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Review article

REST: An epigenetic regulator of neuronal stress responses in the young and ageing brain

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ABSTRACT

The transcriptional repressor REST (Repressor Element-1 Silencing Transcription factor) is a key modulator of the neuronal epigenome and targets genes involved in neuronal differentiation, axonal growth, vesicular transport, ion channel conductance and synaptic plasticity. Whilst its gene expression-modifying properties have been examined extensively in neuronal development, REST's response towards stress-induced neuronal insults has only recently been explored. Overall, REST appears to be an ideal candidate to fine-tune neuronal gene expression following different forms of cellular, neuropathological, psychological and physical stressors. Upregulation of REST is reportedly protective against premature neural stem cell depletion, neuronal hyperexcitability, oxidative stress, neuroendocrine system dysfunction and neuropathology. In contrast, neuronal REST activation has also been linked to neuronal dysfunction and neurodegeneration. Here, we highlight key findings and discrepancies surrounding our current understanding of REST's function in neuronal adaptation to stress and explore its potential role in neuronal stress resilience in the young and ageing brain.

1. Introduction

Stress resilience can be defined as "achieving a positive outcome in the face of adversity" (McEwen et al., 2015). However, successfully adapting to stressful experiences does not necessarily ensure a positive response to further challenges later in life. This is partly because stressful episodes, especially during vulnerable developmental stages in life, can imprint lasting alterations on a person's emotional resilience and ability to cope with subsequent intrinsic and extrinsic stressors. Whilst behavioural changes triggered by stress are mostly reversible, underlying epigenetic changes remain present on the DNA and act as modulators of subsequent gene expression (Bloss et al., 2010; McEwen et al., 2015). The human epigenome is, therefore, strongly dependent on one's environment and cumulative life-experiences. This implies that

Abbreviations: 4-AP, 4-aminopyridine; 5-HT, 5-hydroxytryptamine/serotonin; ACTH, adrenocorticotropic hormone; AD, Alzheimer's disease; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ANS, autonomic nervous system; AVP, arginine vasopressin; BDNF, brain-derived neurotrophic factor; CK1, casein kinase-1; cKO, conditional knockout; CNQX, cyanquixaline (AMPAR antagonist); CNS, central nervous system; CRH, corticotropin-releasing hormone; CTBP1, C-terminal-binding protein 1; CTDSP1, carboxy-terminal domain RNA polymerase II polypeptide A small phosphatase 1; DBD, DNA-binding domain; DCTN1, dynactin Subunit 1; DDX3, DEAD Box Protein 3; DGCs, Dentate granule cells; DKK1, Dickkopf-related protein 1; DLB, dementia with Lewy bodies; DNA, deoxyribonucleic acid; EPSC, excitatory postsynaptic potential; ESCs, embryonic stem cells; G9A, histone lysine methyltransferase/EHMT2: Euchromatic histone-lysine N-methyltransferase 2; GABA, gamma-aminobutyric acid/γ-aminobutyric acid; GC, glucocorticoid; GFAP, GLIAL fibrillary acidic protein; GR, glucocorticoid receptor; GSK3, glycogen synthase kinase 3; GRIN2A, encodes GluN2A subunit of NMDAR; HAP1, huntingtin-associated protein 1; HCN1, potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1; HD, Huntington's disease; HDAC, histone deacetylase; HIPPI, huntingtin interaction protein 1 (HIP1) protein interactor; HPA, hypothalamic-pituitary-adrenal stress axis; HTT, huntingtin; IL-1β, interleukin 1 beta; iPSC, induced pluripotent stem cells; KCC2B, potassium-chloride transporter member; LRP6, low-density lipoprotein receptor-related protein 6; LSD1, lysine-specific histone demethylase 1A; LTP, long-term potentiation; MAPK, mitogen-activated protein kinase; MCI, mild cognitive impairment; MeCP2, methyl CpG binding protein 2; MK801, dizocilpine (NMDAR antagonist); MPTP, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; MR, mineralocorticoid receptor; NLS, nuclear localisation signal; NMDAR, N-methyl-D-aspartate receptor, glutamate receptor; NPAS4, neuronal PAS domain protein 4; NRSE, neuron restrictive silencer element; NRSF, neuron restrictive silencing factor; NSCs, neural stem cells; ODN, oligodeoxynucleotide; ORF, open reading frame; PFC, prefrontal cortex; PD, Parkinson's disease; PVN, paraventricular nucleus of the hypothalamus; RD, repressor domain; RE-1, repressor element-1; REST, RE1-Silencing Transcription factor; RILP, REST/NRSF-interacting Lin-11, Isl-1 and Mec-3 (LIM) domain protein; ROS, reactive oxygen species; SMCX, lysine-specific demethylase 5C; SVZ, subventricular zone; TNF-α, tumour necrosis factor alpha; TPH2, tryptophan hydroxylase 2; VGNa, voltage-gated sodium channel; ZF, zinc finger

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certain homeostatic and reactionary transcriptional programmes do not return to their naïve baselines and, therefore, may cause increased vulnerability to subsequent stressors, as is often observed in the ageing population after a lifelong accumulation of stress (Bloss et al., 2010).

The brain is the ultimate regulator of the body's molecular, cellular and behavioural responses to stress and whether those adaptations promote stress resilience or vulnerability. Stress-responsive neuronal circuits react very differently in stress-vulnerable individuals versus those who are stress-resilient (Franklin et al., 2012; McEwen et al., 2015; Pfau and Russo, 2015). Within the brain, post-mitotic neurons are the essential mediators of thought and behaviour. These long-lived cells are physically and biochemically protected by the skull and blood-brain-barrier but, despite this safety-mechanism, are often subjected to a wide variety of stressful insults, including injury, disease, persistent glucocorticoid signalling and oxidative stress. It is therefore unsurprising that neurons utilise an adaptive stress response mechanism to preserve neuronal function and intrinsic homeostasis. However, neuronal stress responses can also be detrimental and can contribute to a range of neuropathological diseases, accelerated ageing and loss of resilience (Farley and Watkins, 2018). As such, stressful stimuli not only significantly modify the brain's cytoarchitecture but also regulate neuronal homeostasis and neuronal plasticity circuits, which regulate important functions such as memory, sleep and reward responses (McEwen et al., 2015). In addition, stress-induced epigenetic chromatin remodelling is a major regulator of neuronal gene expression and influences phenotypic responses, i.e. resilience or vulnerability (Borrelli et al., 2008; Hunter and McEwen, 2013; Nasca et al., 2013).

A key initiator of epigenetic neuronal gene-expression modification is the transcriptional repressor REST (Repressor Element-1 Silencing Transcription factor). Also known as NRSF (Neuron Restrictive Silencing Factor), REST was first described in 1992 by Mori et al., who identified the transcription factor as a silencing factor for type II sodium channels (Mori et al., 1992). In the following years, REST was found to be implicated in the transcriptional regulation of more than 2000 neuron-specific target genes, encoding proteins involved in synaptic plasticity, neurotransmitter receptors, ion channel proteins and adhesion molecules participating in axon guidance during developmental stages (Andres et al., 1999; Chong et al., 1995; Kuwabara et al., 2004; Roopra et al., 2004; Schoenherr and Anderson, 1995). Emerging evidence has shown that REST also plays a pivotal role as the master transcriptional regulator of neuron-specific genes in the postnatal, adult and ageing brain following stress (Lu et al., 2014; Orta-Salazar et al., 2014; Otsuki et al., 2010; Singh-Taylor et al., 2018; Uchida et al., 2010). REST ensures neuronal specificity and cell type-specific gene expression during brain development and can orchestrate large-scale, experience-dependent neuronal plasticity and synaptic remodelling to generate different behavioural phenotypes. REST-mediated transcription is, therefore, an ideal candidate to fine-tune neuronal gene expression that shapes neuronal homeostasis following stressful experiences (Bithell, 2011; Noh et al., 2012; Qureshi et al., 2010; Stankiewicz et al., 2013).

