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Review:

Emerging relationship between RNA helicases and autophagy*

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Abstract: RNA helicases, the largest family of proteins that participate in RNA metabolism, stabilize the intracellular environment through various processes, such as translation and pre-RNA splicing. These proteins are also involved in some diseases, such as cancers and viral diseases. Autophagy, a self-digestive and cytoprotective trafficking process in which superfluous organelles and cellular garbage are degraded to stabilize the internal environment or maintain basic cellular survival, is associated with human diseases. Interestingly, similar to autophagy, RNA helicases play important roles in maintaining cellular homeostasis and are related to many types of diseases. According to recent studies, RNA helicases are closely related to autophagy, participate in regulating autophagy, or serve as a bridge between autophagy and other cellular activities that widely regulate some pathophysiological processes or the development and progression of diseases. Here, we summarize the most recent studies to understand how RNA helicases function as regulatory proteins and determine their association with autophagy in various diseases.

Key words: RNA helicase; Autophagy; Homeostasis; Regulation
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1 Introduction

Autophagy is a highly evolutionarily conserved physiological process that represents a cellular degradation pathway. Currently, autophagy is divided into three types: chaperone-mediated autophagy, microautophagy, and macroautophagy. Macroautophagy (hereafter referred to as autophagy) has been widely studied and much is currently known about this process. Autophagy is mainly supported by transient double-membrane vesicles called autophagosomes. The outer membrane of the autophagosome differs in different species, and it fuses with the lysosome in mammals and consists of a vacuole in yeast and plants, where acidic hydrolases degrade the autophagic cargo and these macromolecules are recycled (Yang and Klionsky, 2010; Wen and Klionsky, 2016). As a cytoprotective pathway, autophagy not only degrades superfluous components of cells but also recycles energy or nutrients (Yang and Klionsky, 2010). Autophagy occurs constitutively under basal conditions, but it is further induced by various stresses (Frankel et al., 2017). The process consists of four steps: the formation of phagocytic vacuoles, formation of autophagosomes, fusion of autophagosomes and lysosomes to form autolysosomes, and degradation of autolysosomes. Defective or excessive autophagy is associated with many types of diseases, such as viral infection (Huang et al., 2014), cancers (Lan et al., 2014; Sutton et al., 2018), and some chronic diseases (Kaniuk

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et al., 2007; Yang et al., 2010; Su et al., 2017). In addition, mitophagy is a selective type of autophagy that targets mitochondria, and it is involved in innate response (Wang and Klionsky, 2011), inflammation (Zhou et al., 2011), and neuronal diseases (Teodorof-Diedrich and Spector, 2018; Corti, 2019; Wang et al., 2019).

RNA helicases play vital roles in maintaining cellular homeostasis, where they are involved in disposing nucleic acids and their related complex proteins (Hardwick and Luisi, 2013). On the one hand, RNA helicases that regulate endogenous RNAs are divided into six superfamilies (SF1 to SF6) based on their conserved sequences and structures (Gorbalenya and Koonin, 1993; Singleton et al., 2007). The majority of RNA helicases belong to the SF2 superfamily, which is composed of DEAD (Asp–Glu–Ala–Asp)-box RNA helicases and the related DEAH (Asp–Glu–Ala–His), DE*x*H and DE*x*D RNA helicases (Hardwick and Luisi, 2013). All members of the DEAD family possess a conserved amino acid motif (Asp–Glu–Ala–Asp) and have NTPase activity. DEAD-box and DEAH-box proteins are the largest family of RNA helicases in humans (Jankowsky, 2011; Linder and Jankowsky, 2011; Putnam and Jankowsky, 2013; Jarmoskaite and Russell, 2014; Leitão et al., 2015; Ozgur et al., 2015). These proteins contain nine highly conserved motifs (designated Q, I, Ia, Ib, II, III, IV, V, and VI) (Rocak and Linder, 2004; Tuteja and Tuteja, 2004; Linder, 2006) and two characteristic tandem RecA domains that are mainly involved in adenosine 5'-triphosphate (ATP) binding and hydrolysis, and their structures are conserved among these enzymes (Jankowsky, 2011; Linder and Jankowsky, 2011; Putnam and Jankowsky, 2013; Jarmoskaite and Russell, 2014; Leitão et al., 2015; Ozgur et al., 2015). On the other hand, exogenous RNAs are regulated by retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), which belong to the RNA helicase family. Three types of RNA helicases have been reported to recognize exogenous RNAs: DEAD-box helicase 58 (DDX58)/RIG-I, interferon (IFN) induced with helicase C domain 1 (IFIH1)/melanoma differentiation-associated 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2). These three RNA helicases are implicated in viral double-stranded RNA (dsRNA) recognition and the modulation of the immune response. Specifically, RIG-I and MDA5 both contain N-terminal caspase activation and recruitment domains (CARDs) and control downstream signal transduction (Rodriguez et al., 2014; Chan and Gack, 2015). However, LGP2 lacks a CARD and mainly plays an auxiliary or suppressive role in RNA virus responses. Therefore, RNA helicases play vital roles in RNA metabolism. In addition to participating in regulating the level of gene transcription, RNA helicases are also implicated in human diseases, such as various types of tumors (Ito et al., 2017; Jing et al., 2018; Xu et al., 2018; Zhang et al., 2019) and viral diseases (Santiago et al., 2014; Wang et al., 2015; Pattabhi et al., 2019).

