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Emerging roles of long non-coding RNAs in the pathogenesis of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a heterogeneous neurodegenerative disorder and represents the most common form of senile dementia. The pathogenesis of AD is not yet completely understood and no curative treatment is currently available.

With the recent advancement in transcriptome-wide profiling approach, several non-coding RNAs (ncRNAs) have been identified. Among them, long non-coding RNAs (lncRNAs), which are long transcripts without apparent protein-coding capacity, have received increasing interest for their involvement in a wide range of biological processes as regulatory molecules. Recent studies have suggested that lncRNAs play a role in AD pathogenesis, although their specific influences in the disorder remain to be largely unknown.

Herein, we will summarize the biology and mechanisms of action of the best characterized dysregulated lncRNAs in AD, focusing the attention on their potential role in the disease pathogenesis. A deeper understanding of the molecular mechanisms and the complex network of interactions in which they are implicated should open the doors to new research considering lncRNAs as novel therapeutic targets and prognostic/diagnostic biomarkers.

1. Introduction

Alzheimer's disease (AD; MIM#104300) is an irreversible progressive neurodegenerative disorder with a complex etiology and represents the most prevalent form of dementia in elderly individuals, accounting for up to 80% of all diagnoses (Crous-Bou et al., 2017). AD is clinically characterized by a progressive memory deterioration and other cognitive functions, resulting in autonomy loss which ultimately requires full-time medical care (Anand et al., 2014).

The neuropathological hallmarks are characterized by the presence of senile plaques constituted by the amyloid-β (Aβ) peptide and neurofibrillary tangles (NFTs) composed of hyper-phosphorylated paired helical filaments of the microtubule-associated protein tau (MAPT) (Huang and Mucke, 2012). Aβ plaques form as a result of the sequential proteolytic cleavage of Aβ precursor protein (APP) by β-site APP-cleaving enzyme 1 (BACE1) and γ-secretase. It has been reported that dysregulation of BACE1 contribute to AD pathogenesis, leading to Aβ overproduction (Modarresi et al., 2011).

During the early stage of the pathology, extraneuronal Aβ plaques, intraneuronal NFTs and neuritic threads are observed in the entorhinal cortex and in the hippocampus, the key regions of memory and learning functions. Dysfunction of neurotransmission, loss of synapses and neuroinflammation are also involved in the AD pathogenesis (Reddy, 2017). Whereas the original clinical criteria for AD stated that the definitive diagnosis can only be achieved through post-mortem identification of the NFTs and/or abnormal plaque deposits in brain tissue (McKhann et al., 1984), the new 2011 guidelines recognized the potential use of brain imaging studies and cerebrospinal fluid (CSF) biomarkers to diagnose AD in living patients (McKhann et al., 2011).

The majority of AD cases are sporadic with a late-onset (LOAD), usually occurring in individuals aged 65 and older. Conversely, the early-onset AD (EOAD) forms are more commonly inherited with an autosomal dominant pattern and affect people under 65 years of age, generally presenting a positive family history. Genes associated to familial forms are involved in the maturation and processing of APP, resulting in production or aggregation of Aβ peptide (Campion et al., 1999).

In spite of AD prevalence, the etiology of the disease is not

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completely understood and there no effective therapeutic methods. Although behavioral symptoms can be alleviated by the currently therapeutic strategies, drugs that prevent or modify the disease course are not available (Mangialasche et al., 2010). So, a better understanding of molecular mechanisms underneath AD pathology could contribute to the discovery of novel therapeutic targets.

The recent progress of sensitive, high-throughput genomic technologies such as microarrays and next-generation sequencing (NGS) has resulted in the discovery of non-coding RNAs (ncRNAs), as novel regulators of gene expression at epigenetic, transcriptional and post-transcriptional levels (Wilusz et al., 2009; Bhan et al., 2017). Among them, long non-coding RNAs (lncRNAs), a subclass of ncRNAs, are typically defined as transcripts longer than 200 nucleotides, structurally resembling messenger RNAs (mRNAs) but with no protein-coding capacity (Mercer et al., 2009). Several studies have reported that lncRNAs participate in many biological phenomena: genetic imprinting, genome rearrangement, splicing, mRNA decay, immune response, pluripotency and development (Wu et al., 2013; Zhu et al., 2013). Moreover, aberrant expression of lncRNAs has been implicated in several human diseases, including cancer, cardiovascular and neurological disorders (Hu et al., 2014, 2018). Concerning AD, many lncRNAs have been found to be dysregulated (Table 1), mainly involved in processes such as regulation of Aβ accumulation/production, neuroinflammation, synaptic failure, neurotrophin depletion, mitochondrial dysfunction and stress responses to AD (Luo and Chen, 2016) (Fig. 1). The Table 2 summarizes the characteristics of samples used in the most relevant studies on AD-associated lncRNAs that are described below.

