REVIEW ARTICLE

Noncoding RNAs in protein clearance pathways: implications in neurodegenerative diseases

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Abstract

The importance of noncoding genome has become more evident in recent years. Before genome sequencing, the most well studied portion of our genome was protein coding genes. Interestingly, this coding portion accounted only for 1.5% of the genome, the rest being the noncoding sequences. Noncoding RNAs (ncRNAs) are involved in normal cell physiology, stress, and disease states. A class of small ncRNAs and miRNAs has gained much importance because of its involvement in human diseases such as cancer. Involvement of long ncRNAs have also been acknowledged in other human diseases, especially in neurodegenerative diseases. Neurodegenerative diseases are characterized by the presence of abnormally folded proteins that are toxic to the cell. Several studies from model organisms suggest upregulation of pathways that clear this toxic protein may provide protection against neurodegeneration. In this review, I summarize the importance of ncRNAs in protein quality control system of cell that is implicated in this fatal group of neurodegenerative diseases.

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Introduction

A large portion of the eukaryotic genome is transcribed as noncoding RNAs (ncRNAs). NcRNA can be defined as products of genes that make transcripts which functions directly as RNA rather than encoding proteins. Recent studies indicate that a large number of these RNAs play central roles in regulating gene expression at multiple levels. Vast majority of long ncRNA (lncRNA) are yet to be characterized, although many are involved in important cellular processes and are linked with human diseases (Amaral *et al.* 2011; Lakhotia 2012). Discovery of micro RNA (miRNA) led to a refinement of our understanding of posttranscriptional gene regulation. Some candidate miRNAs are expressed in central nervous system and are known to regulate some of the important brain functions. Dysregulation of miRNA and other ncRNA can be attributed for the development of human diseases like cancer and neurodegenerative disorders (Esteller 2011). Neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), spinocerebellar ataxia and Huntington's disease (HD) are characterized by a set of proteins that misfold and aggregate in specific tissues, and are thus categorized as 'proteinopathies' (Dantum and Bott 2014).

Protein quality control system of cell is very stringent and important to maintain cellular homeostasis. Imbalance in this process due to proteasomal stress or defects in protein folding is associated with numerous human diseases (Carrell and Lomas 1997). Protein quality control system is maintained by ubiquitin-proteasomal system (UPS), autophagy and endoplasmic reticulum associated degradations (ERAD) (Vembar and Brodsky 2008). UPS degrades mainly ubiquitinated proteins, in which ubquitin molecule is transferred to the protein molecule in enzyme dependent steps, whereas autophagy is a bulk cellular degradative pathway that degrades proteins, cellular organelles and cytoplasmic components by delivering them to lysosomes (Levine and Kroemer 2008; Dantum and Bott 2014). In this review, I discuss on the role of ncRNA in clearing aggregate prone proteins and their role in human diseases, particularly in neurodegenerative diseases.

Polyglutamine expansion diseases

Polyglutamine diseases constitute a family of neurodegenerative conditions that are caused due to dynamic mutation in CAG triplet repeats in a specific gene. Since CAG codes for glutamine, these groups of trinucleotide repeat disorders are collectively known as polyglutamine diseases. Till date, nine human neurodegenerative diseases are known, they

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include HD, several spinocerebellar ataxias, (SCA-1, 2, 3, 6, 7 and 17), dentatorubropallidoluysian atrophy and spinobulbar muscular atrophy (SBMA) (Bates 2005; Gatchel and Zoghbi 2005). All the above polyglutamine expansion diseases are autosomal dominant except SBMA which is X-linked. A pathological hallmark that characterizes these polyQ expansion disorders is the presence of intracellular protein aggregates also called as inclusion bodies in neurons of affected patients, *in vitro* cell cultures and also in mouse and fly models (Perutz *et al.* 1994; Davies *et al.* 1997; DiFiglia *et al.* 1997; Scherzinger *et al.* 1997; Warrick *et al.* 1998; Kim *et al.* 2002; Mallik and Lakhotia 2010; Sosa *et al.* 2012). A direct correlation between inclusion bodies in diseased tissue and toxicity is elusive. Inclusion bodies contain chaperone, ubiquitin and components of proteasome indicating that formation of inclusion bodies inside the cell triggers stress response (Warrick *et al.* 1999). Neuronal cells in particular are very sensitive to cellular stress and hence maintaining cellular protein homeostasis is very important, and is achieved through a delicate balance between protein synthesis and protein degradation (Cortes and La Spada 2015). In the following, I discuss the protein clearance pathways and relate their relevance to neurodegenerative diseases.

