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Insights into the involvement of noncoding RNAs in autophagy

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1.Abstract

Macroautophagy/autophagy is a catabolic process that is widely available in nature. From the past few decades, mounting evidence has demonstrated that noncoding RNAs, which ranging from small noncoding RNAs to long noncoding RNAs (lncRNAs) and even circular RNAs (circRNAs), interfere the transcriptional and posttranscriptional regulation of autophagy-related genes by participating in autophagy regulatory networks. The different expression of noncoding RNAs affects autophagy levels at different physiological and biological stages, including embryonic proliferation and differentiation, cellular senescence, and even diseases such as diabetes. We summarize the current knowledge regarding noncoding RNA dysregulation in autophagy and investigate the molecular regulatory mechanisms which underlying noncoding RNA involvement in autophagy related networks. After that, we investigate normal available resources to predict autophagy-related noncoding RNAs across species and discuss common way for and the challenges of identifying autophagy related noncoding RNAs. The aim of this article is tobe understanding of the relationship between noncoding RNAs and autophagy, and provide new path to specifically target noncoding RNAs in autophagy-associated therapeutic strategies.

Keywords: Autophagy, microRNA, long noncoding RNA, circRNA

2. Introduction

Noncoding RNAs, which is nearly 98% of the transcriptome, lack the capacity to be translated into proteins. Noncoding RNAs were bounded to rRNA and tRNA for a long period of time, and indeed, two of these noncoding RNAs play irreplaceable roles in the translation of protein-coding genes[1].However, with respective knowledge, previously identified yet disregarded noncoding RNAs are now receiving new role[2]. Noncoding RNAs participate in many of biological processes, which include modulating gene expression both at the transcription and post-transcription area, protecting genomes from exogenous nucleic acids to guide genome rearrangement or DNA synthesis, and others[3,4,5].Additionally, noncoding RNA dysfunction is related to imbalances in cellular homeostasis and leads to pathologies such as tumorigenesis.

Macroautophagy, hereafter referred to as autophagy, is a highly preserve for catabolic process that is essential for maintaining homeostasis[2,6]. The scientist, de Duve named the phenomenon “autophagy” to describe cellular self-destruction[7]. Autophagosomes, the major units in the autophagy process, are characterized by the formation of double-membrane vesicles.

Intracellular phagophores inside damaged proteins and organelles to generate autophagosomes and then combine with lysosomes to formautolysosomes[8,9,10]. The consume cargoes are degraded by lysosomal hydrolases, and the decomposition products are reused or further decomposed[9,11]. The degradation of intracellular material enables cell survival to cope with external stress. At the same time, outside stresses also affect cellular autophagic reaction. Stresses such as starvation or glucagon enhance cellular autophagy levels compared with reductions by exogenous insulin or amino acids[12]. After studying the structure of lysosomes and the mechanisms underlying cytoplasmic component sequestration into lysosomes, autophagy itself can be subdivided into few specific subgroups[13]. Mammalian cells primarily undergo macroautophagy and also experience other types of autophagy, such as microautophagy and chaperone-mediated autophagy[14]. Among these subgroups, the major differences are the types of cargo to be degraded and the mode of transportation for cargo into the lysosomes[15]. Since the initial identification of Atg5, more than 40 Atg genes have been found in yeast, and many of these have mammalian orthologs. Autophagy deregulation due to ATG genes is related to various pathological states in humans, such as neurodegeneration, cardiovascular disease, pathogenic infections and cancer. In some breast cancers, autophagy is restored by exogenous BECN1 to suppress tumorigenesis[16]. At the same time, autophagy itself is also beneficial for tumor cells to survive metabolic stresses. For example, the accumulation of SQSTM1/p62, which is important for autophagosome maturation, promotes tumorigenesis[17,18,19]. Thus, the exact role of autophagy is still open for doing research. Increasing evidence suggests noncoding RNAs are associated with autophagy regulation[5,20,21]. The first small noncoding RNA identified as an autophagy regulator was MIR30A, whichaim is the BECN1 gene in a variety of cancer cells.Numerous researchers have reported the ability of lncRNAs to regulate miRNAs by binding to and separating them from their binding sites on mRNAs to affect autophagic role in organism[22]. In this review, we focus on summarizing the important roles of noncoding RNAs and their diverse regulatory mechanisms in autophagy. Additionally, we integrate public resources to predict autophagy- related noncoding. A profound understanding of the interactions between noncoding RNAs and autophagy may benefit clinical therapeutics.