2. Long non-coding RNAs: characteristics and classification

As mentioned above, lncRNAs constitute a class of endogenous regulatory RNA molecules longer than 200 nucleotides. The estimated number of human lncRNA genes reported by the current GENCODE version is 15,779 and, interestingly, they display tissue-specific patterns with a large amount of them expressed in the brain (Derrien et al., 2012).

They are generally transcribed by RNA polymerase II or III and lack Kozak consensus sequence and a stable open reading frame (ORF). LncRNAs share some common features with mRNAs: they undergo the post-transcription modifications such as 5'-capping, polyadenylation and alternative splicing (Ponting et al., 2009). Unlike mRNAs, lncRNAs are shorter, expressed at lower levels, show a less efficient co-transcriptional splicing and display just an intron and fewer but longer exons (Ulitsky and Bartel, 2013). They are generally located in the nucleus, but some of them are enriched in the cytosol fraction and localized with ribosomes (Van Heesch et al., 2014; St Laurent et al., 2015). Surprisingly, some lncRNAs have been reported to be generated from mitochondrial genome and regulated by nuclear-encoded proteins (Rackham et al., 2011).

LncRNAs are broadly classified into four major classes, based on their biogenesis and genomic position and orientation in respect to protein-coding genes: (i) natural antisense transcript (NATs) or antisense RNAs, (ii) bidirectional RNAs, (iii) long intergenic RNAs (lincRNAs) and (iv) sense-intronic RNAs (Esteller, 2011; Peng et al., 2013) (Fig. 2). NATs are endogenous RNAs which partially or completely overlap genes transcribed from the opposite strand. Slightly diverse from NATs, bidirectional RNAs are transcribed in the opposite direction relative to the protein-coding gene within 1 kb of its promoter region. LincRNAs are transcribed in the genomic regions between two protein-coding genes and the majority of them are enhancer RNAs (eRNAs), generally located in the enhancer regions acting *in cis* on the promoters of the downstream genes. Finally, sense-intronic RNAs are transcribed from the sense strand of introns with no overlap of exonic sequences (Lanzafame et al., 2018). In addition to these main categories, several other subclasses have been proposed, including transcribed pseudogenes (Pei et al., 2012), transcribed ultra-conserved regions (Mestdagh et al., 2010) and eRNAs (Kim et al., 2010). Among them, pseudogenes are genomic DNA sequences resembling functional genes but which have lost their protein-coding ability because of mutations. Owing to the fact that they still share a high sequence similarity, pseudogenes are therefore able to regulate their parental genes through the generation of pseudogene-expressed lncRNAs. They represent an emerging novel group of lncRNAs which function as competing endogenous RNAs (ceRNAs) regulating other RNA transcripts by competing for microRNAs (miRNAs), a class of conserved small ncRNAs (18 to 25 nucleotides) (Barbash et al., 2017). Moreover, pseudogenes can act as a source of endogenous small-interfering RNAs (siRNAs) to silence protein-coding transcripts (Poliseno and Marranci, 2015).

3. Aβ plaques formation

3.1. β-site APP-cleaving enzyme 1 antisense RNA (BACE1-AS)

BACE1-AS is transcribed by RNA polymerase II from the antisense strand of *BACE1* locus mapped on chromosome 11 and, like mRNA, it has a 5'-capping and a poly-A tail. So, *BACE1* mRNA and *BACE1-AS* represent two transcripts from the same locus and together expressed in different human tissues, comprising brain and placenta. *BACE1-AS* is highly expressed in AD patients as well as in the APP transgenic mice. *BACE1-AS* is able to regulate both *BACE1* mRNA expression and its protein levels *in vitro* and *in vivo*. Unlike other NATs inhibiting mRNA translation by forming duplex with the sense mRNA, *BACE1-AS* modulated *BACE1* mRNA expression increasing its stability with additional Aβ production. Faghihi and collaborators reported that when *BACE1-AS* is silenced in mouse brain by siRNA, levels of *BACE1* mRNA were also significantly reduced in the cortex, central and dorsal

Table 1
Main dysregulated long non-coding RNAs in Alzheimer's disease.

