Non-Coding RNAs in Autophagy Regulation

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Non-Coding RNAs

The human genome contains around 20,000 protein-coding genes, accounting for 2% of the genome. The rest of the genome was considered evolutionary junk until the last 20 years. With the publication of the first draft of the human genome project about 20 years ago, it was revealed that the sequences considered as junk in the genome constitute a large part of the genome. When these sequences, defined as garbage, were identified as Non-Coding RNAs (ncRNAs), they have attracted attention in the RNA world. The genome Tilling Array method revealed that non-coding sequences were at least four times more abundant than coding sequences (Consortium, 2004; Ezkurdia et al., 2014). Considering the great influence amount of ncRNAs in the organism on the complex molecular mechanisms of complex organisms, it is suggested that it might be directly proportional to the level of development of the organisms. Although the C-value paradox was largely unknown before the discovery of noncoding RNAs, it has been partially resolved with the completion of the human genome project (Gall, 1981; Kung et al., 2013).

Studies on ncRNAs have revealed many unknowns about the genome and brought new complications. It is sometimes difficult to distinguish between ncRNAs and protein-coding sequences. Although protein-coding sequences have an open reading frame (ORF) longer than 100 amino acids, they can be distinguished from non-coding RNAs. However, rarely some long ncRNAs (lncRNAs) may also contain ORFs longer than 100 amino acids. There is still no definition of ncRNA that can distinguish between coding and non-coding sequences with sharp lines (Chooniedass-Kothari et al., 2004; T. Kondo et al., 2007).

Various classifications have been made to partially facilitate the complex world of ncRNAs. However, ncRNAs are commonly classified according to their length. ncRNAs are classified as lncRNAs that are longer than 200 nucleotides and short ncRNAs (sncRNAs) that are shorter than 200 nucleotides. Ribosomal RNAs (rRNA), small nuclear RNAs (snRNA), carrier RNAs (tRNA) and small nuclear RNAs (snoRNA) are also members of sncRNAs and are classified as housekeeping ncRNAs. In addition, microRNA, piRNA, siRNA, CrasiRNA, snoRNA and tel-sRNAs are also members of

sncRNAs and have regulatory functions. (Katsarou et al., 2015).

LncRNAs

lncRNAs, a fairly broad subclass of ncRNAs, are generally non-protein-coding transcripts which are poorly conserved across species. Compared to sncRNAs, lncRNAs are more structurally and functionally diverse. Most of the transcripts identified in the literature as lncRNAs are transcribed by polymerase II, similar to mRNAs. LncRNAs can undergo 3' polyadenylation (poly(A)), 7-methyl-guanine cap insertion and cleavage, similar to mRNAs. Although lncRNAs are very similar in structure to mRNAs, the signals that direct them to their cellular localization are still enigmatic. In addition, lncRNAs have lower expression levels than protein-coding transcripts. However, many lncRNAs show tissue-specific expression profiles and function as regulatory specific to developmental processes (Katayama et al., 2005).

The functions of lncRNAs depend upon their localization in the cell. Cellular localization of lncRNAs can provide information about their functions. Some of the lncRNAs are localized in the cytoplasm and some in the nucleus. LncRNAs in the cytoplasm might be involved in expression regulation at the mRNA level. LncRNAs that are localized in the nucleus could bind directly to the target gene and inhibiting or activating gene expression (Taft et al., 2010).

LncRNAs could regulate gene expression in various ways and levels and also interact with RNA-binding proteins. LncRNAs could inhibit mRNA expression by binding to transcription factors which bind target mRNA, or they could act as decoys by mediating the degradation of target mRNA. Some LncRNAs that could interact with the PRC2 complex lead to histone modifications and play an important role in epigenetic regulation (Hajjari & Salavaty, 2015). LncRNAs contain several potential binding sites for miRNAs. Complementary base pairing between lncRNAs and miRNAs, RNA-RNA interaction causes lncRNAs functions as a sponge to miRNAs and inhibits miRNA expression. Another group of lncRNAs acts as a scaffold, facilitating the interaction of various proteins and playing a role in the regulation of cellular processes (Y. Kondo et al., 2017).