3. miRNAs and the regulation of autophagy

As an important member of noncoding RNAs, miRNAs have been confirmed to take part in each phase of autophagy, which also include phagophore induction, nucleation and expansion, and autophagosome and autolysosome maturation, and play regulatory roles[23]. The details are as follows:

3.1) Phagophore induction

The ULK1 complex integrates upstream nutrient and energy signals to coordinate phagophore induction, and phosphorylation of the ULK1 complex is controlled by MTOR, a major nutrient/energy sensor[16,24,25]. The upstream nutrient signaling pathways include the class I phosphoinositide 3-kinase (PI3K)-AKT-MTOR, Ca2C -AMPK-MTOR, TP53-MTOR and others. Few miRNAs interfere with upstream nutrient signaling pathways to affect downstream phagophore induction[26,27]. For example, MIR451, MIR155 and MIR21 regulate the expression of certain key enzymes such as TSC1, RHEB and PTEN in the PI3KAKT- MTOR signaling pathway (Fig.1). During the period of hypertrophic cardiomyopathy, MIR451 is downregulated to activate autophagy by suppressing TSC1, which forms a heterodimer with the product of TSC2[17,28,29]. In different study of Mycobacterium tuberculosis infection in macrophages, MIR155 induces autophagy to decrease the survival of intracellular Mycobacteria by interfering with RHEB , which is a negative regulatory factor in autophagy. However, TSC1 and RHEB negatively regulate each other[30,31,32]. The phosphorylation of AKT prevents TSC1 from inhibiting RHEB (Fig. 1).In this way, MIR451 and MIR155 interactively regulate the upstream signaling pathway[29,33]. Some calcium-metabolizing enzymes such as TRPM3 and Drosophila IP3K2 are conditioned by MIR204 and Drosophila mir-14 in the Ca2C -AMPK-MTOR pathway (Fig. 1). In clear renal carcinoma, TRPM3, which is enriched in cells to raise the AMPK-activing Ca2C influx, promotes tumor growth. MIR204 represses TRPM3 to inhibit autophagy and shorten tumor cell survival[34]. In a separate study of Drosophila, mir-14 was vital to salivary gland cell death by inhibiting IP3K2 , the product of which phosphorylates inositol trisphosphate (IP3) to prevent the release of calcium, leading to improved autophagy[35,36,37]. Intriguingly, TP53, which is involved

in the crosstalk between autophagy and apoptosis, exerts dual properties in terms of autophagy regulation. Under genotoxic stress, TP53 and HMGB1 form complexes in the cytoplasm and nucleus, respectively, and lead to opposing outcomes[25,38,39]. Confirmed miRNAs such as MIR212, MIR144 and MIR129–5p regulate autophagy through the TP53-MTOR pathway (Fig.1). In prostate cancer, MIR212 is downregulated both in cancer tissues and blood serum and disrupts the upstream signaling pathway by antagonizing SIRT1 to inhibit cellular autophagy[40,41]. In addition, upstream nutrient and energy signals are also affected by ambient stresses such as hypoxia[42,43,44]. Hypoxia caused by oxygen deprivation in the intracellular environment attenuates aerobic oxidation, leading to a lack of energy supply[26,45,46]. For example, MIR301A/ B targets the 30 transtranslated region of NDRG2 to decrease it's expression, causing an increase in autophagy as opposed to the reduced apoptosis observed under hypoxia[47,48,49].

