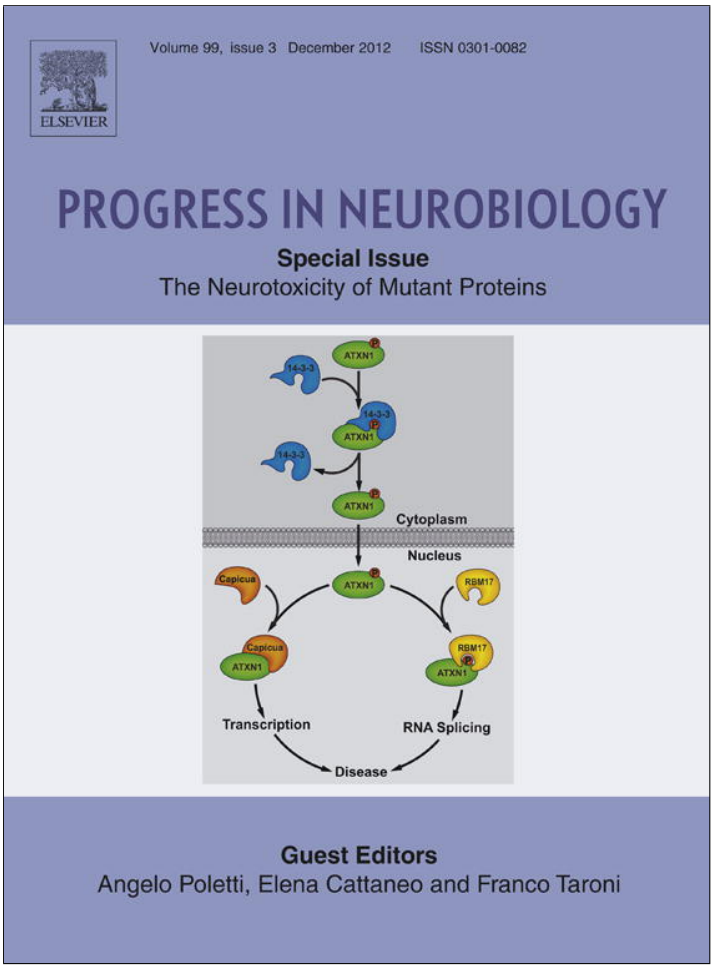

Progress in Neurobiology 99 (2012) 293–315

Contents lists available at SciVerse ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Neurodegeneration as an RNA disorder

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ARTICLE INFO

Article history:
Received 31 May 2012
Received in revised form 14 September 2012
Accepted 26 September 2012
Available online 10 October 2012

Keywords:
Neurodegeneration
Neurodegenerative disease
Non-coding RNA
Alzheimer's disease
Parkinson's disease
Huntington's disease
Trinucleotide repeat disorder
BACE1
REST
Long non-coding RNA
microRNA
HAR1
SOX2OT
mir-9
mir-132
mir-124

ABSTRACT

Neurodegenerative diseases constitute one of the single most important public health challenges of the coming decades, and yet we presently have only a limited understanding of the underlying genetic, cellular and molecular causes. As a result, no effective disease-modifying therapies are currently available, and no method exists to allow detection at early disease stages, and as a result diagnoses are only made decades after disease pathogenesis, by which time the majority of physical damage has already occurred. Since the sequencing of the human genome, we have come to appreciate that the transcriptional output of the human genome is extremely rich in non-protein coding RNAs (ncRNAs). This heterogeneous class of transcripts is widely expressed in the nervous system, and is likely to play many crucial roles in the development and functioning of this organ. Most exciting, evidence has recently been presented that ncRNAs play central, but hitherto unappreciated roles in neurodegenerative processes. Here, we review the diverse available evidence demonstrating involvement of ncRNAs in neurodegenerative diseases, and discuss their possible implications in the development of therapies and biomarkers for these conditions.

Contents

Abbreviations: NDDs, neurodegenerative disorders; AD, Alzheimer's Disease; HD, Huntington's Disease; PD, Parkinson's Disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; CFTR, cystic fibrosis; CSF, cerebrospinal fluid; SOD1, superoxide dismutase 1; TARDBP, TAR DNA binding protein; PSEN-1, presenilin 1; PSEN-2, presenilin 1; MAPT, microtubule-associated protein tau; SNCA, α-synuclein; UPS, ubiquitin-proteasome system; Aββ, -amyloid; ER, endoplasmic reticulum; BER, base excision repair; PARP-1, poly-ADP ribose polymerase-1; lncRNAs, long non-coding RNAs; miRNAs, microRNA; ncRNA, non-coding RNAs; NGS, next generation sequencing; PCR, Polymerase chain reaction; SARS, Severe Acute Respiratory Disorder; SCA, spinal cerebellar ataxia; DM, myotonic dystrophy; HDL2, Huntington's disease-like 2; TNDs, trinucleotide repeat disorders.

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http://dx.doi.org/10.1016/j.pneurobio.2012.09.006

1. Introduction

Neurodegenerative disorders (NDDs) represents one of the greatest challenges to neurobiology and impose a rapidly increasing social and financial burden upon society. Although neurodegenerative disorders are variously classified according to symptomology, natural history, genetics and neuronal loss, there is an emerging consensus that the underlying molecular mechanisms are common to many NDDS. The vast majority of the literature addresses the roles of specific proteins in mediating neurodegeneration. Here, we review the groundswell of data that supports the view that RNA dysfunction plays a central role in NDDs. We start by providing a brief overview of the types of molecular mechanisms that have been implicated in NDD, then discuss the role of non-coding RNA transcripts in the nervous system and the various ways in which they are implicated in disease mechanisms.

2. The molecular basis of neurodegeneration

NDDs, including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD) and Huntington's disease (HD) are a family of disorders in which progressive deficits in neuronal function or structure lead to sustained and relentless neuronal death. The brain region and neural cell types affected gives rise to a set of behavioural, cognitive and/or motor deficits somewhat specific to each disease; however there is considerable heterogeneity of clinical symptoms within and among the common NDDs. Indeed, a definitive diagnosis can usually only be given upon histopathological examination of brain tissue at post-mortem examination.

For most NDDs, only a small proportion of cases are familial, with disease being caused by a few rare and highly penetrant pathogenic mutations, including amyloid precursor protein (*APP*), presenilin (*PSEN*)-*1* and -*2* in AD (Bekris et al., 2010) and superoxide dismutase 1 (*SOD1*), TAR DNA binding protein (TARDBP) and fused in sarcoma (*FUS*) in ALS (Kiernan et al., 2011). The single biggest common risk factor for developing a NDD is age. However, association studies have identified several genetic risk factors that increase the likelihood of developing NDDs (Crosiers et al., 2011; Holtzman et al., 2011; Lill et al., 2011; Ross and Tabrizi, 2011). Since the phenotype observed in sporadic and familial forms of single diseases, and in some cases by disparate mutations, is very similar, this suggests that the pathogenesis of NDDs share common underlying mechanisms. Genetic association studies, combined with known environmental risk factors and evidence from neuropathological examinations, have implicated a number of common molecular events in the development and/or progression of several neurodegenerative diseases. These are discussed briefly below.

2.1. Oxidative stress

Oxidative stress responses are observed in postmortem NDD brain and in many rodent mouse models of NDDs (Coppede and Migliore, 2010). Oxidative stress responses affect, and are influenced by, several neural processes implicated in the progression of NDDs including protein folding, aggregation and the degradation of abnormal protein species, membrane lipid peroxidation, calcium homeostasis and DNA repair (Jellinger, 2009). Reactive oxygen species are predominantly produced during mitochondrial respiration and during periods of prolonged inflammation, thereby providing a link between oxidative stress, mitochondrial dysfunction and neuroinflammatory responses (Coppede and Migliore, 2010).

2.2. Protein oligomerisation and aggregation

The abnormal accumulation of protein oligomers and aggregates is a common feature of many NDDs. Oligomeric and aggregated species of β-amyloid (Aβ) and tau, α-synuclein, and huntingtin are found in AD, PD and HD brain, respectively, whereas aggregated deposits of TDP-43, SOD-1 and neurofilaments characterise affected regions of ALS brain (Gadad et al., 2011). It should be noted that these pathologies are not exclusive to individual NDDs; TDP-43 positive inclusions are apparent in PD, AD and related tauopathies (Warraich et al., 2010; Cohen et al., 2011), and neurofibrillary pathology is observed in PD and other Lewy body dementias (Wray and Lewis, 2010) where *MAPT* haplotype is known to affect disease risk (Simon-Sanchez et al., 2009). Indeed, recent evidence suggests that there may be synergistic interactions between several disease-associated proteins in NDDs (Elbaz et al., 2011; Herman et al., 2011; Waxman and Giasson, 2011).

Until recently it was widely believed that filamentous protein aggregates were directly responsible for neuronal toxicity. However, at least in AD, there is now substantial evidence that oligomeric protein species are more closely associated with synaptic dysfunction, functional deficits and neuronal loss (Walsh et al., 2002; Berger et al., 2007). Indeed, filamentous aggregates may simply represent an inert end-product as suggested by the

prolonged presence of neurofibrillary tangles in otherwise healthy and functioning neurons (Morsch et al., 1999; Santacruz et al., 2005). Alternative interpretations suggest that the assembly of protein filaments is a protective response mounted by degenerating neurons in NDDs (Ross and Poirier, 2005).

Model-based assays indicate that protein oligomerisation and aggregation in NDDs is likely to arise through a number of pathways. Huntingtin aggregation results from either transglutaminase-catalysed cross-linking or polar zipper formation in the expanded polyQ sequence (Jellinger, 2009), while *MAPT* and *SNCA*[N4] mutations, in addition to phosphorylation and conformational change, promote the misfolding of tau and α-synuclein into pro-aggregatory secondary structures (Hanger et al., 2009; Gadad et al., 2011). Proteolytically cleaved fragments of tau, α-synuclein, TDP-43, and possibly huntingtin promote aggregation (Lunkes et al., 2002; Dufty et al., 2007; Zhang et al., 2009; Wang et al., 2010), perhaps by nucleation-dependent seeding. In addition, failures in the ubiquitin-proteasome system (UPS) and/or lysosomal autophagic clearance pathways are suggested to increase cytosolic protein concentrations and promote the aggregation of these key disease proteins (Bove et al., 2011; Nijholt et al., 2011) And this may be influenced by post-translational modifications of the target proteins (Nijholt et al., 2011).

The mechanism by which abnormal oligomeric protein species cause cell death remains the subject of intensive research, although the conformation-dependent structure shared by many amyloid proteins suggests that that they confer toxicity by a common mechanism (Dobson, 1999; Kayed et al., 2003; Luheshi et al., 2007). Although multimeric and misfolded proteins may gain toxic properties (Gadad et al., 2011), there is also substantial evidence that oligomer and/or aggregate-induced synaptic and neuronal toxicity results from a loss of normal function in specific NDDs, for example as a result of cytoskeletal instability and axonal transport deficits upon tau detachment from microtubules in AD and related tauopathies (Brunden et al., 2010).

2.3. Axonal transport deficits

Axonal transport defects occur early in NDD, and are believed to contribute to disease progression (reviewed by De Vos et al., 2008). Disruption to axonal transport can result via several mechanisms. Reduced tubulin acetylation in HD can disrupt binding of the molecular motor, kinesin, to microtubules and slow axonal transport (Dompierre et al., 2007), whereas Aβ, and mutant TDP-43, huntingtin and SOD1 disrupt the transport of mitochondria (Schon and Przedborski, 2011), thereby reducing ATP supply, including that to molecular motors. Aberrant kinase and phosphatase activities also contribute to axonal transport deficits in NDDs since increased phosphorylation of both motors and cargoes reduces their ability to interact. For example, glutamate excitotoxicity, inflammation, and increased expression of Aβ, mutant presenilin-1 and CAG expanded huntingtin, stimulate the activity of several protein kinases in NDDs, leading to phosphorylation of kinesin and cargoes such as tau and neurofilaments (De Vos et al., 2008; Morfini et al., 2009). Tau is also proposed to compete with kinesin for binding to microtubules (Hagiwara et al., 1994; Wagner et al., 1996), and phosphorylation of tau results in its detachment from microtubules, which causes destabilisation of the microtubule cytoskeleton (Wagner et al., 1996).

2.4. Mitochondrial dysfunction

In addition to the detrimental effects of altered mitochondrial transport, mitochondrial dysfunction may contribute to the progression of NDDs through a number of different mechanisms. Indeed, a significant proportion of genetic loci associated with common familial forms of neurodegenerative disease are either directly or indirectly related to mitochondrial function, dynamics, energy production, turnover or interactions between mitochondria and ER (Schon and Przedborski, 2011).

