Blockage of autophagy in intestinal epithelial cells, decline of autophagosome and autolysosome formation, downregulation of IκBα Promotion of pro-inflammatory cytokine expression: IFN-γ, TNF-α, and IL-8	Lin et al. (2018)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-423-3p	Up	Bim	Induction	Gastric cancer	Increase of cell proliferation, invasion and migration, upregulation of LC3, and decrease of P62 and apoptosis	Kong et al. (2017)
miR-135a	Up	Atg14	Inhibition	HCC	Factor VII-increased miR-135a, decrease of LC3A/B protein level, promotion of mTOR activation	Huang et al. (2017)
miR-34a	Down	HMGB1	Induction	Acute myeloid leukemia (AML)	Inhibition of apoptosis Increase of LC3 level, enhancement of chemoresistance	Liu et al. (2017b)
miR-34	Down	Notch 1	Induction	Ovarian cancer cell lines	miR-34 can be inhibiting ovarian cancer cells proliferation by triggering apoptosis and autophagy. It suppresses cell invasion through targeting Notch 1	Jia et al. (2019)
miR-142-3p	Down	HMGB1	Induction	Non-small-cell lung cancer (NSCLC)	Promotion of mTOR, AKT, and P13K activation, increase of chemoresistance	Chen et al. (2017a)
miR-142-3p	Down	HMGB1	Induction	Acute myelogenous leukemia (AML)	Increase of drug resistance in AML cells, inhibition of apoptosis	Zhang et al. (2017a)
miR-142-3p	Down	KLF9	Inhibition	Human ectopic endometrial tissues	Upregulation of mir-142-3p levels can restrict autophagy and induce apoptosis of CRL-7566 cells	Ma et al. (2019)
miR-30b	Down	Atg12, Atg5	Induction	Hepatic ischemia-reperfusion injury (IRI)	Upregulation of LC3-II and increase of autophagosomes	Li et al. (2016b)
miR-30b	–	–	Induction	Vascular calcification	Restoring of miR-30b expression can promote autophagy	Xu et al. (2019a)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-199a-5p	Down	Rheb	Inhibition	Ankylosing spondylitis (AS)	Enhancement of mTOR signaling pathway, decrease of LC3, Beclin-1, and ATG5 expression, Increase of pro-inflammatory cytokines: TNF-α, IL-17, and IL-23	Wang et al. (2017a)
miR-320	Up	HIF-1α	Induction	Retinoblastoma (RB)	Upregulation of HIF-1α and hypoxia, increase of LC3 and Beclin-1 expression, decrease of p62 and p-mTOR	Liang et al. (2017)
miR-32	Up	DAB2IP	Induction	Gastric cancer	Increase of radioresistance in GC, decline of apoptosis and mTOR	Wu et al. (2016a)
miR-224	Up	Smad4	Inhibition	Hepatitis B Virus-associated HCC	Hepatitis B reducesAtg5 and Beclin-1, increase p62, inhibits the formation of autophagosome, blocks TGF-β signaling pathway, and promotes cell proliferation and metastasis	Lan et al. (2014)
miR-181a	Down	p38 JNK	Induction	Parkinson	Enhance p38 MAPK/JNK signaling pathways and apoptosis	Liu et al. (2017c)
miR-410	Down	ATG16L1	Induction	Osteosarcoma	Increase of chemoresistance and inhibition of apoptosis	Chen et al. (2017b)
miR-449a	Down	CISD2	Inhibition	Glioma	Increase level of BCL-2 and cell proliferation, downregulate Beclin-1	Sun et al. (2017a)
miR-378	Up	ATG12	Inhibition	Cervical cancer	Increase migration, invasiveness, proliferation, and metastasis	Tan et al. (2018)
miR-33	Up	ABCA1	Inhibition	Atherosclerosis	Decrease autophagosome formation and LC3 in macrophage	Ouimet et al. (2017)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-32	Up	DAB2IP	Induction	Prostate cancer	Increase radioresistance in prostate cancer cells, promote autophagy through the mTOR-S6K pathway	Liao et al. (2015)
miR-7	Down	mTOR	Inhibition	HCC	Increase cell proliferation	Wang et al. (2017b)
miR-26b	Down	DRAM1	Induction	Breast cancer	Increase radioresistance in breast cancer cell	Meng et al. (2018)
miR-20a	Up	BECN1 ATG16L1 SQSTM1	Inhibition	Breast cancer	C-myce promotes miR-20a and elevates ROS level and DNA damage	Liu et al. (2017a)
miR-638	Up	TP53INP2	Inhibition	Melanoma	Inhibit apoptosis via block p53, increase methylation at CpG islands, enhance melanoma metastasis	Bhattacharya et al. (2015)
miR-212	Down	SIRT1	Induction	Prostate cancer	Increase angiogenesis and cellular senescence	Ramalinga et al. (2015)
miR224-3p	Down	ATG5 FIP200	Induction	Glioblastoma	Hypoxia inhibits miR224-3p and mTOR activity, increase levels of ATG 16,12,13 and ULK1	Guo et al. (2015)
miR-183	UP	UVRAG	Inhibition	Colorectal cancer	Decrease of apoptosis and autophagosome formation, increase of cell proliferation	Huangfu et al. (2016)
miR-183	Down	SIRT1	Induction	Gastric cancer tissue and cell lines	miR-183 can enhance gastric cancer cell viability and inhibit cell apoptosis by promoting autophagy MALAT1-miR-183-SIRT1 axis and PI3K/AKT/mTOR pathway are involve in autophagy of gastric cancer cells	Li et al. (2019a)
miR-29	Down	–	Induction	Retinal pigment epithelial cells	Overexpression of miR-29 can induce autophagy of ARPE-19 cells and primary human retinal pigment epithelial cells	Cai et al. (2019)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-29a	Down	ATG9A TFEB	Induction	Pancreatic cancer	Increase resistance to gemcitabine, autophagy flux, autophagosome formation and autophagosome-lysosome fusion, overexpression of LC3B and decrease p62, promote cell proliferation, migration and invasion	Kwon et al. (2016)
miR-29a	Up	PTEN	Inhibition	Pathological cardiac hypertrophy (rat model)	miR-29a can inhibit autophagy by regulating the PTEN/AKT/mTOR signaling pathway	Shi et al. (2019)
miR-29b-3p	Down	SPARC	Inhibition	Blood samples of heart failure (HF) and hypoxia-induced H9c2 cells	Hypoxia led to downregulation of miR-29b-3p level and induces autophagy and apoptosis of H9c2 cells miR-29b-3p suppresses apoptosis and autophagy by targeting SPARC in hypoxia-induced H9c2 cells	Zhou et al. (2019)
miR-30a	Down	BECN1	Induction	Diabetic cataract	Hgh glucose-promoting apoptosis	Zhang et al. (2017b)
miR-24-3p	Up	DEDD	Induction	Bladder cancer	Increase of cell proliferation, invasion, migration and LC3, decline of apoptosis and p62	Yu et al. (2017a)
miR-138	Down	Sirt1	Induction	Lung cancer	Increase cell proliferation, invasion, metastasis, EMT and AMPK signaling pathway, decrease apoptosis and mTOR activity	Ye et al. (2017)
miR-490-3p	Down	ATG7	Induction	HCC	Increase cell proliferation, decrease apoptosis	Ou et al. (2018)
miR-20a-5p	Down	ATG7	Induction	Neuroblastoma	Increase of LC3-II/ LC3-I and autophagosome formation, decline of apoptosis	Yu et al. (2018b)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-23a	Down	ATG12	Induction	Melanoma	Increase cell proliferation, invasion and metastasis	Guo et al. (2017b)
miR-138	Down	PDK1	Inhibition	Malignant melanoma	Promote PI3K/ AKT/mTOR signaling pathway, decrease levels of LC3, caspase-3 and Bax	Meng et al. (2017)
miR-181a	Up	Atg5	Inhibition	HCC	Decline of apoptosis	Yang et al. (2018)
miR-489	Down	ULK1 LAPTM4B	Induction	Breast cancer	Increase of chemoresistance	Chen et al. (2018)
miR-30a	Down	Beclin-1	Induction	Medulloblastoma	Increase cell proliferation and LC3B level	Singh et al. (2017)
miR-214-3p	Down	Atg12	Induction	Sporadic Alzheimer's disease	Increase levels of LC3bII and Beclin-1, and enhance number of GFP-LC3-positive autophagosome vesicles and apoptosis	Lv et al. (2016)
miR-214	–	PTEN	Induction	Ischemic heart disease (H9c2 cell line)	Oridonin can induce apoptosis and autophagy by regulating PI3K/ AKT/mTOR pathway via overexpression of miR-214	Gong et al. (2019)
miR-20a	Down	RB1CC1/ FIP200	Induction	Breast cancer	Decrease of mTOR activity	Li et al. (2016c)
miR-20b	Down	RB1CC1/ FIP200	Induction	Breast cancer	Decrease of mTOR activity	Li et al. (2016c)
miR-181b	Down	PTEN	Induction	Parkinson	Decrease of PI3 K/Akt/mTOR signaling pathway	Li et al. (2018a)
miR-181b	Up	CREBRF	Induction	Gallbladder cancer	miR-181b inhibits tumor suppression mediated with ginsenoside Rg3 of gallbladder carcinoma through inducing autophagy flux by targeting CREBRF	Wu et al. (2019)
miR-20	Up	ATG10	Inhibition	Osteoarthritis (OA)	Decrease of PI3 K/Akt/mTOR signaling pathway and enhancement of proliferation in chondrocytes	Vojtechova and Tachezy (2018)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-222	Up	PPP2R2A	Inhibition	Bladder cancer	Increase of Akt/mTOR signaling pathway, enhanced resistance of bladder cancer cells to cisplatin	Zeng et al. (2016)
miR-125b	Up	APC	Induction	Colorectal cancer	CXCL12/CXCR4 promotes miR-125b expression and elevates Wnt/β-catenin signaling pathway, EMT and cell invasion, enhances resistance of colorectal cancer cells to fluorouracil	Yu et al. (2017b)
miR-125a	Up	–	Inhibition	Thyroiditis (mice)	Overexpression of miR-125a can be inhibits autophagy by targeting PI3K/ Akt/mTOR signaling pathway in mouse model of thyroiditis	Chen et al. (2019a)
miR-218	Down	YEATS4	Induction	Colorectal cancer	Increase resistance to the oxaliplatin (L-OHP), inhibit of apoptosis	Fu et al. (2016)
miR-22	Down	HMGB1	Induction	Osteosarcoma	Increase drug resistance in osteosarcoma cells, promote cell proliferation, migration, and invasion	Guo et al. (2014)
miR-1	Down	ATG3	Induction	Non-small-cell lung cancer (NSCLC)	Increase drug resistance in NSCLC cells	Hua et al. (2018)
miR-27a	Down	FoxO3a	Induction	Traumatic brain injury (TBI)	Increase level of Beclin-1 and decrease p62	Sun et al. (2017b)
miR-27a	Up	SYK	Inhibition	Melanoma tissues	Depletion of miR-27a lead to induced autophagy and apoptosis of melanoma cells through the activation of the SYK-dependent mTOR signaling pathway	Tang et al. (2019)
miR-31	Down	–	Induction	Colorectal cancer-associated fibroblasts (CAFs)	Elevation of levels of Beclin-1, ATG, DRAM, and LC3, decrease of apoptosis, increase of radioresistance	Yang et al. (2016a)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-140-5p	Down	Smad2 ATG12	Induction	Colorectal cancer	Decrease of TGF-β signaling pathway and necrosis, increase of cell proliferation, metastasis, and invasion	Zhai et al. (2015)
miR-let-7a	Down	Rictor	Inhibition	Gastric cancer	Upregulation of Akt/mTOR signaling pathway	Fan et al. (2018)
miR-221	Up	TP53INP1	Inhibition	Colorectal cancer	Increase cell proliferation, decrease level of LC3	Liao et al. (2018)
miR-107	Down	HMGB1	Inhibition	Breast cancer tissue and cell line	miR-107 can suppress autophagy, migration and proliferation of breast cancer cells through targeting HMGB1	Ai et al. (2019)
miR-107	Down	TRAF3	Induction	Osteoarthritis chondrocytes	Upregulation of miR-107 can inhibit the activation of NF-κB and AKT/mTOR pathway by targeting TRAF3 genes. Also, miR-107 overexpression suppresses apoptosis and promotes autophagy	Zhao et al. (2019a)
miR-223	Up	Atg16l1	Inhibition	Brain microglial cells (BV2 cells) and	miR-223 can inhibit autophagy and induce CNS inflammation by targeting ATG16L1 Expression level of miR-223 was upregulated in CNS and spleen during experimental autoimmune encephalomyelitis (EAE) progression	Li et al. (2019c)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-365	–	ATG3	Inhibition	HCC tissue and cell line	Enforced expression of miR-365 led to significant inhibition of the ATG3 expression in hepatocellular carcinoma cells LncRNA PVT1 can promote autophagy by sponging miR-365 in HCC	Yang et al. (2019a)
miR-206	Down	STC2	Induction	Head and neck squamous cell carcinoma (HNSCC) tissue and cell line	Enforced expression of miR-206 can lead to enhanced autophagy of HNSCC cells	Xue et al. (2019)
miR-206	–	–	Inhibition	Osteoarthritis (rat model)	miR-206 can inhibit autophagy and apoptosis of osteoarthritis cells by activating the IGF-1-mediated PI3K/AKT-mTOR signaling pathway	Yu et al. (2019)
miR-93	–	BECN1, SQSTM1, ATG5, ATG4B	Inhibition	Glioblastoma cancer	miR-93 can inhibit autophagy activity by downregulation of autophagy regulatory genes level	Huang et al. (2019a)
miR-99a and miR-449a	Down	Beclin-1	Inhibition	Thrombosis (serum sample)	Upregulation of miR-99a and miR-449a can inhibit beclin-1 expression levels and autophagy	Zeng et al. (2019)
miR-216a	Down	MAP1S	Inhibition	Colorectal cancer	miR-216a can act as a tumor suppressor miRNA and inhibit autophagy through the TGF-β/MAP1S pathway	Wang et al. (2019a)
miR-18a	Up	BDNF	Inhibition	Cardiomyocytes (from an acute myocardial infarction (AMI) rat model)	miR-18a can lead to inhibiting autophagy and promoting senescence of cardiomyocytes after AMI by targeting BDNF	Lin et al. (2019)