LncRNAs could be categorized according to their transcript length, their relationship to protein-coding genes, and their relationship to DNA elements (Laurent et al., 2015). The most widely used lncRNA categorization is based on their association with protein-coding genes. LncRNAs to their relationship with protein-coding genes; classified as intergenic lncRNAs, antisense lncRNAs, and intronic lncRNAs (Jarroux et al., 2017).

Intergenic lncRNAs (lincRNAs) are synthesized from the region that does not overlap with protein-coding genes. To date, 13,105 lincRNAs have been identified in the genome

(Cabili et al., 2011). While the distance of lincRNAs to protein-coding genes can be up to 3 Mb, their average distances is 40 kb (Hon et al., 2017).

Intronic lncRNAs are transcribed from the intronic regions of protein-coding genes. Circular RNA (circRNA), circular intronic RNA (ciRNA), exonic circRNA (ecircRNA), exon-intron circRNA (EIcircRNA) and switch RNA are the major types of intronic RNA (Jarroux et al., 2017). CircRNAs have a tissue-specific expression profile and the vast majority are ecircRNAs. While ecircRNAs are mostly located in the cytoplasm, ciRNAs are localized in the nucleus and may play a role in gene regulation at the transcriptional level (Jeck et al., 2013; Memczak et al., 2013).

Antisense lncRNAs are transcribed from the opposite strand of protein-coding genes. Antisense lncRNAs are common in the genome and have complementary sequences with other transcripts. Antisense lncRNAs can be divided into two subgroups, cis and trans. Trans-antisense lncRNAs are transcribed from different genomic regions, while cis-antisense lncRNAs are transcribed from the opposite strand in the same genomic region. Cis-antisense lncRNA pairs contain exactly overlapping regions. Antisense lncRNAs could regulate gene expression at the pre-transcriptional, transcriptional, and post-transcriptional levels (Villegas & Zaphiropoulos, 2015).

LncRNAs are classified as long intergenic RNA (lincRNA), very long intergenic RNA (vlincRNA), macro RNA and promoter-associated long RNA (PALR) according to their transcript length. ANRIL, H19, HOTAIR, HOTTIP, lincRNA-p21 and XIST are well-studied lincRNAs. vlincRNAs are RNAs encoded from an intergenic space with transcript lengths ranging from 50 kb to 1 Mb (Laurent et al., 2015). Over 2000 vlincRNAs have been identified, accounting for approximately 10% of the genome in humans (Laurent et al., 2015; St Laurent et al., 2013). Macro RNAs are also quite large like vlincRNAs, they are transcripts larger than approximately 10 kb. Airn, Nespas, KCNQOT1, Gtl2lt, Lncat transcripts are examples of macroRNAs (Laurent et al., 2015).

MicroRNAs

MicroRNAs (miRNAs) are single-stranded sncRNAs about 22 nucleotides in length. miRNAs interact with target sequences through complementary base pairing. Target sequences of miRNAs could be ncRNAs or protein-coding transcripts. miRNAs can shorten the poly(A) tails of target mRNAs, thus destabilizing the mRNA leading to degradation of the target mRNA or suppressing translation (Cai et al., 2009). miRNAs interact with mRNAs in different ways, acting as key molecules responsible for regulating much of the genome. As a result of broad-spectrum gene regulation of miRNAs, they have a regulatory role in cell growth, apoptosis, cellular differentiation, and the performance of various cellular functions (Bushati & Cohen, 2007). Moreover, studies have shown that miRNAs have an important role in autophagy control (Su et al., 2015).