LncRNA	Target	AD-related process	Biological function	References
BACE1-AS	*BACE1*	Aβ deposition	Upregulating *BACE1* mRNA stability	Faghihi et al., 2008; Modarresi et al., 2011
51 A	*SORL1*	Aβ deposition	Downregulating *SORL1* variant A	Ma et al., 2009; Ciarlo et al., 2013
17 A	*GPR51* (*GABBR2*)	Neuroinflammation	Impairing the GABAB signaling pathway	Massone et al., 2011
NDM29	BACE, γ-secretase	Neuroinflammation	Promoting the cleavage activity of BACE and γ-secretase	Massone et al., 2012
BC200	eIF4 A	Neuronal plasticity	Modulating local protein synthesis to maintain the long-term synapse plasticity	Mus et al., 2007; Lin et al., 2008
GDNFOS	*GDNF*	Neuronal plasticity	Regulating the expression of endogenous GDNF in human brain	Airavaara et al., 2011
BDNF-AS	*BDNF*	Neuronal plasticity	Inhibiting *BDNF* mRNA transcription by altering chromatin at the *BDNF* locus	Modarresi et al., 2012
Sox2OT	*Sox2*	Neuronal differentiation	Regulating co-transcribed *Sox2* gene to down neurogenesis	Arisi et al., 2011
EBF3-AS	*EBF3*	Neuronal apoptosis	Promoting neuronal apoptosis in AD	Magistri et al., 2015; Gu et al., 2018
NAT-Rad18	*RAD18*	Neuronal apoptosis	Causing neurons more sensitive to apoptosis	Parenti et al., 2007

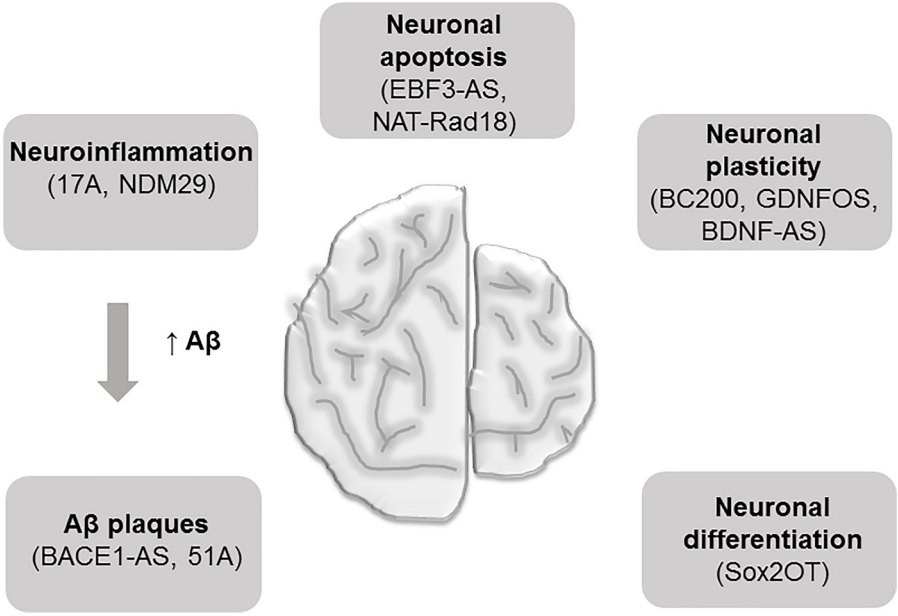

Fig. 1. A summary of the most dysregulated lncRNAs in Alzheimer's disease. Each AD-related lncRNA is grouped according to the area of the disease pathogenesis in which it has been implicated.

hippocampus, regions that are involved in AD progression.

Furthermore, *BACE1-AS* expression can be induced by various cell stressors (Aβ, high glucose, serum starvation, H_2O_2), resulting in an increased *BACE1* mRNA stability which in turn enhanced APP processing and the toxic Aβ generation by a post-transcriptional feed-forward mechanism (Faghihi et al., 2008). Indeed, cell stressors have long been involved in AD pathogenesis (Boland et al., 2008; Shah et al., 2012): an increase in *BACE1-AS* expression due to its stress response may contribute to AD development through enhancing *BACE1* expression. Furthermore, *BACE1* loss in animal models resulted in several physiological and behavioral deficits, such as decreased synaptic plasticity, memory and emotional loss (Laird et al., 2005; Ma et al., 2007).

Liu et al. observed that also in Aβ-induced cell AD model the expression of both *BACE1-AS* and *BACE1* mRNA increases, analogous to what happens in human AD brains. Moreover, siRNA-mediated silencing of this lncRNA resulted in the attenuation of BACE1 ability to cleave APP, reducing thus the formation on senile plaque in this model (Liu et al., 2014). It has been pointed out that in *APP* transgenic mice, hippocampal neurogenesis is increased at an early age before AD symptoms exhibit probably because of detectable Aβ levels in the brains (Jin et al., 2004). In this regard, it has been hypothesized that BACE1-AS can have a role as modulator of adult neurogenesis: knocking down *BACE1* or *BACE1-AS*, it was possible not only to change Aβ aggregation pattern, but also to increase the expression of several neurogenesis markers in hippocampus (Modarresi et al., 2011).