Protein clearance pathways and their disruption in neurodegenerative diseases condition

Autophagy

Autophagy is an evolutionary conserved process activated by amino acid starvation, growth factor removal, or high energy demands inside the cell (He and Klinosky 2009). In the initial steps, it involves the formation of isolation membrane also called as phagophore. The edges of this phagophore then fuse (vesicle completion) to form a double membrane vesicle called autophagososme that sequesters cytoplasmic components. Once autophagosome is formed, it will deliver its components into lysosome by fusing with them (i.e. forming autolysosomes), where the captured contents along with the inner membrane of the autophagosome are degraded (Rubinsztein *et al.* 2005; Levine and Kroemer 2008; Pattingre *et al.* 2008). Prior to their fusion with lysosomes, autophagosomes can also fuse with other vesicular structures in cell, such as endosomes and multivesicular bodies, forming amphisomes (Levine and Kroemer 2008). Autophagy can be pharmacologically induced by rapamycin, lithium chloride and xestospongin B and can be inhibited, by 3-methyladenine (3MA), bafilomycin A1, chloroquine and 3-hydroxychloroquine (Rubinsztein *et al.* 2005; Levine and Kroemer 2008; Menzias *et al.* 2015).

Autophagy plays a critical role in clearing aggregate prone proteins that accumulates in several human neurodegenerative diseases. Aggregate prone mutant proteins involved in neurodegenerative diseases are believed to be more toxic in their oligoform and autophagy acts as a quality control mechanism in removal of these toxic proteins as sometimes these proteins cannot pass through narrow proteasomal barrel (Sarkar *et al.* 2007). Many reports have suggested presence of autophagosome in brains of patients with different neurodegenerative disorder, such as HD, PD and AD (Williams *et al.* 2006; Rubinsztein *et al.* 2007). This association led to the initial assumption of involvement of autophagy with the pathogenesis of this disorder. Recent studies in model organisms provide convincing evidence that autophagy protects against neurodegeneration and accumulation of autophagosomes represent activation of autophagy (Williams *et al.* 2006; Sarkar *et al.* 2007). Autophagy can be induced by rapamycin that leads to reduction in the levels of soluble and aggregated huntingtin, different ataxins (proteins mutated in SCAs), alpha synuclein and tau mutant proteins. Additionally, rapamycin also reduce toxicity of these misfolded proteins in cells as well as in *Drosophila* and mouse models. Interestingly, *ATG* gene knockdown was associated with increased aggregate formation and toxicity induced by polyQ expansion proteins in *Caenorhabditis elegans* (Jia *et al.* 2007). Autophagy induced by overexpression of histone deacetylase 6 (HDAC6) also compensates for impairment in the UPS in a fly model of spinal bulbar muscular atrophy (Pandey *et al.* 2007).

UPS

Maintaining protein quality control by UPS is one of the important ways used by mammalian cells to regulate cytosolic and nuclear protein levels. UPS degrades misfolded, defective and aggregate prone proteins which accumulates under stress and neurodegenerative diseases (Ciechanover and Brundin 2003). UPS works in two steps: ubiquitylation and proteasomal degradation. Ubiquitin activator, conjugase and ligase are involved in the covalent attachment of ubiquitin to a substrate protein (Hershko and Ciechanover 1998; Kleiger and Mayor 2014). Ubiquitination involves the activity of three enzymes, E1, E2 and E3, in three different steps. During the ubiquitination process, E1 can bind with dozens of E2s and E2s in turn can bind with hundreds of E3 enzymes in a hierarchical pattern. In the final step, an isopeptide bond is created between the lysine residue of the target protein and the C-terminal glycine of ubiquitin, and requires the activity of one of the three E3 ubiquitin, protein ligases (Pickart 2001). Some of the proteins that are an integral part of UPS have been genetically linked to neurodegenerative disorders (Ciechanover and Brundin 2003). For example, Parkin, an ubiquitin ligase has been linked to neurodegeneration, mutations of which cause an autosomal recessive juvenile, onset PD (Kitada *et al.* 1998). Second example is ubiquilin, a ubiquitin-binding protein. Ubiquilin overexpression has a neuroprotective effect in mice expressing truncated huntingtin protein (Elsasser and Finley 2005; El Ayadi *et al.* 2012).

