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Review

Gene regulation by antisense transcription: A focus on neurological and cancer diseases

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ABSTRACT

Advances in high-throughput sequencing over the past decades have led to the identification of thousands of non-coding RNAs (ncRNAs), which play a major role in regulating gene expression. One emerging class of ncRNAs is the natural antisense transcripts (NATs), the RNA molecules transcribed from the opposite strand of a protein-coding gene locus. NATs are known to concordantly and discordantly regulate gene expression in both *cis* and *trans* manners at the transcriptional, post-transcriptional, translational, and epigenetic levels. Aberrant

Abbreviations: ncRNAs, non-coding RNAs; rRNAs, ribosomal RNAs; tRNAs, transfer RNAs; snRNAs, small nuclear RNAs; snoRNAs, small nucleolar RNAs; mRNA, messenger RNA; miRNA, microRNA; siRNA, small interfering RNA; PIWI, P-element-induced wimpy testis; piRNAs, PIWI-interacting RNAs; lncRNAs, long non-coding RNA; lincRNA, long intergenic ncRNA; circRNAs, circular RNAs; CARs, chromatin-associated RNAs; ceRNAs, competing endogenous RNAs; NATs, natural antisense transcripts; ORF, open reading frame; CNS, central nervous system; AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; SMA, spinal muscular atrophy; APP, amyloid precursor protein; PS1, presenilin 1; PS2, presenilin 2; BACE1, beta-site APP cleaving enzyme 1; IRES, internal ribosome entry site; MIR, mammalian-wide interspersed repeat; AAV, adeno-associated virus; BDNF, brain-derived neurotrophic factor; RGCs, retinal ganglion cells; GDNF, glial cell line-derived neutrophic factor; UCHL1, ubiquitin carboxy-terminal hydrolase L1; HTT, huntingtin; SMN1, survival motor neuron 1; PRC2, polycomb repressive complex-2; ASO, antisense oligonucleotide; SSO, splice-switching oligonucleotide; ATXN8, ataxin 8; FXS, fragile X syndrome; UTR, untranslated region; FXTAS, fragile X-associated tremor and ataxia syndrome; NSCLC, non-small cell lung cancer; HIF-1α, hypoxia inducible factor-1α; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; AS1, antisense RNA 1; TBX5, T-box transcription factor 5; ox-LDL, oxidized low-density lipoprotein.

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expression of NATs can therefore cause dysregulation in many biological pathways and has been observed in many genetic diseases. This review outlines the involvements and mechanisms of NATs in the pathogenesis of various diseases, with a special emphasis on neurodegenerative diseases and cancer. We also summarize recent findings on NAT knockdown and/or overexpression experiments and discuss the potential of NATs as promising targets for future gene therapies.

1. Introduction

The central dogma of molecular biology, first proposed by Francis Crick in 1958 and later reiterated in 1970, posits that biological information flows along the DNA-RNA-protein axis [1]. However, it has become clear since the 1980 s that not all DNA codes for a protein. Through advances in genomic and transcriptomic technologies in the past decades, it has been revealed that although up to 90% of the human genome is transcribed, about 99% of these are not translated into proteins [2,3]. In fact, the human genome contains only about 20,000 protein-coding genes, which constitute less than 2% of the entire genome [4–6]. The considerably greater proportion of non-coding sequences relative to protein-coding genes is also commonly observed in other species, particularly in complex eukaryotic organisms (but less so in simple organisms such as *Caenorhabditis elegans* and *Schizosaccharomyces pombe*; a phenomenon termed the G-value paradox) [7,8].

Until the 21st century, most non-protein-coding DNA sequences had received little attention and were often regarded as "junk" DNA. This is further corroborated by the observation that most mutations responsible for various human genetic diseases are found in protein-coding sequences or their regulatory regions. However, it has long been known that many of the non-protein-coding sequences are conserved across different species, which suggests that they may have important roles in maintaining normal biological functions [9]. Furthermore, it soon became clear that these non-protein-coding sequences often serve as a template for transcription into functional RNA transcripts, collectively known as the non-coding RNAs (ncRNAs) [10–16]. In the current era of high-throughput sequencing, tens of thousands of ncRNAs have been identified, and several databases have been created to curate the overwhelmingly increasing number of the identified ncRNAs [17,18]. These ncRNAs can be classified into either housekeeping ncRNAs or regulatory ncRNAs. Housekeeping ncRNAs, including ribosomal RNAs (rRNAs), transfer RNAs (tRNAs), small nuclear RNAs (snRNAs), and small nucleolar RNAs (snoRNAs), are required for crucial cellular functions such as gene splicing and messenger RNA (mRNA) translation [19–22]. On the other hand, regulatory ncRNAs are involved in modulating and fine-tuning gene expressions and are expressed differentially in various tissue conditions [8,23–25].

Regulatory ncRNAs play important roles in influencing the expression of essentially all genes in the genome, including those involved in key biological processes, such as cell growth and development, apoptosis, inflammation, and DNA repair. For this reason, dysregulation in the cellular levels of ncRNAs has been observed in many disorders, including but not limited to cancers, neurodegenerative diseases, and cardiovascular diseases [26–36]. Given this, it has been suggested that ncRNAs may potentially serve as biomarkers for disease diagnosis, prognostication, and therapy [37–40]. Several ncRNA-based therapeutics have been developed and some are gradually being adopted into clinical practice, such as inotersen for the treatment of familial amyloid polyneuropathy and patisiran for the treatment of transthyretin amyloidosis [41].

Based on their size, regulatory ncRNAs can be categorized into either short ncRNAs (<200 nucleotides) or long ncRNAs (>200 nucleotides). Some examples of short ncRNAs include the microRNAs (miRNAs), small interfering RNAs (siRNAs), and P-element-induced wimpy testis (PIWI)-interacting RNAs (piRNAs) [42–44]. On the other hand, long ncRNAs (lncRNAs) consists of a large heterogeneous class of RNAs, which are categorized conveniently based on various attributes such as the transcript length and location (e.g. long intergenic ncRNAs, lincRNAs), structure (e.g. circular RNAs, circRNAs), association with subcellular structures (e.g. chromatin-associated RNAs, CARs), function (e.g. competing endogenous RNA, ceRNAs), and orientation relative to the protein-coding genes (e.g. natural antisense transcripts, NATs), among others [42,43,45–48]. Among these mentioned lncRNAs, this review mainly focuses on NATs. It begins by describing NATs and summarizing their functions and mechanisms. Moreover, their roles in the pathophysiological processes associated with neurodegenerative disorders and cancers have been addressed, as well as current advancements in the development of NAT-based therapeutics.

2. The natural antisense transcripts (NATs)

Although DNA transcription is frequently thought to occur in a unidirectional manner (on the 'sense' strand), research since the 2000 s has found that bidirectional transcription, which produces antisense transcripts, is not uncommon [49]. NATs, as the name suggests, are single-stranded RNAs transcribed from a DNA template strand in the opposite direction to that of its sense transcript [50]. NATs are typically 200–400 nucleotides in length and usually do not contain an open reading frame (ORF), although some exceptions have been documented [51,52]. For example, genes encoding for deoxyhypusine synthase, erythropoietin receptor, basic fibroblast growth factor, and thymidylate synthase, which contain an ORF, have been found to function as NATs to regulate the expression of their target genes [9,53]. Transcriptomic studies have demonstrated the presence of more than 5500 NATs in the eukaryotic genomes, particularly in humans, rats and mice. In fact, they make up approximately 30% of annotated human genes and are expressed abundantly in eukaryotic organisms [54].