Recent evidences reported a novel functional role of lncRNAs, suggesting that they are able to interact with other classes of ncRNAs, including miRNAs and thus modulate miRNA-mediated regulation (Jalali et al., 2013). Interestingly, miR-485-5p has been found to be involved in *BACE1* post-transcriptional regulation. *BACE1-AS* prevented *BACE1* mRNA repression induced by this miRNA, masking its binding site and therefore promoting Aβ synthesis. Indeed, *BACE1-AS* and miR-485-5p compete for binding to the same region of *BACE1* mRNA (Faghihi et al., 2010). Kang and collaborators observed that both *BACE1-AS* and *BACE1* transcripts can bind HuD, a primarily neuronal RNA-binding protein involved in memory and learning. HuD also stabilized and associated with *APP* mRNA, promoting thus Aβ generation by increasing APP and BACE1 protein as well as *BACE1-AS* levels. Importantly, both cortical tissue from AD patients and brains of HuD-overexpressing transgenic mice displayed high levels of BACE1, BACE1-AS, APP and Aβ (Kang et al., 2014). All these considerations further support a role of BACE1-AS as a fine regulator of BACE1 expression by different mechanisms.

Recently, because of their stability in plasma, lncRNAs have been

Table 2
A summary of the most relevant studies performed on AD-associated lncRNAs.

LncRNA	Species	N	Sex (m:f)	Clinical manifestation	Population of origin	References
BACE1-AS	human	35	n.a.	AD	n.a.	Faghihi et al., 2008
	human	88	57:31	Moderate and severe AD	China	Feng et al., 2018
51A	human	23	15:8	Mild and moderate AD	USA	Ma et al., 2009
	human	23	n.a.	Mild, moderate and severe AD	USA	Ciarlo et al., 2013
	human	70	33:37	Moderate AD	China	Deng et al., 2017
17A	human	18	n.a.	Mild, severe and moderate AD	USA	Massone et al., 2011
NDM29	human	13	n.a.	Moderate and severe AD	USA	Massone et al., 2012
BC200	human	10	6:4	AD	Canada	Lukiw et al., 1992
	human	9	n.a.	AD	Switzerland	Mus et al., 2007
GDNFOS	human	20	4:16	AD	USA	Airavaara et al., 2011
Sox2OT	mouse	30	0:30	n.a.	n.a.	Arisi et al., 2011
EBF3-AS	human	25	11:14	Moderate and severe AD	USA	Magistri et al., 2015
NAT-Rad18	rat	5	5:0	n.a.	n.a.	Parenti et al., 2007

N: number; n.a: not available.