Evidence suggests that polyglutamine expansion increases the probability that the protein will attain an abnormal conformation. This accumulation of misfolded proteins result in dysfunction of UPS. Inclusion bodies have been shown to

be associated with various molecular chaperones and proteasome components (Davies *et al.* 1997; Chai *et al.* 1999; Warrick *et al.* 1999; Mitsui *et al.* 2002; Cowan *et al.* 2003; Mallik and Lakhotia 2010; Yang *et al.* 2014). The association of inclusion bodies with proteasome components impair the function of UPS (Bence *et al.* 2001; Jana *et al.* 2001). Since the UPS normally controls the quality of proteins by degradation, a blockage of UPS might result in accumulation of misfolded proteins. Thus, it appears that cells recognize aggregated disease protein as abnormal protein and recruitment of chaperone and proteasome to the inclusion bodies is for refolding and or degradation of the mutant protein (Sherman and Goldberg 2001; Sakahira *et al.* 2002). This view is supported by the fact that overexpression of molecular chaperones results in suppression of the neurotoxicity associated with these diseases (Warrick *et al.* 1999; Cummings *et al.* 2001).

ERAD

ERAD is a quality control process that results in the clearance of aberrant proteins in the endoplasmic reticulum (ER). Soluble protein, polypeptides that have not been posttransitionally modified or any other misfolded protein are potential ERAD substrate. ERAD substrates are ubiquitylated and degraded by proteasome. Molecular chaperones within the ER lumen recognizes and binds to the substrates, and retranslocates them to cytoplasm where they are degraded by the proteasomal machinery. It is interesting to note that ERAD pathway is conserved from yeast to humans (Vembar and Brodsky 2008).

NcRNAs and neurodegenerative diseases

NcRNAs are enriched in brain, studies have revealed dynamic expression profile of several lncRNA in specific neuronal subtypes. Some brain associated lncRNAs play crucial roles in hippocampal development, myelination of oligodendrocyte and also in ageing (Mercer *et al.* 2010; Qureshi *et al.* 2010). Thus it is not surprising that dysregulation of ncRNAs affect specific brain function and leads to neurological and psychiatric diseases. In the following section, I provide a summary of lncRNAs and miRNAs that are involved in human neurological diseases.