Depending on the location of their target genes, NATs can be classified into either *trans* or *cis* types (Fig. 1). *Trans*-NATs are transcribed from a genomic locus that is a distance away from their target genes and often have imperfect complementarity to their target transcripts. On the other hand, *cis*-NATs are transcribed from the same genomic locus as their targets and show a perfect complementarity to the latter [52,54]. *Cis*-NATs can be further categorized into several different subtypes based on how they overlap with their target transcripts: (i) head-to-head (divergent) NATs, whose 5' end overlaps with the 5' end of the target; (ii) tail-to-tail (convergent) NATs, whose 3' end overlaps with the 3' end of the target; (iii) overlapping (embedded) NATs, which bind to their targets in entirety; and (iv) nearby NATs, which do not overlap with their targets but are located very close to them [55].

3. The role of NATs in physiology and pathology

A series of experiments in the 1980 s, pioneered by Lacatena and Cesareni [56], provided the first clue that NATs play an important function in regulating gene expression. According to their findings, an RNA transcript transcribed in the opposite direction to that of ColE1 plasmid could inhibit the replication of the latter [56,57]. Subsequent research over the years demonstrated that NATs could either increase or decrease the gene expression (termed concordant and discordant regulation, respectively), although the former is less common [58,59]. NATs can be found in both the nucleus and cytoplasm and may therefore participate in the regulation of gene expression via several mechanisms [60]. Thus far, NATs are known to alter gene expression at the transcriptional, post-transcriptional, and translational levels and may also

affect RNA stability and transport [61–64]. For example, at the transcriptional level, NATs are known to be co-expressed with the sense transcripts and form RNA hybrids or duplex structures with it, thus preventing the sense transcripts from being transcribed [57]. To achieve this, NATs usually, but not always, possess stem-loop motifs, which not only allow complementary base pairing with their targets but also enhance their stability [65]. Apart from that, NATs can achieve gene expression regulation via epigenetic changes, such as by mediating chromatin remodeling and recruiting enzymes involved in methylation and histone modification [8,55,64,66–70]. Commonly, NATs influence gene expression by more than one mechanism. This is exemplified by *Tsix*, which originates from downstream of *Xist* locus that is responsible for the X chromosome inactivation. *Tsix* mediates the *cis*-inhibition of *Xist* gene not only via the formation of RNA duplex which facilitates *Xist* degradation but also by modulating the process of chromatin modification [71]. Besides, it has been proposed that *Tsix* contains DNA elements that could inhibit *Xist* transcription at long range [72].

Genetic interaction networks are highly complex in eukaryotic organisms. Aberrant expression of a single gene can potentially wreak havoc on the downstream gene expression, which eventually leads to diseases. Indeed, genetic diseases are typically characterized by dysregulated gene expression [74,75]. Thus, regulatory factors, including NATs, must be kept at an optimal level to ensure an overall ideal target gene expression. This is especially true considering that about 70% of mammalian genes are known to produce NATs. For this reason, NATs are constantly found to have tissue-specific expression, which provides a clear indication that there are important evolutionarily-conserved functional roles for NATs [76–78]. In fact, dysregulation in the NATs expression has been linked to various pathological conditions [66,79,80]. Thus, the expression levels of NATs have been proposed to serve as promising biomarkers for the diagnosis, prognosis, and therapy of many human diseases, notably neurodegenerative diseases and cancer [81,82]. Table 1 shows preclinical studies on NATs for the treatment of various diseases.

4. NATs in neurodegenerative diseases

Neurodegenerative diseases are a group of disabling disorders involving progressive deterioration in diverse neurological manifestations due to structural damages in the central nervous system (CNS) [102,103]. The major characteristics of these diseases include abnormal conformation and/or spatial distribution of numerous proteins, such as amyloid in Alzheimer's disease (AD), tau in Pick bodies, α-synuclein in Lewy bodies, and TDP-43 in neuronal inclusions [104]. Thus, based on their pathophysiology, neurodegenerative diseases can be classified into either amyloidoses, tauopathies, synucleinopathies, or TDP-43 proteinopathies [104]. Some common examples of neurodegenerative diseases include AD, Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), spinal muscular atrophy (SMA), and spinocerebellar ataxias [105–109]. Neurodegenerative diseases are most common among the elderly, with the highest prevalence observed in late life [106]. Given the rising life expectancy, the incidence of these diseases is expected to be continuously increased [110].

lncRNAs are expressed abundantly in the CNS, and dysregulation of many lncRNAs has been associated with neurodegenerative diseases [111]. Some NATs commonly found to be expressed aberrantly in neurodegenerative diseases include *BACE1-AS*, *GDNF-AS*, *BDNF-AS*, *HTT-AS*, and *LOXL1-AS1* [112]. *In vitro* and in vivo experiments have indicated that targeting NATs may reduce the severity of these diseases. For example, inhibition of *BDNF-AS* has been shown to improve neuron survival [113]. Therefore, NATs may serve as a potential therapeutic target for neurodegenerative diseases, as detailed below.

4.1. Alzheimer's disease (AD)

AD is the most common neurodegenerative disease and a leading cause of dementia in adults older than 65 years [114]. The worldwide prevalence of AD is estimated to be 50 million cases in 2018 [115]. Approximately 90–95% of the cases are sporadic, while the remaining are hereditary [116,117]. Abnormal deposits of proteins, particularly the amyloid β-peptide (Aβ) and tau protein are the main causative mechanism for AD [118–120]. Two of the most crucial enzymes that can lead to abnormal protein aggregation are β-secretase and γ-secretase, which sequentially cleave the amyloid precursor protein (APP) to release the Aβ that eventually accumulates in the brains of AD patients [121–124]. Thus, these secretases are often found at an elevated level in the plasma of AD patients [121–124]. In addition, mutations in several genes have been known to increase the risk of AD at high penetrance. These include the *APP*, *presenilin 1* (*PS1*) and *presenilin 2* (*PS2*) genes which have been associated with an increased susceptibility to early-onset AD via A®42 isoform generation, and the *APOE* gene

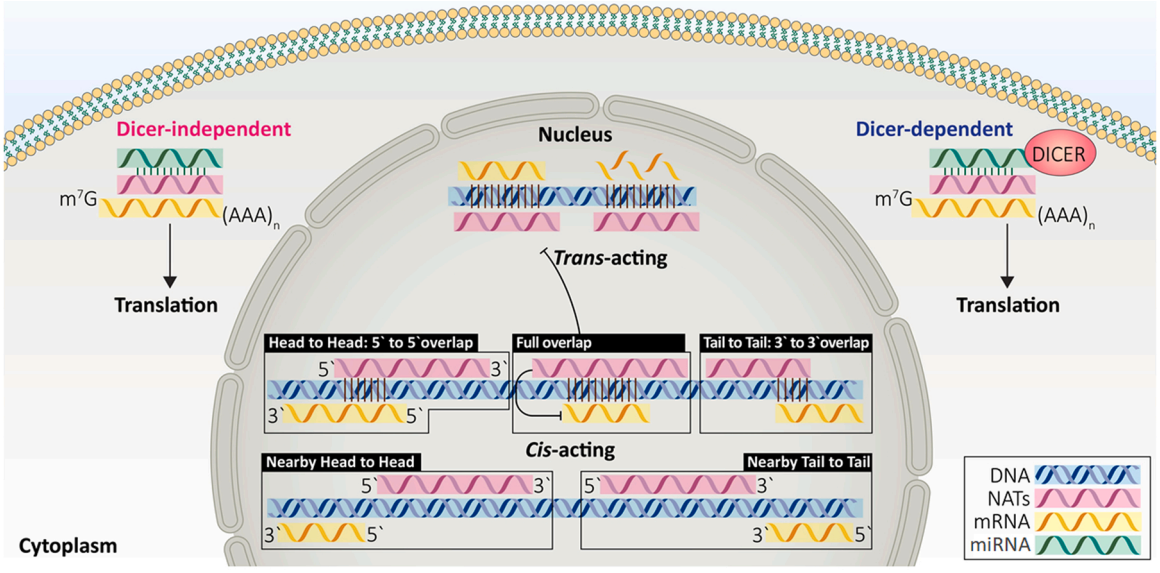

Fig. 1. The function of NATs in regulating gene expression. NATs function occurs in both nucleus and cytoplasm and can be Dicer-dependent and -independent. Redrawn from [73].