Like lncRNAs, miRNAs can act as tumor suppressors or oncogenic depending on the functions of their target mRNAs (ARMAN et al., 2016). Although it is known that the region selection of miRNAs on the target mRNA is often in favor of the 3'UTR, there are studies showing that they can also bind to regions other than the 3'UTR (Bartel, 2009).

Similar to lncRNAs, miRNAs can be synthesized from intergenic and intronic regions. However, although rarely, miRNAs synthesized from exonic regions are also available. About one-third of miRNAs are synthesized from the intronic region (Olena & Patton, 2010; J. Xu et al., 2012). Most miRNA genes are synthesized by RNA polymerase II in the nucleus, but few miRNAs synthesized by DNA polymerase III have also been identified (Vishnoi & Rani, 2017). Biogenesis of miRNA is a multi-step process. In the first step, the miRNA gene is converted to pri-miRNA by the enzyme RNA polymerase II. Although there is insufficient information about the effects of pri-miRNAs on transcriptional regulation, they are only a few kb in length. pri-miRNAs usually have a 7-methyl guanosine cap at the 5' end and a poly(A) tail at the 3' end and are similar to protein-coding mRNAs. Whether these RNAs contain an ORF (open reading frame) or not, they are spliced and became a loop as the poly(A) tail is attached. After the cleavage of pri-miRNAs is carried out in the nucleus by the Pasha (Drosha/DGCR8) enzyme, the pre-miRNA formed is transferred from the nucleus to the cytoplasm via Exportin-5-Ran-GTP. The loop portion of the pre-miRNA is cleaved by the Dicer/TRBP complex in the cytoplasm. The mature miRNA duplex structure obtained after cutting is transferred to the RISC complex together with Ago2 proteins. In the final step, one of the strands of the RISC complex mature miRNA is selectively digested (Winter et al., 2009).

Autophagy

The dictionary meaning of the word autophagy in the Greek language is self-digestion. The term was coined in 1963 by C. de Duve, who discovered lysosomes in 1955. Then, G. Mortimore revealed the inhibitory effect of amino acids and insulin on autophagy. The relationship between autophagy and insulin have suggested that diabetes may have an effect on autophagy. With the beginning of the 2000s, the molecules involved in the autophagic mechanisms and their roles have begun to be clarified (Ohsumi, 2014). With its current definition, the autophagic process is the directing of damaged proteins and organelles in the cell to the lysosome within the autophagosome vesicles, their destruction by the lysosomal enzymes in the lysosome, and the reuse of the building blocks that emerge after the destruction of the cell. In many studies have shown that autophagy is triggered under cellular stress conditions such as oxygen deficiency, growth factor deficiency and starvation (Klionsky, 2007). As a result of the stimulation of autophagy under cellular stress conditions, organelles and proteins as well as pathogens are destroyed. Building blocks obtained after autophagic destruction play an important role in cell homeostasis by providing nutrients and energy to the cell (Ravikumar et

al., 2010). On the other hand, in cases where apoptosis is not possible, it has also been reported that autophagy leads to cell death, depending on variables such as the type, duration and amount of the stimulator. Therefore, to distinguish autophagic cell death from apoptosis, it is also called type II cell death. Autophagy can also be defined as a mechanism that plays a role in deciding whether the cell will survive or die according to the conditions of the cell (Shintani & Klionsky, 2004; White & DiPaola, 2009).

Anomalies in the autophagy pathway have revealed that autophagy is closely related to cancer, neurodegenerative diseases such as Parkinson's and Huntington's, and infectious diseases. Therefore, it is possible to say that autophagy has an effect on pathophysiological conditions. (Jiang & Mizushima, 2014; Levine & Kroemer, 2008).