LncRNAs and neurodegenerative diseases

LncRNA make up the largest portion of mammalian trascriptome. They are heterogeneous group of noncoding transcripts more than 200-nt long and are involved in several cell signalling pathways (Jolly and Lakhotia 2006; Sengupta *et al.* 2009; Lakhotia 2012; Böhmdorfer and Wierzbicki 2015; Chujo *et al.* 2015; Fatima *et al.* 2015; Iyer *et al.* 2015; Jose 2015; Quan *et al.* 2015; Hirose and Nakagawa 2016). LncRNAs are disrupted in many human diseases. The first and foremost is the example of a lncRNA implicated in polyQ expansion diseases is hsrω-n, a lncRNA in *Drosophila melanogaster* (Sengupta and Lakhotia 2006). hsrω-n is a stress inducible ncRNA that interacts with several hnRNPs and RNA-binding protein and organize them in nucleoplasmic omega speckles (Prasanth *et al.* 2000; Lakhotia 2011, 2016). Overexpression of hsrω-n RNA dominantly enhanced neurodegeneration caused by polyglutamine expansion in a fly model of expanded polyQ and HD (Sengupta and Lakhotia 2006). Interestingly, downregulation of hsrω-n transcripts rescued pathogenesis in several models of human polyQ expansion diseases (Mallik and Lakhotia 2009). Although hsrω-n transcripts did not colocalize with polyQ aggregates, the suppression of toxicity was associated with decrease in the number of polyglutamine aggregates (Mallik and Lakhotia 2009). Another example of lncRNA involved in neurodegeneration is BACE1-AS, a conserved antisense transcript that modulates BACE 1 gene expression and influences the pathogenesis of AD. β-Site amyloid precursor protein-cleaving enzyme 1 (BACE 1) cleaves amyloid precursor protein (APP) and leads to the formation of amyloid plaques in brains of patient with AD. BACE 1 AS is transcribed from the opposite strand of BACE 1 locus and is ~2-kb RNA. Studies have shown that BACE 1-AS and BACE 1 messenger RNA (mRNA) form a duplex, which in turn increases the stability of BACE 1 mRNA. As compared to control, AD patients show increased levels of BACE1-AS RNA in affected brain regions (Faghihi *et al.* 2008). Another lncRNA, BC200 is also linked to AD. BC200 levels were found to be increased in Brodmann's area 9, a brain region that is mostly affected by AD (Mus *et al.* 2007). The BC200 plays an important role in regulating protein synthesis in dendrites and overexpression of this ncRNA in AD and in ageing can lead to synaptodendritic detoriation (Mus *et al.* 2007). Spinocerebellar ataxias are a varied group of slowly progressing neurological disorder affecting cerebellum (Orr *et al.* 1993; Paulson 2009). Spinocerebellar ataxia type 8 is caused by a CTG/CAG trinucleotide repeat expansion on chromosome 13q21 (Moseley *et al.* 2006). Repeat expansion region in SCA8 harbours two transcripts that are expressed in opposite directions: ATXN8 protein-coding gene as well as in the ATXN8OS antisense-noncoding gene. The protein-coding RNA ATXN8-containing CAG repeats are translated into a polyglutamine expansion protein, while the antisense transcript expresses CUG repeats. The lncRNA, that harbours a CUG expansion, regulates the expression of sense transcript and is thus implicated in the pathophysiology of the disease (Moseley *et al.* 2006). LncRNAs are also involved in the pathogenesis of HD, a neurodegenerative disorder. A study conducted by Johnson *et al.* (2010) found that expression of human accelerated region 1 (HAR1) to be significantly reduced in HD brain tissue. The Human accelerated region contains lncRNA, HAR1F and HAR1R, which are expressed in neurons during human cortical development. HARs are mainly associated with genes involved in transcriptional regulation and neuronal development. Huntingtin antisense transcript, a natural AS transcript at HD repeat locus is downregulated in human HD frontal cortex. There

Table 1. LncRNA in human neurodegenerative diseases (according to Wan *et al.* 2016).

NcRNAs	Relevant information	Disease/disorder
BACE1-AS	Transcribed from antisense strand of protein-coding *BACE1* gene	AD
BC200	Regulates protein biosynthesis in dendrites	AD and PD
GDNF-AS	Transcribed from opposite strand of *GDNF* gene	AD
17A	Located in the human G-protein-coupled receptor	AD
SOX 2OT	Affiliated with the antisense RNA class	AD and PD
NAT-Rad 18	Transcribed from the antisense of *Rad18* gene	AD
BDNF AS	An antisense lncRNA of *BDNF* gene	HD
HAR1	Human accelerated region 1	HD
HTT-AS	Natural antisense transcript of HD repeat locus	HD
Abhd11os	The expression of Abhd11os is accumulated in mouse striatum	HD
TUG1	TUG1 expressed in brain and retina	HD
NEAT1	Forms paraspeckle or act as a transcriptional regulator	HD
MEG3	Interacts with the tumour suppressor p53. Its deletion enhances angiogenesis *in vivo*	HD
DGCR5	DiGeorge syndrome crucial region gene 5	HD
PINK1-AS	Transcribed from the antisense of PINK1 locus	PD
AS Uchl1	An antisense to the mouse ubiquitin carboxy-terminal hydrolase L1 (Uchl1)	PD
AS C9ORF72	An antisense transcript at the C9ORF72 locus	ALS
ATXN8OS	An antisense transcript to the *KLHL1* gene	SCA 8
ATXN7L3B	A conserved lncRNA	SCA
Hsr-omega	A stress inducible lncRNA in *Drosophila*	*Drosophila* models of polyQ diseases

are reports of another four lncRNAs whose expression is altered in affected HD brain region: TUG1 and NEAT1, whose expression is upregulated, and MEG3 and DGCR5, whose expression is downregulated (Morais *et al.* 2009; Sunwoo *et al.* 2009; Mondal *et al.* 2010; Michelhaugh *et al.* 2011).