Table 1
Preclinical studies on natural antisense transcripts for treatment of different diseases.

Disease	Natural antisense transcript	Treatment strategy	*In vivo*/ *In vitro*	Cell line	Animal model	Delivery	Remarks	Ref.
AD	*BACE1-AS*	*BACE1-AS* siRNA	*In vitro* and in vivo	Primary hippocampal neurons	SAMP8 mice (Alzheimer model) and SAMR1 (Healthy mice)	Lentivirus	*In vitro*: Enhanced proliferation of primary hippocampal neurons and improved survival. *In vivo*: Improvement of memory and learning behaviors, inhibition of BACE1 and amyloid precursor protein production, and au protein phosphorylation in the hippocampus.	[83]
	BACE1-AS	*BACE1-AS* siRNA	*In vitro*	$A\beta_{1-42}$-treated SH-SY5Y cells	–	Lipofectamine 2000	Reduction in APP-cleaving activity of *BACE1* and delayed induction of SP formation	[84]
	BACE1-AS	*BACE1-AS* shRNA	*In vitro* and in vivo	$A\beta_{1-42}$-treated SH-SY5Y cells	APP/PS1 mice (Alzheimer model)	Lipofectamine 2000 (in vitro) Glass pipette using a Nanoliter 2010 Injector (in vivo)	Attenuated neuronal damage by autophagy regulation through the miR-214–3p/ATG5 signaling pathway.	[85]
	BACE1-AS	*BACE1-AS* siRNA and berberine	*In vitro*	$A\beta_{25-35}$-treated HPN cells and $A\beta_{25-35}$-treated SK-N-SH cells	–	Lipofectamine 2000	Alleviated $A\beta_{25-35}$-induced neuronal damage by regulation of miR-132–3p expression in neuronal cells	[86]
	SOX21-AS1	*SOX21-AS1* siRNA	*In vitro* and in vivo	Primary hippocampal neurons	AD mice	Lipofectamine 2000	Reduced neuronal oxidative stress and apoptosis in AD mice through FZD3/5-Wnt signaling axis.	[87]
	SOX21-AS1	*SOX21-AS1* siRNA	*In vitro*	$A\beta_{1-42}$-treated SH-SY5Y cells and $A\beta_{1-42}$-treated SK-N-SH cells	–	Lipofectamine 2000	Sponging miR-107-mediated attenuation of $A\beta_{1-42}$-induced neurotoxicity	[88]
	MAGI2-AS3	MAGI2-*AS3* siRNA	*In vitro*	$A\beta_{25-35}$-treated SH-SY5Y cells	–	Lipofectamine 3000	Decreased Aβ-induced neuronal injury (SH-SY5Ycells) and neuroinflammation (BV2 cells)	[89]
	ANRIL	ANRIL shRNA	*In vitro*	$A\beta_{1-42}$-treated PC12 cells	–	Lipofectamine 2000	Suppression of apoptosis and inflammation, induction of neurite outgrowth through binding of miR-125a in AD.	[90]
Ischemic Injury	*Bdnf-AS*	*Bdnf-AS shRNA*	*In vitro*	Primary retinal ganglion cells (under oxygen and glucose deprivation conditions)	–	Lentivirus	Protection of retinal ganglion cells against ischemia by raising BDNF levels	[91]
PD	*MAPT-AS1*	*MAPT-AS1*	*In vitro*	SK-N-MC cells and HEK293	–	Lipofectamine 2000	*MAPT-AS1* and *DNMT1* were found to be potential regulators of MAPT expression in PD across four distinct regions of the brain. The lncRNA can be used as a biomarker of disease status in PD and a potential therapeutic target to inhibit MAPT expression.	[92]
	UCHL1-AS1	*UCHL1-AS1*	*In vitro* and in vivo	MPP^+-treated iMN9D cells	MPTP mouse models	–	Induction of *Uchl1* overexpression (can be beneficial in neurodegenerative disorders.). The application of *AS Uchl1*-based	[93]

(*continued on next page*)

Table 1 (*continued*)

Disease	Natural antisense transcript	Treatment strategy	*In vivo*/ *In vitro*	Cell line	Animal model	Delivery	Remarks	Ref.
							medication can be used a novel therapeutic strategy.	
	BDNF-AS	*BDNF-AS* siRNA	*In vitro* and in vivo	MPP^+-treated SH-SY5Y cells	MPTP mouse models	Lipofectamine 3000 (in vitro) and injection si-*BDNF*-AS-1 and si-*BDNF*-AS-2 into the midbrain of PD mice (in vivo)	Improved viability of SH-SY5Y cell, inhibition of autophagy and apoptotic cascade in mouse models via miR-125b-5p regulation	[94]
HD	*HTTAS_v1*	*HTTAS_v1* siRNA	*In vitro*	HEK293 cells and SH-SY5Y cells	–	Lipofectamine 2000	Substantial reduction of *HTT* expression, implying that manipulation of antisense expression can have clinical implications.	[95]
ALS and FTD	*C9orf72-AS*	ASOs targeting antisense *C9orf72* RNA (*C9orf72-As)* and ASOs targeting sense *C9orf72* RNA	*In vitro* and in vivo	Neurons and glial cells	C57BL/6 mice	Single intracerebroventricular (ICV) stereotactic injection (in vivo)	Administration of ASO reduced hexanucleotide repeat-containing RNAs and highlighted the potential significance of targeting expanded RNAs transcribed in both directions.	[96]
SMA	*SMN-AS1*	*SMN-AS1* ASO and *SMN2* Splice-switching oligonucleotides	*In vitro* and in vivo	HEK293T cells, SMA patient cells, and human neuroblastoma cells	SMA mice	Subcutaneous injection	*In vitro*: Targeted degradation of *SMN-AS1* with ASO increases the expression of SMN. *In vivo*: Combination therapy with *SMN-AS1* ASOs and *SMN2* Splice-switching oligonucleotides leads to amelioration of SMA.	[97]
HNC	*TCAB1* (except *WRAP53α)*	*TCAB1* shRNA	*In vitro* and in vivo	HSC-3 cells, Cal-27 cells, and ACC2 cells	shScra cells-bearing mice	Lentivirus	Knockdown of *TCAB1* significantly reduced cell proliferation and invasion both in vitro and in vivo. Based on this study, *TCAB1* may contribute to the development of carcinomas of head and neck. *TCAB1* can be a promising prognostic biomarker or a potential target for the diagnosis and treatment of neck and head carcinomas.	[98]
Different types of cancers	*TALAM1*	*TALAM1* ASO	*In vitro*	Hela cells	–	–	Knockdown of *TALAM1* results in defective 3′ end cleavage reaction and compromises *MALAT1* accumulation in the cell. On the other hand, *TALAM1* overexpression leads to the facilitation of the cleavage reaction. It is worth noting that MALAT1 positively regulates this transcript.	[99]
BC	*TALAM1*	MALAT1/TALAM1 Knock down by LNA Gapmers	*In vitro* and in vivo	MDA-MB-231 and MCF7	MDA-MB-231 cells-bearing mice	Lipofectamine RNAiMAX	Considerably reduced ability of breast cancer cells migration potential in vitro, reduced capacity to populate the lungs of immunodeficient mice. *TALAM1* collaborates with *MALAT1* to regulate the properties that guide the aggressiveness and malignancy of breast cancer.	[100]
LPS-induced osteoarthritis	*MFI2-AS1*	*MFI2-AS1* siRNA	*In vitro*	C28/I2 cells	–	Lipofectamine 2000	miR-130a-3p/TCF4-mediated Inhibition of LPS-induced osteoarthritis progression	[101]