Whilst REST is normally quiescent in differentiated neurons, the transcriptional repressor can be upregulated following various intrinsic and extrinsic neuronal insults. Following ischaemia, hypoxia and epileptic seizures REST nuclear upregulation generally appears to elicit a harmful response in the hippocampal neuron through repression of synaptic signalling genes (Table 1) (Calderone et al., 2003; Kaneko et al., 2014; McClelland et al., 2014; Noh et al., 2012; Patterson et al., 2017). Also, following psychological and physical stress REST was reported to be upregulated in the neuronal nucleus in various rodent brain regions. In this context, the nuclear translocation was reported to blunt the glucocorticoid response towards future stressors (Korosi et al., 2010; Singh-Taylor et al., 2018). Furthermore, increased nuclear REST was found to decrease the survival of adult-born dentate granule cells (DGCs) and to accelerate the maturation of the remaining DGCs following psychological and physical stress (Table 1) (Chen et al., 2015). In contrast, neuronal REST was also found to translocate to the nucleus during healthy ageing in the human brain, thereby repressing ROS-induced cell death genes, and was shown to protect ageing neurons from amyloid-β pathology (Kawamura et al., 2019; Lu et al., 2014). Furthermore, physical activity was shown to boost REST expression, which attenuated age-related neuroinflammation in the ageing rodent hippocampus (Dallagnol et al., 2017). Interestingly, in neuropathological states, such as Alzheimer's disease and Parkinson's disease, which are both hallmarked by protein misfolding and aggregation, REST fails to translocate to the neuronal nucleus (Table 1) (Kawamura et al., 2019; Lu et al., 2014). Additionally, mice with a neuron-specific REST conditional knockout presented with depleted levels of striatal dopamine, an increase in glial fibrillary acidic protein (GFAP) and elevated levels of the pro-inflammatory cytokine IL-1β, following injection of the dopaminergic neurotoxin MPTP (Yu et al., 2013). These studies highlight the complexity of REST as a multifaceted regulator of neuronal gene expression following intrinsic and extrinsic insults and perturbations of homeostasis. Therefore, this review is focussed on reporting recent findings regarding REST as an epigenetic regulator of neuronal equilibrium in normal and pathological conditions throughout the neuronal lifespan.

Here, we will first summarize REST's complex characteristics, including its expression throughout the lifespan, DNA binding properties, distinct splice variants, availability and nuclear trafficking, transcriptional regulation of the protein itself, and recruitment of REST co-factors that are crucial for its gene-repressive function. Furthermore, we review REST's intricate activity following stressful stimuli and explore its downstream targets and the potential mechanisms through which REST protects neuronal homeostasis following intrinsic and extrinsic stressors. Because of REST's epigenetic influence on genes critically involved in neuronal function, including genes that regulate synaptic plasticity, neuronal differentiation, axonal growth, vesicular transport and ion conductance, REST is a prime candidate to study in relation to stress-induced changes in neuronal gene expression and in the maintenance of neuronal function in the young and ageing brain. Lastly, we review how REST's functions could be harnessed through novel REST-modifying therapeutic strategies with the aim of enhancing its protective mechanism of action and potentially promoting resilience in the young and ageing brain.

2. REST

REST function is strongly dependent on the stimulus and cell-type, in addition to its cellular localisation, the splice variants present and their chromatin binding affinities, its cooperation with other transcription factors and co-factors, and the accessibility of its target genes (Coulson and Concannon, 2016). In order to contextualise the involvement of REST in mediating stress responses later in this review, we will first provide a brief overview of the characteristic features of REST and the protein complexes it engages with.

2.1. Expression

REST epigenetically represses a cohort of neuronal genes in embryonic stem cells (ESCs) during embryogenesis, preventing neuronal gene expression in non-neuronal precursor cells (Jorgensen et al., 2009). REST was found to repress a subset of genes common to ESCs, neuronal stem cells (NSCs) and even differentiated cells. However, an additional subgroup of genes was found to be repressed by REST solely in ESCs, where REST forms a part of the Oct4, Sox2 and Nanog autoregulatory network controlling differentiation and pluripotency in ESCs (Johnson et al., 2008). Whilst REST levels are also high in NSCs, here the transcription factor only causes repression of a subset of the genes it controls in ESCs (Ballas and Mandel, 2005; Johnson et al., 2008). During the final stages of neuronal differentiation, timed and regulated downregulation of nuclear REST is critical for acquisition of the

Table 1
Overview of REST expression levels and its downstream transcriptional role in modulating gene expression following different forms of cellular, neuropathological, psychological and physical stress in different regions of the human and rodent brain.

Context	REST	Source	Target gene expression	Epigenetic markers	Reference
Ischaemia, hypoxia and seizures					
Global ischaemia	REST ↑	Hippocampal CA1 neurons Rat	CK↓	N/A	Kaneko et al. (2014)
Global ischaemia	REST ↑	Hippocampal CA1 neurons Rat	GluR2 ↓	N/A	Calderone et al. (2003)
Ischaemic stroke	REST ↑	Hippocampal CA1 neurons Rat	Gria2, Grin1, Chrb2, Nefh, Trpv1, Chrm4, Syt6 ↓ GluA2, GluN1, GluN2B ↓	H3K9ac ↓ H3K14ac ↓ H3K9me2 ↑	Noh et al. (2012)
Hyperthermia-induced epilepsy	REST ↑	Hippocampal neurons Rat	Hcn1 ↓	N/A	Patterson et al. (2017)
Kainic acid-induced epilepsy	REST ↑	Hippocampus Rat	Calb1, Glra2, Grin2a, Hcn1, Kcnc2, Klf9, Lrp11, Myo5b, Stmn2 ↓	N/A	McClelland et al. (2014)
Neurodegenerative diseases					
Alzheimer's Disease	*Rest* ↓	PFC neuronal nuclei Mouse	Bcl2, Sod1, Foxo1 ↓	H3K9ac ↑	Lu et al. (2014)
Alzheimer's Disease	*Rest* ↓	Neuron-derived extracellular vesicles Human	N/A	N/A	Ashton et al. (2017)
Parkinson's Disease	REST↓	Dopaminergic neurons Human	N/A	N/A	Kawamura et al. (2019)
Huntington Disease	REST ↑	Cerebral cortex Human	Bdnf ↓	N/A	Zuccato et al. (2007)
Prion Diseases	REST ↑	Primary cortical neurons Rat	FOXO1, cytochrome *c*, Caspase 3 ↑	N/A	Song et al. (2016)
Psychological and physical stress					
Chronic social defeat	*Rest* ↑	Dentate granule cells Mouse	GluN2B↓	N/A	Chen et al. (2015)
Chronic traumatic stress	*Rest* ↑	Prefrontal cortex Rat	CCR5 ↑	N/A	Mou and Zhao (2016)
Augmented maternal care	*Rest* ↑	Neuronal Rat	Crh ↓	MeCP2 ↑ H3K27me3 ↑ H3K9me2 ↑	Singh-Taylor et al. (2018)
Augmented maternal care	*Rest* ↑	Hypothalamic PVN Rat	Crh ↓, vGlut2 ↓	N/A	Korosi et al. (2010)
Maternal Separation	*Rest4* ↑	mPFC Rat	Glur2, Nr1, Chr, CamKIIα, L1, Adcy5, 5Htr1a, Kcnc1 ↑ Nav1 ↓	Mir132, -124, -9-1, -9-3, -212, and -29a ↑	Uchida et al. (2010)

neuronal phenotype and lifting its repression then allows the formation of important neuronal processes such as axonal growth, synaptic signalling and membrane excitability (Baldelli and Meldolesi, 2015; Ooi and Wood, 2007; Paquette et al., 2000).