Deficits in mitochondrial energy production and NDDs have been established in PD, where the risk of developing disease is strongly associated with genes encoding electron transport chain proteins (Zheng et al., 2010). In addition, a small number of mutations in mitochondrial DNA (mtDNA), which encodes several polypeptides essential for mitochondrial oxidative phosphorylation and ATP production, have been identified in association with ALS and some less common NDDs (De Coo et al., 1999; Silvestri et al., 2000). Altered mitochondrial quality control mechanisms, whereby the contents of damaged mitochondria are either 'diluted' via fusion and fission with healthy mitochondria or are cleared via mitoautophagy, are also implicated in HD (Shirendeb et al., 2011) and PD (Vives-Bauza and Przedborski, 2011). Finally, recent studies suggest that disruptions in mitochondria-ER communications, mainly via damaged mitochondria-associated ER membranes, also contribute to neurodegeneration (Schon and Przedborski, 2011).

2.5. Excitotoxicity and calcium dysregulation

Perturbed cellular Ca^{2+} regulation and resulting excitotoxicity in NDDs is strongly associated with alterations to several pathogenic events including oxidative stress and mitochondrial dysfunction. In most NDDs elevated cytosolic Ca2+ concentration is observed in either neurons or glia. Mutations in *PS* and *Htt* alter endoplasmic reticulum (ER) Ca2+ content (Leissring et al., 2000; Vidal et al., 2011), and both Aβ and α-synuclein increase cytosolic Ca2+ concentrations by promoting mitochondrial Ca2+ accumulation (Gibson et al., 2008; Parihar et al., 2008). In AD, cytosolic Ca2+ content is elevated by the release of Ca^{2+} from intracellular stores, Aβ-induced Ca2+ influx through native ion channels, pumps, receptors, and/or as a result of membrane thinning or amyloid pore formation (Small, 2009). Similarly, in ALS the sustained excitotoxicity leading to motor neuron loss is likely mediated by Ca2+ influx through Ca2+-permeable AMPA receptors (Van Damme et al., 2005), subsequent ER Ca2+ depletion (Grosskreutz et al., 2010) and/or altered mitochondrial Ca2+-content (Carriedo et al., 2000; De Vos et al., 2011).

2.6. Neuron–glial interactions and neuroinflammation

There is considerable evidence that the local inflammatory environment is affected in NDDs. Genetic variations in clusterin and CR1, both associated with the complement system, confer risk of developing late onset AD (Harold et al., 2009; Lambert et al., 2009), and both microglial and astrocytic inflammatory responses are observed early during NDD development and likely modulate the progression and severity of disease (Khandelwal et al., 2011).

A number of signalling pathways involving glutamate transporters, glutathione uptake, BDNF release and cytokine signalling, amongst others, have been implicated in the neurotoxic influence of astrocytes during the progression of NNDs (Garwood et al., 2011; Khandelwal et al., 2011). However, the contribution of astrocytes during neurodegeneration is likely two-pronged, since a protective influence of wild-type astrocyte transplantation into the brain of mouse models of AD has been reported (Hampton et al., 2010). Similarly, in mouse models of AD, microglial infiltration to regions of plaque deposition may be protective through their phagocytosis of accumulated A((Simard et al., 2006), at least in younger animals (Hickman et al., 2008). However, neuronal loss also results from increased pro-inflammatory cytokine production by microglia in models of AD (Hickman et al., 2008). The

potentially toxic influence of microglia during ALS progression is believed to be T-cell dependent, and also appears to involve the increased expression of several inflammatory cytokines (Beers et al., 2008).

2.7. DNA damage

Several components of DNA repair pathways are altered in NDDs. This includes modulation of pathways involved in the base excision repair (BER) machinery that targets single strand breaks in AD and PD (Kisby et al., 1997; Lovell et al., 2000), homologous recombination and non-homologous end joining mechanisms that repair double strand breaks in ALS (Martin, 2007), mismatch repair that arise during DNA replication and recombination in HD (Jeppesen et al., 2011), and altered activity of enzymes such as poly-ADP ribose polymerase-1 (PARP-1) that detect DNA damage in several NDDs (Coppede and Migliore, 2010; Jeppesen et al., 2011).

The accumulation of damaged neuronal DNA is believed to cause the formation of oxidative DNA adducts in the genome that lead to neuronal death, perhaps by preventing the transcription of genes required for neuronal maintenance (Hetman et al., 2010), whereas damaged mtDNA can alter the transcription of genes encoding parts of the electron transport chain, causing mitochondrial dysfunction, oxidative stress, further oxidative DNA damage and subsequent neurodegeneration (de la Monte et al., 2000; Jeppesen et al., 2011). Polymorphisms in genes that modulate mitochondrial BER can influence the risk of sporadic AD (Zhang et al., 2011), and altered mitochondrial transport and reduced mitochondrial BER protein amounts contribute to age-related decline in mouse models of AD (Gredilla et al., 2010).

2.8. Aberrant RNA processing

For the majority of NDDs, disruptions in alternative splicing, RNA editing, and mRNA stabilisation and localisation are closely associated with disease, and likely contribute to disease onset and/or progression. For example, some rare neurodegenerative disorders, such as Fragile X syndrome, lethal congenital contracture syndrome 1, and lethal arthrogryposis with anterior horn cell disease are caused by gene deletions or mutations that influence nuclear RNA export (Zhang et al., 2007; Nousiainen et al., 2008). In addition, several mutations in the *MAPT* gene that cause the onset of frontotemporal dementia with Parkinsonism associated with tau mutations on chromosome 17 (FTDP-7T) alter the alternative splicing of tau exon 10, which encodes a repeat domain important for the binding of tau to microtubules (Rademakers and Hutton, 2007).

In ALS, substantial evidence indicates that abnormal RNA processing may contribute to both sporadic and familial forms of disease. The selective vulnerability of motor neurons to degenerative mechanisms in sporadic ALS may arise from altered RNA editing of AMPA receptor subunits (Kawahara et al., 2004) and cytoplasmic accumulations of the splicing factors TDP-43 and FUS likely influence familial neurodegenerative processes through their effect on target RNAs (Anthony and Gallo, 2010a), in addition to the stabilisation of neurofilament mRNA induced by TDP-43 (Strong et al., 2007). Perhaps most strikingly, several genes recently identified as causing or being risk factors for ALS encode RNA binding proteins (Sreedharan et al., 2008; Vance et al., 2009; Couthouis et al., 2011).

3. ncRNAs in the human nervous system

Thus far, we have considered mechanisms by which protein coding genes influence neurodegenerative processes. However, one of the most exciting recent developments in biology has been the recognition of the importance of non-coding RNAs (ncRNAs) in genome regulation (Table 1). Rapidly advancing technological innovation – most obviously in the area of high throughput sequencing (HTS) – has delivered us new views of the regulation and expression of the human genome (Garber et al., 2011). One of the most compelling and unexpected discoveries resulting from this, has been that our genome produces huge numbers of RNA molecules that do not encode protein: non-coding RNAs (ncRNAs) (Lipovich et al., 2010). In fact, together these newly discovered ncRNAs are likely to equal, if not exceed, the number of protein-coding genes in our genome. Therefore, understanding the role of ncRNAs in human biology and disease represents one of the great challenges – and opportunities – of contemporary biomedical research.

Until recently, the human genome was thought to comprise of around 21,000 protein coding genes occupying less than 2% of the genome, dispersed as oases in a genomic landscape that was largely seen as a gene desert, consisting of large regions of non-functional, often repetitive DNA. However, this view was completely undermined in the course of the past decade as a number of large consortia, most notably FANTOM (financed by the Japanese government) (Carninci et al., 2005) and ENCODE (financed by the National Institutes of Health) (2004), carried out large scale sequencing of the human transcriptome. These and subsequent studies revealed a stunning and unexpected result—that the majority of the human genome is in fact transcribed into many thousands of previously unknown RNA molecules, both long and short. Importantly, most of these RNAs do not encode protein, and are transcribed from both "intergenic" and previously described protein-coding loci. These RNAs can be classified by their size: "short" RNAs, including well-known classes such as microRNAs (miRNAs) or snoRNAs, and "long" RNAs which are defined as any transcript >200 nt that does not have a functional open reading frame (ORF). Current, conservative estimates indicate the existence of ~10,000 long non-coding RNAs (Derrien et al., 2012), and 1424 microRNAs (mirBase Release 17). Many other unrecognised short and long RNA almost certainly remain to be found. At present the full repertoire of non-coding RNAs in the human genome is unclear—ever deeper RNAseq analyses of human short and long transcriptomes does not appear close to saturation outside of protein-coding exons, suggesting that many more low expressed or cell-type specific ncRNAs remain to be discovered, particularly in the poorly explored non-polyA fraction (Kapranov et al., 2010). As for their function, our working hypothesis is that most ncRNAs serve to regulate gene expression in some way (Wang and Chang, 2011). This would be consistent with the notion that importance of ncRNAs has increased over evolutionary time to enhance the regulatory complexity of the genome (Mattick, 2003).

Table 1
Classes of ncRNAs in the nervous system.

Type	Examples	Molecular Function
microRNA	mir-9, mir-124, mir-132	Posttranscriptional gene repression, many target mRNAs.
antisense	NKX2.2AS, BDNF-AS1, HTTAS, antiNOS2A	Post transcriptional activation or repression of associated sense gene.
overlapping	SOX2OT, SOX8OT	Regulation of associated sense gene?
lincRNA	HAR1F, DGCR5, RMST, MEG3, TUG1, MIAT	Various, including cis and trans epigenetic regulation

The best understood class of small RNAs are the microRNAs (miRNAs), initially discovered in 1993 (Lee et al., 1993). These are 21–22 nucleotide single stranded RNAs that function in post-transcriptional repression of gene expression through semi-complementary targeting of mRNA transcripts (reviewed in Bartel, 2004). miRNAs are almost ubiquitous in eukaryotes and are found from man to some single celled eukaryotes (Molnar et al., 2007). They undergo a sequential biogenesis pathway, with the majority initially transcribed as a long, spliced and transient "primary" miRNA (pri-miRNA), which is processed by the Drosha nuclease to yield a short hairpin "pre-miRNA". This in turn is processed by Dicer, yielding a double-stranded partially overhanging RNA, one of whose strands is preferentially loaded in the so-called Argonaute (Ago) complex. Ago thus employs the miRNA "guide" antisense strand to select partially complementary mRNA molecules for degradation or translational repression. In the past decade, miRNAs involvement has been demonstrated throughout almost the full range of biological processes and disease states. Nevertheless, major questions remain unresolved, amongst them exactly how miRNAs recognise their target transcripts, and what is the exact significance of their widespread, and weak repression of target genes. The more recent discovery of analogous small RNA pathways in *E. coli* would seem to suggest that widespread repression of gene expression by small RNA may have some fundamental role in correct signal processing or noise suppression in complex gene networks (Shimoni et al., 2007; Raghavan et al., 2011). In addition to miRNAs, numerous other classes of small RNAs have been discovered in the mammalian genome, such as the piRNAs which are involved in host genome defence (Aravin et al., 2007) and snoRNAs which play a role in post-transcriptional RNA modification (Hamma and Ferre-D'Amare, 2010).

In contrast to the wealth of information on the miRNA mechanism of action, we know very little about lncRNAs (Ponting et al., 2009). Few lncRNAs have been functionally characterised, despite the large number that have recently been catalogued (Jia et al., 2010; Cabili et al., 2011; Derrien et al., 2012) but the widespread assumption is that many act as regulators of gene expression. However, unlike miRNAs, lncRNAs seem to employ a variety of mechanisms to regulate gene expression (Wang and Chang, 2011). They may act at a singular locus in *cis* or multiple loci in *trans*, by forming epigenetic regulatory complexes with transcription factors and cofactors (Gupta-Rossi et al., 2001; Feng et al., 2006) and/or control the subcellular localisation of transcriptional regulatory factors (Willingham et al., 2005). Evidence also exists that they can specifically bind to regulatory DNA sequences and recruit chromatin modifying complexes (Schmitz et al., 2010). They can act as decoys by (i) binding to RNA binding proteins (Bernard et al., 2010) (ii) binding to RNA competing with RNA binding proteins or miRNAs (Cesana et al., 2011) or (iii) regulating alternative promoter usage (Martianov et al., 2007). As well as acting as simple binding site 'competitors' or sponges, lncRNAs can act as scaffolds and recruit chromatin modifying machinery to regulate transcription (Sunwoo et al., 2009). Of this myriad of mechanisms, probably the latter presents the most opportunity for manipulation since the scaffolds are often under regulatory control by cell signaling pathways, rendering them amenable to small molecule intervention (Wang and Chang, 2011). In addition there is a relatively substantial literature describing antisense lncRNAs (also known as Natural Antisense Transcripts, or NATs) that are transcribed from the opposite or antisense strand of a protein coding gene, where there is overlap between exonic regions of the two. In these cases, the NAT may hybridise with protein-coding mRNA, either resulting in its stabilization or destabilisation (Katayama et al., 2005; Korneev et al., 2005). The following sections contain examples of all these mechanisms.

These findings are of fundamental significance for understanding neurodegeneration for a number of reasons. First, as will be discussed below, ncRNAs are now considered to be central players in both the development and functioning of the mammalian brain, most notably in their role as regulators of gene expression. Second, their rapid rate of evolutionary appearance and change makes them likely to have been central to the genetic rewiring that must have taken place during evolution of the human brain. And third, ncRNAs represent new biomarkers and targets for intervention in diseases of the human brain. Some examples of the various ncRNA classes expressed in the nervous system are shown in Table 1.