Abbreviations: AD: Alzheimer's disease; PD: Parkinson's disease; HD: Huntington's disease; ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; SMA: Spinal muscular atrophy; HNC: Head and neck cancer; BC: Breast cancer; LPS: Lipopolysaccharide; ASO: Antisense Oligonucleotide; LNA: Locked nucleic acid; shRNA: Short hairpin RNA; siRNA: Small interfering RNA; lncRNA: Long non-coding RNA.

(specifically the e4 allele), which have been associated with increased susceptibility to late-onset AD [125,126]. These genes and their protein products have been proposed as potential therapeutic targets for AD [125,127]. Apart from mutations in the aforementioned high penetrance genes, NATs of several other genes have also been found to be associated with AD, as described below.

4.1.1. BACE1-antisense RNA (BACE1-AS)

BACE1-AS, first described by Faghihi et al. in 2008, is arguably the best-known NAT in AD [128]. The NAT is transcribed from the opposite strand of *beta-site APP cleaving enzyme 1* (*BACE1*) on chromosome 11, which encodes the β-secretase [128]. *BACE1-AS* is often found at an elevated expression level in the parietal lobes and cerebellum of AD patients and their plasma, hence making it a potential diagnostic biomarker for AD [129,130]. Furthermore, the NAT has been shown to participate in the concordant regulation of *BACE1* expression by increasing its mRNA stability [83,118,128]. Consequently, increased expression of *BACE1-AS* causes further accumulation of $A\beta_{1-40}$ and $A\beta_{1-42}$ via a feed-forward regulatory mechanism at the post-transcriptional level.

It has been shown that *BACE1-AS* promotes neuronal damage mediated by autophagy via the miR-214–3p/ATG5 signaling axis and may confer neurotoxicity by sponging microRNAs [118]. In addition, Ge et al. reported that *BACE1-AS* negatively regulated miR-132–3p and attenuated the protective effects of the latter against $A®_{25-35}$ accumulation [85,86]. The researchers also demonstrated that the administration of berberine, which has a neuroprotective role in AD, reduced the *BACE1-AS* level in vitro [86]. Besides, several other in vitro and in vivo studies also demonstrated that knockdown of *BACE1-AS* using specific siRNA could delay or reduce abnormal protein depositions in cell models, promote the survival of primary neurons, and improve neurogenesis markers, memory, and learning behaviors [84,86,131,132]. A very recent study also demonstrated that *BACE1-AS* silencing exerted its protective effect in AD by inhibiting autophagy through the miR-214–3p/ATG5 signaling axis [85]. Taken together, knockdown of *BACE1-AS* has shown promising results in alleviating the neuronal damage seen in AD, and may therefore be a promising target for AD therapy [128,131].

4.1.2. SOX21 antisense divergent transcript 1 (SOX21-AS1)

SOX21-AS1 is another NAT known to be associated with AD. This NAT is transcribed from the 13q32.1 chromosomal locus and its transcript is 2986 nucleotides in length [133]. *SOX21-AS1* has been shown to be upregulated in cell culture models of AD, and may play a role in regulating tau protein levels via the miR-107 pathway [88]. Thus, knockdown of *SOX21-AS1* has been shown to reverse the neuronal damage induced by Aβ [88]. Further in vivo experiments found that *SOX21-AS1* silencing could improve cell viability, hippocampus lesions, learning, and memory abilities in mouse models of AD, presumably through such mechanisms as inhibition of apoptosis, relief of oxidative stress, and genetic regulation [88]. Although further works are warranted to determine the clinical importance of *SOX21-AS1* in AD, the available in vitro and in vivo studies suggest that it may be a potential target for AD therapy.

4.1.3. MAGI2 antisense RNA 3 (MAGI2-AS3)

Another NAT whose level is significantly increased in AD, both in $A®_{25-35}$-induced cell lines and in the serum samples of AD patients, is *MAGI2-AS3* [87]. This NAT is known to regulate the expression of miR-374b-5p negatively. Furthermore, increased expression of *MAGI2-AS3* is associated with neurotoxic and neuroinflammatory effects in vitro. The overexpression of miR-374b-5p and siRNA-mediated knockdown of this NAT enhanced cell survival and reduced $A®_{25-35}$-induced neurotoxicity and neuroinflammation. Based on these facts, it can be postulated that AD progression may be promoted via the *MAGI2--AS3*/miR-374b-5p axis, and targeting this NAT may improve AD therapy [89].

4.1.4. MAPT antisense RNA 1 (MAPT-AS1)

Abnormal deposits of the tau protein represent one of the mechanisms leading to AD. The tau protein is encoded by *MAPT,* which is located on the 17q21.31 chromosomal locus. Earlier experiments on human brain tissues and neuroblastoma cell lines had identified several alternatively spliced NATs transcribed from the opposite strand of the *MAPT* gene [134]. These NATs were demonstrated to diminish the *MAPT* gene activity at the transcriptional and translational levels [134,135]. One of these NATs is an 840-nucleotide long transcript named *MAPT-AS1*, which has been shown to repress tau mRNA translation in mouse models of AD [136]. In addition, the NAT is known to regulate the *MAPT* level by forming a complementary base pairing between its 5' region and the 3' region of *MAPT*, specifically at the internal ribosome entry site (IRES) and the mammalian-wide interspersed repeat (MIR) element of the latter [135]. Recently, de Silva et al. showed that delivery of full-length *MAPT-AS1* vectors into the hippocampus of mice models via an adeno-associated virus (AAV) resulted in a decrease of tau levels by as much as 70% [136]. This suggests that augmentation of *MAPT-AS1* may serve as a potential therapeutic approach to cure AD.

4.1.5. LRP1 antisense RNA (LRP1-AS)

LRP1-AS was first described by Yamanaka et al. in 2015 [137]. It is transcribed from the locus containing the *LRP1* gene, which encodes the low-density lipoprotein receptor-related protein 1 involved in the clearance of A® deposits [137,138]. *LRP1-AS* has been shown to negatively regulate the *LRP1* expression, resulting in the accumulation of Aβ plaques in the brain of AD patients [137,139]. Therefore, targeting *LRP1-AS* may serve as a potential therapeutic strategy for the treatment of AD [137].