Types of Autophagy

There are 4 different types of autophagy in generally: macroautophagy (lysophagy), microautophagy, RN/DNotophagy, and chaperone-mediated autophagy (Yim & Mizushima, 2020). In addition, there are different types of lysosomalphagia named according to the type of digested substrate and digestive vesicle. E.g; the direct digestion of mitochondria by the lysosome is defined by micromitophagy, while autophagosomal digestion is expressed by macromitophagy. The terms lysosomal digestion of the endoplasmic reticulum are reticulophagy, and the terms xenophagy are used for the lysosomal digestion of bacteria and viruses (W. Li et al., 2012).

The process of macroautophagy is one that may also involve digestion of various cytosolic residues and damaged organelles. At the beginning of macroautophagy, the phagophore fuses with the lysosome after maturation to the autophagosome, forming the autolysosome (Yim & Mizushima, 2020). Autophagosome formation is not observed in the microautophagic process. Autophagic material is digested by taking it into the lysosome by forming an inward pocket of the lysosome (W. Li et al., 2012).

In the chaperone-mediated autophagic process, Hsc70 chaperones play an active role in recognizing the substrates to be degraded by their lysine, phenylalanine, glutamic acid, arginine and glutamine sequences and directing them to the lysosome. Substrates transferred to the LMP-2A protein in the lysosomal membrane trigger multimerization of LMP-2A so that the substrate can be translocated across the lysosomal membrane. After translocation, the substrate is digested by lysosomal enzymes (Rios et al., 2021).

In RN/DNautophagy, RNA and DNA bind directly to the receptor on the lysosomal membrane and are transferred by the receptor to the translocon protein. The translocon protein SIDT2 transports nucleic acids directly into the lysosomal lumen and the nucleic acids are digested (Yim & Mizushima, 2020).

Steps of the Autophagic Process

The autophagic process is a multistage and complex set of mechanisms consisting of induction, vesicle nucleation, vesicle elongation, retrieval, and fusion phases (Frankel & Lund, 2012). The first step of this process, the induction step, is the stimulation for the formation of a double-layered membrane structure called the autophagosome. When cells need food or energy, mTORC1, which is active under normal conditions, becomes inactive. Inactive mTORC1 cannot suppress the ULK1/2-ATG13 complex and autophagic stimulation occurs (Mizushima et al., 2002).

Vesicle nucleation, the second step of autophagy, is the nucleation of the membrane structure derived from the membrane of the endoplasmic reticulum, golgi, or mitochondria. This step occurs with the establishment of the PI3KC3 complex. The PI3KC3 complex is formed by the interaction of the proteins PI3KC3, Beclin1, Bcl-2, UVRAG, Atg14, Atg9, Atg2 and Vsp15. Inactivation of mTORC1 as a result of stress conditions such as starvation or hypoxia activates PI3KC3, thereby producing phospholipids required for vesicle nucleation (Y. Yang & Liang, 2015). The Rubicon protein functions as a repressor of the PICKC3 complex (Frankel & Lund, 2012).

In the third step of autophagy, membrane elongation takes place for vesicle formation. In this step, ubiquitin-like conjugation systems take place. In the first of these systems, ATG5 and ATG12 are linked together, via ATG10 and ATG7. Following ATG5 and ATG12 binding, ATG16 binds to this complex. In the second conjugation system, ATG4 cleaves the terminal portion of LC3 to expose the glycine residue. Thus, phosphatidyl ethanolamine can bind to cleaved LC3. The phosphatidylethanolamine binding process to LC3 is activated by the ATG5-ATG12 conjugation system. Added phosphatidyl ethanolamine induces LC3 phagophore formation (Frankel & Lund, 2012; Y. Yang & Liang, 2015).

In the fourth step of autophagy, the ATG9-ATG2-ATG18 complex promotes the expansion of lipids and proteins by incorporating them into the phagophore membrane (Frankel & Lund, 2012).

In the last step of autophagy, the lysosome and autophagosome fuse and the substrates are degraded by lysosomal enzymes and the building blocks are reused by the cell. The fusion of the lysosome and autophagosome is accompanied by the Rab and SNARE proteins (Nakamura & Yoshimori, 2017).