3.1. ncRNAs in mammalian neurodevelopment

During embryonic and postnatal development, the nervous system is built up by progressive waves of cellular proliferation, migration and differentiation (Edlund and Jessell, 1999). The genome of precursors cells integrate a variety of external and internal signals to make discrete lineage decisions, which directs them along well-defined and (usually) unidirectional phenotypic pathways, culminating in terminal-differentiation. This process is accompanied by the establishment of highly complex intercellular contacts (Kwan et al., 2012), mediated by dendrites and synapses, that underlie all neuronal signal processing. This latter process is also associated with enormous amounts of regulated cell death. The gene networks that control this process have been intensively studied for three decades (Guillemot, 2007). Such networks are important not only in creating a functional, differentiated cell, but also in the maintenance of the cells phenotype and viability. It is recognition of this 'maintenance function' that renders it impossible to ignore the processes of regulation of neurodevelopment when considering the molecular mechanisms underlying neurodegeneration (Bothwell and Giniger, 2000; Grilli et al., 2003).

3.1.1. Ghosts in the machine: ncRNA expression in the nervous system

Until recently, attempts to identify gene regulatory programmes during neural development have largely focussed on identifying transcription factors, and understanding their ability to regulate gene expression by sequence specific targeting of genes (Guillemot et al., 2006). However in recent years it has been demonstrated that ncRNAs are also key players in neurodevelopment. The first inkling of this came in early studies on the regulated non-coding transcriptome in the developing rodent nervous system (Sempere et al., 2004; Mercer et al., 2008). These studies have invariably demonstrated, with increasing levels of sophistication, that widespread transcription of ncRNA both long and short takes place in the developing mammalian brain, usually with complex spatial and temporal dynamics. Studies began with individual cloning efforts on human and mouse tissues, discovering some of the most highly expressed miRNAs (Lagos-Quintana et al., 2002). Amongst these were examples that would become archetypal neuronal specific miRNAs, such as mir-9, mir-29 and mir-124. Soon after, microarray profiling revealed enormous diversity of microRNA expression in the brain (Krichevsky et al., 2003; Sempere et al., 2004; Smirnova et al., 2005; Bak et al., 2008). Not only are individual miRNAs expressed at particular developmental time points, but also within different subregions of the brain. Most recently, next generation sequencing (NGS) methods have afforded the deepest yet view of the small RNA transcriptome of the brain, confirming the unparalleled richness of this organ (Landgraf et al., 2007). These studies have allowed us to identify a set of miRNAs that are strongly associated with the brain. This has proved extremely valuable, not least because it seems that many of these neuronal specific miRNAs also play roles in a wide range of neuropathologies. Studies in human and mouse generally show that orthologous miRNAs have similar expression profiles

(Sempere et al., 2004). Far less is presently known about other classes of small RNAs, but they are also likely to have similar behaviour. This is true at least for snoRNAs, where many neuronal specific cases have been found (Leung et al., 2009) and some are associated with mutations that cause behavioural phenotypes (Sahoo et al., 2008).

Research into long ncRNAs has lagged behind the miRNAs by several years, meaning that only recently have equivalent neurodevelopment expression profiles become available. In a landmark paper in 2008, John Mattick and colleagues profiled the lncRNA transcriptome in differentiating mouse embryonic stem cells (Dinger et al., 2008a). More importantly, they used a similar microarray to profile lncRNA expression during directed differentiation of neural stem cells to neurons and glia (Mercer et al., 2010). Not only are many lncRNAs upregulated during neurodevelopment, but many are also expressed in highly circumscribed neuronal populations within the mammalian brain (Mercer et al., 2008). LncRNA probes in existing commercial microarrays also detect multiple lncRNAs in the human brain (Michelhaugh et al., 2011). It is important to mention that many of the lncRNAs regulated in this way are associated with known protein genes that also have roles in the nervous system. For example, both the gene encoding the neurodevelopmental transcription factor Dlx1 and an antisense lncRNA overlapping it, Dlx1AS, are upregulated during the differentiation of GABAergic neurons (Mercer et al., 2010). Another Dlx paralogue, Dlx6, is contained within the intron of a well-known neuron-specific lncRNA, Evf2, which is transcribed from an anciently conserved enhancer region and functions as a transcriptional coactivator (Feng et al., 2006). More recently, we have carried out transcriptional profiling in human differentiating dopaminergic neurons, and discovered many hundreds of dynamically induced lncRNAs (Ng et al., 2012).

A large subclass of lncRNAs is represented by intergenic lncRNAs, also known as "lincRNAs" (long intergenic non-coding RNAs) or macroRNAs (Latos and Barlow, 2009) although it remains unclear whether the division of lncRNAs between intergenic lincRNAs and other "genic" lncRNAs (i.e. antisense or intronic to protein coding genes) is meaningful, and whether they in fact have similar functions. There are many thousands of lncRNAs in the mammalian genome, and many can be distinguished by the presence of chromatin modification patterns of active genes (Guttman et al., 2011). We are beginning to see that substantial numbers of lincRNAs are expressed during neural development and in the mature brain. At present we have little direct information on the function of these RNAs, although it has been widely speculated that many of them act as scaffolds and nucleate and target epigenetic regulatory complexes that regulate gene expression in trans (Guttman et al., 2011). These include RMST, an approximately 2 kb transcript that is highly expressed in the developing mouse brain, and eye (Leung et al., 2009; Uhde et al., 2010). Interestingly, the human orthologue, called NCRMS, is regulated by paired-box transcription factor PAX2 (Bouchard et al., 2005). Given that PAX2 regulator of neuronal development in multiple regions of the nervous system and is conserved from fly to human (Huang et al., 2008; Shi and Noll, 2009), this would suggest that NCRMS is an important neuronal regulatory lncRNA whose expression is regulated by high level transcriptional programmes. An analogous situation is found for another neural specific transcript located in the DiGeorge critical locus is DGCR5, a deletion of which was found to underlie mental retardation in one family (Sutherland et al., 1996), and is regulated by the neural transcriptional repressor REST (Johnson et al., 2009b). In addition, the lincRNAs, Neat1 and Neat2 (Clemson et al., 2009) have recently been shown to be necessary structural components of subnuclear bodies (Sunwoo et al., 2009) that are upregulated during neuronal differentiation (Mercer et al., 2010).

Most recently, RNAseq analysis has been carried out on dissected layers of mouse cortex to generate a fine grained layer-specific map of the transcriptome. This study has identified 1055 layer-specific transcripts of which 66 were lncRNAs (Belgard et al., 2011). Given the low expression of lincRNAs in general, these figures are likely to be underestimates. Nevertheless, they underline the likely importance of lncRNAs in establishment and maintenance of neural identity. The advent of various genomic technologies, most importantly RNAseq, makes it likely that in the near future extremely sensitive, genome-wide maps of the brain transcriptome will become available. This will likely be accompanied by innovations allowing for measurements in extremely small samples – even single cells (Tang et al., 2006) – given the heterogeneity of cell types in the brain, this will be crucial to gleaning a clear picture of the human neuronal transcriptome.

In summary, abundant and regulated expression of ncRNA in the mammalian nervous system, including their direct targeting by known regulatory pathways, points to the importance of ncRNA in this organ. In the next section, we discuss evidence for how ncRNAs contribute to the regulation of gene expression in the nucleus.

3.2. ncRNAs in the gene regulatory networks controlling neuronal differentiation

So what are the functional implications of ncRNA expression during neurodevelopment? While this is an immature field, there is growing evidence that neuron-specific ncRNAs have indispensable roles in neuronal development. Although few mouse knockout models have yet been published, compelling evidence exists that loss of neuronal miRNAs has major impacts on brain development. The lncRNA Evf2, as mentioned above, is expressed from a highly conserved enhancer element at the Dlx5/Dlx6 locus. Originally discovered in rat, but also conserved in mouse, it apparently can function as a transcriptional cofactor to the Dlx2 transcription factor that regulates this locus during GABAergic development (Feng et al., 2006). Jhumku Kohtz and colleagues recently managed to knock out Evf2, generating an animal with reduced GABAergic signalling (Bond et al., 2009). The animals displayed reduced numbers of GABAergic neurons postnatally, resulting in adults with impaired synaptic inhibition. Another neural specific lncRNA is the imprinted Meg3 (Manji et al., 2006). It is capable of activating the p53 tumour suppressor gene, by an unknown mechanism (Zhou et al., 2007). The knockout mouse lacking Meg3 displayed a subtle yet clear phenotype of upregulated angiogenic gene expression in its brain (Gordon et al., 2010). Based on a functional genomics approach, we have recently found even more extreme phenotypes for loss of lncRNA during neurogenesis, at least in vitro, and have found at least four lncRNAs that are apparently indispensable for terminal differentiation of neurons (Ng et al., 2012). Another example is MIAT (also known as Gomafu and RNCR2), a neural-restricted lncRNA with orthologues in mouse and human (Sone et al., 2007). This nuclear-retained transcript was one of several ncRNAs discovered in a screen for genes involved in retinal development. Its loss, or even forced relocation to the cytoplasm, upregulates the production of amacrine cells and Muller glia (Blackshaw et al., 2004; Rapicavoli et al., 2010). Thus, MIAT appears to function in cell fate specification in retinal precursor cells, and this function depends on its nuclear localisation. It will be fascinating to find out whether MIAT is in fact involved in gene regulation.

Amongst the best studied ncRNAs in neural differentiation is the miRNA mir-124. This miRNA is massively expressed in brain, accounting for up to a half of all miRNAs in this organ at any time (Lagos-Quintana et al., 2002). This high expression is accounted for by the existence of three distinct loci that express the miRNA. Further evidence for the importance of mir-124 in the nervous

system is its conservation between human and mouse, and the fact that all three of its host loci appear to be regulated by the master neural regulator, REST (Conaco et al., 2006; Johnson et al., 2008). In recent years, a number of studies have investigated the roles of mir-124 in neurodevelopment, leading to the view that it functions by controlling several distinct gene regulatory pathways during this process. Studies from the Crabtree group have shown that ATP-dependent SWI/SNF chromatin remodelling complexes are key mediators of neuron-specific gene expression programs, and the composition of these complexes change dynamically during development. Mir-124 controls this switch, by switching expression of subunits characteristic of the npBAF (neural precursor specific form) to the nBAF (neuronal form) at the stage of terminal neuronal differentiation (Yoo et al., 2009). In addition to facilitating chromatin remodelling, mir-124 expression also switches genome-wide splicing patterns during neuronal differentiation. This is achieved through the downregulation of the non-neuronal splicing regulator PTB1 (Makeyev et al., 2007). In an elegant model, PTB1 itself promotes the nonsense mediated decay of its neuronal specific paralogue, PTB2. Thus, expression of mir-124 leads to a bistable switch from non-neuronal to neuronal splicing patterns. Mir-124 also directly targets transcription factors to facilitate terminal neuronal differentiation: the HMG-box transcription factor Sox9 is expressed in neural precursor cells, and prevents their terminal differentiation. Induction of expression of mir-124 thus facilitates terminal differentiation by repressing Sox9 levels. Finally, mir-124 is also capable of repressing components of the REST regulatory complex, which represses it and other neuronal specific genes in immature neuronal cells: mir-124 directly targets the small phosphatase SCP1, which is recruited by REST for repression of target genes (Visvanathan et al., 2007). Thus, mir-124 targets multiple distinct components of the gene regulatory network in undifferentiated neural cells to effect a switch to expression patterns characteristic of differentiated neurons. It is unclear whether other miRNAs behave in the same way. However, many of the findings with mir-124 are also mirrored by mir-9, in its ability to shift chromatin remodelling complex expression and the targeting of various transcription factors (Yoo et al., 2009; Shibata et al., 2011).

Quite apart from these defined pathways of control, it appears that mir-124 has so many mRNA target genes that its presence has a profound effect on the cellular transcriptome, so that exogenous expression of mir-124 in a non-neuronal cell type results in widespread transcriptome changes of 100 or more genes (Lim et al., 2005). These findings are underlined by the recent stunning finding that overexpression of mir-124 and mir-9 alone is sufficient to reprogram mouse fibroblasts into functional neurons (Yoo et al., 2011).

One numerous subclass of the lncRNAs are *cis*-antisense transcripts (Katayama et al., 2005). These are lncRNAs that are transcribed from the opposite (non-template) strand of the genome from protein-coding genes, and which have at least some exon-to-exon overlap. Such sense–antisense pairs have been studied for some time, and it is estimated that the majority of genes have some kind of antisense transcript (Katayama et al., 2005). The functional consequences of antisense transcripts on the sense, protein-coding gene appear to be diverse, with cases of both positive and negative regulation reported in the literature (Faghihi et al., 2008; Annilo et al., 2009). There are presently several documented cases of antisense transcripts having important regulatory roles in neural development. The transcription factor Nkx2.2 is expressed in neural precursor cells where it promotes differentiation down the oligodendrocyte lineage. An antisense transcript to this gene, Nkx2.2AS, upregulates levels of the sense transcript, and thus promotes oligodendrocyte differentiation (Tochitani and Hayashizaki, 2008). Interesting, Nkx2.2AS also has significant antisense homology to other paralogous homeobox transcription factors from the Nkx and Hox families, suggesting that antisense may serve to regulate many genes. This is an important observation since it underlines that ncRNAs that act in *cis* may no be limited to regulation of one target. Other examples of antisense expression in the nervous system include negative regulation of Zfh-5 by its own antisense (Komine et al., 2006).