Disorders of autophagy and RNA helicases disrupt the balance of cellular homeostasis. However, the mechanisms of autophagy and RNA helicases are elusive. The interplay between autophagy and RNA helicases in many physiological or pathological processes has been reported in recent studies (Yang et al., 2013; Chan and Gack, 2015; Hu et al., 2015; Zhang ZX et al., 2016; Kim et al., 2017; Jin and Cui, 2018; Zhou et al., 2018; Zhang H et al., 2019). In this review, we focus on the molecular mechanisms linking RNA helicases and autophagy and also discuss the interplay between RNA helicases and autophagy in tumorigenesis and antiviral responses in humans.

2 Regulation of autophagy by RNA helicases in different stages

DEAD-box RNA helicases have been shown to play a mechanical role in RNA metabolism, such as RNA splicing and RNA decay. However, recent studies have focused on how RNA helicases regulate autophagy at different stages. Autophagy contributes to the removal of cellular waste and saves energy to ensure survival when cells are under stress. In fact, this effect is similar to the function of RNA helicases in regulating RNA metabolism. Both RNA helicases and autophagy supervise and execute cellular regulation. In this section, we discuss evidence that RNA helicases closely regulate autophagy (Fig. 1).

2.1 DEAD-box helicases regulate autophagy by modulating the transcription of autophagy-related genes

DDX6 is a member of the DEAD-box helicase family, and its homologues in *Saccharomyces cerevisiae*