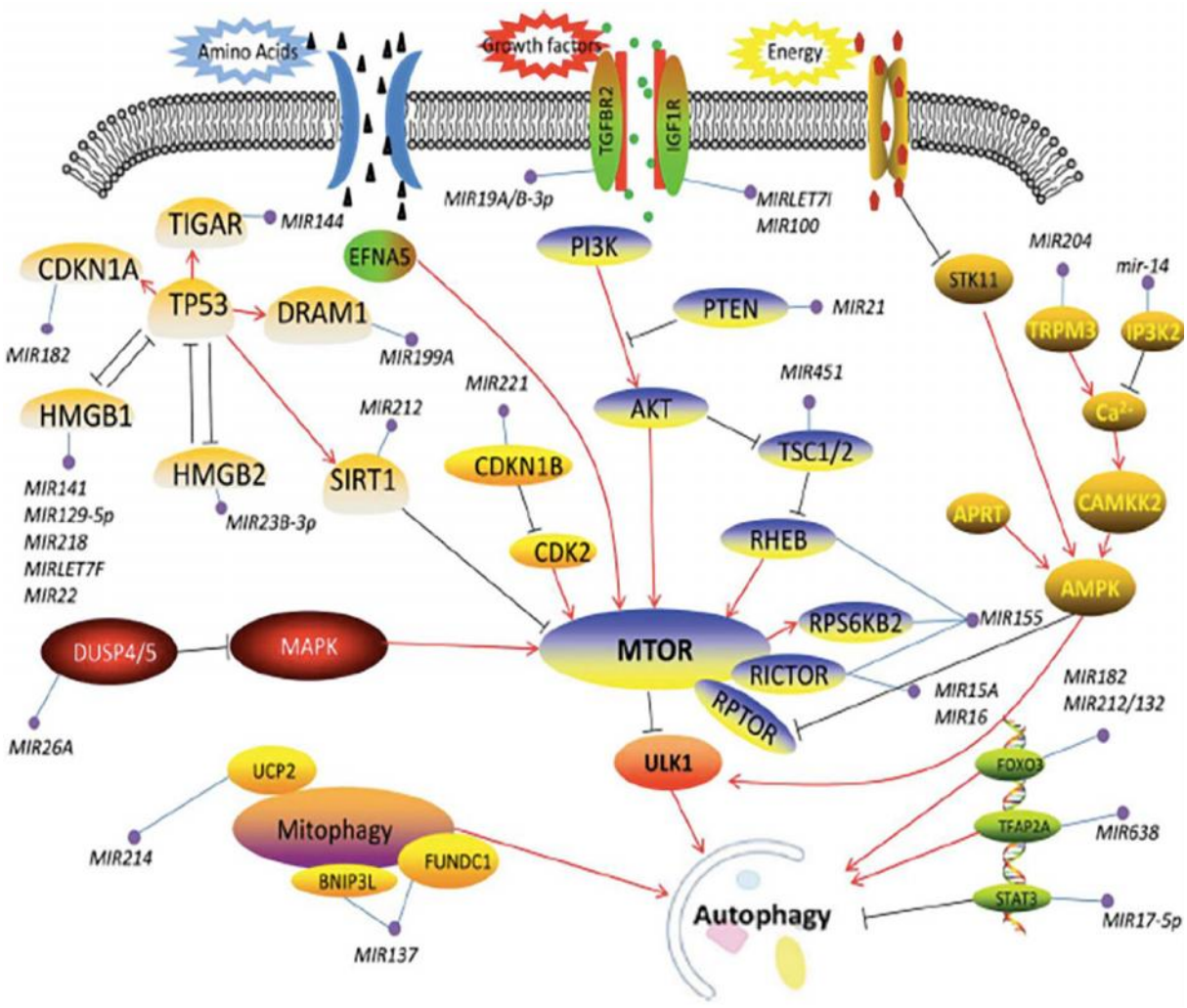

Figure 1: Overview of the miRNAs involved in the regulation of autophagy related signalling pathways. The interplay of autophagy with multiple upstream signalling pathways occurs through MTOR, which is a master regulator of autophagy that is involved in several regulatory pathways including PI3K-AKT-MTOR.

3.2) Phagophore nucleation

In one model of autophagosome biogenesis, isolated membranes gather and assemble into phagophores. The PtdIns3K complex, which is recruited by the activated ULK1 complex, plays an essential role in phagophore nucleation[50,51]. Among the components of this complex, BECN1 has an irreplaceable role and functions as a scaffolding protein to recruit and assemble cofactors such as ATG14, UVRAG and others[51,53]. The importance of BECN1 is also reflected in the crosstalk between autophagy and apoptosis[54,55,56]. BECN1 and BCL2 are mutually antagonistic such that BCL2 suppresses autophagy by sequestering BECN1, and BECN1 potentiates apoptosis by binding to BCL2[56,57]. Many miRNAs, such as MIR30, MIR376A/B and others, target the BECN1 gene to affect autophagy and for example, MIR376B attenuates starvation-induced autophagy by blocking BECN1 in some disease[56,58,59]. Furthermore, miRNAs enhance autophagy by interfering with the BCL2gene.Preferably, the downregulation of MIR21 and MIR497 promotes autophagy while reducing apoptotic injury by inhibiting the BCL2 gene. MCL1, an antiapoptotic BCL2 homolog, also accelerates autophagy[34,48,60]. In macrophages infected by Mycobacterium tuberculosis, the upregulation of MIR17 5p accelerates protective autophagy to eliminate infection by downregulating MCL1[24,61]. In both autophagy and apoptosis, the role of the tumor suppressor TP53 cannot be ignored[62,63]. The dual regulatory roles of this protein facilitate it's interaction with HMGB1 in the cytoplasm and nucleus[61,64]. TP53 knockout enhances the expression of cytosolic HMGB1, which induces autophagy by directly binding with BECN1 to replace BCL2, compared with autophagy inhibition by HMGB1 in the nucleus[64,65]. Several miRNAs target HMGB1 and TP53 to regulate autophagy, including MIR22, MIR218, MIR23B-3p and others[62,66].