Another class of lncRNAs are "overlapping" transcripts (OT) defined as those that contain a protein-coding gene within their intron, but with no exon–exon overlap. We are not aware whether a strict definition requires the OT transcript to lie on the same strand as the protein coding partner, although in the case described here both indeed are transcribed from the same genomic strand. Importantly, the OT transcript and sense gene do not have any overlapping exonic regions. This distinction may be important, given that there is evidence that in the case of cis-antisense genes, the functional interaction may occur through RNA–RNA hybridisation of the processed transcripts (Annilo et al., 2009). At least one OT transcript pairs has been described in the nervous system, both for the SRY-box type transcription factor, SOX2, involved in embryonic stem cell pluripotency and neural differentiation (Amaral et al., 2009). The OT transcript positively correlates in expression with the sense gene, although it remains unclear whether there is a regulatory interaction between the two, or if they are simply coregulated. Overall, overlapping transcripts are rather rare compared to other classes of lncRNA: in a recent analysis we identified 52 same-sense and 115 antisense OT-protein coding gene pairs, representing 0.35% and 0.77% of annotated lncRNAs, respectively (Derrien et al., 2012).

Thus it is clear that the study of ncRNA in neuronal regulatory circuits is at an early stage, particularly in the case of lncRNAs where we have very little idea of how many are operating, nor their mechanism of action.

3.3. ncRNAs in neuronal excitability and function

The excitability and connectivity of the nervous system is maintained by synaptic contacts between neurons. The establishment, maintenance and loss of synapses is fundamental to understanding normal behaviour as well as many neurological and psychiatric diseases and addictive behaviours. Synaptic behaviour is controlled by gene regulatory networks operating both in the nucleus of neurons, and within the neurites themselves where locally regulated translation is particularly important for mediating rapid responses to synaptic activity and extracellular signalling events (Bothwell and Giniger, 2000; Grilli et al., 2003).

The first studies on transcriptional regulatory pathways that mediate synaptic plasticity were carried out by Eric Kandel and colleagues (Dash et al., 1990). These pioneering studies isolated the widely conserved leucine zipper transcription factor CREB (CAMP responsive element binding protein 1). Nuclear CREB is activated by synaptic activity, thereby binding to the regulatory regions of many other genes that it upregulates. Amongst the first evidence for ncRNAs in synaptic activity came with the discovery that CREB directly targets several miRNAs, including mir-132 (Vo et al., 2005). Not surprisingly, mir-132 is highly expressed in the mammalian nervous system, and is induced by synaptic activity (Nudelman et al., 2010). Functional studies showed that expression of mir-132 promotes neurite outgrowth, at least in part through the suppression of the mRNA encoding p250GAP (Vo et al., 2005). Consistent with this, mir-132 levels are upregulated in response to active synaptogenesis (Impey et al., 2004). Like other miRNAs, mir-132 is likely to function through multiple pathways, and evidence has been found for targeting of several other relevant genes including MeCP2 (Klein et al., 2007), which is an intensively studied gene regulator in neurons, and mutations in which are associated with the neurodevelopmental disorder, Rett's syndrome

(Amir et al., 1999). In addition to mir-132, several other miRNAs have been shown to regulate synaptic structure and function: mir-125b and mir-134 (Schratt et al., 2006; Edbauer et al., 2010). In contrast to mir-132, both of these miRNAs negatively regulate synaptic function. Mir-134 is a negative regulator of dendritic spine size, through the repression of the mRNA encoding Limk1 (Schratt et al., 2006). Importantly, this interaction seems to be downstream of the neurotrophic factor BDNF, which relieves this repression of Limk1. Mir-125b acts by targeting the NMDA receptor subunit NR2A (Edbauer et al., 2010). Surprisingly, there is evidence from the aquatic snail, *Aplysia*, that mir-124, a positive regulator of neurodevelopment, may also function as a negative regulator of activity dependent modulation of synapses, possibly through repression of CREB mRNA (Rajasethupathy et al., 2009). Another microRNA, mir-138 also negatively regulates dendritic spine size (Siegel et al., 2009).

Are other types of ncRNA involved in neuronal function and behaviour? Certainly, if the hypothesis that ncRNAs underlie the evolution of human cognition is correct, then we would expect them to be intimately involved in learning and behavior. At present at least two distinct cases of this have been described. The 152 nt RNA called BC1 was identified in the rodent brain more than two decades ago (Sutcliffe et al., 1982). This RNA Pol III-transcribed gene is localised in presynaptic terminals and is upregulated in response to synaptic activity (Muslimov et al., 1998) where it plays a key role in regulating activity-dependent translation of proteins. Specifically, BC1 inhibits translation by binding to specific translational regulatory proteins (Wang et al., 2005). Detailed functional studies have been carried out showing that loss of BC1 causes aberrant translation of synaptic proteins, including the fragile X protein FMRP (see Fig. 1 and Section 5.1), resulting in hyperexcitability (Zhong et al., 2010). At a behavioural level, mice

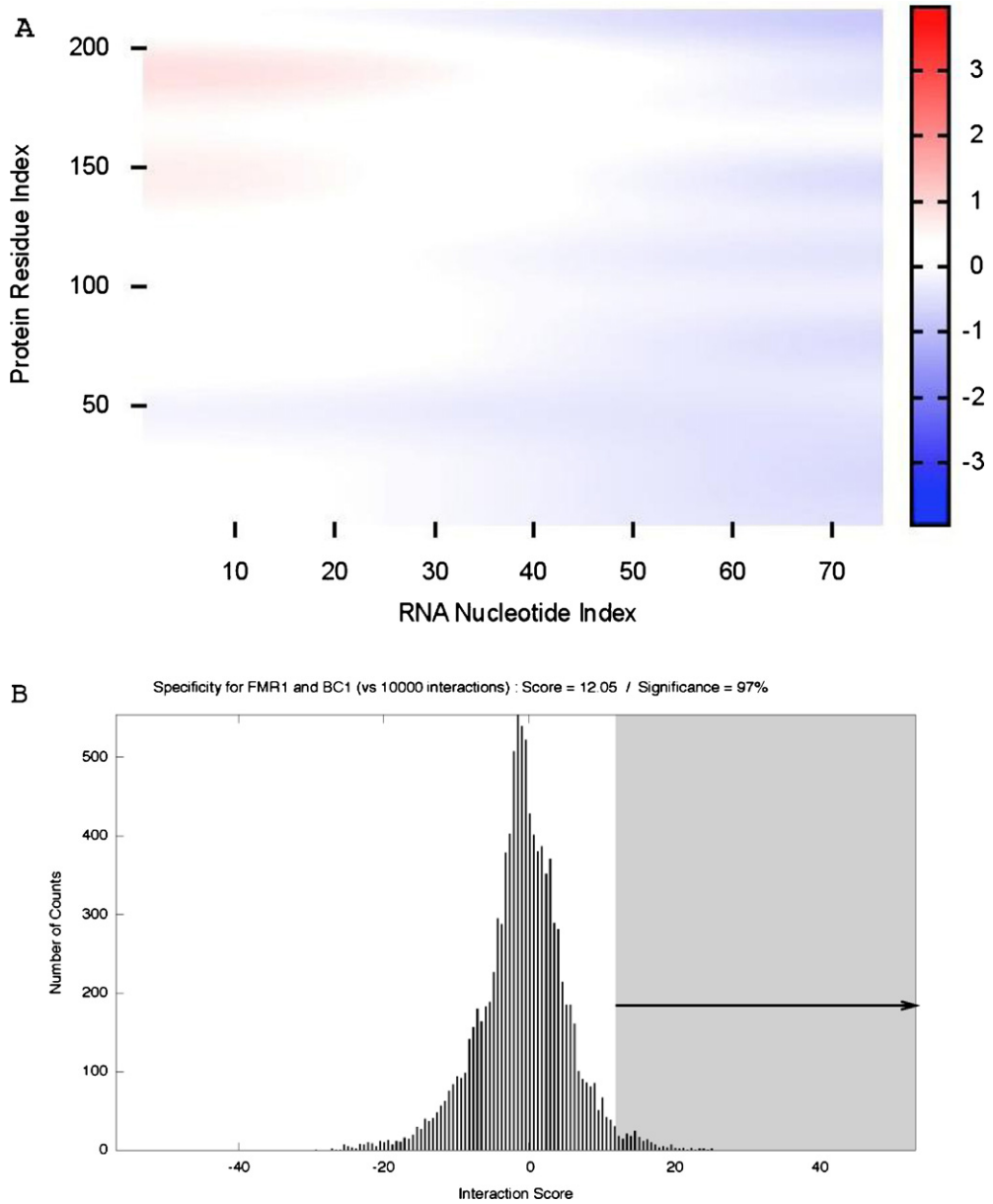

Fig. 1. Prediction of FMRP ncRNA interactions. It has been shown that the N-terminus of Fragile X mental retardation protein FMRP interacts with the 5′ of the dendritic non-translatable brain cytoplasmic RNA BC1 (Zalfa et al., 2005). The FRMP-BC1 complex interacts with targeted mRNAs that are translationally repressed (see ncRNAs in neuronal excitability and function). Computational methods such as catRAPID can be employed to characterize ribonucleoprotein associations, which will help unravel the role of non-coding transcripts in protein networks (Bellucci et al., 2011b): (A) In agreement with experimental evidence, catRAPID predicts the binding site of FMRP at position 150–217. (B) The interaction between FMRP and BC1 is predicted to be 97% significant when compared with other ribonucleoprotein associations.

lacking BC1 display altered exploratory behaviour and increased mortality in open field survival tests (Lewejohann et al., 2004) and have elevated susceptibility to epileptogenesis (Zhong et al., 2009). There also exists an analogous primate-specific ncRNA transcript called BC200, which is also expressed in human dendrites and seems to interact with the same repertoire of proteins as BC1 in rodents, and is also capable of repressing translation (Martignetti and Brosius, 1993).

There is some evidence for the involvement of antisense transcription in learning and memory: Korneev and colleagues have shown that in the snail model Lymnaea stagnalis, associative conditioning is accompanied by induction of two nitric oxide synthase (NOS) paralogues (Lum-nNOS1/2) (Korneev et al., 2005). The authors identified an additional expressed pseudogene containing antisense homology to both NOS1 and 2. This antisense thus should be termed an "antisense NAT", since it is transcribed from a distal genomic locus, although it is likely that it operates through similar mechanisms as cis-encoded equivalents. Intriguingly, this anti-NOS transcript is capable of hybridizing to and inhibiting translation of sense NOS transcripts, and is repressed during memory consolidation (Korneev et al., 2005, 1999). It is also intriguing to note that an analogous antisense regulatory system exists in the human genome with the gene NOS2A (Korneev et al., 2008). There is also evidence that enhancer elements, long range regulatory elements that positively regulate gene expression, may function through the production of ncRNAs (Carninci et al., 2005; Ponjavic and Ponting, 2007; Guttman et al., 2009; Orom et al., 2010). The Greenberg group recently showed that when mouse neurons are depolarized, the resulting changes in transcriptional programs are accompanied by (and likely controlled by) the activation of thousands of enhancer elements. Their novel finding was that these enhancer elements are then transcribed into double stranded RNA molecules, termed "eRNAs" (enhancer RNAs), whose expression correlates with the induction of nearby target genes (Kim et al., 2010). The key question is now whether eRNAs are simply a byproduct of enhancer activation, perhaps due to non-specific transcription due to elevated recruitment of RNA Pol II following gene activation, or whether eRNAs are mechanistically required for enhancer-mediated gene activation. There is some evidence that the RNA molecule itself is, in some cases, necessary for the activation by enhancers, although further experiments will be required to demonstrate this conclusively (Orom et al., 2010). Nevertheless, the profound changes in ncRNA expression observed in depolarised mouse neurons is highly suggestive that they have some important role in activity-dependent genome regulation.