4.1.6. Antisense non-coding RNA in the INK4 locus (ANRIL)

ANRIL, also known as the cyclin-dependent kinase 4 inhibitor antisense RNA (*CDKN2B-AS*), is a 3.8 kb-long NAT transcribed from the 9p21 locus [140]. The NAT is upregulated in the $A\beta_{1-42}$-induced plaque tissues, suggesting that it may play a role in the neurodegeneration of AD. Knockdown of *ANRIL* has been shown to decrease cell viability, suppress apoptosis, inhibit cytokine expression, and enhance neurite outgrowth in cellular models of AD, indicating that it might be a good target for AD therapy [90].

4.1.7. BDNF antisense RNA (BDNF-AS)

Brain-derived neurotrophic factor (BDNF) is a neurotrophin involved in nerve cell growth and survival and is critical for neural development [141]. It has been found to be downregulated in neurodegenerative brain samples [142], and its antisense transcript (*BDNF-AS*, also known as *BDNF-OS*) discordantly regulates its expression levels at the transcriptional level, which subsequently influences the production of BDNF-associated cytokines [91,143]. A recent study showed that inhibition of *BDNF-AS* elevated the *BDNF* levels and subsequently promoted the survival of retinal ganglion cells (RGCs) in ischemic conditions, as well as increased neuronal outgrowth [91]. This indicates that targeting *BDNF-AS* may be a feasible approach for AD therapy.

4.1.8. GDNF antisense RNA (GDNF-AS)

Glial cell line-derived neurotrophic factor (GDNF) is critical for the development and normal functioning of the CNS [144]. Its downregulation has been observed in the serum samples of AD patients and has been associated with AD pathogenesis [145]. *GDNF-AS* also referred to as *GDNFOS*, is the NAT transcribed from the opposite strand of the *GDNF* locus. Several isoforms of *GDNF-AS* have been identified, and they have been shown to negatively regulate the level of *GDNF* [146]. *In vitro* and in vivo experiments conducted by Modarresi et al. demonstrated that knockdown of *GDNF-AS* resulted in a significant increase in the level of *GDNF* and induced neurogenesis, thus making the NAT a

potential therapeutic target for AD (Fig. 2) [143].

4.2. Parkinson's disease (PD)

PD is another common type of neurodegenerative disease, with a prevalence of approximately 100–200 cases per 100,000 individuals [147]. Annually, more than 6 million people are diagnosed with PD worldwide, making it the second most prevalent neurodegenerative disease after AD [148]. A great majority of PD occurs in individuals above 65 years old, and the disease is slightly more prevalent in men than women [147]. The main histological feature of PD is the formation of Lewy bodies, which are a marker of neuronal degeneration [149]. The disease is characterized by movement impairments and cognitive dysfunctions, including tremor and bradykinesia caused by the loss of brain dopaminergic neurons. Thus, the aim of current therapeutic regimens focuses on improving the secretion of dopamine in the brain.

Numerous environmental and metabolic risk factors have been identified for PD, including but not limited to cigarette smoking, alcohol consumption, vitamin D exposure, and urate levels [147]. However, these environmental and metabolic risk factors explain only a subset of the cases, and it has been hypothesized that genetic risk factors play an equally important role in the pathogenesis of PD [150]. The genetic heritability of PD is estimated to be approximately 22% [151]. Over the past decades, several genes have been found to be associated with PD (many of which overlap with AD). These include *MAPT*, *UCHL1*, *BDNF*, *CDKN2B*, *PINK1*, *PARK1,* and *PARK2*. More recently, the role of NATs of some of the genes mentioned above in PD has become increasingly evident [80].

4.2.1. MAPT antisense RNA 1 (MAPT-AS1)

Similar to AD, the abnormal accumulation of tau protein in the brain is also responsible for the pathogenesis of PD [152]. Thus, *MAPT-AS1*, which discordantly regulates the tau-encoding gene *MAPT*, serves as a potential therapeutic target for PD. An in vitro study on cellular models of PD demonstrated that *MAPT-AS1* exhibited its inhibitory effect via promoter methylation of *MAPT* gene, which provides a similar neuroprotective effect as vitamin E [92].

4.2.2. UCHL1 antisense RNA 1 (UCHL1-AS1)

Ubiquitin carboxy-terminal hydrolase L1 (UCHL1) is one of the most abundant proteins in the brain. The protein plays a crucial role in the development of the nervous system by regulating the turnover of ubiquitin. Thus, in many neurodegenerative diseases, including PD, the protein is downregulated [93]. *UCHL1-AS1*, a NAT transcribed from the opposite strand of the *UCHL1* gene, is known to stabilize the *UCHL1* mRNA, which helps to ensure a high cellular level of UCHL1. Downregulation of both *UCHL1* and *UCHL1-AS1* has been observed in neurochemical PD models; hence, targeting the NAT may represent a new therapeutic strategy in PD [93].

4.2.3. BDNF antisense RNA (BDNF-AS)

BDNF-AS is known to be upregulated in PD, both in vitro and in vivo, which led to increased cellular apoptosis and autophagy. The NAT is a negative regulator of BDNF, which plays a crucial role in improving the survival of dopaminergic neurons, dopaminergic neurotransmission, and motor performance in PD [153]. A recent study has therefore investigated the effects of *BDNF-AS* knockdown on PD and their underlying molecular mechanisms. It was shown that *BDNF-AS* knockdown could increase the level of miR-125b-5p, which contributed to enhanced cell viability and suppressed autophagy and apoptosis, indicating that the NAT could be a potential therapeutic target for PD [94].

4.3. Huntington's disease (HD)

HD is a hereditary neurodegenerative disorder with autosomal dominant inheritance characterized by variable clinical manifestations, notably choreic movements. The disease is caused by a CAG trinucleotide repeat expansion in the first exon of the huntingtin (*HTT*) gene located on chromosome 4p16.3. The wild-type huntingtin protein regulates the transcription of BDNF, which is necessary for the survival of striatal neurons [154]. However, the abovementioned trinucleotide repeat sequence results in the production of a dysfunctional HTT protein which interferes with the delivery of BDNF to the striatum, thereby causing the disease [155]. Given the important role of *HTT* and *BDNF* in HD, NATs of these two genes have been linked to the pathogenesis of the disease.