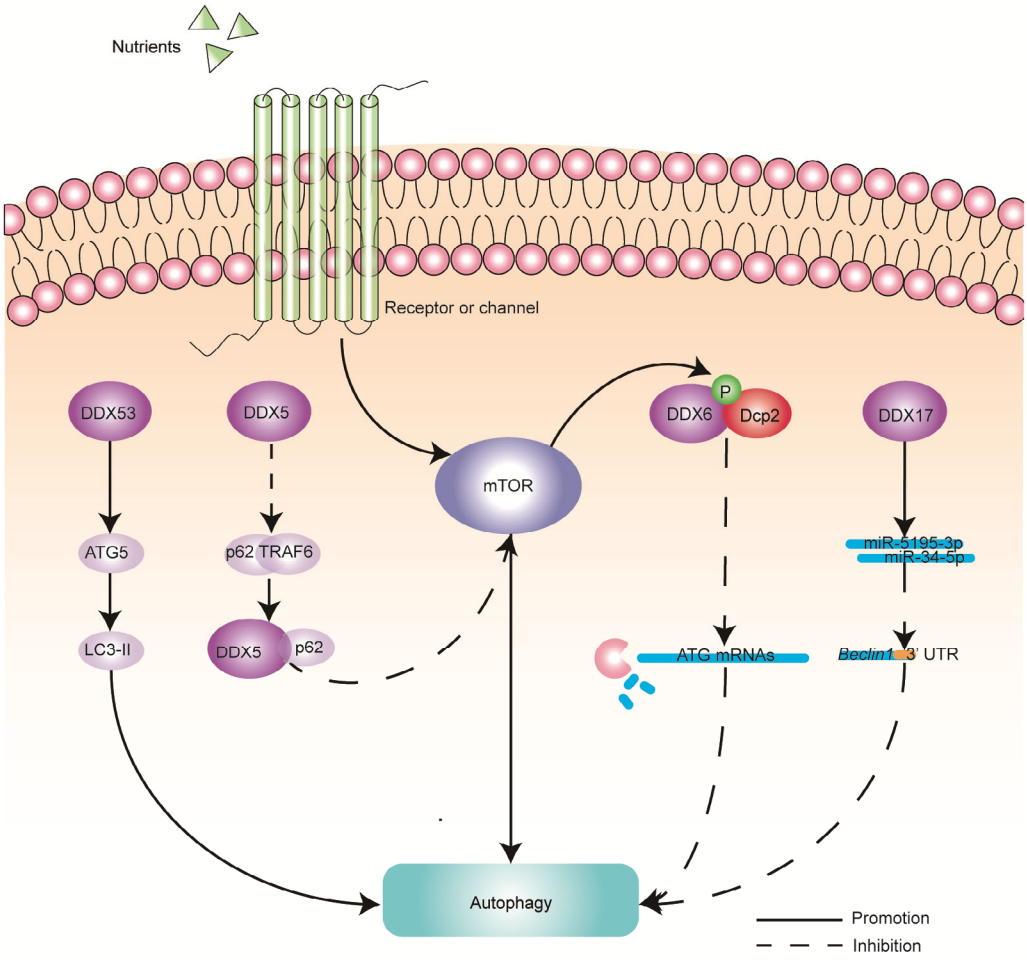

Fig. 1 Regulation of autophagy by RNA helicases at different stages

DEAD (Asp–Glu–Ala–Asp)-box helicase 6 (DDX6) suppresses autophagy by degrading autophagy-related (ATG) protein messenger RNAs (mRNAs) when nutrients are adequate. DDX5 interacts with p62 to inhibit mammalian target of rapamycin (mTOR) and then activate autophagy. DDX17 reduces the expression of *Beclin1* by increasing miR-34-5p and miR-5195-3p expression. DDX53 promotes autophagy by increasing the expression of ATG5 and then increasing the conversion of microtubule-associated protein 1 light chain 3-I (LC3-I) to LC3-II. TRAF6: tumor necrosis factor (TNF) receptor-associated factor 6; P: phosphorylation; Dcp2: decapping enzyme; UTR: untranslated region

and *Cryptococcus neoformans*, Dhh1 and Vad1, respectively, were shown to participate in messenger RNA (mRNA) decapping in a previous study (Presnyak and Coller, 2013). A conserved mechanism was identified, in which DDX6 and its homologues mediate mRNA degradation-regulated autophagy with the decapping enzyme Dcp2 (Hu et al., 2015). Dhh1 and Dcp2 coordinately repress the transcriptome of autophagy-related genes in *S. cerevisiae*, which is consistent with the actions in *C. neoformans* controlled by Vad1. More importantly, the transcripts of autophagy-related protein 8 (*ATG8*) were obviously degraded by Vad1 upon nutrient repletion. In addition, target of rapamycin (TOR)-dependent phosphorylation of Dcp2 played a crucial role in this mechanism. The pathway of Dhh1/Vad1-mediated suppression of autophagy was also detected in mammalian cells and was controlled by the mammalian homologue DDX6 (Hu et al., 2015). However, this process was reversed under starvation conditions, which led to mRNA accumulation and autophagy activation (Hu et al., 2015). In addition, the modulation of fungal virulence and the mammalian inflammasome by this conserved mechanism (Hu et al., 2015) indicated the possibility of studying autophagy-related pathological processes.

DDX53 (also known as cancer antigen cancer-associated gene (CAGE))-mediated processes associated with RNA helicase activity are preferentially activated in various tumors, such as gastric and haematological malignancies, and are involved in DNA hypomethylation in the angiogenesis of cancers (Cho et al., 2002; van Tongelen et al., 2017). First, small interfering RNA (siRNA)-mediated knockdown of DDX53 reduces the levels of ATG5–ATG12, microtubule-associated protein 1 light chain 3 (LC3)-I/II, and pBeclin1Ser15 on western blot (Kim et al., 2017). Then, the punctate pattern of LC3-I/II is decreased following the depletion of DDX53 (Kim et al., 2017). These results suggest a positive role for DDX53 in autophagy. More important, DDX53 directly increases the transcription of ATG5 by binding to ATG5 promoter sequences in breast cancer cells, and this process is inhibited by miR-200b or miR-217 (Kim et al., 2017). ATG5 plays a crucial role in the conversion of LC3-I to LC3-II and participates in the formation of autophagosomes. In addition, a decrease in DDX53 levels induces breast cancer cell resistance to chloroquine (an inhibitor of autophagy) treatment (Kim et al., 2017). In summary, DDX53 positively regulates autophagy by increasing ATG5 expression in breast cancer cells (Kim et al., 2017).