Nuclear REST protein expression is low in mature neurons, however its expression is preserved in NSCs (Singh et al., 2008). Despite the low levels of REST in adult neurons, overall REST levels in the adult brain remain relatively high due to the high expression of REST in most non-neuronal glial cells, endothelial cells and neurogenic areas of the brain, including the subgranular zone of the dentate gyrus and subventricular zone (SVZ) of the lateral ventricles (Gao et al., 2011; Prada et al., 2011).

Interestingly, nuclear REST can be re-expressed in differentiated neurons during critical moments of experience-dependent synaptic remodelling to fine-tune genes involved in synaptic remodelling (Rodenas-Ruano et al., 2012). REST was shown to be reactivated in response to neuronal insults such as ischaemia and seizures, where REST-dependent epigenetic remodelling was causally linked to neuronal death of post-ischaemic, mature hippocampal neurons (Calderone et al., 2003; Kaneko et al., 2014; McClelland et al., 2014; Noh et al., 2012; Schiffer et al., 2014). However, neuronal REST was also found to be re-expressed in the nucleus during healthy ageing, where it suppresses genes involved in neuronal death thereby providing neuroprotection to the ageing brain (Lu et al., 2014). The protein was found to be primarily located in the neuronal cytoplasm in the cortex, caudate nucleus, hippocampus, cerebellum and substantia nigra of middle-aged healthy controls (44–61 years old) (Kawamura et al., 2019; Schiffer et al., 2014). However, in elderly healthy controls (72–91 years old) REST accumulated in the nucleus (Kawamura et al., 2019). To date, there is no evidence of clear sex differences in the spatiotemporal pattern of REST expression levels either in developing or adult brains (Moravec et al., 2016). However, this is an area ripe for future research given the documented sex differences in the susceptibility of males and females to stress and depression in adolescence and adulthood, as well as in age-related cognitive decline (Verma et al., 2011).

Moreover, loss of neuronal REST expression is widely associated with several neurodegenerative diseases (Hwang and Zukin, 2018). For instance, the loss of neuronal REST in ageing prefrontal cortex and hippocampal neurons was associated with the onset of Alzheimer's disease (AD) in humans (Lu et al., 2014). In Parkinson's disease (PD) and dementia with Lewy bodies (DLB), REST was also found to be absent from the nucleus in human dopaminergic neurons in the substantia nigra and cortical neurons (Kawamura et al., 2019). Given recent evidence that women are more susceptible to developing AD and accelerated cognitive decline in old age (Zhao et al., 2016), a pertinent question that requires addressing in the near future will be the analysis of sex differences in stress-induced modulation of REST transcriptional activity within neurons of the male and female brain, particularly in key stress-responsive structures such as the hippocampus, amygdala, prefrontal cortex and hypothalamus.

2.2. DNA binding properties

Full-length REST protein contains three functional domains, including a DNA binding domain (DBD) and two repressor domains at the N-and C-terminals. The DBD contains eight zinc fingers (ZFs) which allow binding of the protein to its 21-base pair consensus motif for repressor element-1 (RE1) or neuron restrictive silencer element (NRSE) (Ooi and Wood, 2007). The RE1 consensus motif {TTCAGC ACCatGGACAGcgcC} was constructed by aligning the sequences of known REST binding sites. Nucleobase variations within the RE1 motif strongly affect binding affinity and REST clearance (Bruce et al., 2009) (Fig. 1).

Initially, REST target genes were thought to contain one to five RE1-binding elements within their promotor region. Later, the use of

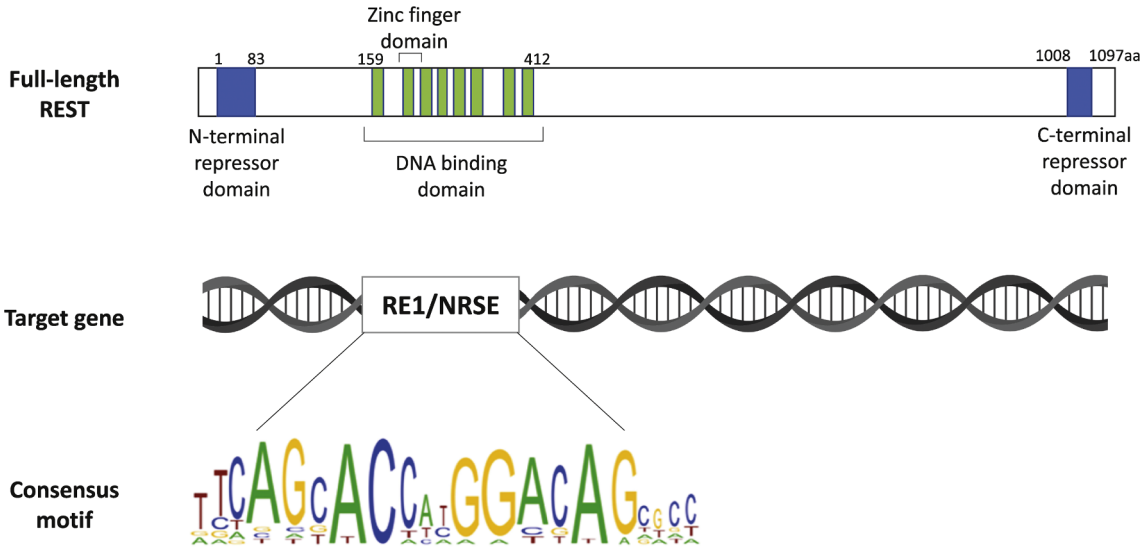

Fig. 1. The modular structure of full-length REST protein. The DNA binding domain contains eight C2H2 zinc fingers near the N-terminal repressor domain. The other repressor domain is located at the C-terminal. REST binds to its targets genes which contain the RE1/NRSE consensus motif, however other binding partners have been identified (Bruce et al., 2009; Ooi and Wood, 2007).

chromatin immunoprecipitation sequencing (ChIP-seq) revealed numerous other REST binding motifs besides the RE1-sequence, which increased the REST-dependent gene pool markedly (Bruce et al., 2009; Otto et al., 2007; Satoh et al., 2013). Furthermore, presence of RE1-binding sites in potential target genes does not necessarily implicate REST-mediated repression, as only RE1-containing genes with mid-range binding properties are subjected to selective REST regulation. Whilst this mechanism of 'dynamic repressor binding' was only examined in an epileptic context, a similar mechanism might apply to other physiological and pathological conditions (McClelland et al., 2014).