(continued)

Table 1 (continued)

miRNA	Expression	Target	Inhibition/ induction	Disease	Note	Ref
miR-155	–	–	Inhibition	Human umbilical vein endothelial cells (HUVECs)	Downregulation of miR-155 expression can lead to decreasing oxidant-induced injury and inducing cell proliferation by upregulating autophagy	Chen et al. (2019b)
miR-506-3p	–	SPHK1	Inhibition	Osteosarcoma cancer cell	miR-506-3p can initiate epithelial-to-mesenchymal transition (EMT) and inhibit autophagy of osteosarcoma cancer cells by targeting SPHK1	Wang et al. (2019b)
miR-326	–	XBP1	Induction	Parkinson's disease (mouse model)	miR-326 can inhibit nitric oxide synthase (iNOS) expression and induce autophagy of dopaminergic neurons via targeting XBP1	Zhao et al. (2019b)
miR-1251-5p	Up	TBCC	Induction	Human ovarian cancer cell lines and tissues	miR-1251-5p can induce autophagy and act as an oncogene to suppress TBCC and α-/β-tubulin expression	Shao et al. (2019)
miR-217	–	NAT2	Induction	CCL4-induced liver injury (rat models)	miR-217 can induce apoptosis and autophagy and inhibit proliferation of hepatocytes by targeting NAT2	Yang et al. (2019b)
miR-34a-5p	Up	–	Induction	CIH-induced HCAECs	Overexpression of miR-34a-5p can contribute to chronic intermittent hypoxia (CIH)-induced human coronary artery endothelial cell (HCAEC) autophagy by Bcl-2/ Beclin-1 pathway	Lv et al. (2019)

pathway (Yang et al. 2020). It was suggested that neuronal deficit and autophagy in ischemic stroke could be abolished by miR-378 trough targeting GRB2, while lncRNA MEG3 could sponge the miR-378 and activate the expression of GRB2 (Luo et al. 2020).

Shi et al. clarified that miR-126 loss of function could activate myocardial autophagy induced by Beclin-1 and contributed in acute myocardial infarction (AMI) development (Shi et al. 2020). In contrast, miR-18a downregulation had protective effects against AMI via activation of BDNF expression and inhibition of Akt/mTOR axis (Lin et al. 2019). In the Su et al. study (Su et al. 2020), it was manifested that downregulation of miR-30e-3p lessened autophagy and activated apoptosis and injury in cardiomyocytes under ischemia/hypoxia conditions potentially through Egr-1 regulation (Su et al. 2020). MiRNA-regulated abnormal apoptosis and autophagy of cardiomyocyte have a great of importance in heart failure (HF). Alongside with reduced expression of miR-29b-3p in HF patients, the level of this miRNA was decreased in an in vitro HF model under hypoxia condition followed by elevated apoptosis and autophagy via inactivation of SPARC and regulation of TGF-β1/Smad3 cascade (see Table 1) (Zhou et al. 2019).

In the liver complications such as liver fibrosis characterized by hepatic stellate cell (HSC) activation, the regulation of HSC autophagy has attracted research interests. There is line of evidence shown that introduction of miR-96-5p into HSCs (LX-2 cells) is accompanied by repressing autophagy in the cells via ATG7 regulation (Yu et al. 2018c).

In the renal problems including renal tubulointerstitial fibrosis (TIF) as a main result of diabetic nephropathy (DN), accumulating data implicated the major role of miRNAs in the autophagy regulation. Zhang et al. findings represented that miR-22 partially targets PTEN-blocked autophagy followed by TIF development (Liu et al. 2018a). Furthermore, p53/miR-214/ULK1 axis affects autophagy dysregulation in diabetic kidney disease (DKD) (Ma et al. 2020). Moreover, Liu et al. disclosed that the expression of miR-25-3p was increased in polycystic kidney disease (PKD) model via interacting with ATG14-activated autophagy as well as promoting proliferation of renal cell (Liu et al. 2020d). Table 1 lists some miRNAs regulating autophagy in some human cancer cells.

2.2 MiRNAs Interactions in Chemo-Induced Autophagy

Increasing data have reported that autophagy, along with chemotherapy and its association with chemoresistance can be a new therapeutic platform to succeed in cancer treatment. To find the correlation between miRNAs and chemotherapy-induced autophagy, experimental investigations were reviewed. More importantly, the cross talk between miRNAs (modulators of multiple pathways) and autophagy holds promise to overcome chemoresistance in malignancies (Soni et al. 2018b).

Chen and colleagues found that *miR-519a not only plays a role in* glioma by regulating STAT3-mediated autophagy pathway but also affects autophagy in glioblastoma multiforme (GBM) cells and also temozolomide (TMZ) chemosensitivity. The results showed that miR-519a enhanced the sensitivity of GBM cells to TMZ. Also, a significant association was found between miR-519a effects and autophagy. Overall, miR-519a promoted autophagy in glioblastoma through targeting STAT3/Bcl-2 signaling pathway (Li et al. 2018b). Besides, overexpression of miR-29b in GBM cells inhibited cell survival, activated apoptosis and autophagy, and sensitized tested cells to TMZ (Xu et al. 2021). Because of TMZ importance in the treatment of glioblastomas and its ability to induce autophagy, Xu and colleagues assessed the regulatory role of miR-30a in glioblastoma cells treated with TMZ. They revealed that miR-30a increases U251 glioblastoma cells' chemosensitivity to TMZ through direct target of Beclin-1 and inhibition of autophagy (see Table 2) (Xu et al. 2018a). In an in vivo study, Chakrabarti and colleagues proved that antitumor activities of luteolin and silibinin, chemotherapeutic agents, were augmented due to the overexpression of miR-7-1-3p leading to

Table 2 Dysregulated expression of miRNAs in chemotherapy and their function in autophagy cascade

MicroRNA	Expression	Target	Drug/chemotherapy/radiotherapy	Inhibition/induction of autophagy	Type of disease	Ref
miR-519a	Up	STAT3 Bcl-2	Chemotherapy (temozolomide)	Induction	Glioblastoma	Li et al. (2018b)
miR-199a-5p	Down	Beclin-1	Chemotherapy (cisplatin [also known as diamminedichloridoplatinum (II) (DDP)]	Induction	Osteosarcoma (OS)	Li et al. (2016d)
miR-18a	Up	mTORC1	Radiotherapy	Induction	Colon cancer	Qased et al. (2013)
miR-22	Up	HMGB1	Chemotherapy	Inhibition	Osteosarcoma (OS)	Li et al. (2014a)
miR-22	–	MTDH	Chemotherapy (cisplatin)	Inhibition	Osteosarcoma cancer cells	Wang et al. (2019c)
miR-155	Up	–	Chemotherapy	Induction	Osteosarcoma (OS)	Chen et al. (2014a)
mIR-152	Up	ATG14	Chemotherapy (cisplatin)	Inhibition	Ovarian cancer	He et al. (2015b)
miR-214	Up	UCP2	Chemotherapy (tamoxifen, fulvestrant)	Inhibition	Breast cancer	Yu et al. (2015a)
miR-30a	Down	Beclin-1	Chemotherapy (temozolomide)	Induction	Glioblastoma	Xu et al. (2018a)
miR-7-1-3p	Up	XIAP	Luteolin Silibinin	Inhibition	Glioblastoma	Chakrabarti and Ray (2016)
miR-199a-5p	Down	ATG7	Chemotherapy (cisplatin)	Induction	HCC	Xu et al. (2012)
miR-199a-5p	Down	DRAM1	Chemotherapy (Adriamycin)	Inhibition	Acute myeloid leukemia (AML)	Li et al. (2019d)
miR-423-5p	Up	p-ERK 1/2	Chemotherapy (sorafenib)	Induction	HCC	Stiuso et al. (2015)
miR-125b	Up	EVA1A	Chemotherapy (oxaliplatin)	Inhibition	HCC	Ren et al. (2018)
miR-216a	Up	Beclin-1	Radiotherapy	Inhibition	Pancreatic cancer	Zhang et al. (2015a)
miR-410-3p	Up	HMGB1	Chemotherapy (gemcitabine)	Inhibition	Pancreatic ductal adenocarcinoma (PDAC)	Xiong et al. (2017)
miR-140-5p	Up	IP3k2	Chemotherapy	Induction	Osteosarcoma	Wei et al. (2016)
hsa-miR-302a-3p	Down	ULK1	Chemotherapy (5-fluorouracil)	Induction	Colon cancer	Hou et al. (2014b)
hsa-miR-548ah-5p	Down	ATG16L1	Chemotherapy (5-fluorouracil)	Induction	Colon cancer	Hou et al. (2014b)

hsa-miR-30a-5p	Up	PIK3R2	Chemotherapy (5-fluorouracil)	Induction	Colon cancer	Hou et al. (2014b)
hsa-let-7c-5p	Up	BCL2L1	Chemotherapy (5-fluorouracil)	Induction	Colon cancer	Hou et al. (2014b)
hsa-miR-99b-5p	Up	mTOR	Chemotherapy (5-fluorouracil)	Induction	Colon cancer	Hou et al. (2014b)
hsa-miR-23a-3p	Up	BCL2	Chemotherapy (5-fluorouracil)	Induction	Colon cancer	Hou et al. (2014b)
hsa-miR-195a-5p	Up	BCL2	Chemotherapy (5-fluorouracil)	Induction	Colon cancer	Hou et al. (2014b)
miR-34a	Up	FoxO3	Lipopolysaccharide (LPS)	Induction	Acute lung injury (ALI)	Song et al. (2017)
miR-15a-3p	Up	Bcl-2	Polygonatum odoratum lectin (POL)	Induction	Lung adenocarcinoma	Wu et al. (2016b)
miR-1290	Down	GSK3β	Polygonatum odoratum lectin (POL)	Induction	Lung adenocarcinoma	Wu et al. (2016b)
miR-193b	Up	–	Chemotherapy (5-fluorouracil)	Induction	Esophageal cancer	Nyhan et al. (2016)
miR-193b	Down	FEN1	Chemotherapy (epirubicin)	Induction	Osteosarcoma cells	Dong et al. (2019)
miR-384-5p	Down	Beclin-1	Streptozotocin (STZ)	Induction	Diabetic encephalopathy	Wang et al. (2018b)
miR-101	Up	STMN1 RAB5A ATG4D	Chemotherapy (cisplatin)	Inhibition	HCC	Xu et al. (2013)
miR-30a	Up	Beclin-1	Chemotherapy (doxorubicin)	Inhibition	Osteosarcoma	Xu et al. (2016)
miR-30b	–	ATG5	Chemotherapy (cisplatin)	Inhibition	Gastric cancer	Xi et al. (2019)
miR-221/222	Up	ATG12	Chemotherapy (dexamethasone)	Inhibition	Multiple myeloma	Xu et al. (2018b)
miR-142-3p	Up	ATG5 ATG16L1	Chemotherapy (sorafenib)	Inhibition	HCC	Zhang et al. (2018c)
miR-21	Down	–	Chemotherapy (etoposide, doxorubicin)	Induction	Chronic myeloid leukemia	Seca et al. (2013)
miR-137	–	ATG5	Chemotherapy (doxorubicin)	Inhibition	Pancreatic cancer cells	Wang et al. (2019d)
miR-224-3p	–	ATG5	Chemotherapy (temozolomide)	Inhibition	Glioblastoma and astrocytoma	Huang et al. (2019b)
miR-146a	–	TAF9b/P53 pathway	Doxorubicin (DOX)	Induction	Human AC16 cell line	Pan et al. (2019)

inhibition of autophagy and induction of apoptosis in glioblastoma cells (Chakrabarti and Ray 2016). In addition, miR-224-3p weakened resistance to TMZ in glioblastoma cells (LN229 cells) via abolishing autophagy under hypoxia via ATG5 downregulation (Liu et al. 2020e).