2.2 DEAD-box helicases suppress autophagy by decreasing the post-transcription of *Beclin1* through evaluating microRNAs

DDX17 contains a typical DEAD sequence important for ATP-dependent hydrolysis (Zhang et al., 2016) and is involved in RNA metabolism particularly in microRNA (miRNA) biogenesis (Kao et al., 2019). DDX17 is obviously increased in human glioblastoma cell lines compared to that in control cells, and the silencing of DDX17 increases the accumulation of green fluorescent protein (GFP)-LC3 in glioma cells (Zhang et al., 2016). Overexpression of DDX17 leads to increased miR-34-5p and miR-5195-3p expression in glioma cells, which target the 3'-untranslated region (UTR) of *Beclin1* to repress its expression. *Beclin1* is a core protein in autophagy, which participates in the early stage of autophagosome formation. Based on these results, DDX17 represses autophagy by targeting the post-transcriptional modification of Beclin1, which is regulated by miR-34-5p and miR-5195-3p in glioma cells (Zhang et al., 2016).

2.3 DEAD-box helicases promote autophagy by regulating autophagy proteins

DDX5 induces autophagy in hepatocytes by interacting with the autophagy protein sequestosome 1 (SQSTM1)/p62 (Zhang et al., 2019). p62 is a multifunctional protein related to cellular growth (Moscat et al., 2016), which directly participates in autophagy. DDX5 induces autophagy by interfering with the binding of p62 to tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) (Zhang et al., 2019). The K63-type of polyubiquitination of mammalian target of rapamycin (mTOR) is involved in the stimulation of mTOR complex 1 (mTORC1) by the p62/TRAF6 complex, and TRAF6 knockdown dramatically increases LC3-II levels, indicating that this complex negatively regulates autophagy (Linares et al., 2013). Interestingly, DDX5 promotes autophagy after it induces the dissociation of the p62/TRAF6 complex, because the function of the N-terminus of DDX5 is independent of its RNA binding and helicase activity. Moreover, overexpression of DDX5 reduces the association of p62 with TRAF6 (Zhang et al., 2019). DDX5 also interacts with p62 through its TRAF6 binding site (TBS). Thus, DDX5 plays a role in the competitive inhibition of the TRAF6 interaction with p62. Moreover, p62 is a target of DDX5-stimulated autophagy. In summary, DDX5 promotes autophagy by interacting with p62 and decreasing p62/TRAF6 binding to inhibit mTOR. Another novel role for DDX5 in promoting autophagy to inhibit liver cancer that does not require its canonical function has also been investigated (Zhang et al., 2019). Therefore, DEAD-box helicases might function as regulators by interacting with other proteins rather than enzymes.

In addition to DDX5, Dhh1, which is a homologue of DDX6 in *S. cerevisiae*, promotes autophagy based on the translation of autophagy proteins during nitrogen starvation (Liu et al., 2019). Dhh1 coordinates with Dcp2 to repress autophagy by degrading ATG mRNAs, particularly ATG8 transcripts, which has been further discussed in a previous study (Hu et al., 2015). According to a novel study, Dhh1 positively regulates autophagy by increasing the translation of Atg1 and Atg13 under nitrogen-starvation conditions (Liu et al., 2019). Atg1 and Atg13 proteins are essential components of a kinase complex that is sensitive to upstream nutrient signals and initiates autophagy (Duprez et al., 2009; Ravikumar et al.,

2010). Furthermore, the mechanism by which Dhh1 modulates autophagy requires structured regions in the open reading frames (ORFs) of Atg1 and Atg13 mRNAs and the helicase activity of Dhh1 under nitrogen-starvation conditions (Liu et al., 2019). In addition, eukaryotic translation initiation factor 4E (EIF4E)-associated protein 1 (Eap1), a TOR-regulated EIF4E-binding protein, is involved in the process of Dhh1-induced autophagy upon nitrogen starvation and promotes the translation of Atg1 and Atg13 (Liu et al., 2019).

In summary, DEAD-box helicases exert different effects on regulating autophagy and function by activating different pathways in different stages. Other members of this family require further study, and the potential functions of their relationships with autophagy in autophagy-related diseases require further discussion.

3 RNA helicases associated with autophagy upon exogenous stimuli

Except directly regulating autophagy, the roles of some RNA helicases in autophagy are unclear, but these proteins regulate autophagy upon exposure to exogenous stimuli.