2.3. Co-factor recruitment

The full-length REST protein contains two repressor domains (RDs), an N-terminal (RD1) and a C-terminal repressor domain (RD2). As a bipartite repressor, REST can directly or indirectly interact with various transcriptional and epigenetic cofactors at its repressor domains. As REST binds to its target genes, the protein acts as a scaffold to recruit a DNA-modifying complex. REST-mediated chromatin modifications are highly dependent on the recruitment of its epigenetic cofactors, i.e. REST alone cannot exert gene repression (Yu et al., 2011).

The N-terminus recruits the corepressor Sin3a, which then serves as a binding site for histone deacetylases 1 and 2 (HDAC1/2) (Huang et al., 1999). The C-terminus is responsible for binding with a second corepressor CoREST, which in turn can recruit a variety of chromatin remodelling proteins, such as HDAC1/2, histone methyltransferase (G9A), lysine-specific demethylase 1 (LSD1), methyl-CpG-binding protein (MeCP2), carboxy-terminal binding protein 1 (CTBP1) and/or various chromatin remodelling proteins (Brg1, Braf35, Baf170, Baf57) (Andres et al., 1999; Lunyak et al., 2002; Ooi et al., 2006) (Fig. 2).

Importantly, REST can recruit different combinations of corepressor complexes to mediate context-specific gene expression modification. A striking characteristic of REST cofactors is that they can maintain their position on the DNA of their target genes, even after dissociation of the protein (Ballas et al., 2005). REST and CoREST have been reported to interact with a large variety of additional epigenetic modifying agents, including DNA methyltransferases and chromatin remodelling enzymes (SMCX and CDYL). A large RNA polymerase II activity modifying complex has also been reported to associate with REST (Ding et al., 2009).

2.4. Splice variants

The ability to mediate gene repression varies greatly between REST splice variants. Context-dependent pre-mRNA splicing creates alternate REST isoforms lacking key regulatory domains (Chen and Miller, 2013a). Chen et al. (2017) recently proposed that the widespread variability in reported REST function is determined by alternative splice variants, which alter the proteins physiological requirements leading to differential data interpretation (Chen et al., 2017). For example, elevated nuclear REST was reported to be neurotoxic and harmful in ischaemia and Huntington's disease (HD), whereas Lu et al. (2014) demonstrated neuroprotective effects for increased nuclear REST during healthy ageing (Kaneko et al., 2014; Lu et al., 2014; Zuccato et al., 2007).

REST4 was the first reported alternative splice variant and is formed by inclusion of an additional exon ($N3_a$, $N3_b$, $N3_c$, $E4_c$ or E5) which causes incorporation of a premature stop codon (Lee et al., 2000). Consequently, the translated REST4 protein contains only five of the eight original zinc finger domains, which reduces its binding affinities in competition with the full-length REST protein. At least 45 different predictive REST isoform variants can be produced by partially or complete skipping of the three constitutive exons (E2, E3, E4) (Fig. 3) (Chen and Miller, 2013a). Furthermore, various mRNA variants reported as REST4 are predicted by different mRNA sequences, (e.g. JX896958, JX896971 and JX896983). This suggests that there are far more REST splice variants than those currently recognized.

On the one hand, mRNA variants lacking E3 are predicted to encode for the N-terminal REST isoform, REST1. E2-skipping variants, on the other hand, lack the conventional start codon which leads to translation of a C-terminal isoform, $REST^c$ (XP_005265817) (Nechiporuk et al., 2016). Moreover, short open reading frame (ORF) mRNAs, which were previously described as noncoding RNAs, are likely to be involved in the context-dependent formation of numerous REST variants (e.g. JX896962, JX896965, and JX896967) (Fig. 3) (Olexiouk et al., 2016).

Due to the existence of multiple REST protein isoforms it is highly likely that different primers and antibodies can target various splice variants. Furthermore, REST interference by conditional knockout (cKO) or siRNA may not be specific for all isoforms. As Chen et al. (2013) concluded, REST isoforms might be differentially assayed or manipulated in different studies, leading to inconsistent results and data misinterpretation. Their assay of two commonly used REST

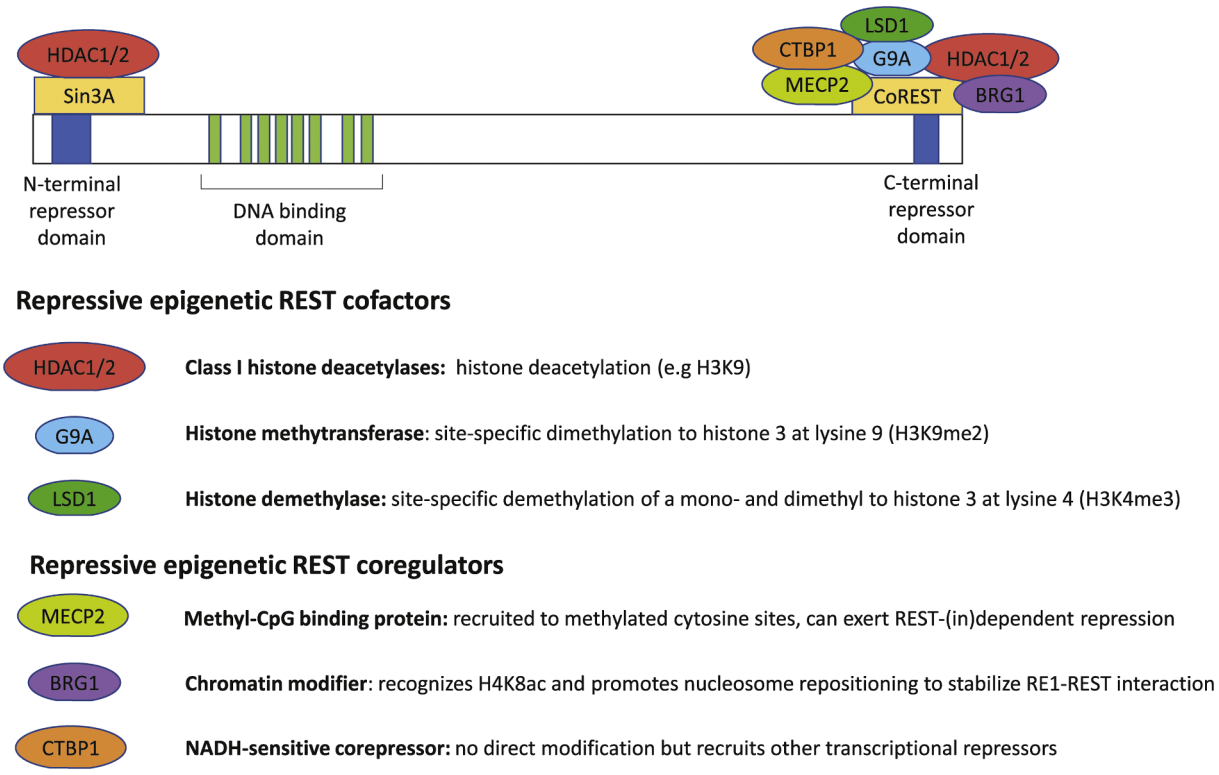

Fig. 2. REST-mediated epigenetic remodelling. REST-mediated epigenetic repression is attained through the recruitment of two corepressor complexes (Sin3A and CoREST), which in turn recruit various other epigenetic modifying proteins. The N-terminal repressor domain recruits Sin3A and subsequently class I histone deacetylases HDAC1 and HDAC2 (potentially also class II histone deacetylates HDAC4/5). The CoREST complex at the C-terminal repressor domain can recruit a variety of different modifiers (e.g. HDAC1/2, methyl-CpG binding protein (MECP2), histone demethylase (LSD1), histone methyltransferase (G9A), carboxy-terminal binding protein 1 (CTBP1)) (Qureshi et al., 2010). CoREST also assembles with BRG1, which stabilizes the interaction between REST and the RE1 binding site (Ooi et al., 2006).

antibodies, yielded inconsistent results regarding the subcellular location of REST protein (Chen and Miller, 2013a).