3.4. Implications of ncRNAs in evolution of the brain

A major corollary of studies on the genomic basis of human brain complexity, is to understand what genomic elements underlie this complexity. This analysis relies on identifying function elements in the human genome that have arisen, or mutated under selection, since our last common ancestor with chimpanzees or other primates. For a variety of reasons, the general feeling is that much of the genetic basis of human-specific phenotypic traits, including cognition, lies in non-protein coding regions of the genome, since protein-coding regions have undergone little change during recent evolution (King and Wilson, 1975; Knowles and McLysaght, 2009). ncRNAs, particularly lncRNAs, appear to undergo rapid evolution. This may be due to the lack of strict nucleotide spacing and conservation that is necessary for an open reading frame. Rather, lncRNAs may function through modular secondary structure features that are less sensitive to mutations, insertions or deletions in the primary RNA sequence (Pang et al., 2006). Quite a number of studies have examined the evolutionary conservation of lncRNAs (Carninci et al., 2005; Ponjavic and Ponting, 2007; Guttman et al., 2009; Orom et al., 2010). While their exonic sequence is under far less selection compared to protein-coding exons, nevertheless they do have a significantly non-random selection when compared to neutrally evolving ancestral repeats, indicative of functional RNA. Intriguingly, lncRNA promoter regions are under selection almost as strong as protein-coding gene promoters (Carninci et al., 2005; Ponjavic and Ponting, 2007; Guttman et al., 2009; Orom et al., 2010; Derrien et al., 2012). These findings are consistent with lncRNAs being functional RNA products that have less constraint on their primary sequence. This observation, coupled with their widespread expression in the human brain, have led to the proposal that lncRNAs have been key players in the molecular rewiring associated with human brain evolution (Mehler and Mattick, 2007). This idea was given a significant boost by the work of David Haussler and colleagues in their 2006 discovery of Human Accelerated Region 1 (HAR1) lncRNA locus (Pollard et al., 2006). In a genome-wide search for human non-coding loci that are under significant positive selection specifically in the human evolutionary branch, the HAR1 cis-antisense non-coding gene pair (that is, two lncRNAs overlapping each other on opposite strands) had the strongest signal. Such regions of positive selection would be expected to include functional genomic elements that have contributed to the emergence of human-specific, adaptive traits including intelligence. Importantly, the elements investigated in this study, including HAR1, have orthologous regions in other species, but these elements have undergone a significant acceleration in evolution specifically after divergence of human and chimp. What was most intriguing was that when the authors investigated the expression of the HAR1F (forward strand) transcript, they found it to be brain specific in human and other primates. Closer examination showed it is also coexpressed with reelin in developing cortical neurons in both human and macaque foetuses. Thus, these findings provided the first candidate lncRNA that may have contributed to human specific neurodevelopmental processes. Follow up studies have shown that HAR1F folds into complex secondary structure, and that human specific mutations may alter these structures, presumably affecting the RNAs function (Beniaminov et al., 2008). It is important to state that subsequent studies have challenged the basis of nucleotide substitutions

Table 2
Neurodegenerative processes that may involve misregulation of indicated RNA.

	LncRNA	miRNA
Alzheimer's	BACE1AS (Faghihi et al., 2008)	Mir-137/181b (Geekiyanage and Chan, 2011), mir-29a/29b-1 (Hebert et al., 2008), mir-107 (Wang et al., 2008c)
Parkinson's	BC200 (Mus et al., 2007), SOX2OT (Arisi et al., 2011)	mir-34b/c (Minones-Moyano et al., 2011), mir-7 (Doxakis, 2010), mir-153 (Doxakis, 2010), mir-433 (Wang et al., 2008a), mir-133b (Kim et al., 2007)
Huntington's	HAR1 (Johnson et al., 2010), DGCR5 (Johnson et al., 2009b), TUG1(Johnson, 2011), NEAT1(Johnson, 2011),	Mir-7 (Johnson and Buckley, 2009), mir-9 (Packer et al., 2008), mir-34b (Gaughwin et al., 2011), mir-124 (Johnson et al., 2008), mir-132 (Lee et al., 2011)
Amyotrophic lateral sclerosis		Mir-206 (Williams et al., 2009)

Table 3
Neurodegenerative process with evidence for toxic RNA species. RAN: Repeat-associated non-ATG translation.

	Antisense transcription	Toxic RNA	RAN	Expansion in non-coding region
DM1			Yes (Zu et al., 2011)	Yes (Brook et al., 1992)
DM2				Yes (Ranum et al., 1998)
FXTAS	Yes (Ladd et al., 2007)			Yes (Verkerk et al., 1991)
HD		Yes (Banez-Coronel et al., 2012)		
HDL2	Yes (Wilburn et al., 2011)		Yes (Zu et al., 2011)	Possibly (Margolis et al., 2001)
SCA3		Yes (Li et al., 2008)	Yes (Zu et al., 2011)	
SCA7	Yes (Sopher et al., 2011)			
SCA8		Yes (Mutsuddi et al., 2004)	Yes (Zu et al., 2011)	
SCA10				Yes (White et al., 2012)
SCA12				Yes (Holmes et al., 1999)

occurring in HAR1, and at present this debate remains unresolved (Galtier and Duret, 2007). Interestingly, not only has the sequence of HAR1 itself undergone evolutionary change, but also the regulatory pathways controlling its expression: while studying the regulation of this gene by the neural repressor protein REST, we found that this regulation is not conserved (Johnson et al., 2010). While human HAR1 is controlled by proximal REST binding sites, the mouse orthologue shows little evidence of such regulation. Thus, neural-specific regulatory evolution of lncRNAs may also evolve rapidly (Johnson et al., 2009a).

It remains unclear how much we can extend the findings from HAR1 to other lncRNAs. At present we do not have accurate data on the phylogeny of human lncRNAs, although it would appear that a sizable fraction of them are primate specific (Derrien et al., 2012). As a general trend, however, the amount of non-coding DNA, and hence presumably ncRNA, scales with organismal complexity from prokaryotes to humans (Mattick, 2004).

One particular subset of lncRNAs that seems to be intimately linked to neurodevelopment has been described by Chris Ponting's group (Ponjavic et al., 2009; Chodroff et al., 2010). This group identified a category of lncRNAs in mouse that have been under significant evolutionary selection. Interestingly, these genes are more likely to be located in genomic proximity to protein-coding genes associated with development, and particularly those encoding transcription factors involved in neural development. Some of these lncRNAs are conserved and transcribed from mouse to chicken, underlining their importance in development. It remains unclear how exactly these RNAs function, although one might expect that they are involved in the cis-regulation of nearest protein coding genes, possibly through some kind of enhancer function (Orom et al., 2010).

4. ncRNAs and neurodegeneration

As mentioned above, the various neurodegenerative processes that affect the human brain have enormous and growing social and economic implications for human society. For this reason, much effort is being spent on understanding the molecular pathways underlying NDDs, with the hope of eventually being able to predict susceptibility, allow early diagnosis, and develop effective therapies that modify the course of disease progression.

While neurodegeneration is highly prevalent in human, it remains unclear whether the molecular pathways governing this process have commonalities between disease types (see Section 2). In addition to the loss of neurons in defined regions of the nervous system, these diseases are almost all characterised by the extracellular and/or intracellular accumulation of aggregated protein species. Furthermore, the various dominantly inherited trinucleotide repeat disorders are all characterised by triplet expansions within a particular gene locus. Nevertheless, at present it is not clear what universal pathways operate across these diseases. Indeed, it may be the case that the only fact that unites the neurodegenerative conditions may be the extremely long lifespan that we as humans – and thus our neurons – experience. Indeed, age is the greatest risk factor for developing a NDD. Nevertheless, the difficulty of studying this disease has meant that, in spite of commendable work from hundreds of labs around the world, distinguishing the actual aetiology of these conditions from simply bystander phenotypes or protective cellular responses, remains a major challenge. Thus, much work remains to be done in discovery the genetic pathways underlying these conditions. Given the recent discovery of ncRNAs, their fundamental roles in neurodevelopment and neuronal function, and particularly their likely evolutionary non-conservation, it is essential to investigate their likely roles in neurodegeneration.

In recent years, evidence for a role of RNA in neurodegeneration has been growing rapidly. We may divide this role into two distinct categories, which are elaborated below. First, cases where the dysregulation of an endogenous ncRNA causes a disease phenotype. These pathways are relevant to both spontaneous and genetic neurodegenerative conditions. Second, where a genetic mutation causes a disease phenotype (summarised in Table 2), a situation that appear to be highly prevalent, if not universal, in triplet-associated neurodegeneration (summarised in Table 3).

4.1. ncRNA dysregulation in neurodegeneration

As described in the preceding sections, short and long ncRNAs are expressed throughout the nervous system. With the recent discoveries of ncRNAs, first the microRNAs and more recently the lncRNAs, not surprisingly attention has shifted to ask whether these genes expression may also play some role these disease conditions.

In the past five years or so, it has been shown that miRNA pathways are affected in almost all neurodegenerative conditions, both spontaneous and familial: Alzheimer's (Wang et al., 2008b), Parkinson's (Kim et al., 2007), Huntington's (Johnson et al., 2008), ALS (Williams et al., 2009), and spinal cerebral ataxia (SCA1) (Lee et al., 2008). This is perhaps not unexpected given the central importance of miRNAs in shaping the neuronal transcriptome. Quite a number of reports have now shown that miRNA expression is altered in neurodegenerative conditions, but also that these miRNAs often include those that are most highly and specifically expressed in the nervous system. Furthermore, evidence is becoming available suggesting that some miRNAs may be common to several distinct neurodegenerative pathways, offering hope to find unifying mechanisms amongst these diseases.

What are phenotypic consequences of miRNA changes in neurodegeneration? Given our relatively better understanding of miRNA mechanisms of gene regulation, progress on this question has been quite rapid. For the main neurodegenerative conditions – AD and PD – as well as for HD and some other trinucleotide repeat disorders, we have an increasingly detailed picture of the changes in miRNA–mRNA networks that accompany neurodegeneration.

While the large number of individual miRNAs that have been discovered in these studies precludes a detailed discussion here, we will cover the most important information hereafter.

The miRNA-ome in AD has been intensively studied by several groups, revealing a large catalogue of dysregulated miRNAs (Satoh, 2010) Amongst these at least three pathways appear to be important, two of which converge on the BACE1 gene, encodes a secretase that processes the amyloid precursor protein to generate β-amyloid (A(), the principle component of senile plaques in AD brain. In a microarray screen of postmortem brains, mir-107 was shown to be down-regulated in AD brains (Wang et al., 2008b). Interestingly, its expression was down-regulated even in early stage patients, suggesting that it may play a causative role in pathology. Most importantly, the authors showed that mir-107 targets the BACE1 mRNA, supplying a plausible mechanism for the upregulation of this gene. Another likely regulator of BACE1 is the miRNA cluster mir-29a/b-1, which is also decreased in AD (Hebert et al., 2008). In a separate study, it was found that the inflammatory brain response in AD may be regulated by another miRNA, mir-146a, which itself is controlled by the transcription factor NFkB (Ghose et al., 2011). The important downstream target here appears to be complement factor H (CFH).

Similar evidence exists for a role of miRNAs in PD. Here, the key players so far appear to be mir-133b, mir-34b/c and mir-7. Mir-133b plays an intimate role in the gene regulatory circuit controlling dopaminergic neuronal differentiation, through negative regulation of Pitx3 (Kim et al., 2007). Moreover, loss of mir-133b seems to be an important contributory factor in PD. More recently it has been demonstrated that mir-34b/c RNAs contribute to the mitochondrial dysfunction phenotype in PD (Minones-Moyano et al., 2011). The neural specific miRNA mir-7 regulates levels of SNCA, making it a clear candidate in PD. There is also some evidence that mir-7 is down-regulated in mouse models of PD, although clear data on its expression from human PD patients has not yet been presented (Junn et al., 2009).

miRNA pathways are also affected in trinucleotide-associated neurodegeneration. At least in the case of HD, we have strong evidence that multiple neuronal specific microRNAs are repressed, many of them through specific targeting of the transcriptional repressor REST (Johnson et al., 2008). Several groups have carried out bioinformatic prediction, or transcriptomic studies, to show that some of the most neural-specific miRNAs are repressed including mir-7, mir-9, mir-124 and mir-132 to name a few (Johnson et al., 2008; Packer et al., 2008). There is also some evidence that HTT protein itself may be involved in miRNA processing, and furthermore that components of the miRNA pathway are lost in HD (Lee et al., 2011). Together these data provide numerous, non mutually exclusive hypotheses as to potential ways that miRNAs may cause neurodegeneration in HD: either through the loss of one or several neuronal specific miRNAs which are necessary for maintenance of neuronal phenotype or else the wholesale loss of miRNA processing, which itself causes neurodegeneration (Schaefer et al., 2007).

Apart from the specific miRNA pathways mentioned above, there is various evidence that the miRNA pathway as a whole is neuroprotective. Loss of this pathway in flies leads to neurodegeneration (Bilen et al., 2006), and more recently a similar phenomenon has been demonstrated in mammals: targeted loss of the Dicer miRNA processing enzyme in mouse forebrain results in neurodegeneration (Schaefer et al., 2007). It remains unclear whether this process occurs due to the loss of a finite number of miRNAs, or else whether this pathway has some intrinsic neuroprotective role in and of itself, perhaps through the maintenance of the neuronal phenotype.