MDA5 mainly plays a role in recognizing exogenous RNAs, particularly viral RNAs, to activate innate immune responses, and it is particularly sensitive to dsRNA (Takeuchi and Akira, 2008; Rodriguez et al., 2014). MDA5 drives autophagosome formation following the exposure of melanoma cells to $[pIC]^{PEI}$ (the dsRNA mimic polyinosinic-polycytidylic acid (pIC) coadministered with polyethyleneimine (PEI) as a carrier) (Tormo et al., 2009; Inao et al., 2012). Specifically, the transfection of melanoma cells with $[pIC]^{PEI}$ substantially activates MDA5 and stimulates autophagy and cell death in melanoma (Fig. 2). Both MDA5 activation and autophagy are required for $[pIC]^{PEI}$-mediated cell death. Importantly, MDA5 participates in the focal aggregation of LC3 in melanoma cell lines stimulated with $[pIC]^{PEI}$, revealing the role of MDA5 in $[pIC]^{PEI}$-induced autophagy (Tormo et al., 2009). In summary, this study showed that MDA5 participates in $[pIC]^{PEI}$-induced autophagy and leads to melanoma cell death. However, further studies are required to determine whether it possesses the ability to directly induce autophagy and to identify the specific target. Another exogenous stimulant, carbonyl cyanide *m*-chlorophenylhydrazone (CCCP, a mitochondrial protonophore), interacts with MDA5 (Xu et al., 2016). Knockdown of MDA5 led to reduced autophagy in CCCP-stimulated cells, indicating that MDA5 promotes autophagy in response to CCCP stimulation (Xu et al., 2016).

Overall, MDA5 has been verified to be implicated in $[pIC]^{PEI}$-induced autophagy and is activated upon CCCP stimulation. Although its precise role in directly inducing autophagy remains elusive, current research suggests that the role of MDA5 in autophagy triggered by exogenous stimuli is not its main function and that it may function as an RNA sensor under some conditions. MDA5 is considered to serve as a bridge between autophagy and innate immunity, which is a novel function that requires additional study.

4 Interplay between RNA helicase and autophagy in various diseases

4.1 Virus-induced autophagy regulates the expression of RNA helicases in viral infections

Autophagy is induced by various types of viral infections, and two aspects are important to consider regarding viruses and autophagy. First, autophagy benefits some viruses, such as hepatitis C virus (HCV) (Fang et al., 2017). RNA helicases play a vital role in antivirus immune responses by recognizing virus components and then activating innate immunity or specific responses in humans. RNA helicases have been reported to serve as a bridge to autophagy for viruses, although the precise function requires further elucidation. In this section, we summarize recent studies on this topic and discuss new directions for investigating RNA helicases and autophagy in viral diseases.

Based on emerging studies, autophagy is involved in the antiviral function of RNA helicases. RIG-I (DDX58) is the most important RNA helicase and its antiviral effects are mediated by the RLR signalling pathway. In most cases, the RLR pathway is induced as a defence against viral infection via the activation of mitochondria-associated antiviral signalling (MAVS) (Kato et al., 2005), promoting the expression of downstream genes. MAVS was recently

shown to link autophagy to antiviral effects via the RLR signalling pathway. RIG-I (DDX58) plays a significant role in the RLR signalling pathway (which is involved in viral RNA binding and immune activation) (Kato et al., 2005; Melchjorsen et al., 2005). According to recent data, autophagy is potently stimulated upon RLR activation by dsRNA transfection (Yang et al., 2013). Indeed, the transfection of mesenchymal stem cells (MSCs) with dsRNA activates RLRs, which obviously induces LC3 conversion (Yang et al., 2013). This phenomenon suggests an interaction between RIG-I and autophagy during RLR activation.

Severe fever caused by thrombocytopenia syndrome virus (SFTSV) is a type of RNA virus with a nonstructural protein (NS) that induces the formation of vesicles and inhibits the activation of type I IFN responses by RIG-I (Santiago et al., 2014). Some specific cytoplasmic vehicles are induced by RNA viruses that have a similar morphology and function to autophagosomes (Miller and Krijnse-Locker, 2008). Interestingly, the number of autophagosomes is substantially increased following SFTSV infection and the NS-induced vesicles have been shown to colocalize with GFP-LC3 (Santiago et al., 2014). However, the inhibition of RLR proteins by these structures is not influenced by defects in autophagy. Accordingly, these particular vesicles are considered to be unconventional autophagosomes that participate in the resistance to host responses (Santiago et al., 2014). Overall, both autophagosomes and NS-induced vesicles are generated upon SFTSV infection, and the two structures commonly sequester RIG-I and its RLR signalling adaptors (Santiago et al., 2014). Thus, autophagy may promote SFTSV infection by digesting RIG-I. In addition to SFTSV, several viruses, such as classical swine fever virus (CSFV) and the Edmonston strain of the measles virus (MV-Edm), induce autophagy to inhibit RIG-I during the process of infection (Xia et al., 2014; Pei et al., 2016). Moreover, a similar inhibitory effect has been observed in cells infected with some viruses, such as MV-Edm. MV-Edm-induced autophagy decreases the levels of cytokines that inhibit virus infections (Xia et al., 2014) and the levels of RLRs are reduced during ATG5-induced autophagy after an infection (Xia et al., 2014). In summary, autophagy controls innate immune responses in infected cells by attenuating the positive feedback from RLR signalling (Xia et al., 2014). Moreover, the innate immune response to MV-Edm infection is reduced by SQSTM1-mediated mitophagy but not macroautophagy. Taken together, RNA helicases are regulated by virus-induced autophagy.