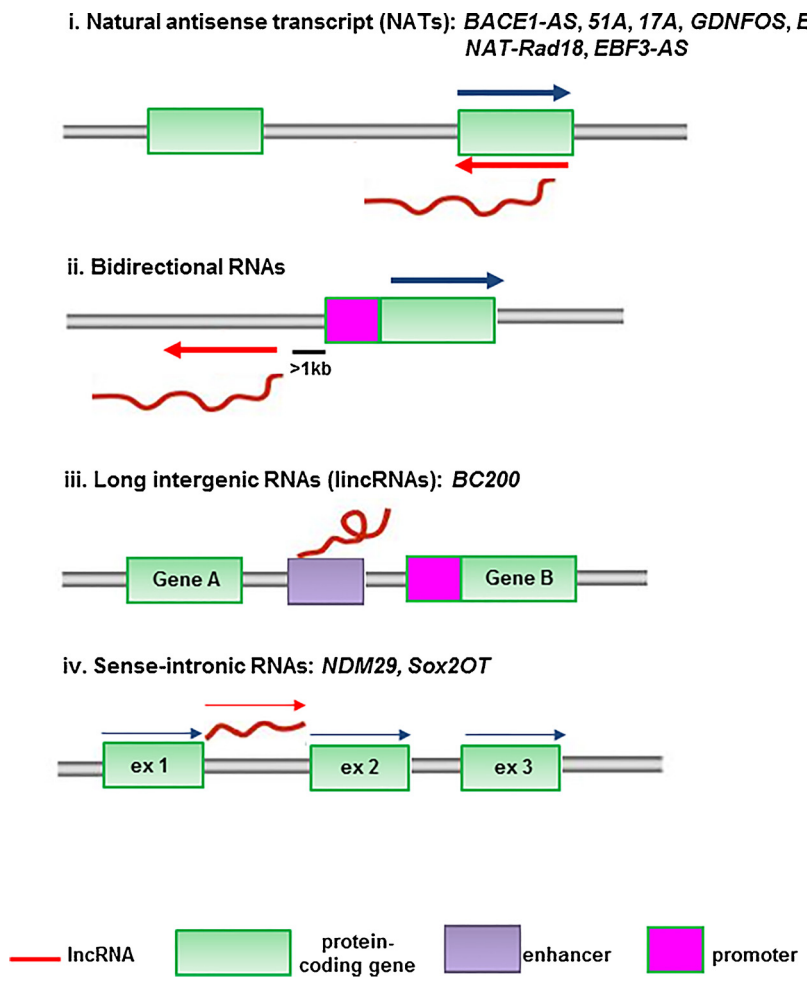

Fig. 2. Classification of lncRNAs according to the their genomic position and orientation in respect to protein-coding genes. (i) NATs partially or completely overlap genes transcribed from the opposite strand; (ii) bidirectional RNAs are transcribed from the opposite strand relative to the protein-coding gene within 1 kb of its promoter; (iii) lincRNAs are transcribed in the genomic regions between two protein-coding gene, usually located in the enhancer region; (iv) sense-intronic RNAs are transcribed from the sense strand of introns with no overlap of exonic sequences.
Each AD-associated lncRNA is associated to the corresponding subtype.

proposed as novel peripheral biomarkers for AD. *BACE1-AS* was found to be increased in plasma of AD patients with high specificity, proposing its role as potential biomarker for diagnosis of this disorder. However no correlation was found between the expression of this lncRNAs and the mini-mental state examination (MMSE), a brief cognitive test used to estimate the severity of cognitive impairment (Feng et al., 2018).

3.2. 51A

51A is transcribed by polymerase III and mapped to the first intron of sortilin-related receptor 1 (*SORL1*, also known as *LR11* or *SORLA*) gene on the antisense strand. SORL1 is a transmembrane neuronal sorting protein with an unknown function which is expressed in neurons of the central and the peripheral nervous system. Ma et al. reported that the expression of *SORL1* is reduced in cerebrospinal fluid (CSF) of patients affected by AD, suggesting its potential role in the pathogenesis of this disorder (Ma et al., 2009). The link between AD and SORL1 was also supported by the demonstration that this protein, acting as a sorting receptor during APP translocation, affects its cleavage and trafficking in endosomes and the trans-Golgi network. A decreased or absent *SORL1* expression impairs APP cleavage pathway and promotes neurotoxic Aβ formation (Andersen et al., 2005). A further evidence strengthening its role as AD susceptibility factor was the association of *SORL1* allelic variants with AD-related brain morphologies (Assareh et al., 2014).

51A changes the splicing pattern of *SORL1,* promoting the expression of the alternatively spliced variant instead of the canonical long protein variant A. Under these conditions, APP processing is impaired, resulting in an increase of Aβ deposition. Moreover, it has been reported that 51A is upregulated in the brains of AD post-mortem patients (Ciarlo et al., 2013). All these considerations suggest that 51A may be involved in AD pathology, acting as a regulator of *SORL1* alternative splicing which in turn leads to an increased Aβ formation.

A recent study showed that *51A* is upregulated in plasma from sporadic AD patients, suggesting its possible role as a stable diagnostic biomarker for this disorder. Importantly, the same authors found that the expression of this lncRNA negatively correlates with the disease progression evaluated by MMSE score (Deng et al., 2017).

4. Neuroinflammation

4.1. 17A

17A is a 159-nt lncRNA, so it does not strictly belong to the lncRNA classification according to its length. However, it is transcribed by RNA polymerase III and embedded in an antisense orientation of intron 3 of the human G-protein coupled receptor 51 (*GPR51*, also named

GABBR2) gene, affecting *GPR51* alternative splicing and promoting the formation of the alternative and unfunctional splicing isoform of GABAB R2 receptor. LncRNA 17A decreases the transcription of the canonical isoform of GABAB R2, so significantly impairing the GABAB signaling pathway (Zhou et al., 2014). Massone and collaborators reported that 17A is expressed in AD brain in response to inflammation stimuli, thereby promoting Aβ secretion and increasing its accumulation. Furthermore, *17A* has been found to be upregulated in cerebral cortices from AD patients, suggesting its direct or indirect role in the disease pathogenesis (Massone et al., 2011).