Xiao et al. (2016) investigated the role of miR-199a-5p in reducing chemoresistance to cisplatin or diamminedichloridoplatinum (II) (DDP) in OS. They showed that treatment of OS cells with DDP attenuated the expression level of miR-199a-5p; increased the level of various proteins, such as Beclin-1 and LC3; and induced autophagy machinery, which highlights the relationship between treatment cytotoxicity, autophagy inhibition, and their effects on chemoresistance (see Table 2) (Li et al. 2016d). Chen and colleagues observed that overexpression of miR-155 during chemotherapy induced autophagy leading to mediate chemoresistance in OS (Chen et al. 2014a). Wang et al. noted that upregulation of miR-22 in OS cells (MG-63) increased *sensitivity to cisplatin* mediated via negative regulation of autophagy by down-expression of MTDH (Wang et al. 2019c). Alongside, miR-193b/FEN1 axis ameliorated the epirubicin sensitivity of OS cells through autophagy induction (Dong et al. 2019). miR-375 could be another target to sensitize OS to cisplatin as its overexpression in cisplatin-resistant OS models delayed tumor progression and autophagy via targeting ATG2B (Gao et al. 2020a). Qased et al. investigated the role of miR-18a in autophagy process in HCT116 (human CRC cells). To do so, HCT116 cells were irradiated, and the expression levels of miR-18a were subsequently measured in the cells. The results showed that the radiation led to increased expression level of miR-18a and enhanced autophagy induction (Qased et al. 2013). Li et al. showed that the expression levels of miR-22 are enhanced during chemotherapy and target HMGB1, which results in inhibition of HMGB1-induced autophagy (see Table 2) (Li et al. 2014a).

He et al. reported that miR-152 plays an important role in autophagy regulation and drug resistance in ovarian cancer (OC) (He et al. 2015b). They showed that miR-152 was significantly downregulated in cisplatin-resistant cells. It has been reported that overexpression miR-152 leads to induction of apoptosis in cisplatin-resistant cancer cells as well as a decrease of cisplatin-induced autophagy. In this in vitro study, it was documented that ATG14 downregulation by EGR1-miR-152 sensitizes ovarian cancer cells to cisplatin-induced apoptosis through inhibiting cyto-protective autophagy (He et al. 2015b). Vescarelli et al. verified that miR-200c considerably sensitized chemoresistant OC cells to olaparib via regulating NRP1 (Vescarelli et al. 2020). In addition, miR-29c-3p overexpression inhibited autophagy which in turn reversed cisplatin resistance of OC by downregulation of FOXP1/ATG14 pathway (Hu et al. 2020). Esfandyari et al. (2021) demonstrated that miR-143 overexpression in cervical cancer cells (CaSki cells) could increase cisplatin sensitivity of treated cells via induction of apoptosis and autophagy (Esfandyari et al. 2021). Tamoxifen (TAM) and fulvestrant (FUL) are considered as effective drugs for patients with ER-positive breast cancer, but the rate of response to these therapies is limited because of various barriers, such as endocrine resistance. In this regard, Yu and colleagues found that miR-214 enhanced breast cancer cells sensitivity to TAM and FUL through autophagy inhibition (Yu et al. 2015a). In a comparable study on breast cancer, Soni et al. identified that miR-489 enhanced sensitivity to doxorubicin (Dox) as a result of autophagy inhibition dependent to LAPTM4B downregulation (Soni et al. 2018b).

Xu et al. reported that miR-199a-5p downregulation induced by cisplatin enhances drug resistance through activating autophagy in HCC (Xu et al. 2012). Soni et al. evaluated the role of miR-155-5p on Adriamycin (ADR)-resistant liver carcinoma cells (HepG2/ADR), and their findings indicated the effects of miR-155-5p as sensitizer of ADR, activator of apoptosis, and inhibitor of autophagy via attaching to ATG5 3UTR (Soni et al. 2018b). Also, higher expression of miR-541 inhibited the autophagy in HCC cells by targeting ATG2A and RAB1B leading to promising response to sorafenib (Xu et al. 2020a). In another

study, it was revealed that upregulated miR-142-3p increased sensitivity of HCC cells to sorafenib by targeting ATG5 and ATG16L1 as negative modulators of autophagy (Zhang et al. 2018b). Similar findings have been reported for miR-101/RAB5A/STMN1/ATG4D axis in the HCC cells (HepG2) which improved the response to cisplatin due to inhibition of autophagy mechanism (Xu et al. 2013). Consistently, Ren et al. demonstrated that miR-125b/EVA1A axis-mediated autophagy reversed resistance of HCC cells to oxaliplatin (Wei-Wei et al. 2018).

Chemoresistance of nasopharyngeal carcinoma (NPC) has been investigated by Zhao et al. (2020) study in which they verified that miR-1278 expression was decreased in NPC tissues associated with worse chemotherapy response. Nonetheless, upregulation of miR-1278 dramatically raised anticancer effects of cisplatin in NPC cells together with reduced autophagy via inhibiting ATG2B (Zhao et al. 2020).

Yang et al. (2021) showed that miR-136-5p upregulation not only had negative effects on malignant progression of laryngeal squamous cell carcinoma (LSCC) and hypopharyngeal squamous cell carcinoma (HPSCC) cells but also reversed cisplatin resistance in the tested cells via inactivation of ROCK1 Akt/mTOR axis (Yang et al. 2021).

Recently, Xi et al. explored the lncRNA MALAT1/miR-30b/ATG5 axis in cisplatin resistance of GC cells (AGS/CDDP and HGC-27/CDDP) and documented that miR-30b attenuated cisplatin resistance by reduced expression of not only MALAT1-activated autophagy but also ATG5 (see Table 2) (Xi et al. 2019). In another study, Chen et al. (2020a) identified that miR-30a could sensitize gastrointestinal stromal tumors (GISTs) cells to imatinib (IM) via silence of Beclin-1-regulated autophagy (Chen et al. 2020a). Also, He et al. (2020a) discovered that miR-153-5p upregulation in oxaliplatin (L-OHP)-resistant CRC cells could overcome L-OHP resistance via silencing Bcl-2-induced autophagy (He et al. 2020a). Furthermore, Liu et al. (2020f) indicated that lncRNA NEAT1 upregulation sponged miR-34a in CRC. Additionally, NEAT1 inhibition significantly slowed down CRC tumorigenesis and elevated sensitivity of cells to 5-fluorouracil (5-FU). miR-34a overexpression also showed comparable trends with NEAT1 inhibition via binding to autophagy components (HMGB1, ATG4B, and ATG9A) (Liu et al. 2020f). The role of miRNA in chemoresistance of pancreatic cancer (PC) cells was evaluated by miR-137 overexpression in PANC-1 cell lines. The results indicated that miR-137 chemo-sensitized the cells to Dox via ATG5-triggered autophagy (Wang et al. 2019d).

The main hurdle for the proper treatment of multiple myeloma (MM) is still chemoresistance. Of note, the cross talk between miRNA dysregulation and autophagy illustrated that miR-221/222 could suppress dexamethasone (Dex) sensitivity in MM cells via inhibition of autophagy associated with ATG12/p27-mTOR axis (Xu et al. 2019b). In various studies, drug resistance in non-small-cell lung cancer (NSCLC) has been investigated. In a research conducted by Hua et al., overexpression of miR-1 reversed cisplatin resistance in NSCLC by suppression of ATG3-regulated autophagy (Hua et al. 2018). Therefore, miRNAs have regulatory roles in chemoresistance due to their effects on autophagy induction. These mediators should be further investigated in numerous in vivo and in vitro studies to find the molecular mechanisms related to resistance. Table 2 lists the effects of autophagy-related miRNAs on some human cancer chemotherapy.

3 Exosome and Autophagy

Exosomes, membrane-coated vesicles with 30–120 nm size, are released by several cells, such as lymphocytes, platelets, epithelial cells, mast cells, dendritic cells, neurons, and endothelial cells (Théry et al. 2002; Hashemipour et al. 2021). Exosome has main roles in biological events, including inflammation, tumorigenesis, metastasis, and response to therapy (Kharaziha et al. 2012). Various researches have demonstrated that exosomes can also be considered as diagnostic means and targeted drug delivery system. It has been identified that almost all biological body fluids, including blood, serum,

saliva, milk, amniotic fluid, semen, breast milk, and urine contain exosomes (Keller et al. 2011; Lässer 2015).

Exosomes carry diverse unique molecular cargos, including lipids, proteins, and nucleic acid fragment. Some of the proteins are involved in assembly, movement, and organization of exosomes (e.g., annexins, actins, tumor susceptibility gene 101, vesicle-associated membrane protein 8, and fibronectin) and observed in the structures of exosome. Furthermore, a cluster of proteins known as exosome surface markers, such as CD9, CD63, CD81, and CD82, are useful for the detection of exosomes (Zhao et al. 2015b; Barclay et al. 2017). Mounting evidence has established that exosomes have a wide range of roles in human pathological and physiological processes. Since exosomes deliver their constituents into recipient cells, they are able to play a prominent role in cell signaling and local/distant cell-to-cell communication (Lakkaraju and Rodriguez-Boulan 2008; Van Niel et al. 2006). These data demonstrated that exosomal molecular constituents can represent disease conditions (Feng et al. 2013). The idea of the RNAs presence in exosomes has attracted great attention in the research of exosomal RNAs, especially miRNAs as potential diagnostic biomarkers (Taylor and Gercel-Taylor 2008). Recent experiments have demonstrated that exosomal miRNAs are resistant to RNase degradation and thus remain stable in circulating plasma and serum. On the other hand, they are easily evaluated, are minimally invasive, and have high sensitivity and specificity. This evidence indicates that exosomal miRNAs are ideal biomarkers for early clinical diagnostic applications (Lin et al. 2015; Li et al. 2014b).

As cited above, the autophagic process contains five key stages including initiation, nucleation, elongation and maturation, fusion, and degradation (Li et al. 2020c). mTOR acts as the regulator of the initiation stage, and its activation is associated with prohibition of autophagy, whereas its inactivation is able to induce autophagy. It has been revealed that mTOR and the ULK complex (consist of ULK1, FIP200, and autophagy-related protein 13 [Atg13]) is inactivated and activated, respectively, in stress situations. Beclin-1, an essential component for autophagosome formation, in combination with Vps34 and Atg14L produces a complex, which is necessary for induction autophagy nucleation (Liang et al. 1999; Levine et al. 2015; He and Klionsky 2009; Kihara et al. 2001). In the elongation along with maturation stage, two ubiquitin-like conjugation systems are warranted to facilitate autophagosome membrane expansion. The first system involves the microtubule-associated protein light chain 3 (LC3)-phosphatidylethanolamine (PE) complex. LC3 is cleaved by Atg4 at its C terminal to produce intracellular LC3-I, which is conjugated with PE in the ubiquitin-like reactions of Atg7 and Atg3. The lipid form of LC3 (LC3-II) is attached to the autophagosome membrane (Yu et al. 2015b). The second system involves the Atg12-Atg5-Atg16 complex, in which Atg12 is conjugated with Atg5 via ubiquitin-like reactions of Atg7 and Atg10. The Atg12-Atg5 conjugate interacts noncovalently with Atg16 to form a large complex. While lysosomes bind to autophagosomes to form autolysosomes in the fusion stage, cargo within autolysosomes will be degraded in the degradation stage. Autophagy is tightly modulated to keep homeostasis. Following autophagy initiation, lots of Atg proteins collaborate to manage the next stages of autophagy. It is yet not clear that autophagy conveys protective or detrimental effects in diseases (Saha et al. 2018; Xiong 2015). For example, lack of autophagy is associated with excess amount of tau and synuclein proteins, which induces neurodegenerative disorders. Evidences are in support of the fact that autophagy has a dual effects on cancer cells and initially acts as a tumor inhibitor; however, later it defends tumor cells against the immune system's attacks (Sharma et al. 2021; Hassanpour et al. 2020). Likely, it has been demonstrated that autophagy regulates cardiac and hepatic disorders positively and negatively, respectively. Thus, the control of autophagy via exosomes can have various positive and negative effects on a variety of diseases (Xing et al. 2021).

The role of exosomes in cellular stresses has been evidenced. However, some researches

indicate that the interaction between exosomes and autophagy machinery may preserve intracellular protein and homeostasis (Baixauli et al. 2014). In addition, autophagy induction due to nutrient deprivation leads to inhibited exosome secretion (Fader and Colombo 2009). There are some exosomal proteins markers related to autophagy mechanism. Dias et al. showed that PRNP (prion protein gene) is essential to promote the release of exosomes regulating CAV1/caveolin-1-suppressed autophagy (Dias et al. 2016). Moreover, significant levels of autophagy proteins, including WIPI2, LC3, NBR1, and p62, are present in exosomal fractions secreted by apilimod-treated cells (Hessvik et al. 2016). Importantly, different exosomal and autophagic proteins can be applied as potential biomarkers regarding the type of cancer (Salimi et al. 2020).