3.3) Autolysosome maturation

Completion of the autophagic process relies on the fusion of autophagosomes with lysosomes to form autolysosomes[61,67]. The docking and fusion processes are promoted by RAB7, LAMP2 and other proteins[66,68]. MIR207 and MIR352 modulate LAMP2 gene expression to block the lysosomal-autophagy pathway[69,70]. Furthermore, MIR207 mimics also reduce the number of cellular lysosomes and autophagosomes[70,71]. Conversely, MIR4459 inhibits LARP1 expression, which is involved in SQSTM1 protein synthesis to attenuate autophagy in vascular endothelial cells[72,73]. The identification of these miRNAs as regulators of autophagy-lysosomal genes will allow us to identify regulatory mechanisms and may have some importance for further clinical applications[74].

4. Long noncoding RNAs and autophagy regulation

The previousconcepts regarding the sequential transfer of biological information, individual thinking can be constrained by central dogma, which in this case entails the detailed residue-by-residue transfer of sequential information that cannot be transferred back from protein to either protein or nucleic acid[75,76]. However, accumulating evidence indicates that this simplification ignores the existence of reverse information flow from RNA to DNA. Therefore, the central dogma was restated by previous researcher[74,77]. Similar to the complements in central dogma, previous studies on the other forms of noncoding RNAs will supplement the cognition of noncoding RNAs in regulating autophag. Multiple miRNAs are responsible for the regulation of autophagy[78,79]. Emerging evidence indicates lncRNAs act as competitive platforms for both miRNAs and mRNAs. The lncRNA category is diverse and includes not only antisense, intronic and intergenic molecules also pseudogenes and retrotransposons. Meanwhile, lncRNAs demonstrate specificity among diverse tissues and cells in physiological or pathological conditions[80,81].