4.2. Neuroblastoma differentiation marker 29 (NDM29)

Neuroblastoma differentiation marker 29 (*NDM29*) is transcribed by RNA polymerase III from the first intron of the *ASCL3* (achaete scute-like homologue 3) gene and its synthesis is regulated by an extragenic type-3 promoter (Pagano et al., 2007). In humans, *NDM29* maps to a genomic region of chromosome 11, whose deletion is implicated in neuroblastoma development (De Preter et al., 2005). Massone and collaborators showed that high levels of *NDM29* transcripts induce APP synthesis, which in turn lead to an increase of Aβ secretion. Interestingly, like *17A*, the same authors demonstrated that the expression of *NDM29* can be promoted by inflammatory stimuli and inhibited by anti-inflammatory drugs. Finally, they also reported that this lncRNA, normally detected in the cortex, cerebellum and white matter of normal humans, is abnormally expressed in sporadic AD brains (Massone et al., 2011, 2012).

5. Neuronal plasticity

5.1. Brain cytoplasmic 200 RNA (BC200)

As briefly mentioned in the Introduction section, the synapse loss represents a critical feature in AD already occurring in the first stages of the disorder. Synapse plasticity is one of the most important neurochemical foundation of memory and learning and it has been demonstrated that Aβ, Aβ oligomers and hyper-phosphorylated tau impair synapse structure and function in AD brains (Shankar et al., 2008). In this regard, the role of the lincRNA primate-specific *BC200* (also known as *BCYRN1*) and its functional analog in rodents *BC1* in synaptic plasticity has been reported in different studies (Lin et al., 2008; Wang et al., 2002). BC200, expressed in adult nervous system, is transcribed by RNA polymerase III, firstly in the cell body of nerve cells and then transported into the dendrites during the synaptogenesis where it contributes to the regulation of local protein synthesis (Muslimov et al., 1997). It acts as a translational regulator targeting eukaryotic initiation factor 4A (eIF4A), an adenosine triphosphate (ATP)-dependent RNA helicase. The binding between BC200 and eIF4A results in decoupling ATP hydrolysis from RNA duplex unwinding, modulating synapse-related protein synthesis and providing thus to the preservation of long-term plasticity (Lin et al., 2008). In addition to eIF4A, *BC200* interacts with other RNA-binding proteins controlling mRNA translation, such as fragile X mental retardation protein (FMRP), synaptotagmin binding cytoplasmic RNA interacting protein (SYNCRIP) and poly(A)-binding protein (PABP) at the level of post-synaptic dendritic microdomains (Muddashetty et al., 2002; Zalfa et al., 2005; Duning et al., 2008).

BC200 showed a subcellular mislocalization (non-somatodendritic) and abnormal expression levels in brain regions of patients affected by AD. In this regard, although *BC200* expression decreases during normal ageing in frontal cortex, a post-mortem study found high levels of this lncRNA in AD patients and its upregulation was specific to the brain areas involved in the disease. Moreover, the relative *BC200* levels in AD-involved cerebral regions increased in parallel with the progression of the disorder, evaluated by the clinical dementia rating (CDR) score of AD patients. These evidences suggested that BC200 overexpression and its aberrant localization may represent a compensatory response to synaptodendritic deterioration occurring in AD neurons or its cause (Mus et al., 2007). However, a previous study reported opposite results, showing a reduced *BC200* expression in AD brains (Lukiw et al., 1992). This discrepancy may be explained by differences in sampled brain regions or the disease severity, but in any case both studies underline an abnormal *BC200* expression in AD cerebral tissue.

An in vivo study performed on BC1 knockout mice suggested an involvement of this lncRNA in memory and learning processes. Mutant mice, showing normal brain morphology with no apparent neurological defects, displayed behavioral changes, such as increased anxiety and reduced exploration, but the spatial memory was preserved (Lewejohann et al., 2004). Interestingly, a recent study demonstrated that BC1 controls APP mRNA translation through the direct association with FMRP. In particular, BC1 inhibition or BC1-FMRP association repressed the translation of APP, blocking thus the Aβ aggregation in brain and preventing impairments of memory and spatial learning in AD mice (Zhang et al., 2018).