Also, the role of exosomal miRNAs in autophagy regulation has been demonstrated by various investigations. Yang et al. reported that high serum levels of exosomal miR-30a were observed in AMI patients. Also, they observed that inhibition of miR-30a increased the expression level of Beclin-1, Atg12, and LC3-II/LC3-I known as the regulators of core autophagy machinery and contributed to preserve the hypoxia-induced autophagy (Yang et al. 2016b). Liu and colleagues conducted a study on AMI rat model and in vitro model of hypoxic H9c2 cells to investigate the cardioprotective role of miR-93-5p-encapsulating exosomes released from adipose-derived stromal cells (ADSCs) in ischemia-induced cardiac damage. They found overexpression of inflammatory cytokines as well as miR-93-5p in both patients and rat models with AMI. In addition, the comparison of the protective effects of exosomes on infarction-induced cardiac damage revealed that exosomal treatment containing miR-93-5p derived from ADSCs caused more protection than simple exosomes (Liu et al. 2018b). Also, Li et al. highlighted the impact of bone marrow-derived mesenchymal stem cells (BMMSCs)-derived exosomes enriched in miR-29c on negative regulation of autophagy in cardiac ischemia/reperfusion (I/R) injury through PTEN/Akt/mTOR pathway (Li et al. 2020d). Similarly, human umbilical cord mesenchymal stem cells-exosome (hucMSC-ex) abolished coxsackievirus B3 (CVB3)-activated myocarditis due to upregulation of autophagy function mediated by AMPK/mTOR axis and reduction of cardiomyocyte death (Gu et al. 2020). Santoso et al. (2020) demonstrated that induced pluripotent stem cells and their differentiated cardiomyocyte-delivered exosome (iCM-Ex) treatment had cardioprotective effects against post-MI via improvement of autophagy machinery in vivo and in vitro (Santoso et al. 2020). Besides, Li and colleagues isolated exosomes released by human aortic smooth muscle cells and identified that isolated exosomes contained miR-221/222. They found that miR-221/222 could target 3′UTR of PTEN. Also, overexpression of miR-221/222 downregulated the expression of ATG5, LC3-II and Beclin-1, suggestive of the inhibitor role of exosomal miR-221/222 in autophagy process (Li et al. 2016e).

Yuwen et al. (2017) reported that the expression level of exosomal miR-146a-5p in NSCLC is correlated with chemosensitivity and chemotherapy response to cisplatin. Low levels of miR-146a-5p in serum exosomes were detected in advanced NSCLC patients. In both NSCLC cells and exosomes, the expression level of miR-146a-5p was gradually decreased due to chemoresistance to cisplatin. In addition, miR-146a-5p also inhibited the autophagy through targeting Atg12 (Yuwen et al. 2017). Wang et al. investigated the role of tumor environment such as acute shear stress (ASS) in NSCLC invasion. Their data indicated that ASS activated cell death by exerting the secretion of autophagy and exosome components via SIRT2/TFEB axis (Wang et al. 2020a). In the severe lung injury and respiratory deficit, Wei et al. illustrated that huMSC-ex-delivered miR-377-3p could improve acute lung injury (ALI) induced by lipopolysaccharide through targeting RPTOR followed by autophagy activation (Wei et al. 2020).

Exosomal miR-1910-3p derived from breast cancer cell attenuated metastasis, growth, and autophagy via MTMR3 suppression and NF-κB and wnt/β-catenin signaling induction (Wang et al. 2020b). Since exosomes loaded with

miR-1910-3p increased autophagy and breast cancer development via silencing MTMR3 and inducing NF-κB and wnt/β-catenin pathway, it could be considered as a diagnostic biomarker for breast cancer (Wang et al. 2020b). Moreover, hucMSCs-ex transferring miR-224-5p could hamper cellular apoptosis and mount proliferation and autophagy in breast cancer via silence of HOXA5 (Wang et al. 2021a). In another interesting study, Han et al. (2020), showed that exosome-shuttled miR-567 repressed autophagy and chemo-sensitized breast cancer cells to trastuzumab via interacting with ATG5 (Han et al. 2020). Additionally, the anticancer effects of gemcitabine in breast cancer (luminal-b type) could be improved using exosome-overexpressed small interfering RNA (siRNA) MTA1, which suppressed autophagy and EMT/HIF-α pathway (Li et al. 2020e).

In the field of thyroid research, papillary thyroid cancer (PTC) cell exosome-delivered SNHG9 lncRNA could prevent autophagy flux and upregulate apoptosis of human normal thyroid epithelial cell line (Nthy-ori-3 cell) mediated by YBOX3/P21 pathway (Wen et al. 2021).

In cisplatin-resistant GC, Yao et al. manifested that the levels of exosomal circ-PVT1 and miR-30a-5p were respectively upregulated and downregulated, while the silence of Circ-PVT1 reversed cisplatin resistance via reducing autophagy alongside with increasing apoptosis through miR-30a-5p/YAP1 axis (Yao et al. 2021). Comincini et al. evaluated the expression levels of exosomal miR-17 and miR-30a to diagnose celiac disease and discovered that miR-17- and miR-30a-regulated ATG7 and BECN1 known as two key executor of autophagy (Comincini et al. 2017).

Beclin-1 contains three main domains including coiled coil (CCD), evolutionarily conserved (ECD), and Bcl-2-homology-3 (BH3). Several proteins through binding to the various domains of Beclin-1 and forming different complexes regulate autophagy activity (Wirawan et al. 2012). Beclin-1 is encoded by BECN1, which is located on chromosome 17q21 and was shown to be targeted via miR-30a (Zhu et al. 2009). Exosomal miR-30a is capable of prohibiting autophagy via targeting the Beclin-1 pathway and maintains a mandatory role in liver fibrosis and MI. It was revealed by Yang et al. (2016b) that hypoxic cardiomyocytes prohibit autophagy through secreting miR-30a and, thereby, cause cardiomyocyte damage. So, it can be expected that autophagy level can be increased by targeting miR-30a, and, thereby, cardiomyocyte damage will be decreased. In contrast to findings of Yang et al., Zhang et al. found out that epigallocatechin gallate acts as a protective agent for MI through overexpression of exosomal miR-30a and, consequently, prohibiting autophagy and apoptosis (Zhang et al. 2020b). An animal study that was conducted by Xu et al. (2019c) also demonstrated that exosomal miR-30a through prohibiting autophagy decreased the level of cardiomyocyte apoptosis in rats with MI/reperfusion injury. Autophagy becomes active throughout hypoxia and displays protective effects by modifying cell survival. Nevertheless, as myocardial hypoxia continues, excessive autophagy occurs, which causes accumulation of a quite amount of toxic components and, as a consequence, cell death. In Yang et al.'s study, autophagy was inhibited by exosomal miR-30a; hence, there was a lack of protective autophagy in cardiomyocytes, which contributed to cardiomyocyte apoptosis. However, in other studies performed by Zhang and Xu, excessive autophagy was the reason behind cardiomyocytes damage. Exosomal miR-30a is able to decrease the level of cardiomyocyte apoptosis via prohibiting excessive autophagy. Moreover, it has been unveiled that excessive autophagy can induce liver fibrosis. It was shown that in a hepatic fibrosis model that was establish by Chen et al. (2017c), the expression level of exosomal miR-30a, secreting via hepatic stellate cells, was decreased. The upregulation of miR-30a may have the capacity to improve liver fibrosis through prohibiting autophagy mediated by the Beclin-1 pathway.

Li et al. (2021) revealed that osteosarcoma (OS)-secreted exosomal lncRNA OIP5-AS1 regulated autophagy and angiogenesis via reduction of miR-153 and enhancement of ATG5 expressions (Li et al. 2021). In spite of pro-tumor effects of hBMSC-derived exosomes on OS progression via autophagy elevation, knockdown of

ATG5 in OS cells attenuated oncogenic effects of hBMSC exosomes (Huang et al. 2020).

Reportedly, in osteoarthritis (OA) mice model, intra-articular administration of OA exosomes loaded with ATF4 had protective effects against chondrocyte apoptosis via activating autophagy (Wang et al. 2021b). Furthermore, in IVDD model, it was confirmed that normal cartilage end plate stem cell-derived exosomes (N-Exos) had a better therapeutic impact on stopping nucleus pulposus cell apoptosis and delay in IVDD progression in comparison with degenerated cartilage end plate stem cell-derived exosomes (D-Exos) via induction of PI3K/AKT/autophagy pathway (Luo et al. 2021). Also, the effects of human umbilical cord mesenchymal stem cell-derived exosomes (hucMSC-ex) on tissue damages make them as a promising tool in the regenerative medicine. Based, Jia et al. (2018) discovered that hucMSC-ex enriched with 14-3-3ζ reversed cisplatin-activated nephrotoxicity via interaction with ATG16L-induced autophagy (Jia et al. 2018).

It has been made clear that the levels of anti-inflammatory cytokines and miR-30d-5p are reduced following acute ischemic stroke (AIS). Jiang et al. recognized that exosomes derived from miR-30d-5p-overexpressing ADSCs could overcome autophagy-induced cerebral damage via increasing polarization of M2 microglial/macrophage (Jiang et al. 2018). Chen et al. (2020b) noticed that exosome-delivered circSHOC2 released from ischemic-preconditioned astrocyte (IPAS) potentiated neuronal protective effects against ischemic cerebral injury by affecting autophagy through the miR-7670-3p/SIRT1 axis (Chen et al. 2020b). Recently, Pei et al. verified that astrocyte-released exosomes (AS-Exo) suppressed neuronal autophagy and alleviated neuronal injury and apoptosis in an in vitro model of ischemic injury via overexpression of miR-190b and downregulation of Atg7 (Pei et al. 2020). It has been observed that hucMSC-ex could breakdown blood-brain barrier (BBB) and target substantia nigra leading to protection of dopaminergic neurons via activation of autophagy in a PD model (Chen et al. 2020c). Ma et al. (2021) analyzed the amounts of lncRNA LINC00470 in glioma-derived exosomes from patients and concluded that overexpressed LINC00470 could abrogate autophagy and raise glioma cells proliferation via binding to miR-580-3p which in turn inactivated WEE1 and induced the PI3K/AKT/mTOR pathway (Ma et al. 2021). Programmed death-ligand 1-containing exosomes (PD-L1-ex) derived from glioblastoma stem cell (GSC) enhanced autophagy and reduced apoptosis via AMPK/ULK1 pathway cascade resulted in enhanced resistance to TMZ, while knockdown of PD-L1 reversed these effects (Zheng et al. 2021). There is line of evidence shown that Schwann cells (SCs) have regenerative role following peripheral nerve injury. In this context, Yin et al. discovered that ADSC-Exos loaded by miR-26b blocked SC autophagy and improved the myelin sheath regeneration in the sciatic nerve injury model via targeting Kpna2 (Yin et al. 2021). Due to the improvement of inflammation secondary to spinal cord injury (SCI) via anti-inflammatory effects of peripheral macrophages (PMs), Zhang et al. represented that PM-derived exosomes (PM-Exos) could promote spinal cord recovery via enhancement of microglial autophagy and anti-inflammatory microglia polarization mediated through PI3K/AKT/mTOR pathway (Zhang et al. 2021b).

In type 2 diabetes mellitus (T2DM) rats, He et al. uncovered that hucMSC-ex promoted hepatic lipid and glucose metabolism potentially by enhancing the autophagosomes via AMPK pathway (He et al. 2020b). Likewise, Zhang et al. reported that liver I-/R-induced injury could be alleviated by huMSC-ex-transmitted miR-20a via regulating apoptotic and autophagic genes including caspase-3, P62, mTOR, and LC3-II (Zhang et al. 2020c). Further, Zhu et al. (2020) verified that ADSC exosome carrying mmu_circ_0000623 inhibited liver fibrosis through autophagy induction (Zhu et al. 2020). Since liver fibrosis can be driven by HSC activation, Wang et al. (Wang et al. 2020c) displayed that natural killer (NK) cell-derived exosome (NK-Exo) attenuated HSC activation via inhibiting TGF-β1 mechanistically through overexpression of miR-223 and inhibition of ATG7-induced autophagy (Wang et al. 2020c).

All in all, studies have recently demonstrated that autophagy has regulatory properties in exosomal production and its release. The link between Atg5 and V1V0-ATPase and their role in induction of exosome production has been documented by Chen et al. (2018). They found that cells with Atg5 and Atg16L1 deficiency exhibit reduced exosome production, but it's not dependent on Atg7 and canonical autophagy. It has been shown that Atg5 affects the production of exosomes by reducing the acidifying of endosomes and disrupting the acidification of V1V0-ATPase. Because of the role of autophagy and exosomes in metastasis, Atg5 is able to induce invasion and metastasis (Guo et al. 2017c). Abdulrahman et al. evaluated the role of autophagy in exosome production and processing. They found that the induction of autophagy by rapamycin, mTOR inhibitor, suppressed the release of exosomal prions; however, the inhibition of autophagy resulted in increased release of both exosomes and prions (Abdulrahman et al. 2018). Totally, further studies were collected in Table 3.