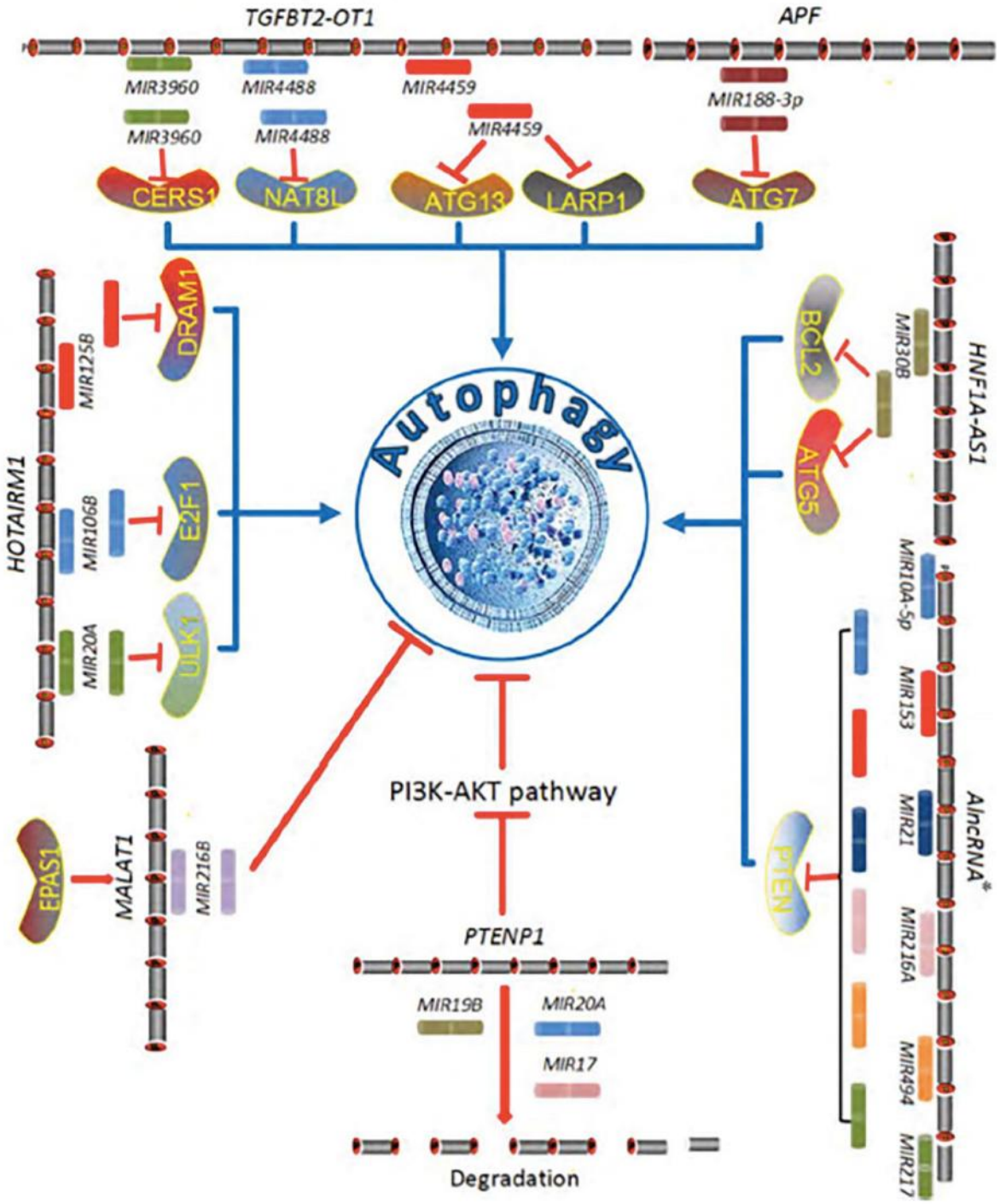

Figure 2: Conceptual diagram of regulation mechanism between miRNAs and lncRNAs in autophagy

5. Circular RNAs and autophagy regulation

Another important and complementary members of the noncoding RNA family, the high-profile discovery of natural circRNAs was met with a great deal of interest. CircRNAs are novel endogenous noncoding RNAs that differ from traditional linearRNAs[82,83]. The biogenesis of circ RNAs is confusing and remains unclear, although circularization signals, exon-skipping events and splicing machinery are thought to participate in the circularizationprocess[35,85]. The exact mechanism by which thesplicing machinery selected regions to circularize hasnot been fully characterized[36,86,87]. Among numerous convincing hypotheses, several theoretical models have been proposed toexplain the possible formation of circRNAs. In theory, any exons kipping event holds the potential to cause cyclization, and a spliced lariat containing skipped exons will rapidly undergo internal splicing[88]. Originally, circularized transcripts were thought to be byproducts of imperfect splicing, like lncRNAs, anotion supported by their low yield, lack of specific protective modifi cations and sequence conservation[38,89,90]. However, this concept has been recently challenged. CircRNAs were not discovered earlier and received less attention because classicRNA detection methods specifically identify only RNA molecules with polyadenylated tails, and the generation of circRNAs involves polyadenylated mechanism[24,88].