5.2. Glial cell line-derived neurotrophic factor opposite strand (GDNFOS)

GDNFOS is a *cis*-natural antisense transcribed from the opposite strand of glial cell line-derived neurotrophic factor (*GDNF*) gene only in primate genomes. GDNF is a member of a group of neurotrophins involved in neuron survival, synaptic plasticity, neurite branching and increase of neural stem cell migration and differentiation. In patients with early AD, GDNF concentration was found to be significantly increased in CSF and reduced in serum, hypothesizing that its regulation may be involved in the pathological processes occurring in AD (Straten et al., 2009). *GDNFOS* contains four exons that are alternative spliced into three different isoforms, including *GDNFOS1*, *GDNFOS2* and *GDNFOS3*. *GDNFOS1*, overlapping with *GDNF* transcript, and *GDNFOS2* are lncRNAs, whereas *GDNFOS3* has a potential ORF, encoding a protein of 105 amino acids with no homologs in GenBank. *GDNFOS1* is differentially expressed in human brain and its transcriptional levels are lower than the *GDNF* isoform encompassing exons 1 and 4, suggesting that this lncRNA may influence the higher amounts of *GDNF* proforms in the cerebral tissue (Airavaara et al., 2011).

5.3. Brain-derived neurotrophic factor antisense RNA (BDNF-AS)

BDNF-AS, also known as *BDNF-OS*, is a lncRNA transcribed from the opposite strand of brain derived neutrophic factor (BDNF), another neurotrophin involved in neuronal growth, maturation, differentiation, memory processes and learning. *BDNF* expression levels are decreased in neurodevelopmental, psychiatric and neurodegenerative disorders (Luo et al., 2010; Gonul et al., 2011). Modarresi et al. observed that this neurotrophic factor is under the control of *BDNF-AS* which represses *BDNF* mRNA transcription by altering chromatin at its locus, thus reducing protein level and function. Therefore, *BDNF-AS* inhibition may represent a good strategy for treating AD by specifically increasing *BDNF* levels (Modarresi et al., 2012).

6. Neuronal differentiation

6.1. Sox2 overlapping transcript (Sox2OT)

Sox2OT embeds the single-exon *Sox2* gene within one of its introns and they are both transcribed in the same orientation (Fantes et al., 2003). Sox2 is a key regulator of the stem cell pluripotency, whose expression may be regulated by the co-transcribed *Sox2OT* gene. This lncRNA is implicated in neuronal embryonic development in several organisms and adult mouse neurogenesis (Amaral et al., 2009). Knauss et al. recently found that *Sox2OT* is expressed in developing mouse cerebral cortex with a regulatory role in promoting neuronal differentiation and cortical neurogenesis through the repression of Sox2 in neuronal progenitors (Knauss et al., 2018). Interestingly, a study

performed by whole genome microarray analysis in an anti-NGF (nerve growth factor) AD11 transgenic mouse model found *Sox2OT* as a potential biomarker for both early and late stages of AD-like neurodegeneration (Arisi et al., 2011).

7. Neuronal apoptosis

7.1. Early B cell factor 3 antisense RNA (EBF3-AS)

Using RNA sequencing in order to discover alterations in lncRNA profile of AD brains, Magistri and collaborators found that *EBF3-AS* is dysregulated in LOAD as compared with healthy controls (Magistri et al., 2015). A recent study performed in an AD transgenic mouse model demonstrated that *EBF3-AS* is upregulated in the hippocampus, suggesting its potential role in the disease pathogenesis. Furthermore, the same authors investigated the function of this lncRNA *in vitro*, observing that *EBF3-AS* is able to stimulate *EBF3* expression which in turn promotes neuron apoptosis in AD. Altogether these evidences may provide novel insights into the pharmacological treatment of the disorder, targeting *EBF3-AS* (Gu et al., 2018).

7.2. NAT-Rad18

NAT-Rad18 is a natural antisense transcript against *Rad18*, encoding a DNA damage repair protein.

One study performed in rats demonstrated that it is expressed in brain tissue and upregulated in cortical neurons after Aβ treatment. This evidence suggests that *NAT-Rad18* decreases the ability of neurons to response to DNA damage-related stress, increasing their susceptibility to apoptosis (Parenti et al., 2007). This finding indicates a possible role of DNA repair system in AD pathogenesis.

8. Other candidate lncRNAs

Single nucleotide polymorphisms (SNPs) within lncRNAs have been also associated with a wide range of human diseases. In particular, the rs1333049 located in the *ANRIL* (*Antisense Noncoding RNA In The INK4 Locus*, also named as *CDKN2B-AS* or *CDKN2B-AS1*) lncRNA gene on chromosome 9 has been found to be associated with AD (Yu et al., 2010; Emanuele et al., 2011). Furthermore, *ANRIL* regulates *CDKN2B* expression which accumulates in Aβ plaques and NFTs in AD brains (Arendt et al., 1998). Another study reported that rs7990916 in the lincRNA 0108001,080 (linc01080) is associated with regional cortical gray matter volume in normal individuals and in patients affected by mild cognitive impairment and AD (Chen et al., 2013).