Table 3 Exosome and autophagy

Type of cargo	Exosome source	Effect on autophagy	Type of disease	Note	Ref
miR-146a-5p	Serum	Inhibition	Non-small-cell lung cancer (NSCLC)	miR-146a-5p upregulated and decrease level of Atg12	Yuwen et al. (2017)
miR-93-5p	Adipose-derived stromal cells (ADSCs)	Inhibition	Acute myocardial infarction (AMI)		Liu et al. (2018b)
miR-30d-5p	Adipose-derived stromal cells (ADSCs)	Induction	Acute ischemic stroke (AIS)	Enhancement of M2 microglial/macrophage polarization and reduce of M1 microglial/macrophage polarization. Inhibition ischemia-induced neuronal damage via decreasing of TNF-α, IL-6, and iNOS secretion from M1 microglial cells. Downregulation of Beclin-1 and Atg5. Induction of expression anti-inflammatory cytokines IL-4 and IL-10 from M2 microglial cells	Jiang et al. (2018)
miR-181-5p	Adipose-derived mesenchymal stem cells (ADSCs)	Induction	Liver fibrosis	miR181-5p-ADSC block of STAT3/Bcl-2/Beclin-1-dependent signaling pathway and decrease liver fibrosis	Qu et al. (2017)
miR-30a	Serum H9c2 cell	Inhibition	Acute myocardial infarction (AMI)	Hypoxia promotes expression of miR-30a in cardiomyocytes and increases apoptosis and elevates Atg12 and Beclin-1 protein levels	Yang et al. (2016b)
miR-17	T98G cells	Induction	Celiac disease (CD)	miR-17 downregulated and increase of expression level of ATG7	Comincini et al. (2017)
miR-30a	T98G cells	Induction	Celiac disease (CD)	miR-30a downregulated and increase of expression level of BECN1	Comincini et al. (2017)
miR-221/222	Human aortic smooth muscle cells (HAoSMCs)	Inhibition	–	miR-221/222 upregulation in HUVECs, reduction of PTEN, LC3-II, ATG5, and Beclin-1protein levels. Increase of SQSTM1/p62 level and Akt signaling pathway	Li et al. (2016e)

(continued)

Table 3 (continued)

Type of cargo	Exosome source	Effect on autophagy	Type of disease	Note	Ref
MSC exosome (miR-125b)	Neonatal mice cardiomyocytes (NMCMs) cell	Inhibition	Myocardial infarction (MI)	Decrease of p53/Bnip3 signaling pathway and save myocardial from death	Monaco et al. (2017)
HucMSC exosome (14-3-3ζ)	NRK-52E cells	Induction	Acute kidney injury (AKI)	HucMSC exosome-delivered 14-3-3ζ attached the ATG16L protein and induced autophagosome formation and as a result elevated cisplatin resistance and cell proliferation and reduced apoptosis	Jia et al. (2018)
Exosomes derived from gefitinib-treated (Exo-GF)	PC9 cells	Induction	Non-small-cell lung cancer (NSCLC)	Enhancement cisplatin resistance, overexpression of Bcl-2 and LC3-II protein levels, decrease of Bax and p62 protein levels	Li et al. (2016f)
NA	H9C2 cells	Induction	Myocardial ischemia-reperfusion injury (MIRI)	Exosomes derived from mesenchymal Stem cells enhance cardiomyocyte autophagy, inhibit cell apoptosis and ROS production through H2O2, promote AMPK pathway and decrease Akt and mTOR pathways	Liu et al. (2017d)
HucMSC exosomes	NRK-52E cells	Induction	–	HucMSC exosomes block cisplatin-induced mitochondrial apoptosis and secretion of inflammatory cytokines, decrease of mTOR and NF-KB, increase levels of ATG5 and ATG7	Wang et al. (2017c)

4 Inhibition or Stimulation of Autophagy by the Virus

Viruses are known as intracellular parasites that are highly dependent on the host for their cell cycle. Hence, after entrance, they reprogram the target host cell to meet their basic needs (Fehr and Yu 2013; Bagga and Bouchard 2014). As we cited before, autophagy has a crucial role in preserving cellular hemostasis by participating in different physiological processes, such as, but not limited to, cell differentiation and development, starvation, and degradation of abnormal products. Additionally, it has been shown that autophagy is produced in response to stress conditions such as infection with viral viruses (Senft and Ze'ev 2015; Mizushima and Levine 2010). Also, in response to viral infections, autophagy becomes active by innate immune system to degrade viruses (Deretic et al. 2013). Additionally, autophagy also takes part in activation of adaptive immune system by accelerating antigen processing (Paludan et al. 2005; Romao et al. 2013). Xenophagy is a type of selective lysosomal degradation pathway that is vital for eliminating pathogens especially bacteria and viruses (Levine 2005). Although autophagosomes potentially are detrimental for invading viruses, several viruses have shown to be able to convert the autophagosome to their home during replication. The autophagosome provides a membrane-bound, protected site to produce their progeny, where their metabolites can be utilized as source of energy for viral replication. Another unique class of autophagy, called lipophagy, targets intracellular lipid droplets, and this process can also be captured by viruses. Lipid droplets are considered as the optimal source for viral assembly since the viruses have the potential to stimulate lipophagy provide the high values of

ATP needed for viral replication (Choi et al. 2018; Heaton and Randall 2011). Taken together, according to recent findings, viruses are developing new strategies to fight or use autophagy to facilitate their replication. Herein, we sought to provide a brief review on how autophagy fights against viral viruses and, thereafter, how the viruses disrupt the autophagic pathway to escape form immune system reactions and prompt their replication.

Recently, several studies have reported that the aim of virus interference with host cell autophagy is to promote the life cycle of virus and avoid detection by the host immune system. The diverse set of viruses are able to dysregulated autophagy machinery (Glick et al. 2010; Jackson 2015). The viral proteins directly or indirectly interact with autophagy components leading to enhance or block autophagy (Mack and Munger 2012). For instance, coronavirus papain-like protease, termed PLP2, induces autophagy via interacting with Beclin-1 (Chen et al. 2014b). Although some viral proteins inhibit the autophagy via interaction with Beclin-1, HIV-Nef and HSV-1 ICP34.5 proteins are capable of inhibiting autophagy-dependent Beclin-1 (Orvedahl et al. 2007; Kyei et al. 2009a; Campbell et al. 2015a). Beclin-1 has Bcl-2 homology 3 (BH3) domain and, through this domain, interacts with anti-apoptotic Bcl-2 family members (Oberstein et al. 2007). This interaction inhibits Beclin-1 assembly to the pre-autophagosomal structure, thereby preventing autophagy (Liang et al. 1998).

The importance of apoptosis and Bcl-2 proteins in immune system regulation and responses to stresses has provided evolutionary pressures on viruses to acquire the genes encoding pro-survival Bcl-2 proteins (Neumann et al. 2015). Large DNA viruses, such as γ-herpesviruses 68 (γ-HV68), adenovirus, Epstein-Barr virus (EBV), and Kaposi's sarcoma-associated herpesvirus (KSAH), mimic the pro-survival Bcl-2 proteins leading to hijack the intrinsic pathway of apoptosis for their purposes (Kvansakul et al. 2017). Liang et al. (2008) reported that murine gamma-herpesvirus 68 (MγHV68) Bcl-2 protected virus-infected cells against apoptosis, also repressed autophagy through its direct binding to Beclin-1 (Liang et al. 2008). In addition to suppressing autophagy by the vBcl2/Beclin-1 complex, KSHV also inhibits this process by viral homolog of cellular FLICE-like inhibitor protein (v-FLIP). Both KSHV v-FLIP and cellular FLIP directly interact with the autophagy-protein ATG3 in competition with LC3 protein. It has been demonstrated that, to suppress autophagic programmed cell death, this interacting ability of KSHV v-FLIP is required (Mack and Munger 2012; Irmler et al. 1997; Thome et al. 1997; Lee et al. 2009). The biochemical evidences show interaction of different HCV and HBV proteins with autophagy machinery components. Nonstructural protein 3 (NS3) of HCV was found to co-localize and associate with the immunity-associated GTPase (IRG) family M that it known autophagy pathway regulator in response to the bacterial infection (Grégoire et al. 2011a; Singh et al. 2006). Core protein of HCV activates autophagy through EIF2AK3and ATF6 UP pathway and/or upregulating Beclin-1 expression (Wang et al. 2014a; Liu et al. 2015b). Moreover, this core protein represses apoptosis and enhances autophagy in hepatocytes through upregulating Beclin-1 (Liu et al. 2015b). Small surface proteins of HBV interact with LC3 and HBV-HBx protein interacts with VPS34 (Sir and Tian 2010; Li et al. 2011a). Sir and colleagues reported that HBx through binding to phosphatidylinositol 3-kinase class III, a critical enzyme in the initiation of autophagy, leads to enhanced activity of this enzyme and thus activates the early autophagic pathway (Sir and Tian 2010).

Espert et al. have shown that autophagy-dependent cell death is activated after binding of HIV envelope glycoprotein to CXCR4 on T cells (Espert et al. 2006; Espert et al. 2007). Bcl-2-associated athanogene 3 (BAG3) is known as a pro-autophagic and anti-apoptotic factor in many normal and neoplastic cells (Rubinstein and Kimchi 2012; Behl 2011; Rosati et al. 2011). Bruno and colleagues reported that transfection of HIV-1 trans-activator (Tat) protein into glioblastoma cells results in increasing BAG3 levels leading to stimulate the autophagic pathway, while silencing of BAG3 results in disrupted balance between autophagy and apoptosis (Bruno et al. 2014). As mentioned earlier, autophagy process involves the formation and maturation of autophagosomes.

Recent studies have showed that interferon-γ (IFN-γ) activates autophagosomes to participate in immunity defense (Deretic 2006). HIV-Tat protein suppresses the formation of autophagosome. In other words, this protein disrupts the IFN-γ signaling pathway through repression of STAT1 phosphorylation and, consequently, inhibits the IFN-γ-induced autophagy (Li et al. 2011b). Additionally, influenza matrix protein 2 and human parainfluenza virus Type 3 phosphoprotein interrupt the maturation of autophagy through blocking autophagosome degradation (Ding et al. 2014; Gannagé et al. 2009).

One of the most important regulators of autophagy is the mammalian target of rapamycin (mTOR), which moderates the balance between autophagy and growth in response to environmental stress and physiological conditions (Cuyàs et al. 2014). Kinase mTOR is the downstream target of PI3K-Akt signaling pathway, which is activated by growth factor receptors and neurotropism as well as promotes cell differentiation, growth, and survival and also reduces apoptosis (Manning and Cantley 2007; Brunet et al. 2001; Hanada et al. 2004). It has been observed that suppression and activation of PI3K/AKT/mTOR pathway lead to promote and inhibit autophagy, respectively (Heras-Sandoval et al. 2014). Surviladze et al. reported that contamination of HaCaT cells with HPV-16 pseudovirions activates thePI3K/Akt/mTOR signaling pathway leading to autophagy inhibition (Surviladze et al. 2013). KSHV-K1, a viral protein, activates thePI3K/Akt/mTOR signaling pathway in endothelial cells and B lymphocytes (Mack and Munger 2012; Tomlinson and Damania 2004; Wang and Damania 2008). Also, HBV induces autophagy in HepG2 cells transfected with HBx through regulating the PI3K/Akt/mTOR pathway (Wang et al. 2013a). It is believed that autophagy plays an important role in the regulation of cancer progression and development and in determining of tumor responses to anticancer treatments. It has been observed that oncolytic viruses (OVs) interact with autophagy in infected tumors to ensure their own survival and replication advantage (Jiang et al. 2011). While an increasing number of OVs are reported to induce autophagy in infected tumors, some OVs choose to subvert or evade it (Zhang et al. 2006; Moloughney et al. 2011). For instance, Rodriguez-Rocha et al. showed that adenoviruses induce autophagy to promote virus replication and oncolysis in lung cancer A549 and H1299 cells (Rodriguez-Rocha et al. 2011). This concept suggests an insightful indication to OV therapy to improve the quality of life and survival of patients with cancer. Therefore, viruses and viral products can effect on the stimulation or inhibition of autophagy. Searching for using these agents to control stress conditions should be more focused.

HCMV belongs to β-herpesvirus family, which has shown to be transmissible via different body fluids. HCMV is known as one of the biggest viruses since its genome contains of 236 kilobases (Plotkin and Boppana 2019). Albeit it has been demonstrated that primary infection mainly is asymptomatic, the congenital form of the virus can be accompanied by several complications including, but not limited to, disabilities and death. HCMV was shown to have the potential to favor cancer through transformation of infected cells when infecting normal tissues by regulating several signaling pathways (Herbein 2018). The virus modulates autophagy in a dual fashion (Joseph et al. 2017; Nahand et al. 2021). At early phases of infection, it contributes to autophagic vesicle formation. On the contrary, later, it inhibits autophagy via producing some proteins (Chaumorcel et al. 2012). By far, two viral proteins, namely, TRS1 and TRS2, that participate in autophagy prohibition in cooperation with Becline-1 have been explored. It has been demonstrated that simultaneous expression of TRS1 and IRS1 is necessary for prohibition of autophagy in virus infection (Mouna et al. 2016). Recently, viral components with the ability of regulating latency and lytic reactivation, especially those in the uLb' gene region, have been at the center of focus. These viral components are capable of limiting virus replication via moderating immune system response and viral latency through expressing quite a few virus proteins. For instance, a viral protein, namely, UL138, through autophagy machinery, can

modulate adaptive immunity of fibroblast when it presents to MHC-1 (Tey and Khanna 2012; Mlera et al. 2020). However, recent evidence clarified that prohibition of autophagy is associated with extreme CD8 + T-cell response because of the internalization of molecules in MHC-I (Loi et al. 2016). Expressing viral proteins derived from HMCV genes 1 and 2 (IE1 and IE2) is essential for immunomodulation and reactivation of host cell virus (Suares et al. 2021; Reddehase and Lemmermann 2019). IE2 is able to modulate gene expression by interacting with UL84 and itself along with a number of cell transcription factors. IE2 protein has a mandatory role in synthesis of viral DNA and was shown to have the potential to counteract host responses (Li et al. 2020f; Møller et al. 2018). Lately, it has been shown that upregulation of IE2 can contribute to autophagy in cells infected with the virus (Zhang et al. 2021c). Briefly, it has been found out that when a cell is infected with HMC, viral proteins result in autophagosomal vesicle formation. Later, the proteins prohibit vesicle-to-lysosome binding, which leads to loss of their degradative capability.