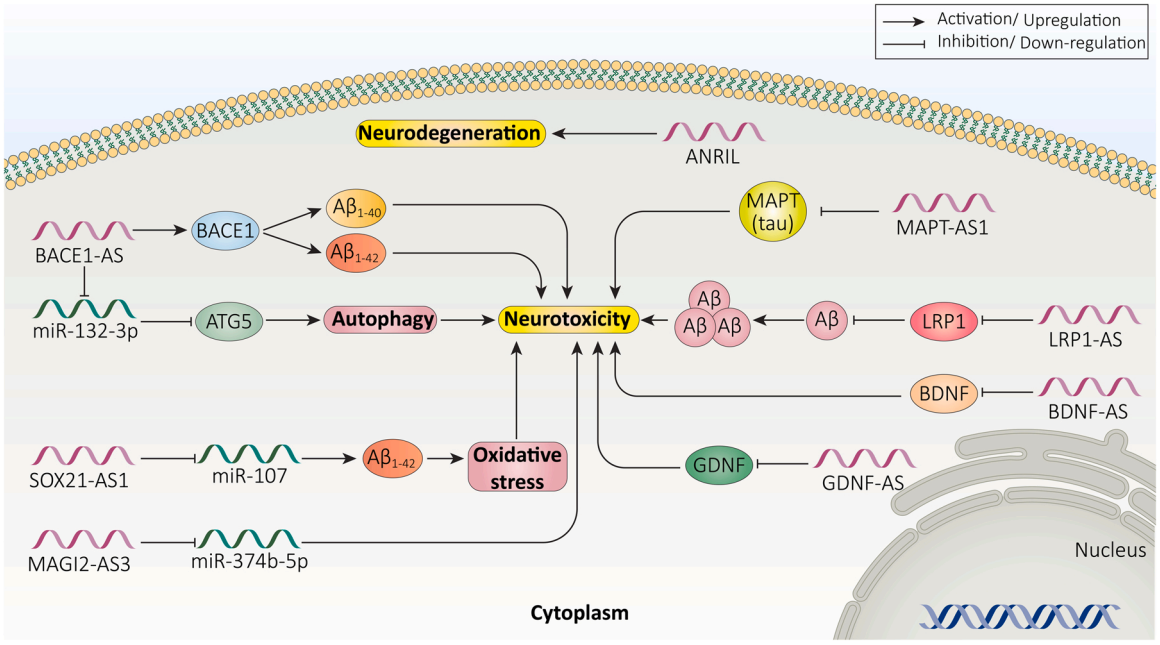

Fig. 2. NATs in Alzheimer's disease. The NATs mainly affect miRNA expression in AD. Furthermore, tau protein and amyloid-beta levels, as factors involved in AD, are affected by NATs in AD.

4.3.1. HTT antisense RNA (HTT-AS)

Two alternatively spliced isoforms of *HTT-AS* are known to be transcribed from the *HTT* locus, namely the *HTT-AS_v1,* which contains exons 1 (including the CAG trinucleotide repeat) and 3, and *HTT-AS_v2,* which contains exons 2 and 3 [156]. Both isoforms of the *HTT* NAT undergo 5′capping and poly-A tailing during maturation. The role of *HTT-AS_v2* in HD is poorly understood, as it appeared to have limited function in regulating the level of HTT. On the other hand, *HTT-AS_v1* has been demonstrated to negatively regulate *HTT* transcription in vitro [95]. Moreover, siRNA knockdown of *HTT-AS_v1* was found to promote HTT transcription. Thus, overexpressing *HTT-AS_v1* may potentially decrease the pathogenic *HTT* transcript levels and reverse HD patients' symptoms [95].

4.4. Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD)

ALS and FTD are two neurodegenerative diseases that are highly similar in terms of clinical and pathological presentations. From the genetics perspective, both diseases are caused by an expanded GGGGCC hexanucleotide repeat in the intron 1 of the *C9orf72* gene located on chromosome 9p21 [157]. It has been shown that both ALS and FTD patients have an increased level of *C9orf72* antisense RNA (*C9orf72-AS)* in their brains [158]. Moreover, elevated levels of both *C9orf72* and its NAT have been observed in the blood samples of the patients. These findings indicate that bidirectional transcription is a hallmark of ALS and FTD pathology [159]. Therefore, targeting the *C9orf72-AS* may be helpful in the treatment of ALS/FTD [96].

4.5. Spinal muscular atrophy (SMA)

SMA is an autosomal recessive neuromuscular disease involving the degeneration of alpha motor neurons, which eventually leads to progressive proximal muscle weakness and paralysis. It is estimated that 1 in 6000–10,000 newborns are affected by the diseases. SMA is caused by the homozygous loss of the survival motor neuron 1 (*SMN1*) gene located on chromosome 5q13 [97,160]. Patients with SMA retain variable copies of the highly homologous *SMN2* gene present on the same chromosomal locus, and the severity of the disease is inversely correlated to the *SMN2* copy number [161]. Recently, a NAT of the *SMN* genes has been described [97]. The NAT denoted *SMN-AS1*, is transcribed from the first intron of the *SMN* genes and can repress the expression of the *SMN* locus by binding and subsequently recruiting the polycomb repressive complex-2 (PRC2) to the transcription start site of the *SMN* gene [97]. Knockdown of *SMN-AS1* was demonstrated to increase *SMN1* expression in vitro and in vivo [97]. More importantly, combination treatment using antisense oligonucleotide (ASO) against *SMN-AS1* (*SMN-AS1 ASO)* and splice-switching oligonucleotide (SSO) for *SMN2 (SMN2 SSO)* promoted survival, increased body weight, and improved motor behavior in SMA mice, suggesting that knockdown of *SMN-AS1* could represent a potential therapeutic strategy for SMA [97].

Apart from that, expression of the SMN protein can be enhanced by inhibiting the scavenger decapping enzyme DcpS, which hydrolyzes the m7GpppN cap on the 5' end of mRNAs as part of the RNA degradation machinery [162,163]. A NAT of the *DCSP* gene has recently been described [164]. The NAT, called *NATTD* (natural antisense transcript to both TIRAP/Mai and DcpS), concordantly regulates the DcpS transcription through epigenetic mechanisms [164]. Thus, theoretically, targeting *NATTD* can inhibit DcpS, which in turn increases SMN protein level and ameliorates SMA. Nonetheless, this hypothesis warrants further investigations.

4.6. Spinocerebellar ataxia type 8 (SCA8)

SCA8 is a very slowly progressive neurodegenerative disease that is inherited in an autosomal dominant manner. The major clinical presentations of the affected individuals include gait, limb, speech, oculomotor incoordination, muscle tightness, and sensory impairment [165,166]. SCA8 is caused by an inherited repeat expansion in the ataxin 8 (*ATXN8*) gene and its antisense counterpart, *ATXN8OS*. The exact molecular mechanisms leading up to SCA8 pathogenesis are not fully understood, but it has been postulated that the repeat expansion in *ATXN8OS* interferes with its *ATXN8* regulatory functions [167]. Thus, targeting the *ATXN8OS* NAT may have significant therapeutic potential.

4.7. Fragile X syndrome (FXS) and fragile X-associated tremor and ataxia syndrome (FXTAS)

Fragile X syndrome (FXS) is an X-linked genetic disorder characterized by a mild-to-moderate form of mental retardation and learning disability. It is caused by a CGG repeat expansion in the 5' untranslated region (UTR) of the *FMR1* gene, which leads to transcriptional silencing of the gene via DNA methylation [168]. On the other hand, fragile X-associated tremor and ataxia syndrome (FXTAS) is a late-onset movement disorder affecting premutation carriers of the same gene. In contrast to FXS, *FMR1* expression is found to be increased in FXTAS patients [169]. In 2007, a NAT of FMR1 was described. This NAT, named *FMR1-AS1*, is an anti-apoptosis factor, and its expression is silenced in FXS and overexpressed in FXTAS patients (Fig. 3) [169,170]. The variable level of expression of this NAT in FXS and FXTAS suggests that it might play a role in the pathology of the disorders, thus making it a potential target for therapy.

5. NATs in cancers

Cancer is a disease characterized by the uncontrolled growth of cells in the body [171–175]. It is one of the most common causes of morbidity and death globally. In 2018 alone, more than 18 million individuals were diagnosed with the disease, and close to 10 million cancer-related deaths were reported [176]. At the molecular level, cancer is essentially a disease of dysregulated gene expression [177–180]. Therefore, regulators of gene expression, including NATs, have been increasingly studied for their roles in various cancers [181]. Cancer cells are consensually defined by eight biological hallmarks, namely (i) sustenance of proliferative signaling, (ii) evasion of growth suppressor, (iii) avoidance of immune destruction, (iv) enablement of replicative immortality, (v) activation of invasion and metastasis, (vi) inducement of angiogenesis, (vii) resistance to cell death, and (viii) deregulation of cellular energetics [182–187]. NATs have been shown to be involved in each of these biological hallmarks, making them a potentially relevant target for cancer therapy [81].