The ability of the host cell to resist viral infection requires the normal functioning of the RLR pathway and autophagy. Indeed, these two mechanisms are closely associated. Autophagy plays a vital role in viral replication in host cells and the inhibition of RLR signalling. Many viruses may have evolved to encode genes that block RLR signalling by activating autophagy in host cells (Fig. 2).

Based on these results, the ultimate goal of RNA helicase regulation by virus-induced autophagy is to escape from host attack, thereby favouring replication. Interestingly, HCV and several arboviruses require autophagy to survive in host cells (Becher et al., 2003; Fang et al., 2017). Thus, virus-induced autophagy exerts completely opposite effects on the virus and host. In summary, the termination of virus-induced autophagy ensures viral replication in host cells by suppressing RNA helicases.

4.2 Autophagy inhibits the antiviral immune response by degrading RIG-I or its adaptors

The host immune system must be activated to clear viruses. However, as excess immune activation is harmful, tight control is required. In this section, we summarize the effect of the interplay between RNA helicases and autophagy on the cellular immune response to a viral infection (Fig. 2).

RIG-I (DDX58) and MDA5, which are major components of the RLR signalling pathway, play pivotal roles in resisting RNA virus-induced immune activation (Loo and Gale, 2011). The two CARDs in RIG-I and MDA5 activate MAVS, which promotes the secretion of type I IFN and related inflammatory cytokines. The C-terminal regulatory domain (CTD) of RIG-I mainly binds to viral RNAs. Emerging evidence has suggested that type I IFN signalling is inhibited by the autophagy-mediated degradation of RIG-I or its adaptors (Jounai et al., 2007; Du et al., 2018; Jin and Cui, 2018). Some adaptors, such as bone marrow stromal cell antigen 2 (BST2)/tetherin, function as negative regulators of the response to various viruses and antiviral immunity (Jin and Cui, 2018). BST2 inhibits DDX58-mediated type I IFN at

the late stage of infection by promoting MAVS degradation in association with calcium binding and coiled-coil domain-containing protein 2 (CALCOCO2)-directed autophagy (Jin and Cui, 2018). Other adaptors, such as leucine-rich repeat containing protein 25 (LRRC25), another inhibitor of type I IFN signalling, promote interaction between RIG-I and the autophagic receptor p62 through IFN-stimulated gene 15 (ISG15), thereby mediating the degradation of RIG-I in autophagy (Du et al., 2018). Therefore, some cellular proteins can lead to the autophagy-mediated degradation of RIG-I or its adaptors to prevent immune activation in the host upon viral infection.

In addition to suppressing RLR signalling, the absence of autophagy leads to substantially increased levels of RLR signalling and increases the production of type I IFN in mouse embryonic fibroblasts (MEFs) (Jounai et al., 2007; Tal et al., 2009; Ke and Chen, 2011). The Atg5–Atg12 conjugate was found to regulate the RIG-I pathway and recognize vesicular stomatitis virus (VSV) in MEFs (Tal et al., 2009). Both Atg5 and Atg12 are autophagy-related proteins that participate in the formation of autophagosomes. While pIC stimulates primary macrophages, IFN-α and interleukin-6 (IL-6) levels are increased in $Atg5^{-/-}$ macrophages, indicating the amplification of RLR signalling in both MEFs and macrophages in the absence of autophagy (Ke and Chen, 2011). Thus, RLR signalling is prolonged in the absence of autophagy. In fact, these phenomena further confirm that autophagy negatively regulates RIG-I and its adaptors.

Although RIG-I-induced activation of the immune response and the regulation of autophagy occur separately, their consequences are tightly connected. In the absence of autophagy, the RLR pathway is amplified, indicating that autophagy is indispensable and strongly governs DDX58-mediated type I IFN signalling by RNA helicases upon viral infection. DDX58 may serve as an intersection between autophagy and antiviral immune responses, which warrants further analysis. The interplay between this RNA helicase and autophagy might be a target of developing new antiviral drugs.