HTLV-1 is a complex type C virus belongs to *Retroviridae* family and contains an envelope which derived from the cell membrane of host (Martin et al. 2016). The virus first was extracted from patients who were suffering from rapidly growing T-cell lymphoma (ATLL) with cutaneous involvement (Martin et al. 2016). Additionally, it has been shown that HTLV-1 has a major role in other diseases including development of poliomyelitis, arthropathy, HTLV-1-associated myelopathy, facial nerve palsy, and infectious dermatitis (Futsch et al. 2018). It has been reported that approximately 5–20 million individuals carry the virus globally; however, a small proportion (3–5%) of them progress secondary ATLL (Gessain and Cassar 2012; Schierhout et al. 2020). Tax is known as a regulatory protein maintaining a crucial role in HTLV-1 replication and, hence, is needed for the virus propagation. It also plays a crucial role in ATLL development since it cooperates with more than 100 cellular proteins to increase cell signaling, inhibit apoptosis, contribute to cell cycle dysregulation, disrupt DNA repair, and stimulate proto-oncogenes (Mui et al. 2017). It was shown that the virus is able to prohibit the binding between autophagosomes and lysosomes through a mechanism involving tax. As a result, quite a few autophagic vesicles, which are not degraded, appear, and these vesicles are great for virus replication (Tang et al. 2013). Hence, Tax protein combines with the IKK complex to induce NF-kB and Beclin-1 activity. Cell adhesion molecule 1 (CADM1) is a glycoprotein belonging to the type 1 transmembrane cell adhesion family, which is part of immunoglobulin superfamily and is taken into account as a marker of T cells infected with HTLV-1 in (Nakahata et al. 2021; Chen et al. 2015). Tax and NF-kB stimulation and degradation of NF-kB negative regulator, namely, p47, are necessary for CADM1 expression. The main mechanism behind p47 degradation is autophagy, and autophagy can be detected in the majority of HTLV-1 infected ATLL cells (Sarkar et al. 2019). HBZ is another crucial essential viral protein for progression of ATLL (Akram et al. 2017). Recent evidence found out that HBZ can prohibit autophagy as well as apoptosis and, in contrast, stimulate brain-derived neurotrophic factor (BDNF) and its receptor expression (Baratella et al. 2017; Mukai and Ohshima 2014). HBZ can exert different effects based on its location; its expression in cell nucleus and cytoplasm is associated with tumor development and stimulation of inflammation, respectively. Its entry to cytoplasm from nucleus is associated with activation of mTOR via PPP1R15A expression, which is a regulator subunit of protein phosphatase1 (Mukai and Ohshima 2014). Same to other viruses, infection with HTLV-1 is associated with formation of autophagosomes and prohibition of binding to lysosomes so as to inhibit degradation. As a consequence, a great amount of autophagosome vesicles will appear, which provides a suitable environment for the virus formation and, moreover, a physical barrier, which limits the progression of cellular processes (Ren et al. 2015).

Since 2019, the world is witnessing a pandemic caused by a new virus called SARS-CoV-2, causing COVID-19 infection (Khatami et al. 2020). It has been reported that at least

270 million individuals infected with SARS-CoV2 and near 5.3 million people have died because of that (Worldometer 2020). Although its mortality rate is not considerably high, it is highly infectious (Sanche et al. 2020). COVID-19 infection symptoms are broad ranging from fatigue, fever, tiredness, and cough to acute respiratory distress syndrome, MI, stroke, renal injury, and death (Xu et al. 2020b). Albeit some mechanisms have been proposed for sever form of the disease, the exact mechanism behind the diseases pathology is yet not clarified and required more studies (Gorshkov et al. 2020). It has been demonstrated that for the virus replication and transcription, there is a need to DMVs to be formed, indicating the fact that the virus may hijack the autophagosomal machinery to assist DMV formation (Carmona-Gutierrez et al. 2020). Hence, autophagosomes play a crucial role in infection replication by using viral replicase proteins (Cottam et al. 2011). In support of that, also, it was found out that NSP6, a viral replicase protein, colocalized with DMVs positive for LC3, showing a probable correlation between the virus replication and autophagy (Cottam et al. 2011; Bello-Perez et al. 2020). Furthermore, Fulvio et al. designed a study to explore the mechanism that coronaviruses such as mouse hepatitis virus and SARS hijack the formation of EDEMosome, and vesicles participate in the regulation of endoplasmic reticulum degradation, in order to produce the DMVs needed for the virus replication. They declared that mouse hepatitis disrupts two endoplasmic reticulum-associated degradation (ERAD) regulatory proteins, namely, EDEM1 and OS-9, degradation via trapping them into DMVs (Reggiori et al. 2010). This represents that SARS-CoV2 is able to facilitate the virus replication within the infected individual by escaping from autophagy.

Enhanced amount of processed form of LC3B and LC3B-II and an accumulation of SQSTM1, supporting the fact that SARS-CoV2 infection contributed to decreased autophagic flux (Hayn et al. 2021). An experimental study illustrated that although stimulation of autophagy using rapamycin cannot affect the virus considerably, activation of innate immune using interferons keeps the virus sensitive. Therefore, the virus escapes from antiviral mechanism of autophagy. In order to understand the mechanism behind anti-autophagy effects of SARS-CoV2, Hayn et al. (2021) evaluated the effect of 29 of the 30 SARS-CoV-2 proteins on autophagy. They found out that while NSP15 expression is associated with reduced number of autophagosomes positive for LC3B, ORF3a, E, M, and ORF7a expression was associated with accumulation of LC3B. Moreover, the authors showed that E, M, ORF3a, and ORF7a inhibit autophagic flux. It is of importance to note that the reduction of autophagosomes for Nsp15 expression was improved following administration of rapamycin, proposing that possibly Nsp15 impacts mTOR axis. While upon E, ORF3a, and ORF7a expression, the values of processed LC3B-II enhanced, Nsp15 expression led to decrease but not substantial in LC3B-II values. In consistent with this finding, ORF3a, ORF7a, E, and Nsp15 expression is associated with higher values of SQSTM1. Noteworthy, while M expression is associated with higher values of processed LC3B, it was not able to prohibit the degradation of SQSTM1, showing that M cannot inhibit autophagy. Immunofluorescence assay demonstrate that although overexpression of ORF3a, E, and ORF7a is associated with higher numbers of LC3B-positive puncta, M expression is associated with elevated LC3B localization. Also, following Nsp15 expression, decrease in number of autophagosomes was observed. Moreover, the authors proposed that the role of SARS-CoV2 proteins including M, ORF3a, ORF7a, and Nsp15 in autophagy is virtually similar to their function in SARS-CoV-1 and bat coronavirus RaTG13 (Hayn et al. 2021; Koepke et al. 2021). A very recent study showed that ORF3a can intensely prohibit autophagic flux by preventing the fusion of autophagosomes with lysosomes (Zhang et al. 2021d). It was shown that ORF3a colocalized with lysosomes and interacted with VPS39, which is a subunit of the homotypic fusion and protein sorting (HOPS) complex. The interaction between VPS39 and ORF3a contributes to inhibition of -HOPS binding to RAB7, which inhibited the assembly of a fusion

machinery, contributing to increase levels of autophagosomes. These findings shed light on the mechanism behind the virus escape degradation, which is disrupting the fusion of autophagosomes with lysosomes (Zhang et al. 2021d). Taken together, the spread of SARS-CoV-2 virus can be limited with using approaches targeting autophagy.

Several drugs, for instance, azithromycin, chloroquine, and hydroxychloroquine, have been considered since these drugs are capable of modulating autophagy signaling pathways (Gao et al. 2020b). The fact that the mentioned medications are able to inhibit endocytic pathway and, thereby, inhibit SARS-CoV2 replication constitute a rational for considering using these drugs in patients who are infected with the virus (Gao et al. 2020b). In clinical settings, inconsistent findings regarding the benefits of these drugs in COVID-19 patients have been reached. Some studies revealed that hydroxychloroquine administration is associated with lower mortality rate in severe COVID-19 patients (Yu et al. 2020; Meo et al. 2020); however, several studies demonstrated that these medications were not able to decrease mortality from infection with SARS-CoV2 (Molina et al. 2020; Singh et al. 2020). Noteworthy, it has been found that these medications are associated with prolonged QT interval, which can lead to cardiac arrhythmia and sudden cardiac death (Chorin et al. 2020; Jankelson et al. 2020). Thus, more investigations are warranted to evaluate the advantageous and disadvantageous of autophagy modulator drugs to limit the virus infection progression. Table 4 lists the effects of viral infection on the regulation of autophagy during some viral diseases.

5 Autophagy Supporting Viral Replication

RNA viruses hijack autophagy for replication. During the autophagy process, DMVs are formed, which maintain a crucial role in poliovirus replication by creating a promising environment for poliovirus replication and keeping polioviruses RNAs away from innate immune receptors recognition and degradation.

Polioviruses, a member of picornavirus family, lack a membrane envelope. Autophagy was shown to be inducer of poliovirus replication, and its inhibition was shown to associated with reduced virus replication (Jackson et al. 2005; Dales et al. 1965). Besides, infection with poliovirus increases the level of LC3 in puncta and expresses two nonstructural poliovirus proteins 2BC and 3A, contributing to lipidation and formation of LC3 and DMVs, respectively, which makes link between the virus replication and autophagy. Similar to polioviruses, foot-and-mouth disease virus and CVB3 exploit autophagy for replication (Berryman et al. 2012; Robinson et al. 2014).

Hepatitis C virus also can trigger autophagy via increasing levels of autophagosomes and using autophagosomal membranes, which is the site for the virus replication (Shrivastava et al. 2011; Dreux and Chisari 2009; Ait-Goughoulte et al. 2008). Nonetheless, the capacity of HCV in stimulating the fusion of lysosome with autophagosomes is still the matter of debate. Several studies have claimed that the virus stimulates autophagosomes and inhibits the autophagosome and lysosome fusion to enhance viral replication and limit virus degradation (Taguwa et al. 2011; Sir et al. 2008a, b). A study stated that HCV enhances the levels of autophagosomes without any change in the levels of autophagy protein degradation, which is (Sir et al. 2008b). Dreux et al. demonstrated that although the autophagy proteins are key components in the translation process of incoming HCV genome, it is not essential for maintenance of the infection (Dreux et al. 2009). However, Ke et al. revealed that the viral replication is totally dependent on the whole autophagic process through complete autolysosome maturation (Ke and Chen 2011b). At early phase of infection with HCV, the interaction between the HCV RNA-dependent RNA polymerase NS5B and ATG5 was observed, which highlights the importance of ATG5 for infection initiation. Blocking ATG5 expression was shown to be associated with the virus replication and maintenance (Guévin et al. 2010).

Table 4 Autophagy and viruses

Virus	Inhibition/ induction	Viral product	Target	Sample	Note	Ref
B19	Induction	–	–	In vitro	B19-infected cells survive by cellular autophagy	Nakashima et al. (2006)
Adenoviruses	Induction	–	–	In vitro	Ad E1a and E1b activate LC3 conversion and Atg12-Atg5 complex formation	Rodriguez-Rocha et al. (2011)
PRRSV	Induction	–	–	In vitro	Autophagy is triggered in pulmonary alveolar macrophages by PRRSV infection	Liu et al. (2012)
HP-PRRSV	Induction	–	–	Bystander cells	Induced apoptosis and autophagy in thymi of infected piglets	Wang et al. (2015b)
Mouse norovirus (MNV)	Induction	–	–	In vitro	MNV infection triggers autophagy in host cells and appears to block the downstream degradation of autophagosomes.	O'Donnell et al. (2016)
Rotavirus	Dysregulation	RV-vsRNA1755	IGF-1R	In vitro	RV-vsRNA1755 targets IGF-1R, blockading the PI3K/Akt pathway and triggering autophagy, but it ultimately inhibits autophagy maturation	Zhou et al. (2018)
Influenza A	Inhibition	Matrix protein 2 (M2)		In vitro	M2 protein blocks autophagosome degradation	Gannagé et al. (2009)
Influenza A	Inhibition	M2	LC3		IAV utilizes a mimicry of host protein short linear motifs (SLiMs) to hijack autophagy	Beale et al. (2014)
HSV-1	Inhibition	ICP34.5	Beclin-1	In vitro	Inhibition of Beclin-1-dependent autophagy	Orvedahl et al. (2007)
Human parainfluenza virus type 3 (HPIV3)	Induction	Matrix protein (M)		In vitro	Viral M protein is sufficient to induce mitophagy by bridging autophagosomes and mitochondria	Ding et al. (2017a)
Zika virus	Induction	NS4A and NS4B		In vitro	Akt-mTOR signaling to inhibit neurogenesis and induce autophagy	Liang et al. (2016)
Coronavirus	Induction	PLP2-TM	Beclin-1	In vitro	PLP2-TM activates autophagosome formation but prevents its fusion with lysosomes	Chen et al. (2014b)

(continued)

Table 4 (continued)