More recently, details have begun to emerge about possible roles of lncRNAs in NDDs. So far the best documented cases involve antisense transcripts to known neurodegeneration-related genes, although this is likely to be due to bias for practical reasons (since these transcripts, by virtue of their close proximity, have a clear a priori case for being regulators of those genes), and many more lncRNAs are likely to be operating in trans in these diseases. A clear demonstration again involves BACE1, a gene that plays a key role in AD. The group of Claes Wahlestedt showed recently that an antisense transcript to BACE1, BACE1AS, is widely expressed and is capable of up-regulating levels of the sense mRNA. Furthermore, BACE1AS expression is elevated in post-mortem AD patient brains (Faghihi et al., 2008). Interestingly, expression of BACE1AS itself is induced in response to Aβ, suggesting that a positive feedback mechanism may exist to drive amyloidogenesis. BACE1AS is also a promising candidate for therapeutic knock down using antisense locked nucleic acid (LNA) oligonucleotides (Modarresi et al., 2011). There is also evidence that the BC200 RNA, the human analogue to the mouse synaptic-activity regulated BC1, is upregulated significantly and proportionally in Alzheimer's brain (Mus et al., 2007) although it remains unclear whether this phenomenon is a cellular response to cell death or contributes to neurodegeneration.

There is also evidence from mouse models of AD that other lncRNAs' expression is altered in AD (Arisi et al., 2011). A recent microarray analysis of AD11 mice, which express a recombinant antibody against NGF, showed that lncRNA expression is specifically altered in the brains of these mice, compared to controls. Remarkably, of the 15 genes that serve as the best biomarkers of neurodegeneration in this system, two are lncRNAs: Sox2ot and 1810014B01Rik. Both transcripts are significantly upregulated in the brain of diseased mice. This is rather surprising, since lncRNAs are likely to be underrepresented amongst the genes included in the mouse microarrays used in this study, suggesting that lncRNAs have similar, if not higher probability of being altered in AD compared to protein-coding genes. At least Sox2ot is likely to have brain specific expression and functions (Amaral et al., 2010), while nothing is yet known about 1810014B01Rik.

In order to search for additional signatures of lncRNA expression in AD, we mined previous microarray data from (Bossers et al., 2010). This study was carried out on a cohort of post-mortem brain samples, AD brain samples at various stages of disease severity as assessed by Braak staging (Braak and Braak, 1995), hybridised to Agilent whole genome microarrays. The authors used statistical methods to identify ~1000 genes and transcripts showing significantly different expression levels amongst Braak stages. Amongst unannotated transcripts in this set, we found at least eight lncRNAs (Fig. 2). These lncRNAs display a range of expression profiles, including some that decrease steadily during disease progression, others that peak sharply at intermediate disease stages, and others that increase with disease severity. Interesting, the two known lncRNAs amongst this set have both been previously implicated in neurodegeneration. The precursor transcript of the microRNA mir-9 peaks strongly at intermediate Braak Stage III, implying that the mature microRNA also increases in a similar fashion. Mir-9 has previously been shown to be repressed in Huntington's disease (Packer et al., 2008). The other lncRNAs is the Human Accelerated Region 1 transcript (Table 2), a neural-specific lncRNA of unknown function (Pollard et al., 2006), that was the first lncRNA shown to be repressed in Huntington's disease (Johnson et al., 2010). It is unclear whether this commonality between AD and HD is significant.

A recent reanalysis of microarray data in HD revealed large numbers of lncRNAs are likely to be altered in this disease (Johnson, 2011). Misannotated lncRNAs within conventional Affymetrix microarrays were reannotated, and significantly changing transcripts were collected. At stringent levels of statistical significance, this analysis identified four repressed

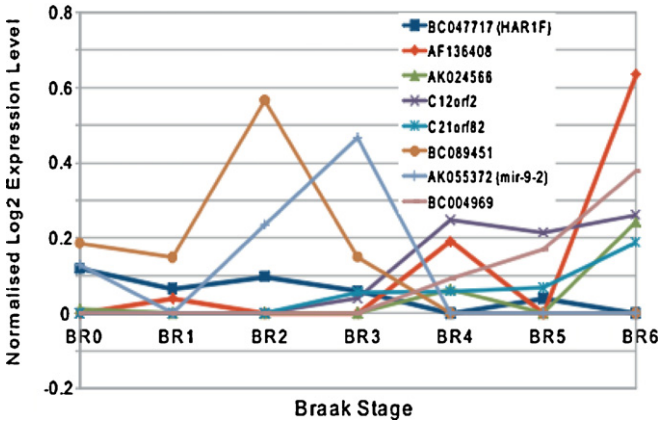

Fig. 2. Long non-coding RNAs in Alzheimer's brain. We searched for evidence of significantly changing lncRNAs in AD subjects in the study of Bossers et al. (2010). Brains were staged according to Braak and Braak (1995) where Braak stage I represents early disease stage and Braak stage VI end stage disease. Amongst the 1071 transcripts found to be changing with statistical significance amongst seven groups of postmortem brains, we identified at least eight lncRNAs. In brief, we manually extracted likely lncRNAs from this set based on ID—those transcripts with IDs commencing in ENST/BC/AK, or with the format "C1orf1", then submitted their sequences to the coding potential calculator (Kong et al., 2007). Transcripts scored as non-coding (CPC score <0) were then manually checked. Any transcripts overlapping protein coding gene exons on the same strand, or immediately downstream of annotated protein coding genes (and therefore potential extended UTR regions) were discarded. We then used published normalised log2 expression data (Bossers et al., 2010) to plot the lncRNA expression level.

and four overexpressed lncRNAs in HD. Consistent with the known role of the transcriptional repressor REST in this disease, the known REST target gene, DGCR5 is repressed in HD, suggesting that this lncRNA is downstream of REST in this disease (Table 2). Another predicted REST target, MEG3 is also repressed. Amongst the upregulated lncRNAs is the known lncRNA TUG1, which is a target of the tumour suppressor p53, which itself is a known transcriptional pathway in HD. An earlier study showed that both the sense and antisense Human Accelerated Region 1 (HAR1) transcripts are also repressed in HD (Johnson et al., 2010). It is unclear at present how many other lncRNAs are misregulated in HD, since the RNAs tested in these studies represent a tiny fraction of the known lncRNAs. It is of note however, that some of the HD-misregulated RNAs have also been implicated in behavioural disorders such as heroin addiction (Michelhaugh et al., 2011). The HTT gene itself is negatively regulated by a recently discovered antisense transcript, HTTAS (Chung et al., 2011). Furthermore, given the crucial role of BDNF in HD, it is worth noting that BDNF has an antisense transcript which may regulate it (Pruunsild et al., 2007). Of course these studies so far yield little functional or mechanistic insight into the roles of lncRNAs in neurodegeneration. However, given the emerging evidence that lncRNAs may serve as chromatin regulatory factors, it is tempting to hypothesise that their dysregulation may be responsible for the alterations in gene regulatory networks observed in these conditions.

4.2. Evidence for a role of RNA toxicity in repeat expansion diseases

One of the most fascinating class of neurological diseases are the trinucleotide repeat disorders. In the course of the past 20 years, a growing number of conditions have been linked to unstable expansions in repetitive DNA regions of various genes. Almost all the trinucleotide repeat disorders are characterised by severe neurological symptoms resulting from neurodegeneration (Everett and Wood, 2004; Anthony and Gallo, 2010b; Todd and Paulson, 2010). In almost all cases the condition results in death, and no therapies or drugs are yet available, although by their nature these diseases are attractive targets for various types of gene therapy (McBride et al., 2011). What is so compelling about these diseases is the fact that all of them result from a highly penetrant mutation at a single genomic locus. How can such a simple mutation give rise to such a slow developing and rather complex phenotype? All the trinucleotide repeat disorders are caused by mutations in distinct genes, which in general are ubiquitously expressed and do not have a function implicated specifically in the nervous system. In this case, why do all of them produce such a strong neurodegenerative effect? The groundbreaking studies demonstrating that various neurodegenerative conditions and ataxias result from such simple, and similar, genetic mutations offered hope that the neuropathogenic mechanism would also be simple. Unfortunately, the passage of time has showed exactly the opposite: that trinucleotide repeats are neurotoxic through a range of plausible mechanisms, and that each trinucleotide disease appears to exhibit various aspects of these mechanisms. In the following section we will attempt to summarise our current understanding of trinucleotide repeat diseases affecting the nervous system in light of recent findings.

By definition, trinucleotide repeat disorders (TNDs) result from variable sized expansions of unstable triplet repeats in the genome. In the majority of trinucleotide repeat disorders, that expansion occurs in a (CAG)n, which is translated into a polyQ (polyglutamine) tract. For example, Huntington's disease is caused by an expanded CAG repeat in the coding region of the first exon of the huntingtin gene (Htt), and spinocerebellar ataxia results from a similar repeat expansion in the Ataxin 7 gene. Initial studies on TNDs focussed on the affected gene, and how the polyglutamine expansion might lead to a toxic gain-of-function in the translated protein. What was clear was that mutant proteins had a tendency to accumulate in intracellular protein inclusions, and to have unnatural interactions with other proteins (Forner et al., 2010; Davranche et al., 2011). These inclusions tend to be populated by highly ubiquitinated proteins, and recruit other proteins with natural polyQ regions (Lee et al., 2004). The expression of transgenes containing polyQ regions alone, or fused to other open reading frames, is neurotoxic in both flies and mouse (Marsh et al., 2000). It has also been suggested that a loss of function of the mutated gene product also contributes to neurodegeneration. For example, the Htt protein has intrinsic neuroprotective characteristics, and polyQ expansion abrogates this function (Cattaneo et al., 2005). Similarly, loss of function in the Ataxin-2 protein has been the candidate mechanism in the cerebellar neurodegeneration in SCA2 (Lastres-Becker et al., 2008b).

However, a number of observations suggest that the combination of toxic gain-of-function of proteins, and loss of function of the wild type allele, is not sufficient to explain the disease mechanism. If loss of function is a general disease mechanism, why do mutations in such a diverse set of proteins result in a broadly similar phenotype? Furthermore, most of the proteins are ubiquitous, and not expressed specifically in the cell type that suffers neurodegeneration. Finally, transgenic mice lacking trinucleotide repeat associated genes generally do not recapitulate neurodegeneration (The Dutch-Belgian Fragile X Consortium, 1994; Nishi et al., 2002; Schmitt et al., 2007; Lastres-Becker et al., 2008a) although in the case of HD the knockout does display characteristic striatal neurodegeneration (Dragatsis et al., 2000). Therefore, we must suppose that some other underlying commonalities link these diseases. The most obvious of these is of course, the homopolymeric protein that is produced. As mentioned above, this is most often comprised of polyglutamine (polyQ), but some disease causing repeat expansions encode polyleucine or polyalanine (van Eyk et al., 2012). Importantly, many proteins in

the genome contain natural polyQ tracts, and the fact that they are under demonstrable evolutionary selection strongly suggests that they serve some kind of function (Mularoni et al., 2010). Examination of the brains of human patients and animals models reveals the presence of nuclear inclusions that contain polyQ protein (DiFiglia et al., 1997). It appears that these inclusion consist not only of the disease-causing polyQ itself, but also other proteins that contain natural polyQ repeats. These include several transcriptional regulatory proteins, such as CBP, and have led to the hypothesis that trinucleotide repeat disorders are disorders of transcriptional regulation—transcriptionopathies (La Spada and Taylor, 2003). Thus, the sequestration of polyQ containing transcriptional regulatory proteins will reduce their available concentration in the nucleus, and consequently lead to transcriptional dysfunction.

In almost all cases where experiments have been carried out on polyglutamine expansions either in vitro or in vivo, DNA constructs have been used that encode the polyQ protein (Mangiarini et al., 1996). Therefore, a major assumption is being made that the primary RNA transcript, from which the protein is translated, is itself not toxic. We now know that this is not always true. This was strikingly demonstrated in a fly model by Nancy Bonini's group (Li et al., 2008). In experiments on polyQ-expanded ataxin-3 induced neurodegeneration in Drosophila, the authors found that the RNA binding protein MBNL1, a known player in neurodegeneration discussed below, enhances toxicity of a CAG-expanded SCA3 transgene. Surprisingly, when the authors then mutated the CAG-repeat region to contain interrupting CAA codons, thereby not altering the polyQ translated product, the authors observed strongly reduced mortality, neurodegeneration and behavioural changes. Furthermore, insertion of CAG repeats into the non-coding region of an unrelated marker gene – DsRed – was still toxic. These results suggests that CAG expansions are toxic through at least two distinct pathways, one involving the production of a polyQ-containing protein, and another involving the RNA-sequence dependent properties of the CAG repeat, independent of gene context. In this regard it is interesting to note that HTT may have a dual function since HTT interacts with ribonucleoprotein particles in cortical neurons. In fact, there is a range of other evidence that trinucleotide expansion in non-protein RNA can give rise to neurodegeneration, ataxia, neuropsychiatric problems or mental retardation. Examples exist of expansions in 5′ or 3′ untranslated regions, introns, or ncRNA transcripts–none of which are translated into any protein product (Campuzano et al., 1996; Davis et al., 1997; Holmes et al., 1999; Koob et al., 1999). One of the spinocerebellar ataxias – SCA8 – is caused by a CTG expansion in a non-coding locus that is transcribed on both strands into ncRNAs (Koob et al., 1999). Indeed, SCA8 is caused by CUG expansion in a non-coding antisense transcript, AXN8OS and expression of this transcript in flies causes neurodegeneration (Mutsuddi et al., 2004). Further, the myotonic dystrophies (DM1, DM2) are caused by expansions in non-coding 3′ UTR and intronic regions, respectively (Brook et al., 1992; Ranum et al., 1998) while Huntington's-like 2 (HDL2) is caused by an expansion in the 3′ UTR region of JPH3 gene (Margolis et al., 2001). Therefore, the production of a expanded, mutant protein is by no means a universal feature of trinucleotide repeat disorders. In the following sections we will discuss various evidence that such repeats function through either the production of a toxic RNA, or through direct translation of small homopolymeric proteins.