Several other neurodegenerative disorder, including Amylotrophic lateral sclerosis, Fragile X syndrome, PD, Schizophrenia and others are also modulated by ncRNAs. For example, DISC1 and DISC2 (disrupted in schizophrenia 1 and 2) has been linked with Schizophrenia. DISC1 is a protein-coding gene, whereas DISC2 encodes an antisense ncRNA. Although function of DISC1 and DISC2 remains to be clearly defined, speculation is that DISC2 acts as a riboregulator of DISC1 (Millar *et al.* 2000). A human specific ncRNA transcribed from the antisense orientation of PINK1 locus, NaPINK1, is implicated in PD. This antisense RNA has the capability to stabilize the expression of PINK1. Loss or overexpression of PINK1 (phosphatase and tensis homologue-induced kinase1) leads to impaired dopamine release and motor defects in PD (Chiba *et al.* 2009). A list of ncRNAs and their involvement in human diseases have been summarized in table 1.

MiRNAs and neurodegenerative diseases

MiRNA are short, endogenously expressed ncRNAs that are involved in posttranscriptional gene regulation (Bushati and Cohen 2007; Bartel 2009). MiRNAs are generally transcribed by RNA Pol II as primary transcripts (pri-miRNAs). Pri-miRNA is then processed by Drosha and Digeorge syndrome critical region gene 8 protein (DGCR 8) and the resulting pre-miRNA is then exported to cytoplasm. In the cytoplasm the pre-miRNA is then cleaved by another RNase III type enzyme Dicer along with its cofactors to yield 20-bp long miRNA duplex. This short miRNA duplex is bound by Ago (Argonaute protein), a part of multisubunit complex, termed as miRNA induced silencing complex (miRNA RISC). In the next step, one strand is selected to function as a mature miRNA where as other strand is selected and degraded. Mature miRNA then becomes a part of miRISC. MiRNAs control gene expression in a wide range of biological processes and are implicated in cell proliferation, differentiation, growth and metabolism, apoptosis, stress response etc. Many miRNAs are highly expressed in brain and their expression is tightly controlled in a temporal and spatial patterns. Recent studies suggest miRNAs to be involved in various stages of the developing nervous system. Interestingly, miRNA metabolism and turn over in retinal, hippocampal and cortical neuron are faster than non-neuronal cells (Persengiev *et al.* 2012a, b). This turnover rate of miRNA is dependent on the activity of neuronal cells. It has been suggested that faster turnover rate of miRNA may be a general property of neurons. This statement is supported by the fact that, mouse embryonic stem cells did not exhibit a faster miRNA turnover, where as pyramidal neurons which are differentiated cells did it. MiRNA dysregulation has been studied in various neurodegenerative diseases. PD is neurodegenerative condition caused by slow loss of dopaminergic neurons from the midbrain region. MiRNA 133b is particularly enriched in the midbrain region of normal individual but is found to be deficient in samples from PD patient (Kim *et al.* 2007). In HD, expression of four miRNAs was found to be significantly reduced. This reduction was seen

in HD mice model where expression of miR-28a, miR-124a, miR-132 and miR-135b was significantly reduced. Study in human samples revealed only miR132 to be downregulated in HD patients (Johnson *et al.* 2008). In another study, Perkins *et al.* (2007) reported 16 miRNAs to be differentially expressed in schrizophrenia patients as compared to control. Studies with AD patients revealed that miRNA, miRNA29a/b is downregulated in a subset of AD patient that showed high BACE-1 expression level. miR 29 and miR 29 a/b targets BACE-1 mRNA. BACE 1 promotes formation of amyloidogenic peptide formation (Hebert *et al.* 2008). Other miRNAs that are downregulated in AD are miR-107, miR-15a, miR-16, miR-106a, miR-520c and miR-153 (Femminella *et al.* 2015). The above studies, thus, highlight the importance of miRNA in regulation of certain proteins that are critical in AD pathogenesis (Femminella *et al.* 2015).