Each step is regulated by many autophagy-related genes and various ncRNAs. This makes the autophagic process very complex and difficult to analyze. However, with increasing studies, new regulatory genes that contribute to the autophagic process are being discovered and their contributions to the process are revealed.

MicroRNAs in Autophagy

ATG6, commonly known as Beclin1, is a member of the ATG family, which are important regulators of the autophagic pathway. Beclin1 plays a scaffold role in the formation and maturation of autophagosome structure (Wirawan et al., 2012). miR-30a (Zhu et al., 2009) and miRNAs such as miR-376b (Korkmaz et al., 2012) and miR-519a (Huang et al., 2012) downregulate autophagy by suppressing the expression of Beclin1. miR-376b, In addition, various modifications of Beclin1 have been associated with various cancers and neurologic diseases such as Alzheimer's and Parkinson's (Wirawan et al., 2012).

ATG5, ATG12 and ATG16 function in triggering autophagic elongation and are promoted by ATG7 and ATG10 (Frankel & Lund, 2012; Noda et al., 2011). miR-519a acts as an inhibitor of autophagic elongation by targeting ATG10 as well as Beclin1 (Huang et al., 2012). miR-199a-5p inhibits autophagosome formation by suppressing ATG7 (N. Xu et al., 2012).

Epidermal Growth Factor Receptor (EGFR) is another protein responsible for the regulation of autophagy. When EGFR is bound by the ligand, autophagic stimulation is inhibited, otherwise autophagic stimulation occurs when the cell is under starvation and stress (Jutten & Rouschop, 2014). miR-7 indirectly contributes to autophagic stimulation by directly targeting EGFR. Upregulation of miR-7 promotes autophagy, whereas inhibition of miR-7 inhibits autophagy (Cao et al., 2019).

LncRNAs in Autophagy

LncRNAs can regulate gene expression of transcripts in many ways. Because of the game-changing role of lncRNAs in gene expression regulation and their effects on genes involved in cellular processes, they are responsible for the development and regulation of various diseases. A large number of lncRNAs have been associated with cancer, various neurologic diseases, autoimmune diseases, muscle diseases, and various physiological conditions (Mathieu et al., 2014). In various cancers, lncRNAs have been identified as tumor suppressor or oncogenic. In addition, some lncRNAs function bifunctionally (Guzel et al., 2020). The diverse nature of lncRNAs makes their interaction with proteins and transcripts in the autophagic pathway inevitable. There are oncogenic and tumor suppressor lncRNAs that induce or inhibit autophagy.

HOTAIR, an oncogenic lincRNA, triggers autophagy by upregulating the autophagy genes ATG3 and ATG7 and promotes cell proliferation in hepatocellular carcinoma (HCC) (L. Yang et al., 2016). Similarly, in HCC, MALAT1 activates autophagy through miR-26b inhibition and promotes multidrug resistance (Yuan et al., 2016). In another study, it was revealed that lincRNA MALAT1 promotes proliferation and metastasis while activating autophagy through LC3 upregulation in pancreatic cancer (L. Li et al., 2016).

HULC associated with autophagy genes activates autophagy in pancreatic cancer and gastric cancer, respectively, by increasing the LC3-II/LC3-I ratio and Sirt1protein levels (Xiong et al., 2017; Zhao et al., 2014). MEG3, a tumor suppressor lncRNA, activates autophagy by upregulating Atg3 in ovarian carcinoma. Upregulation of Atg3 inhibits tumor development in ovarian carcinoma (Xiu et al., 2017). Another study demonstrated that MEG3 suppressed autophagy and cell proliferation (Ying et al., 2013). LncRNA MEG3 exerts a bifunctional effect on autophagy. LncRNA GAS5 suppresses autophagy in non-small cell lung cancer (NSCLC), increases cisplatin drug sensitivity and enhances chemotherapy efficacy (Zhang et al., 2016).

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