4.3. Unconventional mechanisms of trinucleotide toxicity

Given then the possibility that trinucleotide repeat expansions cause disease through pathways other than gain of function effects in protein coding sequences, how do these pathways function? To date there have been a range of compelling proposals including some insights which challenge our understanding of fundamental molecular biological processes. These will be discussed in the following sections. These pathways can be divided into the following main groups: antisense transcription, sequestration of RNA binding proteins, processing into toxic small RNAs, and non-ATG-initiated translation.

4.3.1. Antisense transcripts

As mentioned above, antisense transcription is extremely common in mammalian genomes. In studying the toxicity of trinucleotide repeats, several curious lines of evidence have pointed to a role for antisense transcription in a number of diseases. In most cases, this occurs where a previously identified CTG repeat turns out in fact to be transcribed on the opposite strand into a CAG repeat. This was first discovered in the course of studies on SCA8, where a CTG repeat was mapped in the last exon of a non-coding transcript, ATXN8OS (Nemes et al., 2000). SCA8 belongs to the spinocerebellar ataxias, characterised by loss of physical coordination due to atrophy of the cerebellum, accompanied by loss of Purkinje neurons (Koob et al., 1999). Subsequently, Laura Ranum and colleagues produced a BAC mouse model, which recapitulated the intranuclear inclusions and neurodegenerative phenotype of the disease (Moseley et al., 2006). Mysteriously, brains of the knockouts also contained inclusions staining positive for the antibody 1C2, generally considered to bind to polyglutamine. Since polyQ can only be encoded by CAG, not CTG, the authors looked for an antisense transcript, which they subsequently identified (ATXN8).

An analogous situation occurs in Huntington's-like 2 (HDL2). This disease strongly phenocopies HD with adult-onset degeneration of the medium spiny neurons of the striatum, resulting in personality changes, chorea and dementia (Margolis et al., 2001). Here the disease is caused by a CTG repeat, this time lying within a variably spliced exon that, depending on splicing patterns, falls either within a coding region (encoding polyleucine or polyalanine) or a non-coding region. The mystery of how this apparently weakly transcribed repeat causes disease was to some extent clarified by the demonstration that an antisense transcript also covers this region, resulting in a CAG-containing RNA (Wilburn et al., 2011). Similar to the above work on SCA8, the authors created a BAC mouse, and found that these mice accumulate intranuclear inclusions containing polyQ, originating from unexpected antisense transcription of the repeat region. These mice displayed the expected phenotype of selective neurodegeneration, reduced rotarod performance and nuclear inclusions. However, the authors took one step further and asked whether the sense CTG transcript was required at all for the neurodegenerative phenotype, by creating another mouse model where the sense transcript was silenced. These mice still display the HDL2 phenotype suggesting that indeed the principal disease-causing agent here is the antisense transcript. Furthermore, this transcript produces polyQ, which appears to dysregulate transcription of BDNF through the known CBP pathway. It is however important to state that, despite these findings, there is equivocal evidence supporting the toxicity of CTG transcripts in other situations.

Quite apart from their ability to encode toxic repeats themselves, antisense transcripts have been implicated in the epigenetic regulation of a toxic, sense transcript. This is best documented in a recent paper from the La Spada group, studying spinocerebellar ataxia 7 (SCA7) (Sopher et al., 2011). SCA7 results from a polyCAG expansion just downstream of the initiation codon of the Ataxin-7 gene. SCA7 is rather unusual in that the usual cerebellar neurodegeneration is accompanied by macular

degeneration (Del-Favero et al., 1998). This aspect of the disease would appear to result from altered function of the host SCA7 gene, which encodes a transcriptional regulatory protein (La Spada et al., 2001). Mutant SCA7 interferes with the normal transactivation function of the CRX homeodomain transcription factor, itself containing a natural polyQ tract, which controls numerous genes necessary for photoreceptor cells. It would appear that SCA7 transcript levels are controlled by a complex interplay between a non-coding antisense transcript which overlap the repeat region—SCAANT1. The sense and antisense transcripts have highly anticorrelated expression, and the antisense transcript is driven by two binding sites for the boundary protein, CTCF. Importantly, SCAANT1 regulates Ataxin-7 transcript levels through a cis-mechanism, since exogenous expression of SCAANT1 had no effect on the Ataxin-7 gene. The expression of SCAANT1 results in repressive epigenetic signals in the Ataxin-7 promoter. Interestingly, CTCF regulation of an antisense transcription is also a feature of myotonic dystrophy (DM) type 1 (Cho et al., 2005).

4.3.2. Sequestration of RNA binding proteins and RNA foci

There is now compelling evidence that toxic RNA repeats can act through gain-of-function interaction with RNA binding proteins. The general mechanism involves sequestration of RNA-binding splicing factors, leading to pathogenic changes in mRNA splicing in the affected tissues. The best known players in this are Muscleblind (MBNL1) and CUGBP1, two key regulators of splicing in the developing heart (Kalsotra et al., 2008). The relationship with MBNL1 is particularly important for CTG repeat containing RNAs. Myotonic dystrophy (DM1) is caused by a dominant expansion in a CUG repeat in the 3′ UTR of the DMPK gene (Carango et al., 1993). DM1 patients present with muscle wasting and sometimes cognitive impairment. The molecular mechanism appears to be well understood: The CTG repeat transcript sequesters MBNL1, reducing its effective concentration in the cell and resulting in altered RNA processing, principally splicing (Dansithong et al., 2005). Loss of MBNL1 most importantly switches the pattern of mRNA splicing from adult to foetal form in striated muscle. A secondary effect is the hyperphosphorylation of another RNA binding protein CUGBP1. This results in a dramatic increase of its protein levels, and increase of splicing regulation. A decrease in MBNL1 and increase in CUGBP1 function are characteristic of foetal muscle gene expression programs. Importantly, mouse models lacking MBNL1 suffer myotonia and missplicing consistent with human patients (Kanadia et al., 2003). The CTG expansion in SCA8 also results in MBNL1 sequestration and missplicing, suggesting that this may be a general property of all CTG repeat expansions.

The phenomenon of intranuclear RNA foci characterises most trinucleotide repeat disorders (Wojciechowska and Krzyzosiak, 2011). These foci are enriched in the repeat RNA, as well as associated proteins such as MBNL1 which promote their formation (Querido et al., 2011). Foci are observed in various animal models of DM1 (Orengo et al., 2008). Foci have been detected in MM1 and DM2, SCA8, FXTAS, and HDL2. Taken together, the evidence points directly to repeat-containing RNAs as a common mechanism underlying trinucleotide-repeat disorders.

4.3.3. Toxic small RNAs

There is emerging evidence for involvement of small RNAs in trinucleotide repeat disorders. The first inkling of this came in a study from Tapscott's group, suggesting that siRNA molecules are produced at both wildtype and expanded DM1 locus (Cho et al., 2005). This involves an antisense transcript that overlaps the repeat region, in addition to the known sense transcript of the DMYK gene. These siRNAs appear to play a role in the establishment of the highly localised heterochromatin which covers the normal and expanded repeat regions.

A recent paper from the Bonini lab added more details to this picture, showing evidence that sense/antisense CAG/CTG containing transcripts interact to generate small siRNAs that target CAG-repeat containing mRNAs (Yu et al., 2011). The authors found that simultaneous overexpression in fly of both expanded CAG and expanded CTG transcripts led to an elevated and synergistic toxicity. Northern blots revealed a 21nt small CAG-repeat containing RNA that is created by the *dcr2/ago2* pathway. Finally, the authors demonstrated that these siRNAs can target and repress CAG-containing mRNAs. This suggests that transcriptional dysregulation observed in trinucleotide repeat diseases may be in fact a partial post-transcriptional dysregulation. It has not been demonstrated whether this process actually occurs in human subjects.

The idea that CAG expansions result in neuronal toxicity through the production of small RNA species has been echoed in recent work on HD by Marti and colleagues (NEW REF Banez-Coronel PMID 22383888). Investigating the basis of toxicity due to the mutant poly-CAG expansion in HTT exon 1, the authors created mutant untranslatable versions of HTT that retain expanded CAG tracts but without an initiation codon. The authors showed that expression of untranslatable HTT retains its toxicity, at least in cultured human neural cells, and this is not due to repeat-associated non-ATG translation. These expanded CAG tracts are processed into small RNA species that are toxic specifically to cells of neural origin. The authors propose that these repeat-derived sRNAs are capable of acting as siRNAs to cause a generalized suppression of CTG-containing mRNAs via Ago2. These results must force us to reevaluate previous HD literature where mutant CAG-containing plasmids and gene targeting constructs have always been assumed to function through the expression of protein, rather than the RNA species that are also produced.

4.3.4. Non-ATG-initiated translation

Possibly the most radical discovery in recent research on trinucleotide mechanism, has been the 2011 report from Laura Ranum's group that CAG repeats are in fact translated, even in the absence of ATG start codons (Zu et al., 2011) This surprising discovery has major implications for our basic understanding of translation, quite apart from forcing us to reevaluate much of our understanding of trinucleotide toxicity (Table 3). During the course of studies on ATXN8, the authors investigated the basis of its translation. Previously ATXN8 was shown to generate a polyQ protein (Moseley et al., 2006), from a cryptic open reading frame containing the CAG expansion. However, when the authors mutated the putative start codon, they continued to detect polyQ protein production in transfected cells. Homopolymeric peptides were also detected in the two other possible frames, resulting in polySer and polyAla. The authors present a range of evidence that this repeat-associated non-ATG translation (RAN) is a genuine effect, that occurs for mutations causing DM1, SCA3, SCA8 and HDL2. Finally, by developing specific antibodies to polyGln and polyAla, the authors identified these proteins in inclusions of human patients and mouse models.

How does this RAN translation occur? At present it is too early to say. Ranum and colleagues have speculated that the secondary structure adopted by CAG repeat tracts may be important. Previous work by Kryzyosiak and colleagues has indicated that CAG repeats, and most other trinucleotide repeats, can form hairpin structures, at least in vitro (Sobczak et al., 2003; de Mezer et al., 2011) and Ranum and colleagues have proposed that such structures contribute to non-ATG translation initiation, a process that is known to be influenced by hairpin structures (Zu et al., 2011).

5. ncRNAs as biomarkers and drug targets

It is clear that RNA dysfunction, be it due to loss of function of endogenous ncRNA or gain of toxic function lie at the heart of many, if not all, neurodegenerative disorders. But can this knowledge be translated into either biomarker discovery or therapy? Microarray technology and multiplex amplification techniques have shown that RNA is indeed a valid target for routine molecular diagnostics and testing (Schaaf et al., 2010; Edmonds et al., 2011; Shen et al., 2011). Indeed, RNA-based diagnostics employing reverse transcription PCR are nowadays used for detection of RNA viruses such as Severe Acute Respiratory Syndrome (SARS), hepatitis C (HCV) and influenza (including H1N1), and more recently, they have been applied to detection of NDDs and cancers (Baas et al., 2006; Lemon and Threats, 2007; Danesh et al., 2011). PCR approaches are routinely used for mutation analysis of disease genes such as cystic fibrosis (CFTR), identification of p450 polymorphisms related to adverse drug reactions, and tissue typing during organ transplantation, e.g. human leukocyte antigen (HLA) (Novoyatleva et al., 2006; Wright et al., 2006; del Fresno et al., 2009). More recently, differentially expressed lncRNAs between hepatitis B (HBV)-related hepatocellular carcinoma (HCC) and paired tumoral tissues have been identified by microarray and validated using quantitative PCR (Yang et al., 2011). These studies showed that expression levels of lncRNAs in HBV-related HCC were associated with recurrence, and thus presented a valid prognostic factor for survival (Yang et al., 2011). Furthermore, there are specific known mutations in lncRNAs that are associated with distinguishable phenotypes or that are strongly implicated in altered phenotypes of neurodegenerative disorders. These mutations include a triplet repeat expansion in the ncRNA SCA8, which causes the human neurodegenerative disease Spinocerebellar Ataxia 8 (this gene induces progressive retinal neurodegeneration in Drosophila (Mutsuddi et al., 2004) and other examples of deleterious mutations in lncRNAs associated with diseases such as myotonic dystrophy (Ishii et al., 2006), deletions encompassing ncRNA loci and alterations of splicing patterns (Christov et al., 2008), and a SNP variant in an ncRNA MIAT that confers risk of myocardial infarction (Mattick, 2009). Other examples of lncRNAs implicated in learning, cognition and behaviour, including BC1 have already been discussed earlier.