5.1. WD40-encoding RNA antisense to p53 (WRAP53)

TP53, which encodes for the tumor suppressor protein p53, is the most commonly mutated gene in human cancers [188,189]. A NAT for the *TP53* gene, named WD40-encoding RNA antisense to p53 (*WRAP53*), was described in 2009 [190]. There are three isoforms of *WRAP53*, namely *WRAP53α*, *WRAP53β,* and *WRAP53γ*, which are respectively transcribed in an antisense direction from the 1α, 1β and 1γ exon of the *TP53* gene [190]. The *WRAP53α* isoform is known to stabilize the *TP53* mRNA by forming an RNA duplex with it, thereby preventing the mRNA from degradation [190]. Alterations to *WRAP53α* can therefore reduce *TP53* expression and contribute to tumorigenesis. In non-small cell lung cancer (NSCLC), for example, methylation of *WRAP53α* promoter has been documented and found to be associated with worse overall survival [191]. It is also interesting to note that cisplatin, a chemotherapeutic agent, was found to induce apoptosis in osteosarcoma cells by upregulating *WRAP53α* [192]. These observations suggest that *WRAP53α* could be a promising target for cancer therapy.

Compared to *WRAP53α*, the molecular mechanisms linking *WRAP53β* and *WRAP53γ* to cancer are less well understood, as their

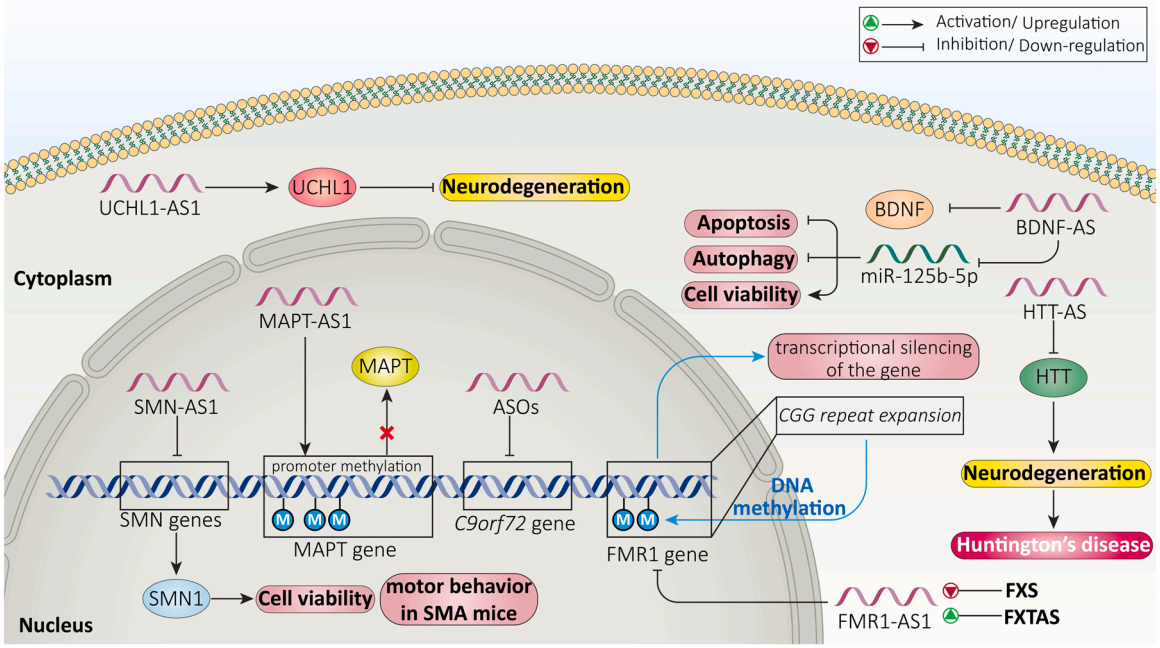

Fig. 3. NATs in other neurodegenerative diseases. As it is shown, NATs function in both nucleus and cytoplasm. Furthermore, proliferation, cell cycle progression and angiogenesis are tightly regulated by NATs via affecting downstream targets.

influence on the p53 level was not observed in knockdown and overexpression experiments [191]. Nonetheless, *WRAP53β* overexpression has been observed in head and neck cancer, esophageal squamous cell carcinoma, and rectal cancer [193,194], and knockdown of *WRAP53β* was found to reduce the proliferative potential and invasiveness of cancer cells in vitro. In addition, depletion of the NAT has also been shown to suppress tumor formation in mice [98]. Hence, there is a huge potential of targeting the NAT for cancer treatment.

5.2. *HIF1A antisense RNA 2 (HIF1A-AS2)*

Since cancer cells proliferate at an elevated rate, oxygen supply becomes rapidly depleted, and cancer cells commonly suffer from hypoxia [195–197]. One of the genes that are being upregulated in response to hypoxia is *HIF1A*, which encodes hypoxia-inducible factor 1 alpha (HIF-1α). HIF-1α is a transcription factor that activates cell proliferation, angiogenesis, and a series of other cancer-related pathways under low oxygen conditions [198–200]. The *HIF1A* locus also transcribes a NAT, named *HIF1A-AS2* (previously known as a HIF), which negatively regulates the HIF-1α level [201,202]. Expression of *HIF1A-AS2* has been observed in many cancer types, including breast, renal and gastric cancers, and has been correlated with a poor prognosis [202–204]. Recently, it was observed that ovarian cancer cells treated with SC144 (an anticancer drug belonging to the small-molecule gp30 inhibitor class) induced the transcription of *HIF1A-AS2* and hence, decreased HIF-1α levels [205]. This suggests that *HIF1A-AS2* may serve as a target in cancer therapy.

5.3. *HOXA11 antisense RNA (HOXA11-AS) and HOX antisense intergenic RNA (HOTAIR)*

HOX genes are a family of transcription factors that play a major role in cellular signaling, differentiation, apoptosis, and many other cancer-related pathways [206]. In humans, four HOX gene clusters have been identified, including *HOXA*, *HOXB*, *HOXC,* and *HOXD*. The *HOXA* and *HOXC* loci respectively harbor *HOXA11-AS* and *HOTAIR* NATs, which have been frequently implicated in oncogenesis. Both NATs are known to regulate gene expressions in both *cis* and *trans* manners. They have also been found in both the nucleus and cytoplasm, suggesting that they can regulate gene expression through multiple mechanisms. In the nucleus, for example, both NATs of HOX genes are known to modulate the recruitment of PRC2, a histone methylase, and lysine-specific demethylase 1A (LSD1, a histone demethylase) to the promoter of their target genes and can therefore epigenetically regulate gene expression [207, 208]. In the cytoplasm, on the other hand, both NATs are known to act as miRNA sponges to regulate target gene expression [209,210]. Dysregulations of *HOXA11-AS* and *HOTAIR* have been observed in many cancer types and are associated with a poor prognosis [207,211–220]. In addition, the knockdown of these two NATs has been shown to reverse many cancer-related phenotypes, making them ideal targets for cancer therapy [212,215,219].