In the years to come, we expect more studies to investigate the diverse properties of distinct REST splice variants. However, this might be a challenging task as post-translational modifications make it exceptionally difficult to distinguish non-specific binding from a REST

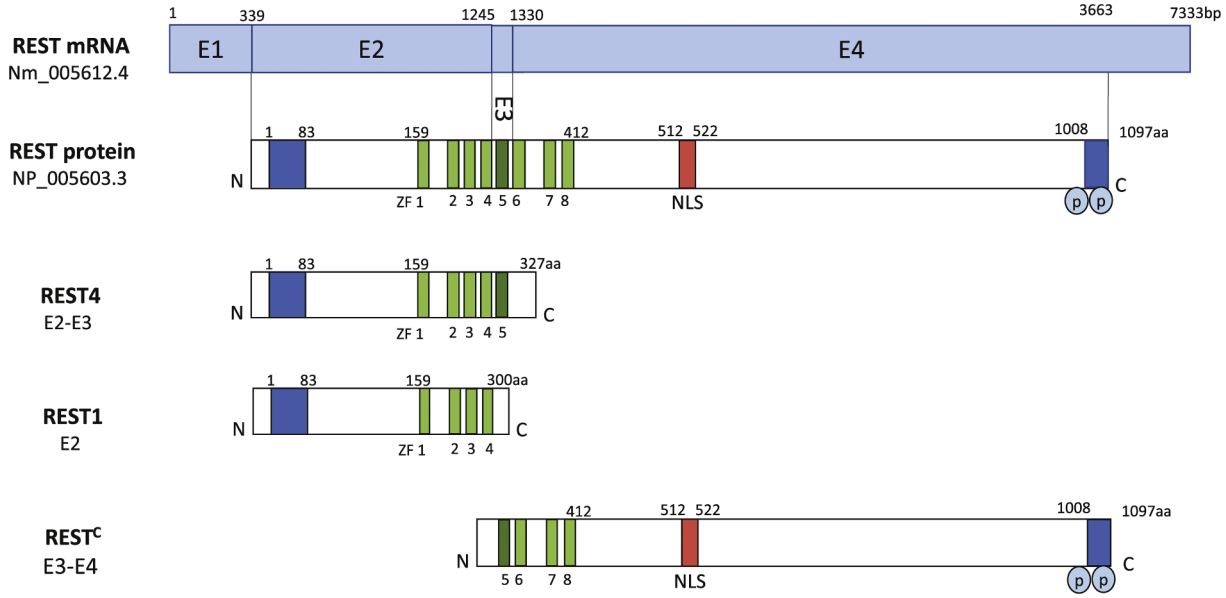

Fig. 3. Full-length REST and its splice variants. The major REST isoform has two repressor domains, eight zinc fingers (ZFs), a nuclear localisation signal (NLS) and a phosphodegron (P) motif, which is required for β-TrCP regulation (Westbrook et al., 2008). Alternative splicing of REST mRNA generates various REST isoforms which lack key regulatory domains, e.g. ZF5 and/or NLS which are thought to be required for nuclear localisation. Known isoform REST4 is read by exon E2-E3 and only contains the N-terminal repressor domain and ZFs 1–5. REST1 is translated through exon E2 and contains N-terminal repressor domain and ZFs 1–4. REST^{c} is read by exon E3-E4 and only consists of the C-terminal repressor domain and ZFs 5–8 (Coulson and Concannon, 2016).

isoform. On top of that, shared epitopes within different REST isoforms can be labelled by the same antibody, which likely discriminate more lengthy isoforms based on the complexity and accessibility of their 3D protein structure.

2.5. REST availability

Maternal genetics and environmental factors have been shown to induce lifelong alterations in immune function and stress responses within their offspring. Maternally supplied mRNA encoding vital transcription factors and chromatin effector genes is deposited in the oocytes before fertilization to modulate developmental gene expression and to regulate the chromatin landscape. Using a zebrafish model, it was shown that maternally supplied REST regulates the expression of its target genes in the developing larvae and that altered levels of maternally supplied REST caused enduring changes in adult behaviour. Interestingly, the behavioural consequences of early maternal REST depletion, observed as erratic swimming behaviour, were more pronounced in male zebrafish (Moravec et al., 2016). Furthermore, zygotic REST was unable to compensate the deficits in maternally supplied REST, indicating novel temporal requirements for the transcription factor's activity (Moravec et al., 2016). Although these findings have only been reported in zebrafish, they might have broad implications for neuronal development in other species, especially following maternal illness or severe psychological stress.

During neurogenesis, REST is widely available. However, inducibility of REST protein expression after neurogenesis is tightly regulated through transcriptional repression and protein degradation via Skp1-Cul1-F-box protein (SCF)/β-TrCP-dependent, ubiquitin-based proteasomal degradation and HAUSP(USP7)-dependent deubiquitination (Ballas et al., 2005; Singh et al., 2011). Two non-canonical degron motifs within the REST C-terminus are responsible for the binding of the E3 ubiquitin ligase β-TrCP, which primes REST for ubiquitin-based proteasomal degradation (Cheong and Virshup, 2011; Weissman, 2008; Westbrook et al., 2008).

Nesti et al. (2014) identified a novel proline-directed phosphorylation sequence, at serine 861/864, upstream of the degron motifs which facilitates the downregulation of REST at the end of neuronal differentiation. The proline-rich motif acts as a substrate for the peptidyl-prolyl *cis/trans* isomerase Pin1 and ERK1/2 kinases. Furthermore, dephosphorylation of the S861/864 sequence by C-terminal domain small phosphatase 1 (CTDSP1) stabilizes REST. Taken together, CTDSP1 stabilizes REST in stem cells during neurogenesis whilst ERK1/2-dependent phosphorylation combined with Pin1 activity promotes REST degradation. Thus, REST abundance during neurogenesis is tightly regulated to prevent untimely downregulation of REST, hindering terminal neuronal differentiation. Furthermore, strict control over REST degradation in neuronal progenitors at the end stages of neurogenesis is essential to promote maturation of the neuronal phenotype (Nesti et al., 2014).