6. Non-coding RNA: The Yin and Yang of gene control

Some of the most studied ncRNA to date have been the long intergenic non-coding RNAs (lincRNAs), which are a heterogeneous group of transcripts involved in epigenetic control of the cell that range in size from ~ 300 nucleotides to several thousands. Currently the human catalog of lincRNAs is thought to be around 3,300 although the true number may be closer to 4,500. Often associated with these ncRNA is an antisense RNA (asRNA) that contains a sequence complementary to the ncRNA and thus may afford the cell another layer of genetic regulation[91]. To date the most studied and well understood lincRNA is the 17,000 nucleotide transcript Xist, which is involved in X chromosome inactivation (for an in-depth review see). Of prime importance in X-inactivation is the X inactivation center (XIC in humans, Xic in mice), which contains at least two ncRNA, the aforementioned XIST (XIST humans and Xist in mice) and its asRNA Tsix. Expressed early on in embryonic development, Xist is weakly expressed by both X chromosomes until cell differentiation when an yet-to-be determined key factor triggers up-regulation of Xist transcription from the future inactive chromosome by progressive coating of the chromosome from the XIC outwards[92,93]. In humans this randomly coats one of the two X chromosomes in females whereas in mice the Xist locus on the maternal X chromosome is always repressed and thus, the maternal X chromosome is always active giving rise to an Xactive and Xinactive[94,95]. Upon differentiation, the histone modification of the active and inactive become significantly altered with the inactive X chromosome exhibiting more repressive chromatin modification, which is thought to play a role in recruitment of proteins, while the active X chromosome exhibits silencing of the Tsix asRNA promoter due to a lack transcriptional machinery recruitment. The result of these eventualities is the alteration of the expression of Xist and the coating of one of the chromosomes by the ncRNA causing inactivation of those chromosome associated genes due to the loss of histone modification by acetylation and methylation[96]. This coating of the chromosome ensures an equal dosage of gene expression between Xlinked genes of males and females[97]. In mice, this inactivation has been shown to require an interaction between the 5′ of Xist, named RepA and the Polycomb Repressive Complex (PRC2, a complex containing histone methyltransferases (HMTases), Enhancer of Zeste (EZH2, a H3K27 histone methyltransferase) and SUZ12 or G9A (both of which are H3K9 histone methyltransferases)). Some of the most studied ncRNA to date have been the long intergenic non-coding RNAs (lincRNAs), which are a heterogeneous group of transcripts involved in epigenetic control of the cell that range in size from ~ 300 nucleotides to several thousands[98,99]. Currently the human catalog of lincRNAs is thought to be around 3,300 although the true number may be closer to 4,500[100,101]. Often associated with these ncRNA is an antisense RNA (asRNA) that contains a sequence complementary to the ncRNA and thus may afford the cell another layer of genetic regulation. To date the most studied and well understood lincRNA is the 17,000 nucleotide transcript Xist, which is involved in X chromosome inactivation[102,103,104]. Of prime importance in X-inactivation is the X inactivation center (XIC in humans, Xic in mice), which contains at least two ncRNA, the aforementioned XIST (XIST humans and Xist in mice) and its as RNA Tsix. Expressed early on in embryonic development, Xist is weakly expressed

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7. Discussion

As described in the sections above, autophagy in response to stress is an evolutionary mechanism for survival that involves protein and organelle recycling. Noncoding RNAs, considered “transcriptional trash,” participate in many biologic processes and play important roles in autophagy. The field investigating autophagy regulation by noncoding RNAs continues to grow both in terms of volume and impact. However, autophagy and noncoding RNA research is still in its infancy, and a great deal of information remains to be elucidated, such as the paradox of autophagy effects versus noncoding RNA control, deficiencies in research methods, imperfect practical applications and others. The effects of autophagy directed by noncoding RNAs have remained controversial for many years. Whether autophagy regulated by noncoding RNAs is a cell death mechanism or cell survival mechanism, both sides of the argument are independent. Meanwhile noncoding RNAs also appear to exert bilateral regulation.The uncertainty of autophagy andthe dual roles of noncoding RNAs complicate our understanding of associated regulatory mechanisms, making explanations difficult. Quality control plays a critical role in cellular autophagy and is involved in protein dynamics. Unfortunately, the concrete mechanism of quality control and the full dynamicprocess by which misfolded or damaged proteins are incorporated into phagophores still remains unclear. Further improvements should allow us to visualize thedynamic machinery of autophagy with higher spatiotemporal resolution. The emergence of circRNAs exhibiting stronger stabilityand cytoplasm localization through molecular engineering will potentially result in the development of capture and imaging devices that are superior to LC3 and SQSTM1 formonitoring dynamics. However, the construction of geneticanimal models remains a research predicament. A major deficitof traditional genetic animal models is the inability to reproducemajor age-dependent characteristics starting from birth. Thus, it is impossible to compare the effects of impairing noncoding RNAs on autophagy over time. The introduction ofconditional knockouts such as through CRISPR/Cas9 may help us overcome this problem. Additionally, previous studies exploring a single autophagy gene have given different results for partial and non systematic interference. We should turn to multidisciplinary and integrated public databases to examine interference by single or multiple factors with noncoding RNAs and to elucidate the multiple genes and steps involved in the complex autophagy

network regulated by noncoding RNAs. In parallel with mechanistic research, the application of dysregulated noncoding RNAs in autophagy has received a great deal of attention.

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Conflict of Interest: Nil

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