Zhou and Xu identified twenty-four upregulated and eighty-four downregulated lncRNAs in post-mortem tissue samples of AD as compared with healthy controls by a reannotation of microarray data (Zhou and Xu, 2015). Among them, the highly upregulated lncRNA, *n336934*, encoded by mitochondrial genome, was significantly associated with cholesterol homeostasis pathway which is implicated in the regulation of Aβ generation in AD (Hannaoui et al., 2014). On the other hand, among the most downregulated lncRNAs, *n341006* was found to the be associated with the ubiquitin pathway. Indeed, increasing evidences pointed out that the ubiquitin-proteasomal system (UPS) pathway is dysregulated in AD brains and several related genes have been found to be involved in the disease pathogenesis (Zhang et al., 2017). Additionally, some ubiquitin-conjugating enzymes such as UBB, UBE2N and UBE3C are involved in AD pathogenesis (De Vrij et al., 2001).

9. Conclusions

Whole-transcriptome analyses have provided important insights into the biological and clinical relevance of lncRNAs in AD. Indeed, they are found to be expressed in the brain and are emerging as key regulators of several neurological and neurodevelopmental processes. To date, many lncRNAs have been found to be involved in the disease pathogenesis and in the regulation of AD-associated gene expression (Table 1), but how they influence AD onset and its progression remains to be discovered. Unraveling the regulatory networks and the molecular mechanisms of lncRNAs in AD will allow the development of innovative pharmacological treatments with lncRNAs as more appropriate drug targets, since no effective therapeutic strategies are currently available. For example, a potential therapeutic use of *UBE3A* antisense transcript (*UBE3A-ATS*) using antisense oligonucleotides (ASOs) has been successfully proposed for the treatment of patients with Angelman syndrome (Meng et al., 2015) and similar ASO-based therapeutic approached have also been proposed for a wide range of disorders. Among them, some of the ongoing phase I/II clinical trials using ASO-mediated therapies have been developed mainly for the treatment of different types of cancers, including chronic lymphocytic leukemia, diffuse large B cell lymphoma and squamous cell lung cancer (Adams et al., 2017). In this way, ASOs are able to correct the specific function/expression of a lncRNA by sterically blocking its activity of inducing RNase H-dependent degradation in the nucleus. Moreover, ASOs should be more efficient than siRNAs to target lncRNAs in the nucleus, the compartment in which the vast majority of them predominantly reside (Lennox and Behlke, 2016). However, ASOs are highly unstable in cells, subjected to nucleases and they show low target affinity and potency, so higher concentrations and chemical modifications are required to avoid incidence of off-target effects, improve their delivery and an adequate cellular uptake. Disorders affecting the central nervous system (CNS) show problems that limit an effective and efficient drug delivery: ASOs are not able to cross the blood brain barrier (BBB) which restricts the entry of certain molecules based on size, solubility or charge, limiting the possibility to use ASOs in the treatment of neurodegenerative disorders. However, it has been proposed to deliver them to the CSF that circulates throughout the CNS by ICT (intracerebroventricularly) or IT (intrathecal) infusions. To date, IT ASO delivery has been implemented in two phase I clinical trials for amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) patients without any major adverse side effects with promising results in terms of safe and adverse side effects (Miller et al., 2013; Chiriboga et al., 2016). Regarding AD, the development of specific ASOs downregulating *BACE1-AS*, *51A*, *17A*, *NDM29* and *BDNF-AS* may represent an innovative therapeutic strategy in order to decrease Aβ generation in AD, as already demonstrated to be efficient in AD cell models and animals (Massone et al., 2011; Modarresi et al., 2011; Massone et al., 2012; Liu et al., 2014). Another therapeutic approach could reside in the pharmacological modulation of lncRNAs in order to change the expression of already known target genes implicated in AD.

Importantly, lncRNAs may be used as potential AD biomarker for early detection of the pathology, the diagnosis and the possible prevention, mainly if their abnormal expression pattern can be easily detected in blood or CSF of AD patients (Ma et al., 2009; Straten et al., 2009, Feng et al., 2018). In this regard, the use of lncRNAs as diagnostic and prognostic markers has already been exploited in the oncology field, in which they have been found to be associated with the prognosis of cancer patients (Xie et al., 2013), including hepatocellular carcinoma, breast and colorectal cancers (Kogo et al., 2011).

In conclusion, the role of lncRNAs in the AD pathogenesis is not completely elucidated, but promises to open more avenues to early diagnosis and setting-up of innovative therapies.

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Declaration of interest

None.

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