4.3 RNA helicases are related to autophagy in cancer

The interplay between RNA helicases and autophagy is also involved in tumorigenesis, representing a possible therapeutic target for the resistance to cancer treatment (Fig. 2).

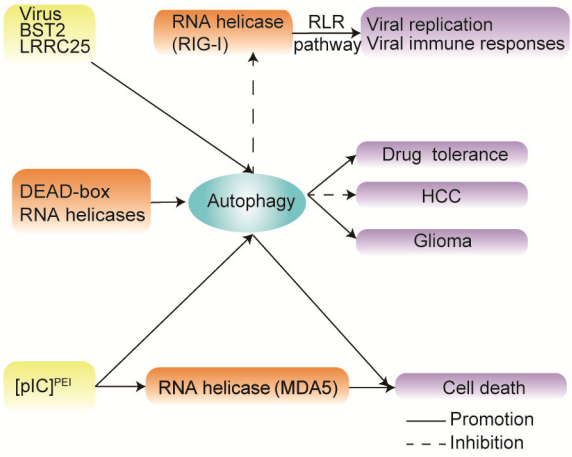

Fig. 2 RNA helicase and autophagy associated with cell death or diseases

DEAD-box RNA helicases directly regulate autophagy, which can be relevant to drug tolerance of cancer and tumorigenesis such as HCC and glioma. Virus-induced autophagy and other immune inhibitor-induced autophagy repress RIG-I, which benefits to viral replication and immune responses. $[pIC]^{PEI}$-induced autophagy is associated with MDA5, which contributes to cell death. DEAD: Asp–Glu–Ala–Asp; HCC: hepatocellular carcinoma; RIG-I: retinoic acid-inducible gene I; $[pIC]^{PEI}$: the double-stranded RNA (dsRNA) mimic polyinosinic-polycytidylic acid (pIC) coadministered with polyethyleneimine (PEI) as a carrier; MDA5: melanoma differentiation-associated 5; BST2: bone marrow stromal cell antigen 2; LRRC25: leucine-rich repeat containing protein 25; RLR: RIG-I-like receptor

DDX5 is expressed at low levels and autophagy is impaired in hepatocellular carcinoma (HCC). DDX5 promotes autophagy by interacting with p62 to inhibit mTOR (Zhang et al., 2019). p62 is not only related to autophagy but is also involved in many types of human cancers, such as HCC. Moreover, DDX5 attenuates p62 accumulation and suppresses tumorigenesis. A low level of DDX5 expression is associated with a poor prognosis for patients with HCC (Zhang et al., 2019). In general, DDX5 is a pivotal protein linking autophagy and HCC, which promotes autophagy in HCC to inhibit tumorigenesis. In addition, the function of DDX5 has also been discussed in other malignant tumors such as oesophageal cancer (Ma et al., 2017), gastric cancer (Sha et al., 2018), and breast cancer (Hashemi et al., 2019). However, the mechanism

by which DDX5 and autophagy regulate other tumors requires additional investigation.

Furthermore, DDX17 increases miR-34-5p and miR-5195-3p expression to target the 3'-UTR of *Beclin1* to repress *Beclin1* expression and inhibit autophagy in glioma cells (Zhang et al., 2016). Indeed, knockdown of DDX17 not only enhances autophagy but also promotes the apoptosis of glioma cells (Zhang et al., 2016). This mechanism reveals that RNA helicase suppresses autophagy to increase the growth of malignant cells by repressing the post-transcriptional modification of *Beclin1*, which is closely related to cancer.

DDX53 is present in the serum of patients with various types of tumors (Iwata et al., 2005). Repression of autophagy reduces the level of DDX53 and increases the sensitivity of breast cancer cells to anticancer drugs (Kim et al., 2017). Down-regulating DDX53 results in a decrease in the levels of autophagic proteins, which indicates the tight relationship between autophagy and DDX53 (Kim et al., 2017). Most importantly, DDX53 dramatically increases the expression of ATG5 by binding to its promoter in breast cancer cells (Kim et al., 2017). The finding that suppression of autophagy modulates RNA helicase expression in human pathological conditions is novel. Compared with DDX5, the terminus of DDX53 promotes autophagy in cancer, thereby enhancing tumor progression. Therefore, various RNA helicases may have specific functions in the same pathological process.

In summary, the interplay between RNA helicases and autophagy in cancer includes not only the antitumor function of RNA helicases but also the resistance of cancer cells. Different RNA helicases may exert common effects on autophagy, thereby leading to different results in cancer. Thus, studies exploring the relationships between RNA helicases and autophagy and their effects on cancer are important.