Virus	Inhibition/ induction	Viral product	Target	Sample	Note	Ref
HIV	Inhibition			CD4+ T cells, U937 cells	The autophagy protein Beclin-1, LC3 II and autophagosomes were found to be markedly decreased	Zhou and Spector (2008)
HIV	Inhibition	Nef	Beclin-1	In vitro	Nef acts as an anti-autophagic maturation factor through interactions with the autophagy regulatory factor Beclin-1	Kyei et al. (2009a)
HIV	Inhibition	Nef	Beclin-1	MOLT-4 cells	During permissive infection, Nef binds BECN1 resulting in mammalian target of rapamycin (MTOR) activation, TFEB phosphorylation and cytosolic sequestration, and the inhibition of autophagy	Campbell et al. (2015a)
Dengue virus	Induction	–	–	Mice	Dengue virus induces amphisome and autophagosome formation as well as the autophagic flux in the brain of infected mice	Lee et al. (2013)
Subgroup J avian leukosis virus (ALV-J)	Inhibition	–	–	In vitro		Liu et al. (2013)
Encephalomyocarditis virus	Induction	2C 3D	–	In vitro	2C and 3D were shown to be involved in inducing autophagy by activating the ER stress pathway	Hou et al. (2014c)
HBV	Induction	HBx	Phosphatidylinositol 3-kinase class III	In vitro Mice	Interestingly, in contrast to starvation-induced autophagy, this enhancement of autophagy by HBV does not lead to an increased autophagic protein degradation rate	Sir and Tian (2010)
HBV	Induction	HBx		HepG2.2.15 cells	Novel function of HBx in increasing autophagy through the upregulation of Beclin-1 expression	Tang et al. (2009a)
HBV	Induction	HBx		HepG2 cells	HBx activates the autophagic lysosome pathway in HepG2 cells through the PI3K-Akt-mTOR pathway	Ju et al. (2013)
HBV	Induction	HBx		Chang cell	HBX induces autophagy via activating DAPK in a pathway related to Beclin-1, but not JNK	Zhang et al. (2014)

HBV		HBx		Huh7 cells	HBx-induced autophagosome formation is MTOR inhibition-independentRepressive effect of HBx on lysosomal function is responsible for the inhibition of autophagic degradation, and this may be critical to the development of HBV-associated HCC	Liu et al. (2014)
HBV	Induction	HBV small surface protein		Huh7 cells	SHBs partially co-localized and interacted with autophagy protein LC3	Li et al. (2011a)
HBV	Induction	HBx	–	Huh7 cells	HBV can be promoting autophagy by the interaction of HBx and c-myc to affect miR-192-3p-XIAP, which in turn regulates Beclin-1	Wang et al. (2019e)
Bluetongue virus (BTV)	Induction	–	–	In vitro	The BTV1-induced inhibition of the Akt-TSC2-mTOR pathway and the upregulation of the AMPK-TSC2-mTOR pathway both contributed to autophagy initiation	Utama et al. (2011)
BTV1	Induction	–	–	BSR cells	BTV1-induced inhibition of the Akt-TSC2-mTOR pathway and the upregulation of the AMPK-TSC2-mTOR pathway both contributed to autophagy initiation	To et al. (2020)
HIV	Induction	Env	CXCR4	In vitro	Autophagy is specifically triggered after Env binding to CXCR4, leading to apoptosis	Espert et al. (2006), Espert et al. (2007)
HIV	Inhibition	Vif	Human autophagy-related protein 8 family proteins	In vitro	The C-terminal part of viral infectivity factor interacts with microtubule-associated protein light chain 3	Borel et al. (2015)
HIV	Induction	Tat	BAG3	Human glial cells	Tat protein is able to stimulate autophagy through increasing BAG3 levels in human glial cells	Bruno et al. (2014)
HIV	Inhibition	Tat		Human primary blood macrophages	HIV-1 Tat protein suppressed IFN-g-induced autophagy processes, including LC3B expression HIV-1 Tat suppressed the induction of autophagy-associated genes and inhibited the formation of autophagosomes	Li et al. (2011b)

(continued)

Table 4 (continued)

Virus	Inhibition/ induction	Viral product	Target	Sample	Note	Ref
HCV	Induction		UPR	In vitro	HCV induces the unfolded protein response (UPR), which in turn activates the autophagic pathway	Ke and Chen (2011a)
HCV	Induction	–	–	Huh7	HC V inhibited the AKT-TSC -MTORC1 pathway via ER stress, and the inhibition of the AKT-TSC -MTORC1 pathway contributed to upregulating autophagy	Huang et al. (2013)
HCV	Inhibition	–	–	Monocyte	HCV-positive sera block autophagy during monocyte differentiation LC3 II level increased in monocytes cultured in the presence of HCV-positive sera	Granato et al. (2014)
HCV	–	NS5B	ATG5	Huh7 and C5B cells	HCV utilizes ATG5 as a proviral factor during the onset of viral infection	Guévin et al. (2010)
HBV	Inhibition	HBeHBc		Human ($n = 40$) In vitro	HBe and HBc proteins of HBV activate the mTOR signaling pathway to inhibit autophagy in neutrophils	Hu et al. (2018)
HBV	Induction	HBx				
West Nile virus (WNV)	Induction			In vitro	West Nile Virus-induced LC3 lipidation	Beatman et al. (2012)
Foot-and-mouth disease virus	Inhibition	$3C^{pro}$	ATG5-ATG12	PK-15 cells	FMDV suppresses NF-κB, IRF3, and autophagy by degradation of ATG5-ATG12 via 3Cpro	Fan et al. (2017)
High-risk HPV	Inhibition	–	–	Tissue sample (uterine cervical cancer, $n = 270$)	Persistent HPV infection may stabilize ATAD3A expression to inhibit cell autophagy and apoptosis as well as to increase drug resistance	Chen et al. (2011)
Influenza A virus	Induction	–	–	Cell lines (A549 cells, MDCK, 293T, WT MEFs, and autophagy-deficient MEFs)	IAV infection increased levels of the autophagosomal marker "microtubule-associated protein light chain 3-II" (LC3-II), at early stage of infection	Khalil (2012)
Human bocavirus (HBoV)	Induction	–	–	Human bronchial epithelial cells	Microtubule-associated protein 1A/1B light chain 3 (LC3) II and autophagy protein 5 were increased in HBoV-transfected HBECs, whereas, the mRNA	Deng et al. (2017)

					and protein levels of LC3-I and sequestosome 1 were decreased	
Porcine hemagglutinating encephalomyelitis virus (PHEV)	Induction	–	–	Neuro-2a cells	PHEV infection induces atypical autophagy and causes the appearance of autophagosomes but blocks the fusion with lysosomes	Ding et al. (2017b)
Bovine viral diarrhea virus (BVDV)	Induction	–	–	MDBK cell	BVDV NADL infection triggers autophagosome formation and increases autophagic activities Beclin-1 and ATG14 expression levels were increased as a result of BVDV NADL infection	Fu et al. (2014a)
BVDV	Induction	E^{rns} and E2		MDBK cell	BVDV-NADL infection induced autophagy and significantly elevated the expression levels of autophagy-related genes, Beclin-1 and ATG14, at 12 h postinfection in MDBK cells	Fu et al. (2014b)
Enterovirus 71 (EV71)	Induction	–	Beclin-1	Hep2, vero	EV71 infection resulted in the reduction of cellular miR-30a, which led to the inhibition of Beclin-1, a key autophagy-promoting gene that plays important roles at the early phase of autophagosome formation	Fu et al. (2015)
EV-71	Induction	–	–	Human rhabdomyosarcoma, neuroblastoma cells and in vivo	The specific viral proteins encoded contributed to the inhibition of the mTOR/p70S6K pathway and the induction of autophagy	Huang et al. (2009)
EBV	Induction	–	–	EBV-associated nasal NKTCL ($n = 35$)	Enhanced autophagy and reduced expression of lysosomal enzymes induced regional ACD under EBV infection in natural killer/T-cell lymphomas	Hasui et al. (2011)
Avibirnavirus	Induction	VP2	HSP90AA1	DF-1 cells, 293T cells	HSP90AA1 binding to the viral protein VP2 resulted in induction of autophagy and AKT-mTOR pathway inactivation	Hu et al. (2015)

(continued)

Table 4 (continued)

Virus	Inhibition/ induction	Viral product	Target	Sample	Note	Ref
HCV	Induction	Core protein		QSG-7701	HCV core protein can enhance hepatocytes autophagy through upregulating Beclin-1	Liu et al. (2015b)
HCV	Induction	Core protein		Huh7 hepatoma cell line	Core protein activates autophagy through EIF2AK3 and ATF6 UPR pathway-mediated MAP1LC3B and ATG12 expression	Wang et al. (2014a)
HCV	Induction	–	Class III PI3K-independent pathway	Huh7 hepatoma cell line	–	Sir et al. (2012)
HCV	Induction	NS4B		Huh7.5 cells	Rab5 and Vps34 are involved in NS4B-induced autophagy	Su et al. (2011)
HCV	Induction	–	–	Huh7.5 cells	HCV induces autophagy by upregulating Beclin-1 and activates mTOR signaling pathway	Shrivastava et al. (2012)
HPV16 and 18	Inhibition	–	–	104 cases of cervical cancer tissues	The expression levels of Beclin-1 and LC3B were significantly lower in cervical cancer cells	Wang et al. (2014b)
Flavivirus	Induction	NS4A		Epithelial cells	Expression of *Flavivirus* NS4A is sufficient to induce PI3K-dependent autophagy and to protect cells against death	McLean et al. (2011)
Simian virus 40	Induction	Small T antigen	–	–	The novel role for the SV40 ST antigen in cancers, where it functions to maintain energy homeostasis during glucose deprivation by activating AMPK, inhibiting mTOR, and inducing autophagy as an alternate energy source	Kumar and Rangarajan (2009)
Varicella-zoster virus	Induction	–	–	Human skin vesicle MRC-5 cells	–	Takahashi et al. (2009)
HHV-8	Induction	RTA	–	RTA-inducible BCBL-1cells (TRExBCBL1-RTA)	Autophagy is involved in the lytic reactivation of HHV-8	Wen et al. (2010)
EBV	Induction	LMP1		B cells		Lee and Sugden (2008)
HCMV	Inhibition	TRS1	Beclin-1	MRC5 cells	The Beclin-1-binding domain of TRS1 is essential to inhibit autophagy	Chaumorcel et al. (2012)

HCMV	Induction	–	–	THP-1 cells	HCMV could induce autophagy, and the capacity of promoting autophagy may be weakened in the latent infection	Liu et al. (2017e)
Porcine circovirus type 2 (PCV2)	Induction	–	–	PK-15 cells	PCV2 might induce autophagy via the AMPK/ERK/TSC2/mTOR signaling pathway in the host cells	Zhu et al. (2012)
HSV-1	Inhibition	Us11	PKR	HeLa cells and fibroblasts		Lussignol et al. (2013)
HPV-16	Inhibition	–	–	HaCaT and 293T cells	The HPV-host cell interaction stimulates the PI3K/Akt/mTOR pathway and inhibits autophagy	Surviladze et al. (2013)
HIV-1	Induction	ASP	LC3	U937 andCOS-7 cells		Torresilla et al. (2013)
Influenza A virus	Induction	NS1	–	CV-1 cells	NS1 stimulates autophagy indirectly by upregulating the synthesis of HA and M2	Zhirnov and Klenk (2013a)
EBV	Induction	Rta	–	293T cells	Autophagic activation is caused by the activation of extracellular signal-regulated kinase (ERK) signaling by Rta	Hung et al. (2014)
HTLV-1	Induction	Tax	–	U251 cells	Tax-triggered autophagy depends on the activation of IKKTax can be degraded via manipulation of autophagy and TRAIL-induced apoptosis	Wang et al. (2014)
HTLV-1	Induction	Tax	–	–	Tax induces Bcl-3 expression Bcl-3 acts as a negative regulator of NF-κB activation and promotes autophagy in HTLV-1-infected cells	Wang et al. (2013c)
HTLV-1	Induction	Tax	–	Human astroglioma cells	HTLV-1 Tax protein induces autophagy via IKK in human astroglioma cells: a protective mechanism against death receptor-mediated apoptosis	Zheng et al. (2014)
EBV	Induction	LMP2A	–	MCF10A cells	MP2A may inhibit anoikis and luminal clearance in acini through induction of autophagy	Fotheringham and Raab-Traub (2015)
DENV	Induction	NS1	–	HMEC-1 cells	–	Chen et al. (2016)
HIV-1	Inhibition	–	–	Monocytic cells		Van Grol et al. (2010)

(continued)

Table 4 (continued)

Virus	Inhibition/ induction	Viral product	Target	Sample	Note	Ref
					HIV-1 impairs autophagy in bystander macrophages/monocytic cells through Src-Akt signaling	
Japanese encephalitis virus	Induction	–	–	N2a cells	–	Jin et al. (2013)
Japanese encephalitis virus	Induction	C, M and NS3		BHK-21, PK-15 and N2A cells	–	Wang et al. (2015a)
Coxsackievirus A16	Induction	2C and 3C		HeLa cells	CA16 infection inhibited Akt/mTOR signaling and activated extracellular signal-regulated kinase (ERK) signaling, both of which are necessary for autophagy induction	Shi et al. (2015)
Coxsackievirus B3	Induction	–	–	HeLa cells	CVB3 might directly or indirectly induce autophagy via AMPK/MEK/ERK and Ras/Raf/MEK/ERK signaling pathways in the host cells	Xin et al. (2015)
Coxsackievirus B3	Induction	2B		HeLa cells	56 V in the loop region of 2B is critical for the induction of autophagy	Wu et al. 2016c)
γHV68	Inhibition	vBcl2	Beclin-1	NIH3T3 cells	Viral Bcl-2s displays enhanced anti-autophagic activity than cellular Bcl-2	Liang et al. (2008), Liang et al. (2006)
γHV68	Inhibition	M11	Beclin-1	COS7 cells	M11-Beclin-1 BH3 domain binding is required for autophagy inhibition by M11	Sinha et al. (2008)
Bluetongue virus	Induction			BSR cells	BTV- induced disruption of cellular energy metabolism contributes to autophagy	(Lv et al. (2016)
Influenza A virus H5N1	Induction		mTOR signaling	MEF cells	H5N1 causes autophagic cell death through suppression of mTOR signaling	Ma et al. (2011a)
Influenza A virus H5N1	Induction			Mouse lungs and human A549 cells	Autophagy induced by live H5N1 virus in human A549 cells depends on signaling through the Akt-TSC2-mTOR pathway The hemagglutinin protein of H5N1 virus may induce autophagy in A549 cells	Sun et al. (2012)