However, in differentiated neurons, REST abundance and stability is regulated through different mechanisms, mainly orchestrated by the serine/threonine kinase casein kinase-1 (CK1) and Wnt-β-catenin signalling. CK1 maintains low REST expression by phosphorylation of the serine residues in two neighbouring degron motifs within the REST C-terminus, which marks the protein for E3 ligase β-TrCP recognition and subsequently ubiquitin-regulated proteasomal degradation (Kaneko et al., 2014). However, global ischaemia has been shown to trigger a decrease in CK1 and β-TrCP, thereby increasing REST in vulnerable hippocampal neurons (Kaneko et al., 2014; Noh et al., 2012). Whilst CK1 was thought to be constitutively active, it appears that its activity is regulated by the DEAD-box RNA helicase 3 (DDX3) which was identified as an upstream positive regulator of CK1 (Huang et al., 2013). Furthermore, DDX3 promotes phosphorylation of the Wnt-β catenin signalling-associated scaffold protein dishevelled (Dsh). Phosphorylated Dsh inhibits glucogen synthase kinase 3 (GSK3) activity, preventing β-catenin destruction and subsequently β-catenin-mediated gene transduction (Cruciat et al., 2013).

Nuclear translocation is essential for REST-mediated transcriptional repression. However, under certain circumstances the protein fails to translocate to the nucleus and gets degraded by autophagy (Song et al., 2017). Serum deprivation in neuron-derived SH-SY5Y cells was shown to activate autophagy, resulting in REST translocation from the nucleus to the cytoplasm where the protein was found to colocalise with autophagosomes (Cruciat et al., 2013). Similar mechanisms were observed in the brain of AD and PD patients, and in a prion disease model, where REST was markedly depleted in the neuronal nucleus and colocalized with autophagosome marker LC3-II (Kawamura et al., 2019; Lu et al., 2014; Song et al., 2017; Song et al., 2016).

The question remains, however, whether REST directly activates/regulates autophagy or if autophagy is activated following REST dysfunction or ubiquitin-proteasome system failure (Hwang and Zukin, 2018; Kawamura et al., 2019). It has been proposed that REST may disrupt the mTOR signalling pathway which is a vital negative regulator of autophagy. This pathway was inhibited in prion disease models, where REST failed to translocate to the nucleus and associated with autophagosomes in primary neurons (Song et al., 2017). Furthermore, REST knockdown demonstrated disruption of the mTOR signalling pathway, causing a reduction in cell viability, apoptosis and DNA fragmentation in human squamous cell carcinoma cells (Cho et al., 2015).

2.6. Nuclear trafficking

As a transcriptional modulator, the availability of REST and translocation of the protein to the nuclear compartment is essential. Shimojo et al. (2001) originally identified the nuclear localisation sequence (NLS) to be responsible for the nuclear distribution signals (Shimojo et al., 2001). However, splice variant REST4 lacks the NLS and still displays nuclear localisation. It was suggested then, that the essential domain for nuclear translocation was ZF5, since REST1 lacks the corresponding amino acid sequence and is not targeted to the nucleus (Shimojo, 2006). Nuclear localisation requires energy-independent nuclear targeting and subsequent docking to nuclear pore complexes, followed by energy-dependent translocation through the nuclear pore. The active translocation through the nuclear pore is thought to be regulated by ZF2 and ZF3 (Shimojo, 2006).

The discovery of a novel protein, REST/NRSF-interacting Lin-11, Isl-1 and Mec-3 (LIM) domain protein (RILP), led to new insights regarding the nuclear trafficking mechanism of REST. Human neurons express REST target protein, RILP or PRICKLE1, on their outer nuclear membrane. Interestingly, siRNA-mediated suppression of RILP caused cytosolic localisation of both full-length REST and REST4, causing loss of REST repressor activity, which suggests that nuclear translocation of both isoforms is regulated by RILP (Bassuk et al., 2008; Shimojo and Hersh, 2006). In non-neuronal cells, the target signal is thought to be DCTN1 (dynactin 1, dynactin p150Glued), a subunit of dynactin complex that can bind dynein motor proteins to be transported along microtubules. However, certain proteins also bind to REST to maintain its cytosolic location and prevent nuclear translocation, including huntingtin (HTT) and huntingtin-associated protein 1 (HAP1) (Shimojo, 2008; Zuccato et al., 2007).

2.7. Transcriptional regulation of REST

Besides the context- and cell type-dependent regulation of REST, it is important to understand the transcriptional regulation to fully appreciate the complexity of REST-mediated repression of its target genes. The Wnt/β-catenin signalling pathway, which is known to be involved in the differentiation of neuronal precursors, dendritic morphology and synaptic function was shown to directly regulate REST to control the stem cell progenitor pool (Inestrosa and Varela-Nallar, 2014; Nishihara

et al., 2003). The REST gene is also positively regulated by Oct4 and Nanog, since knock-down of these transcription factors in mouse embryonic stem cells results in reduced REST expression (Loh et al., 2006).

In addition to REST regulation through non-autonomous Wnt-signalling during embryonic developmental stages, REST is reportedly regulated through the same signalling cascade during ageing and neurodegenerative disease (Lu et al., 2014; Nishihara et al., 2003; Song et al., 2017). Wnt ligands activate the pathway by binding the low-density lipoprotein receptor-related protein 6 (LRP6)/Frizzled co-receptor complex, which stabilizes β-catenin causing nuclear translocation and consequently transcriptional activation (Gruber et al., 2016). Interestingly, REST was found to colocalize with β-catenin in neurons from AD patients and in primary cortical neurons in a prion disease model (Lu et al., 2014; Song et al., 2016).

Exogenous REST was shown to alleviate the synaptic abnormalities and neuronal death in prion disease through LRP6-mediated Wnt-β-catenin signalling (Song et al., 2016). Extracts of aged cortex and stressed cell conditioned medium induced both β-catenin and REST in SH-SY5Y cells. On the one hand, REST expression could be partially inhibited using the Wnt pathway antagonist Dickkopf (DKK1). On the other hand, inhibition of GSK3 using lithium chloride induced REST activation, increased REST-RE1 site binding and increased nuclear translocation of the protein (Lu et al., 2014). These findings indicate that REST is not only regulated by Wnt-β-catenin signalling, but is also reciprocally related to Wnt-signalling (Song et al., 2017).

Ravache et al. (2010) showed that REST mRNA is upregulated in the R6/2 HD mouse model. The observed upregulation at the transcriptional level was mediated by direct binding of specificity proteins, Sp1 and Sp3, to the REST promotor (Ravache et al., 2010). Besides Sp1 and Sp3, the proapoptotic protein HIPPI (huntingtin interaction protein 1 (HIP1) protein interactor) has since been identified as a transcriptional regulator of REST (Datta and Bhattacharyya, 2011).

Furthermore, various epigenetic mechanisms are involved in the regulation of REST mRNA transcription, such as CpG methylation, MeCP2 binding and miRNA mediated processes (Kreisler et al., 2010; Wang et al., 2018). Interestingly, the presence of a RE1-motif within the genomic sequence of REST likely indicates autoregulation (Johnson et al., 2007). Overall, the mechanisms which regulate REST mRNA expression are not fully understood and are likely a close interaction between Wnt-mediated transcription, epigenetic mechanisms and strict (self)regulatory feedback mechanisms (Fig. 4).

3. REST-mediated stress response

Stress can be experienced by virtually all biological systems and is often defined as any external or internal stimulus that forces the system away from its physiological, homeostatic steady state. Homeostasis, the ability to return to baseline or a new steady state following a disruption to normal processes, is a fundamental property that biological systems use to deal with and regain operational balance (Kotas and Medzhitov, 2015). When the homeostatic capacity of an organism is insufficient to cope with the stressor, it engages in a stress response. When this reaction is inadequate to maintain homeostasis and/or when the perturbation is persistent, adverse side-effects of the initially beneficial stress response can emerge. These homeostatic imbalances are widely associated with disease and exacerbation of pathophysiological changes (Chovatiya and Medzhitov, 2014; McEwen, 1998).