5.4. *MALAT1 antisense RNA (TALAM1)*

Metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) is a lncRNA located on chromosome 11q13. The lncRNA was first identified in early-stage NSCLC patients with a higher risk of metastasis [221]. *MALAT1* is known to modulate the alternative splicing process and regulate gene expression at the transcriptional and post-transcriptional levels [222]. The lncRNA has also been found to be overexpressed in many cancer types, suggesting that it could participate in various cancer-related pathways [223–226]. The expression level of *MALAT1* is regulated by, among others, its NAT, which is known as *TALAM1* [99]. *TALAM1* is also concordantly regulated by *MALAT1*; thus, the two lncRNAs form a feed-forward expression loop to ensure a continuously high cellular level during cancer progression. *In vitro* and in vivo works have demonstrated that knockdown of *TALAM1* could significantly impair the ability of cancer cells to proliferate and migrate. Therefore, *TALAM1* shows therapeutic potential for cancer (Fig. 4) [99,100].

6. NATs in other diseases

NATs have also been implicated in a variety of other diseases. In the tetralogy of Fallot, for example, *T-box transcription factor 5 (TBX5) antisense RNA 1* (*TBX5-AS1*) was shown to be downregulated along with its sense transcript, *TBX5* [227]. The NAT concordantly regulates *TBX5*

expression by affecting its mRNA stability through the formation of the RNA duplex. Although the exact function of *TBX5-AS1* in cardiac development remains to be elucidated, knockdown of *TBX5-AS1* by shRNA lentivirus was found to significantly decrease cell proliferation in TOF, suggesting that targeting the NAT may be a feasible therapeutic approach in disorder. Besides, in osteoarthritis, an increased expression of NAT *MFI2-AS1* has been reported. Knockdown of *MFI2-AS1* in vitro was found to increase cell viability and ameliorate lipopolysaccharide-induced arthritis [101]. This suggests that *MFI2-AS1* could be a potential target for osteoarthritis treatment. Similarly, in atherosclerosis, *ZEB1 antisense RNA 1* (*ZEB1-AS1*) has been shown to promote oxidized low-density lipoprotein (ox-LDL)-induced injury (which represents a key contributor to the development of atherosclerosis) by targeting miR-942 [228]. This observation may indicate the possible use of the NAT as a target in the treatment of atherosclerosis.

7. Conclusions and future perspectives

NATs have a multifaceted role in the regulation of the ncRNA network, which is critically important in biological processes. In recent years, many studies have reported that NATs are dysregulated in various human diseases, including several cancers and neurodegenerative disorders. There are several advantages of targeting NATs in the treatment of cancer and neurodegenerative disorders. First, most NATs have high target specificity as they regulate only their sense genes in a *cis*-manner. This ensures that off-target gene regulation is minimal, if it exists at all. Besides, targeting NATs mimics the natural cellular environment closer than targeting protein-coding genes. This can be exemplified by *BACE1*, whose direct inhibition can lead to disruptions to the functionalities of the protein product and causes undesirable side effects [229,230]. Targeting *BACE1-AS*, on the other hand, not only led to the reduction of *BACE1* levels, but also reduced abnormal Aβ depositions in AD, as described above [128].

However, we need to overcome several limitations or challenges before the therapeutic potential of the NATs can be fully exploited. For example, there are also several NATs that participate in the *trans*-regulation of a large number of genes. Thus, while targeting a NAT may restore the expression of certain genes to an optimal level, it remains possible that the approach would lead to dysregulation of other genes at the same time. Besides, many NATs contain overlapping sequences with their sense counterparts. Hence, it is important to ensure that the molecules used for targeting the NATs would not unintentionally act on their sense counterparts [81].

Apart from that, genetic polymorphisms have long been associated with disease susceptibility, presumably by influencing the expression and/or functionality of the protein product [231–239]. Since genetic polymorphisms could also occur in antisense genes, it would be interesting to see whether these polymorphisms have any functional impact on the NATs transcribed. Among the NATs described above, only *HOTAIR* polymorphisms have been regularly investigated concerning their relationship with disease susceptibility [240–245]. It is imperative that polymorphisms in other antisense genes be extensively evaluated in future studies to determine whether the functions and therapeutic potential of these NATs could be affected by the DNA sequence variations.

In summary, NATs are highly promising targets for therapy of many diseases. However, a complete understanding of their functions, mechanisms, and physiological consequences is crucial before NAT-targeting technologies can be widely used in the clinical setting.

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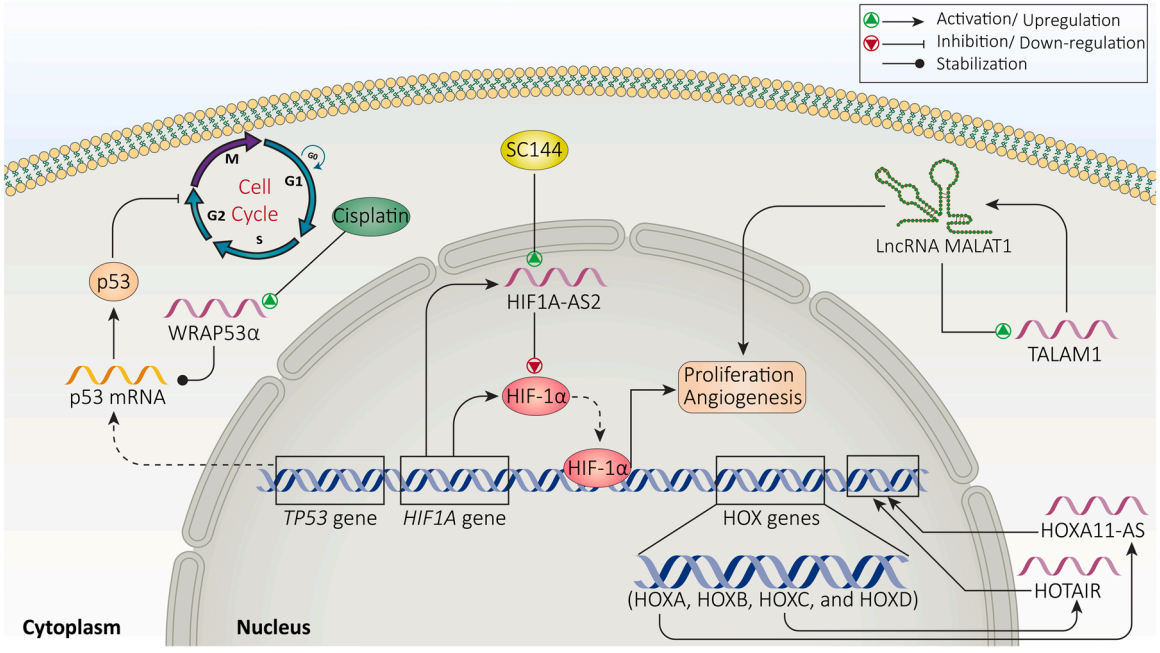

Fig. 4. Several NATs play significant roles in cancer proliferation, progression, and metastasis. *TALAM1* directly interacts with *MALAT1* leading to cancer progression and angiogenesis. *HIF1A-AS2* negatively regulates *HIF1A*. SC144 can induce *HIF1A-AS2* expression resulting in inhibition of proliferation and angiogenesis. Using cisplatin, a chemotherapeutic agent can upregulate the expression of *WRAP53α,* leading to apoptosis induction by stabilizing the *TP53* mRNA. *HOXA11-AS* and *HOTAIR* are important contributors to the regulation of cancer-related gene expression, which can lead to tumorigenesis and progression.

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Conflict of interest statement

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