The main challenge using protein as a target for routine diagnostics is low sensitivity, reproducibility and specificity. By contrast, RNA as a target for routine diagnostics gives the information of clinical activity, regulation or processes in addition to higher or equal sensitivity, reproducibility and specificity compared to DNA as target. New methods of isolation, purification and stabilization of mRNA have been recently developed for routine diagnostics making the RNA very much suited as a marker for new methods and drugs (Bustin, 2002). Non-neuronal cells and tissues such as fibroblasts, lymphoblasts, and muscle biopsies can be explored for RNA expression biomarker discovery. Nucleic acids can be identified in most bodily fluids, including blood, urine, and cerebrospinal fluid (CSF), and have been adopted for use as diagnostic biomarkers for diseases (Xiang et al., 2003; Li et al., 2004). In fact, the composition of fluids reflects levels of hormonal, immunological, toxicological and infectious disease markers. If present, mRNA may provide potential biomarkers to identify populations and patients at high risk for oral and systemic diseases.

In the case of Amyotrophic lateral sclerosis (ALS), a considerable fraction of patients show a loss of the astroglial glutamate transporter excitatory amino acid transporter 2 (EAAT2) protein in motor cortex and spinal cord, which leads to increased extracellular glutamate and excitotoxic neuronal degeneration (Lin et al., 1998). Multiple abnormal EAAT2 mRNAs, including intron-retention and exon-skipping, have been identified from the affected areas of ALS patients, while aberrant mRNAs are highly abundant in neuropathologically affected areas and are detectable in CSF of living ALS patients at the early stages of the disease. This finding indicates that identifying the presence of RNA species in CSF has a potential for diagnostic utility (Lin et al., 1998). A microarray scan was recently employed to discover transcript levels of sortilin-related receptor LDLR class A (*SORL1/LR11*) in lymphoblasts of patients with AD (Scherzer, 2009). Low expression levels of *SORL1/LR11* are present in brains of patients with sporadic AD and of individuals with mild cognitive impairment. Genetic and molecular studies have suggested a mechanistic model linking *SORL1/LR11* to increased production of the neurotoxic peptide Aβ (Scherzer, 2009). When SORL1 is underexpressed, the APP secretory pathway is affected and APP is preferentially sorted into late endosomes, a compartment where it is processed by β- and γ-secretases to generate A((Scherzer, 2009). In the case of PD, a transcriptome-wide scan was performed using microarray technology to investigate the molecular processes in cellular blood of patients with early stage PD (Scherzer et al., 2007). Among the genes differentially expressed in patients with PD (versus healthy individuals) it was found *ST13*, which is a co-chaperone stabilizing heat-shock protein 70, was identified as a modifier of α-synuclein misfolding and toxicity. *ST13* mRNA copies were found to be lower in patients with PD. This finding indicates that gene expression signals measured in blood can facilitate the development of biomarkers for PD.

5.1. Transcriptomic complexity and bioinformatics

Understanding the transcriptome is essential for interpreting the functional read-out of the genome and revealing the molecular constituents of cells and tissues, and also for understanding development and disease. Transcriptomics deals with collection of all species of transcripts, including mRNAs, non-coding RNAs and small RNAs and focuses on the definition of transcriptional structures of genes, splicing patterns and other post-transcriptional modifications as well as quantification of the expression levels of each transcript during development and in association with disease. RNA-Seq is the first sequencing-based method that allows the entire transcriptome to be surveyed in a very high-throughput and quantitative manner (Garber et al., 2011). Transcriptome studies have been dominated by interrogation of microarray-based studies of coding genes inferred from genome annotation. However, this approach largely excludes the vast majority of lncRNAs and most short ncRNAs would have been size-excluded during probe preparation. The advent of RNA-seq has changed this. RNA-Seq offers both single-base resolution for annotation and gene expression levels at the genome scale at a much lower cost than either tiling arrays or large-scale Sanger EST sequencing and could be used to investigate the role of lncRNAs in patients affected by NDDs. The method faces several informatics challenges, including the development of efficient ways to store, retrieve and process large amounts of data, which must be overcome to reduce errors in image analysis and base-calling and remove low-quality reads (Wang et al., 2009). Once high-quality reads are produced, the main task of data analysis is to map the short reads to a reference genome (of healthy individuals), and assemble them into contigs before aligning them to the genomic sequence to reveal transcription structure (there are several programs for mapping reads to the genome, including SOAP31, MAQ32 and RMAP33 (Wu et al., 2006; Smith et al., 2008; Amaral et al., 2010; Cook et al., 2010). However, short transcriptomic reads exon junctions or poly(A) ends that cannot be analysed in the same way. For tissues in which splicing is less frequent, special attention only needs to be given to poly(A) tails and to a small number of

exon–exon junctions (Nagalakshmi et al., 2008). For brain, alignment is complicated by the fact that a significant fraction of sequence reads match multiple splicing variants (Mortazavi et al., 2008; Wilhelm et al., 2008) while databases collecting sequences of non-coding transcripts are becoming increasingly available (Wu et al., 2006; Amaral et al., 2010; Cook et al., 2010). A major goal is now to identify the protein binding partners of lncRNAs in order to understand their mechanism of action and to subsequently manipulate their interaction with their target transcripts. Twinned with this goal is the need to predict target transcripts and methods for prediction of interactions between proteins and RNAs are being currently developed (Perez-Cano et al., 2010; Bellucci et al., 2011a). These goals must be achieved if we are to investigate the interplay of these molecules and characterize their role in NDDs and ultimately target the RNA/protein and/or RNA/protein interactions for therapeutic benefit.

5.2. Therapeutic targeting of RNA

Antisense therapy is a form of treatment for genetic disorders and infections. When the genetic sequence of a particular gene is found to be associated with a particular disease, it is possible to synthesize a strand of RNA that interacts with the messenger RNA produced to inactivate the gene. In general, silencing of gene expression by RNA interference (RNAi) has proven to be a robust and straightforward technique for gene function analysis (Jackson et al., 2003; Machuy et al., 2005). Synthetic small interfering RNAs (siRNAs) have been widely used to transiently knockdown gene expression in cultured cells for loss of function (LoF) analyses. In mammalian cell models it has been shown that allele-specific silencing of disease genes with siRNA can be achieved by targeting either a linked single-nucleotide polymorphism (SNP) or the disease mutation directly (Lapierre et al., 2011). For a polyglutamine neurodegenerative disorder, the SNP was employed to design a siRNA able to silence the mutant Machado–Joseph disease/spinocerebellar ataxia type 3 allele while sparing expression of the WT allele (Miller et al., 2003). In another experiment, a siRNA was employed to target a missense Tau mutation, V337M, that causes frontotemporal dementia (Miller et al., 2003). Taken together, these results indicate that siRNA can be engineered to silence disease genes differing by a single nucleotide and highlight a key role for SNPs in extending the utility of siRNA in dominantly inherited disorders. However, not all siRNAs designed with the currently available algorithms induce efficient silencing of gene expression. Pools of different siRNAs directed against the same gene are in general used to increase the probability of efficient inhibition of gene expression. Nevertheless, recent reports show that siRNAs may reduce the expression of unrelated genes (Jackson et al., 2003). Another potential difficulty in using RNAi for gene function analysis is the induction of the interferon (IFN) response (Sledz et al., 2003).

Inherited neuromuscular diseases are debilitating disorders with no effective treatments avialable to date (Daniele et al., 2007). Several therapeutic approaches involving RNA manipulation have been applied to Duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), myotonic dystrophy type 1 (DM1) and Ullrich disease (UCMD). Following studies that provided proof of concept obtained from patients' cells and in animal models, clinical trials started and encouraging results have been reported. RNA-based strategies exploit knowledge of the molecular mechanisms associated with the genetic defects and the specific nature of the disease-causing gene and rely on three strategies (Le Roy et al., 2009): (i) *Modulation of pre-mRNA quality through exon exclusion or inclusion*. For example, deletion of exon 50 in the DMD gene is known to introduce a premature termination codon (PTC) in exon 51 of the DMD mRNA. Consequently, a truncated, unstable and non-functional dystrophin is produced leading to a DMD phenotype. The antisense oligonucleotide 2′OMePS–PRO051, targeting exon 51, induces specific skipping of this exon during pre-mRNA splicing and can restore dystrophin expression. The dystrophin produced is shorter than the wild type protein but is more stable, and partially functional, producing less severe phenotypes (van Deutekom et al., 2007). (ii) *Modulation of mRNA quantity*. In the case of Ullrich disorders, patients harbor a homozygous 26-bp deletion in exon 18 of the collagen VI (2 (COL6A2) gene that causes a frame shift mutation and introduces a PTC in exon 22. The resulting COL6A2 mRNA is degraded by nonsense-mediated decay (NMD), which decreases COL6A2 protein levels and leads to disease. To re-establish a minimal amount of COL6A2 protein in fibroblasts from this patient, COL6A2 NMD can be blocked by siRNA-mediated knockdown of Upf1 and SMG-1, two major players in the NMD pathway (Usuki et al., 2006). (iii) *Modulation of mRNA translation.* The DMD gene in the mdx mouse contains a nonsense mutation that leads to the introduction of a PTC in DMD mRNA and prevents production of functional full-length dystrophin. PTC124 is a chemical compound that promotes read-through specifically at PTC without affecting normal translation termination or cellular mRNA stability. This molecule induces nonsense suppression at the PTC in exon 23 and allows the translation of a full-length mutated dystrophin that is functional (Welch et al., 2007).

In addition, targeting pre-mRNA to influence alternative splicing may also have therapeutic utility. The microtubule-associated protein tau plays a central neurodegenerative role in AD and related tauopathies. Tau is encoded by the *MAPT* gene, which is alternatively spliced to give rise to six tau isoforms in the adult human CNS. There are two major classes of tau isoforms, with either three (3R) or four (4R) microtubule-binding repeat domains, and elevated 4R tau expression in AD and several related tauopathies is linked to disease pathogenesis. Therefore, correcting aberrant production of 4R tau isoforms may represent another disease-modifying approach for the 4R-dominant tauopathies (Gallo et al., 2007). Some promising evidence for this approach has been demonstrated in cell culture, although it is not clear how such techniques could be adapted for patients. In rat PC12 cells that express predominantly 4R tau, blocking access of the splicing machinery to tau pre-mRNA using antisense oligoribonucleotides that target the 5′ or 3′ splice junction of E10, results in a relative reduction of 4R tau expression (Kalbfuss et al., 2001). Alternatively, tau pre-mRNA can be modified in cells using spliceosome-mediated RNA *trans*-splicing technology (SMaRT^{TM}). A proof of concept study showed that this approach could be used to increase the conversion of 3R tau to 4R tau encoding RNA with approximately 30% efficiency (Rodriguez-Martin et al., 2005).

6. Outlook

Upon reflection, the title of this review 'Neurodegeneration as an RNA disorder' unwittingly polarises the debate into 'RNA' or 'protein'. It is true that the large majority of researchers see neurodegeneration as exclusively a protein disorder but this polarisation breaks down on two fronts. Firstly, it is illuminating to see how many mutant RNAs can precipitate pathology even in the absence of mutant protein, thus undermining the hegemony of protein-mediated pathology, and hinting at the potential for many as yet undiscovered toxic RNA species. Secondly, it is becoming clear that RNA itself cannot be thought of as simply protein-coding or non-coding and that a singular locus can give rise to transcripts that may be translated and not translated (Dinger et al., 2008b). This increasingly complex and subtle RNA landscape will influence our rationale for defining pathways and interactions to target for drug intervention. The ever-deeper sequencing of the human genome using current and emerging technologies will continue to

expand the repertoire of ncRNAs. Hand in glove with this unveiling of the complexity of the genomic landscape there is an urgent need for a suite of bioinformatic tools that accurately and comprehensively predict DNA and RNA targets of ncRNAs, both short and long.

With this awareness of RNA complexity comes opportunity to uncover novel regulatory mechanisms and biomarkers. We have seen already how oligonucleotides can be effectively deployed in animal models such as in mouse models of myotonic dystrophy (Wheeler et al., 2009) and we are beginning to see the generation of small molecules inhibitors of RNA interaction with their protein-binding partners as seen in the nanomolar effiicacy of ligands directed against the expanded rCUG and rCAG repeat RNAs in myotonic dystrophy type 1 and spinocerebellar ataxia type 3 (Pushechnikov et al., 2009).

Much remains to be improved in prediction of target genes of both miRNAs and lncRNAs and it may transpire that the most effective way of interfering with ncRNA action is not through targetting the RNA/target gene interaction itself but to target the recruited epigenetic apparatus; this offers the advantage of exploiting a growing array of chemical compounds aimed at the active site of chromatin modifiers (Kelly et al., 2010) but at the expense of losing gene-specific action. At the very least, this expanded view of the importance of RNA, both protein-coding and non-coding, both small and large offers a host of novel of interactions to target that are distinct from the current focus on protein regulation of neurodegeneration.

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