5 Conclusions and perspectives

An increasing number of novel molecular mechanisms that regulate autophagy have been reported. The involvement of RNA helicases in autophagy has attracted increasing attention over the past several years. However, many gaps in our understanding of the connections between RNA helicases and autophagy still exist. Several members of this enzyme family function as innate sensors that participate in specifically inducing autophagy to recognize viral RNAs and activate immunity. MDA5 is the most extensively studied member of the RNA helicase family (Takeuchi and Akira, 2008; Yang et al., 2013; Rodriguez et al., 2014; Santiago et al., 2014; Szabo et al., 2014; Chan and Gack, 2015; Wu et al., 2017; Ahmad et al., 2018; Devarkar et al., 2018; Ye et al., 2018; Zheng et al., 2018), and it has been shown to recognize dsRNA and exogenous RNAs, such as viral RNA, and then interact with MAVS to activate downstream genes and clear exogenous RNAs (Takeuchi and Akira, 2008; Rodriguez et al., 2014; Ahmad et al., 2018; Ye et al., 2018). MDA5 was recently reported to activate autophagy before, during, or after viral infection according to the type of stimulation (Tormo et al., 2009; Xu et al., 2016). Nonetheless, further studies are required to determine whether MDA5 is a direct participant in autophagy. Unlike MDA5, RIG-I (DDX58) may not directly regulate autophagy, although autophagy may degrade RIG-I and its adaptors during viral infection and thus prevents immune activation (Du et al., 2018; Jin and Cui, 2018). DDX58 is also suppressed in virus-induced autophagy. Based on these results, RIG-I (DDX58) is a bridge linking autophagy and virus-induced immune responses.

The DEAD/H-box family is the largest subfamily of RNA helicases. Members of this subfamily have been extensively studied in recent years. Different RNA helicases modulate different stages of autophagy. DDX6 and its homologues control both the expression of ATG-related transcripts and proteins during nutrient deprivation (Hu et al., 2015; Liu et al., 2019). DDX53 targets the ATG5 promoter sequence to promote autophagy and then improves drug sensitivity in breast cancer cells (Kim et al., 2017; Zhang et al., 2019). DDX17 (p72) represses autophagy by decreasing the post-transcriptional modification of *Beclin1* based on an evaluation of miRNAs (Zhang et al., 2016). DDX5 promotes autophagy by interacting with the autophagy-related protein p62, which suppresses HCC. Moreover, RNA helicases alter the survival, growth, invasion, and metastasis of cancer cells by modulating autophagy. These proteins might represent new targets for cancer therapy or sensitive diagnostic biomarkers for various types of tumors. MDA5 and RIG-I are

associated with autophagy mainly through their involvement in activating or repressing virus-induced immune responses.

The connection between RNA helicases and autophagy has emphasized the close associations of autophagy with tumorigenesis, activation of the immune response, and viral infections. However, the mechanisms of RNA helicases and autophagy have not received sufficient attention compared to the multiple functions of these factors in regulating cell signalling or various diseases. The unique functions of other members of the RNA helicase family have not been discovered. Both RNA helicases and autophagy are highly evolutionarily conserved and contribute to maintaining cellular homeostasis. Finally, these multifunctional proteins and their mechanisms may represent new targets for the treatments of cancer, viral infections, and other diseases; thus, additional studies should be performed.

Contributors

Miao-miao ZHAO wrote the manuscript and prepared figures. Ru-sha WANG and Yan-lin ZHOU amended the grammar of the manuscript. Zheng-gang YANG provided expert comments, project planning, writing and editing. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Miao-miao ZHAO, Ru-sha WANG, Yan-lin ZHOU, and Zheng-gang YANG declare that they have no conflict of interest.

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中文概要

题　目：RNA 解旋酶和自噬之间的新关系

概　要：RNA 解旋酶是参与 RNA 代谢的最大的蛋白质家族，通过翻译和前体 RNA 剪接等各种过程来稳定细胞内环境。这些蛋白质还与一些疾病有关，如癌症和病毒性疾病。自噬是一种自我消化和保护细胞的运输过程，通过降解多余的细胞器和细胞垃圾来稳定内部环境或维持细胞的基本生存，与人类疾病有关。与自噬相似，RNA 解旋酶在维持细胞内稳态中发挥着重要的作用，与多种疾病相关。近年来的研究表明，RNA 解旋酶与自噬密切相关，参与调节自噬或作为自噬与其他细胞活动之间的桥梁，广泛影响了一些病理生理过程。本文总结了最新的研究，以了解 RNA 解旋酶调节自噬的机制以及这些机制与疾病之间的联系。

关键词：RNA 解旋酶；自噬；内稳态；调节