Newcastle disease virus	Induction			U251 cells		Meng et al. (2012a), Kang et al. (2017)
Newcastle disease virus	Induction	NP and P proteins		A549 cells	NDV NP and P proteins induced autophagy through activation of the ER stress-related UPR pathway	Cheng et al. (2016)
Avian reovirus	Induction	–	–	Chicken fibroblast cells and vero cells	The class I PI3K/Akt/mTOR pathway contributes to ARV-triggered autophagy	Meng et al. (2012b)
RABV GD-SH-01	Induction	–	–	Human and mouse neuroblastoma cell lines	Autophagy is induced by GD-SH-01 and can decrease apoptosis in vitro. Furthermore, the M gene of GD-SH-01 may cooperatively induce autophagy	Peng et al. (2016)
HSV-1 HSV-2	Induction	–	–	SIRC cell line		Petrovski et al. (2014)
Enterovirus 71 (EV71)	Induction	–	–	Suckling mouse model	EV71 infection can induce autophagosome, amphisome and autolysosome formation, and the structural protein VP1 and nonstructural protein 2C of EV71 were distributed around the autophagosome and amphisome	Lee et al. (2014)
Pseudorabies virus	Inhibition	–	–	PK-15 cells	Alphaherpesvirus US3 tegument protein may reduce the level of autophagy via activation of the AKT/mTOR pathways in PRV infected cells	Sun et al. (2017c)
Zika virus (ZIKV)	Induction	–	–	Human umbilical vein endothelial cells (HUVEC)	–	Peng et al. (2018)
HIV-1 HIV-2	Induction	–	–	Jurkat and CD4+ T cells	HIV is able to induce the autophagic signaling pathway in HIV-infected host cells, which may be required for HIV infection-mediated apoptotic cell death	Wang et al. (2012)
Sendai virus (HVJ-E)	Induction	–	–	NSCLC cells	HVJ-E could induce autophagy in NSCLC cells via the PI3K/Akt/mTOR/p70S6K signaling pathway	Zhang et al. (2015b)
Rotavirus (RV)	Induction	–	–	HT29 cells, MA104 cells	RV infection can be activating autophagy machinery during RV infection through upregulation and downregulation of miR-99b and let-7g expression levels, respectively	Mukhopadhyay et al. (2019)

HCV dynamically modulates autophagy by expressing ultraviolet radiation resistance-associated gene protein (UVRAG) and Rubicon to increase its replication (Wang et al. 2015c). At the early stages of viral infection, upregulation and downregulation of Rubicon and UVRAG, respectively, by the virus inhibit the autophagosomes maturation and thereby increase the levels of autophagosomes, leading to virus replication (Wang et al. 2015c). Additionally, immunity-related GTPase family M protein (IRGM), an IFN-inducer GTPase, was shown to be able to modulate autophagy process by interacting with several autophagic proteins (Grégoire et al. 2011b). Hansen et al. showed that IRGM by promoting autophagy and Golgi fragmentation induces the virus replication. IRGM stimulates Golgi fragmentation via modulation of Golgi apparatus-specific brefeldin A-resistant guanine nucleotide exchange factor 1 (GBF1) and AMPKα (Hansen et al. 2017). In summary, HCV is able to regulate autophagy process to induce the virus replication.

According to findings of related studies, it can be concluded that flaviviruses take benefits from the close connection between ER and autophagy processes. At first, it was believed that stimulation of autophagy in those infected with flaviviruses is only related to the ER stress-related UPR signaling pathway. On the other hand, it was shown that several nonstructural proteins of West Nile virus (WNV) and DENV are able to stimulate autophagy irrespective of the UPR (Blázquez et al. 2014; Miller et al. 2007). Analyses of neural progenitor cells infected with Zika virus (ZIKV) disclosed that the infection causes a huge remodeling of ER and, moreover, vesicular packet formation, which are assumed to be the spots of ZIKV replication (Offerdahl et al. 2017; Cortese et al. 2017). Infection of skin fibroblast is associated with autophagosomes formation, leading to higher levels of ZIKV replication (Hamel et al. 2015). Furthermore, enhancement in lapidated form of LC3 along with decrement in ATG16L1 expression, a vital autophagy gene, in placentae infected with ZIVK, indicates the fact that autophagy plays a crucial role in vertical transmission of ZIKV (Cao et al. 2017). Liang et al. clarified the mechanism responsible for fetal neurological defects causing by ZIKV. They found out that two proteins exist in ZIKV, namely, NS4A and NS4B, in cooperation with each other inhibit the Akt-mTOR signaling pathway, which contributes to autophagy activation and defective neurogenesis (Liang et al. 2016). Upon early phase of ZIKV and DENV infection, inhibition of FAM134B, which acts as an autophagy receptor, enhances the virus replication. The viruses use their NS3 protease to cleave FAM134B, leading to limit ER and autophagosomes formation (Khaminets et al. 2015; Lennemann and Coyne 2017).

It was shown that two HIV proteins Gag and Nef modulate the autophagy process through interacting with LC3 and Beclin-1, which, finally, causes higher viral replication. During early phase of autophagy, Gag protein interacts with C3, which leads to higher levels of Gag processing and HIV levels in macrophages (Kyei et al. 2009b). Also, during the maturation stage of autophagy, Nef protein of HIV inhibits autophagy maturation via binding to Beclin-1 and, thereby, keeps the virus safe from degradation. Thus, the interaction between the virus and autophagy increases HIV load and replication through inducing early-stage autophagy but prohibits late stages (Kyei et al. 2009b). Nevertheless, it has been detected that during permissive infection, the virus inhibits autophagy so as to prevent the degradation of proteolytic. In the normal situation, mTOR by phosphorylating transcription factor EB (TFEB) limits TFEB translocation. TFEB is able to induce autophagy and lysosomal activation when it transfers to the nucleus. In doing so, TFEB should become dephosphorylated, which is dependent upon mTOR inhibition. For stimulating autophagy within macrophages infected with HIV, the interaction between TLR8 and HIV should be occurred, which is dependent on the dephosphorylation and nuclear translocation of TFEB. The authors also observed that during permissive infection, the interplay between Nef and Beclin-1 contributed to phosphorylation of TFEB, mTOR activation, cytosolic sequestration, and, thereby, autophagy inhibition (Campbell et al. 2015b).

A number of experimental studies have declared that autophagy inhibition causes

prohibition of HBV replication, which represents the fundamental role of autophagy in HBV life cycle (Table 3). The studies have utilized cells that were infected with HBV, or transfected with HBV, or exhibiting HBV DNA replication. It was found out by Sir and his colleagues that triggering autophagy by HBV is dependent on the presence of HBx, which increases its activity through binding to PI3KC3. Therefore, autophagy along with PI3KC3 modulates the majority of HBx impacts on HBV replication (Sir et al. 2010a, b). Either inhibition of PI3KC3 or Atg7 contributes to decrease in HBV replication (Sir et al. 2010b). A study found out that autophagy inhibition decreases pgRNA packaging and HBV RNA values to some extent while inhibited HBV DNA replication remarkably (Tang et al. 2009b). Therefore, it can be concluded that this phenomenon indicates that autophagy exerts its effects on HBV replication mainly at the viral DNA replication stage of the viral life (Sir et al. 2010b). Another study similarly found positive effects of autophagy on HBV replication; however, the effects were mostly seen at the stage of envelopment (Rautou et al. 2010). Li et al. designed a study to evaluate the association between autophagy and HBV by suppressing autophagy using 3-methyladenine and siRNA duplexes that suppress fundamental genes need for autophagosome formation. The investigators explored that autophagy inhibition is able to suppress the virus replication notably and stimulating autophagy using starvation and/or rapamycin increases the virus replication (Li et al. 2011c). These inconsistent findings can be explained by using different HBV strains or sublines of Huh7 cells in the relevant studies. Also, a study unveiled ROS HBV capsid assembly in the existence of Hsp90; however, it was observed that ROS without Hsp90 decreases the virus assembly (Kim et al. 2015). Another pathway responsible for HBV-induced autophagy is ROS/JNK signaling pathway. In doing so, ROS/JNK signaling pathway modulates the interaction between Beclin-1 and Bcl-2, which is crucial for activation of autophagy (Zhong et al. 2017). Additionally, it has been shown that HBV has the potential to favor its replication by subverting autophagy Atg5-12/16L1 complex, without any need for Atg8/LC3 lipidation, which is a vital process for autophagosomes maturation (Döring et al. 2018). At the same time, several studies have claimed that autophagy triggered by HBV inhibits the virus replication. Wu et al. demonstrated that autophagy following infection with HBV is able to degrade envelope proteins (Wu et al. 2016d). For the first time, Lazar et al. demonstrated that HBV decreases the level of envelope protein through that the ERAD signaling pathway. Simultaneous expression of the virus envelope proteins and EDEM1 caused huge envelope protein degradation, which was blocked through EDEM1 inhibition (Lazar et al. 2012). Furthermore, a study revealed that AMPK activation is able to limit the virus production by inducing autophagy, suggesting the therapeutic value of targeting AMPK for HBV management (Xie et al. 2016). Collectively, it can be said that the precise relationship between the virus replication and autophagy merits extra studies.

Also, infection with influenza A virus (IAV) is able to induce enhanced levels of autophagosomes that needed for viral replication (Zhou et al. 2009). A study showed that the virus increases the levels of autophagosomes by inhibition of their fusion with lysosomes, and the presence of matrix 2 (M2) ion-channel protein for prohibition of autophagosomes degradation is pivotal (Gannagé et al. 2009). Another research displayed that M2 escapes from autophagy using its LC3-interacting region (Beale et al. 2014). M2 interacts with LC3 and induces LC3 re-localization to the plasma membrane, and disruption of this interaction downregulates virion budding and stability. The NS1 is another IVA protein that induces autophagy via overexpression of M2 and hemagglutinin (HA) (Zhirnov and Klenk 2013b). Recently, the interplay between M2 protein and MAVS signaling pathway was demonstrated, which leads to MAVS aggregation and, thereby, stimulates MAVS-mediated antiviral innate immunity. Furthermore, it was shown that M2 triggers ROS generation, which is a crucial factor for autophagy activation (Wang et al. 2019f). Additionally, H5N1, a major avian pathogen, has the potential

to induce autophagy via prohibiting mTOR (Ma et al. 2011b).

As we mentioned before, Beclin-1 is a fundamental modifier of autophagy process that forms two distinct complexes, one with Atg14 that is needed for autophagosome formation and the other with UVRAG, which is essential for autophagosome maturation (Levine et al. 2015). In a study that was conducted by Qu and his associates, it was demonstrated that infection with SARS-CoV-2 is associated with incomplete autophagy response, which was shown to be needed for effective virus replication. Moreover, the investigators disclosed that although infection with SARS-CoV-2 stimulates autophagosomes formation, the infection contributes to prohibition of autophagosome maturation and block autophagy by inhibiting fundamental genes involved in the virus replication (Qu et al. 2021). They analyzed expression of 26 proteins expressing by the virus and found out that ORF3a expression is associated with incomplete autophagy. The ORF3a interplays with UVRAG to promote and prohibit expression of PI3KC3-C1 (Beclin-1-Vps34-Atg14) and PI3KC3-C2 (Beclin-1-Vps34-UVRAG), respectively. In summary, the authors shed light on how ORF3a inhibits autophagy and, thereby, prompts SARS-CoV-2 replication, which provides a therapeutic potential of targeting autophagy for COVID-19 treatment (Qu et al. 2021).

6 Conclusion

Autophagy is known as conserved intracellular process which transfers cytoplasmic materials to lysosomes for degradation though autophagosomes. This process emerges to be relevant to the pathogenesis of various diseases, and its regulation could have therapeutic value. It has been indicated that a sequence of cellular and molecular signaling pathways by several internal and external factors is involved in initiation and progression of autophagy. Viruses are one of main factors which exert their pathogenesis effects via affecting on autophagy processes. Besides viruses, a wide range of internal factors including genetic and epigenetic factors could influence on underlying pathways involved in autophagy processes. Very recently, microRNAs and exosomes have been emerged as critical players in the autophagy processes, given that exosomes and microRNAs are able to change behavior of host cells via targeting of a large number of cellular and molecular signaling pathways. Hence, more insights into the various signaling pathways that are targeted by exosomes and microRNAs could pave the way to the finding and designing new therapeutic approaches.

Conflicts of Interest The authors have declared that no competing interest exists.

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