Whilst many biological processes are in place throughout the human body to maintain homeostasis, including the hypothalamic-pituitary-adrenal (HPA) axis, autonomic nervous system, immune, metabolic and cardiovascular systems, the brain specifically is equipped with various response mechanisms to promote survival and adaptation following stress. Our brain can be regarded as the master regulator of the stress response as it both perceives stressors and adapts to them. Furthermore, it determines the origin of the stimulus, orchestrates coping mechanisms and more importantly, changes both functionally and structurally in response to the stressor. These unique processing mechanisms enable the brain to control and coordinate behavioural and physiological outcomes following internal and external challenges to the body's homeostasis. Neurons, in particular, have been identified as major regulators of central nervous system (CNS) homeostasis, as they have an important impact on the physiological response towards changes in internal or external conditions, through epigenetic genomic mechanisms and non-genomic molecular mediators (Farley and Watkins, 2018).

Throughout their entire lifespan, neurons may face various insults that can impact their intrinsic homeostatic balance. Disruption of this balance can lead to severe neuronal dysfunction, including perturbations in synaptic output and neuronal excitability, ultimately affecting behaviour and cognition (Ramocki and Zoghbi, 2008). Unsurprisingly, neurons have demonstrated an exceptional ability to compensate imbalances in their homeostasis through modulation of ion channels, receptors, various signalling pathways and neurotransmitters. Excitatory amino acids and glucocorticoids play a fundamental role in maintaining neuronal homeostasis, along with various extra- and intra-cellular mediators, such as serotonin, brain derived neurotrophic factor (BDNF) and corticotropin releasing hormone (CRH). Furthermore, continuous chromatin remodelling and gene expression changes via epigenetic mechanisms aid in regaining balance following stress (Faye et al., 2018; Franklin et al., 2012; McEwen, 2007).

Because of REST's epigenetic influence on genes critically involved in neuronal function and various stress-related mediators, including CRH, BDNF and the serotonin (5-HT) 1A receptor, the transcription factor recently received an increasing amount of interest regarding its potential influence in modulating the neuronal stress response (Chen et al., 2015; Korosi et al., 2010; Lu et al., 2014; Otsuki et al., 2010; Otto et al., 2007; Singh-Taylor et al., 2018). However, understanding of the physiological mechanisms that REST can control following stress is still in its infancy. Therefore, we will discuss recent findings of how REST could be a key determinant of the neuronal stress response through modulation of the neuroendocrine stress response, neuronal excitability, adult neurogenesis and oxidative stress. An overview of REST expression levels and its downstream effects on gene expression following different forms of cellular, neuropathological, psychological and physical stress in various brain regions is given in Table 1.

3.1. REST and the neuroendocrine stress response

The HPA axis in one of the first systems to respond following perception of a stressor, leading to the activation of the paraventricular nuclear (PVN) neurons within the hypothalamus. These neurons secrete CRH and arginine vasopressin (AVP), which upon binding to their ligand stimulate the production of adrenocorticotropic hormone (ACTH) in the anterior pituitary gland. In turn, ACTH causes the release of glucocorticoids (GCs), cortisol or corticosterone, from the adrenal cortex into the bloodstream (Pfau and Russo, 2015; Ulrich-Lai and Herman, 2009). Besides the modulation of a vast array of physiological processes, both in the periphery and in the central nervous system, these circulating corticosteroids are responsible for initiating a negative feedback loop on the HPA axis via activation of the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) in order to cease GC production. Disturbances in glucocorticoid feedback mechanisms have been widely correlated to negative health outcomes, including an increased risk for cognitive and physical frailty (Johar et al., 2014; Noordam et al., 2012).

REST was first associated with the neuroendocrine response through its ability to modulate CRH. Seth et al. (2001) discovered the presence of the RE-1 sequence within the promotor regions of the *Crh* gene and were the first to show that transcriptional repression of *Crh* was mediated through REST (Seth and Majzoub, 2001). Furthermore, early-life stress has been shown to induce enhanced nuclear levels of REST and recruitment of the transcription factor to *Crh* (Korosi et al., 2010;