Role of ncRNAs in protein clearance pathways

Among the varied function of ncRNAs, many miRNAs and short ncRNAs have been seen to play an essential role in protein clearance pathways. Some examples of roles of ncRNAs in protein clearance are discussed below.

MiRNA and autophagy

Recent studies have shown that miRNAs are involved in autophagy regulation, starting from induction of autophagy to formation of mature autophagosome. Autophagy induction is regulated by ULK complex, composed of ULK1/2, FIP200, ATG101 and ATG13 (Frankel and Lund 2012). MiR-885-3p, a candidate miRNA targets ULK2. MiR-885-3p is also a regulator of vesicle elongation process, as it shown to regulate ATG16L2 (He and Levine 2010; Huang *et al.* 2011). The second step is vesicle nucleation, which involves ClasIII PI3K/Beclin-1-complex and other proteins like hVPS34, Beclin-I and p150. Zhu *et al.* (2009) reported Beclin-I as a direct target of miR-30a. Endogenous levels of miR 30a were altered when autophagy was induced and overexpression of miR-30a could reduce rapamycin induced autophagy (Zou *et al.* 2012). This indicated a direct role of miR-30a in autophagy regulation. MiR-30a has been shown to effectively reduce autophagy levels and tumour size in mice model (Zou *et al.* 2012; Menghini *et al.* 2014). Another miRNA, miR-376b is also known to target Beclin-1 and ATG 4C (Korkmaz *et al.* 2012). In a screen-based assay for detecting miRNAs regulating autophagic flux, MiR-101 that was identified could effectively inhibit basal and induced autophagy (Frankel *et al.* 2011). RAB5A, a small GTPase can induce autophagosome formation and rescue neurodegeneration in fly models. MiR-101 also targets RAB5A (Ravikumar *et al.* 2008). MiR101 is also implicated in regulation of vesicle nucleation. In a study with cardiomyocytes, a miRNA, miR-204 was identified to be involved in vesicle elongation process (Xiao *et al.* 2011). MiR-30a, miR-181a, miR-374a and miR630 have also been shown to be important regulators of ATG5–ATG12 complex, that is involved in vesicle nucleation and elongation process. In addition, miR-591a has also been found to be a regulator of vesicle elongation (Frankel and Lund 2012).

Small ncRNA targets in UPS

Although much information is not available on ncRNA targets in UPS, there are reports of selective activation of small ncRNAs in affected brain regions of SCA1 patients. These small ncRNAs were later found to target members of UPS. In a recent study, HECTD1 and RNF8, two E3 ubiquitin–protein ligases were identified as targets of ncRNA in the cortex and cerebellum of SCA1 patient and also of individuals with AD (Persengiev *et al.* 2012a, b). The HECT family of protein ligase, ubiquinate proteins that are subsequently degraded by the 26S protein complex. It has been seen that deregulation of HECT ligase can have a profound effect on neuronal structure and function that may ultimately lead to complete dysfunction of postmitotic fully differentiated neurons (Persengiev *et al.* 2012a, b).

Concluding remarks

Impairment of ubiquitin-proteosomal pathway and autophagy in neurodegenerative diseases clearly indicates dysregulation of protein clearance pathways. Polyglutamine expansion diseases are caused by expansion of CAG repeat tracts at distinct gene loci, and are characterized by abnormal protein accumulation in neuronal and nonneuronal cells. To identify and develop possible routes of therapeutic strategies, scientists have discovered several modifiers for these fatal diseases. One of the important groups of modifiers are ncRNAs. Importance of ncRNAs and human disease dates to the first discovered mammalian lncRNA H19, which has both oncogenic and tumour suppressor properties (Wrana 1994). Till date many disease related ncRNAs have been studied and the list of ncRNAs implicated in human disease including neurological disorder is constantly increasing (Sengupta and Lakhotia 2006; Sengupta and Ganesh 2008; Amaral *et al.* 2013). Association of miRNAs with autophagy has been demonstrated in recent studies. MiRNAs can be easily manipulated using antisense oligonucleotides making them attractive therapeutic targets. More miRNAs and functions of other ncRNA needs to be discovered, that may help to find a possible cure for this group of fatal diseases.

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