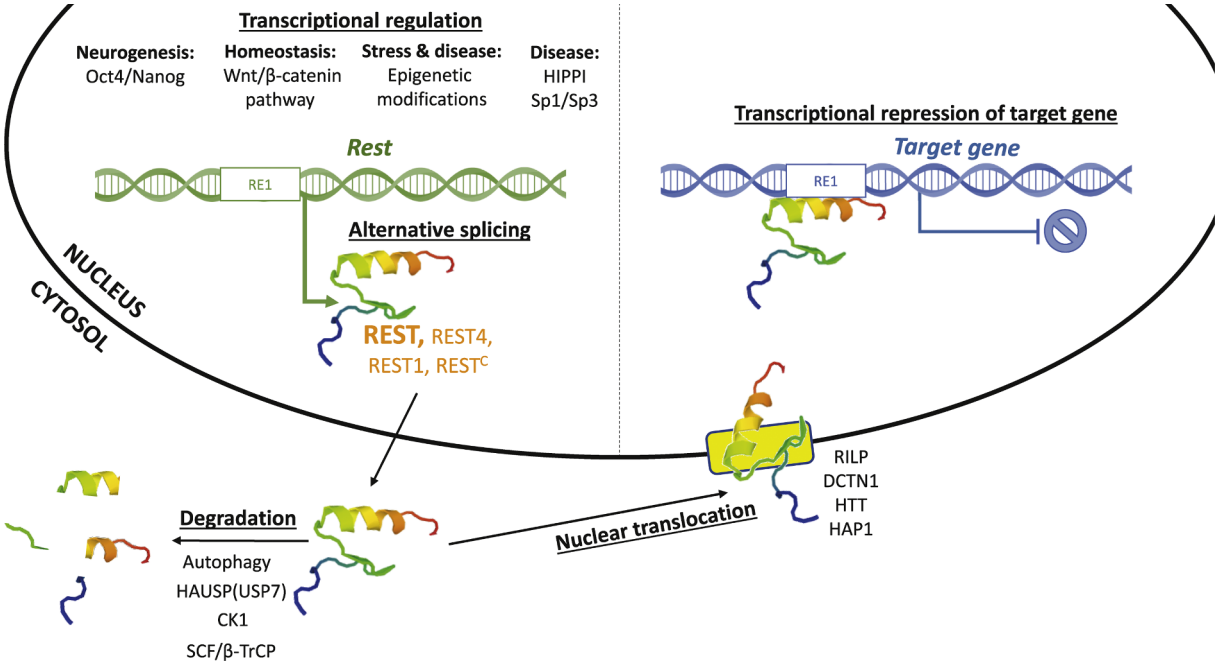

Fig. 4. Brief overview of REST characteristics. *Transcriptional regulation*: The transcription factor itself is regulated through Wnt/β-catenin signalling (Huang et al., 2013; Lu et al., 2014; Nishihara et al., 2003; Song et al., 2017), the embryogenic transcription factors Oct4 and Nanog (Loh et al., 2006; Singh et al., 2008), disease-associated proteins such as the huntingtin interaction protein 1 (HIP1) protein interactor (HIPPI) (Datta and Bhattacharyya, 2011; Ravache et al., 2010) and epigenetic modifications (Ballas et al., 2005; Johnson et al., 2007; Kreisler et al., 2010; Qureshi et al., 2010; Singh-Taylor et al., 2018), which are likely induced by a self-regulatory feedback mechanism (Johnson et al., 2007). *Alternative splicing*: Upon REST transcription, alternative splicing can result in different isoforms with different functional regions, affecting their DNA binding affinities and repressive activity (e.g. REST4, REST1, REST^c) (Chen et al., 2017; Nakano et al., 2018). *Degradation*: In the cytosol REST can be targeted for proteasomal degradation through SCF/β-TrCP (Ballas et al., 2005; Singh et al., 2011; Westbrook et al., 2008) and HAUSP(USP7)-dependent de-ubiquitination (Huang et al., 2011), casein kinase-1 (CK-1) mediated phosphorylation (Kaneko et al., 2014; Noh et al., 2012) and autophagy (Song et al., 2017). *Nuclear translocation*: Nuclear trafficking of the protein is vital for its repressor activity and dependent on various nuclear localization signals, including REST/NRSF-interacting LIM domain protein (RILP) in neurons (Bassuk et al., 2008; Shimojo, 2006, 2008; Shimojo and Hersh, 2006), dynactin 1 (DCTN1) in non-neuronal cells (Shimojo, 2008; Zuccato et al., 2003). Disease-associated proteins such as huntingtin (HTT) (Chen et al., 2017), huntingtin-associated protein (HAP1) (Shimojo, 2008) and likely amyloid-β (Lu et al., 2014) can prevent REST's nuclear translocation. *Transcriptional repression*: As REST binds to its target genes, the protein acts as a scaffold to recruit a DNA-modifying complex of epigenetic cofactors. Through direct or indirect interaction with a variety of transcriptional and epigenetic cofactors REST exerts gene repression (Ballas and Mandel, 2005; Ooi and Wood, 2007; Yu et al., 2011).

Singh-Taylor et al., 2018). Augmented maternal care in rodents, by brief maternal separation and increased maternal licking and grooming upon return, was shown to reduce the number of glutamatergic synapses contacting CRH-expressing neurons in the PVN of the hypothalamus, enough to reduce the expression of CRH in hypothalamic neurons and stress-responsiveness towards future stressors (Faye et al., 2018; Korosi et al., 2010). The change in stress-sensitivity was confirmed by a blunted corticosterone release upon stress later in life, without changes in the basal corticosterone levels. In this case, the authors stated that the early-life modulation of CRH-expressing stress-sensitive neurons contributed to a life-long phenotype of improved memory and resilience to stress. (Singh-Taylor et al., 2018). Of note, adequate functioning of CRH is dependent on a delicate equilibrium, as both hyper- and hypoactive CRH systems have been associated with psychiatric disorders, anxiety and memory impairment (Kasckow et al., 2001; Roozendaal et al., 2002).

Indeed, Uchida et al. (2010) found increased vulnerability towards future stress following maternal separation in rats, alongside increased depression- and anxiety-like behaviour in adulthood. The early-life stressor did not seem to alter full-length REST expression in the medial prefrontal cortex (mPFC), rather it increased the expression of splice variant REST4. The REST4 splice variant lacks functional zinc fingers and the C-terminal RD2. Overexpression of REST4 even significantly increased the expression of *Crh* in the mPFC (Uchida et al., 2010). *In vitro* cortisol was shown to increase only N-terminal REST (REST4) in neural retinal ganglion cells and also in the Neuro2A neuroblastoma cell line REST4 was unable to mediate gene repression in the absence of cortisol (Abramovitz et al., 2008). These findings might indicate that full-length REST is responsive to stress in the hypothalamus, whilst REST4 is the stress-responsive splice variant in the PFC.

Traumatic physical stress, induced by invasive surgery in adult rats, also showed an upregulation in REST which was accompanied by a downregulation of CRH expression in the hypothalamus (Mou and Zhao, 2016). Interestingly, adenovirus-mediated REST overexpression reduced corticosterone secretion in this traumatic stress paradigm, which might be due to REST-mediated repression of CRH (Mou and Zhao, 2016). In humans with depression, REST expression was decreased in peripheral blood cells, alongside increased circulating *Crh* (Otsuki et al., 2010). However, the question remains whether increases in plasma levels of REST protein positively or negatively correlate with REST levels in the CNS.

The neuroendocrine stress response and neuronal function is also mediated by various neurotransmitters and neuropeptides, including serotonin and its receptors. Pharmacologically-induced reduction of serotonin in the hippocampus has been shown to block stress-induced memory dysfunction, implicating a role for serotonin in hippocampal damage following stress (Lemonde et al., 2004; Wang et al., 2013). The expression of tryptophan hydroxylase (*Tph2)*, an enzyme involved in the biosynthesis of serotonin, is under the transcriptional control of REST (Patel et al., 2007). The mechanism through which REST controls the activation of *Tph2* is still unknown. However, it has been suggested that GC mediated induction of gene expression is involved (Chen and Miller, 2013b). Besides the enzyme required for serotonin production, 5-hydroxytryptamine (5-HT) 1A receptor gene (*5htr1a)* is also under

REST-mediated repression (Lemonde et al., 2004). Another predominant neurotrophin in the brain is BDNF. Mature BDNF preferentially binds to the TrkB receptor, which activates downstream signalling pathways involved in neuronal survival, differentiation and learning and memory formation in the hippocampus, such as mitogen-activated protein kinase (MAPK), phospholipase Cγ, and phosphatidylinositol-3 kinase pathway (Leal et al., 2017). REST is known to represses the transcription of an ensemble of neuronal genes, including the gene encoding BDNF through the presence of the RE-1 region (Otto et al., 2007; Zuccato et al., 2007). Chronic stress was shown to substantially lower BDNF, which raises the question whether REST might be involved in this observation (Phillips, 2017). However, Uchida et al. (2010) examined the expression of RE-1-containing genes, including *Bdnf*, following daily maternal separation from postnatal day 2 to day 14. Here, researchers only observed an increase in Rest4, not full-length Rest, mRNA expression in the mPFC in comparison to control and no alternations in *Bdnf* expression were observed (Uchida et al., 2010).

Overall these findings indicate that the levels of neuronal REST are highly responsive to stress stimuli and implicate the involvement of the protein in the neuroendocrine stress response. Furthermore, REST's ability to repress *Crh*, *5htr1a*, *Tph2* and *Bdnf* amongst other genes, indicates how the transcription factor can potentially regulate neurophysiological stress responses.

3.2. REST and neuronal excitability

Intrinsic and extrinsic stressors are known to cause structural remodelling of neurons and to alter neuronal excitation (McEwen et al., 2016). In order to maintain stability, neurons must actively change their output to meet the new requirements within a satisfactory operating range. This balancing is achieved through a combination of synaptic plasticity and changes in intrinsic neuronal excitability (Camp, 2012). Intriguingly, neuronal excitation is actively controlled by REST through modulation of voltage-gated Na^+ channels (Chong et al., 1995). In addition to Na^+-channels, REST also regulates expression of Ca^{2+}-channels, K^+-channels and hyperpolarization-activated cyclic nucleotide-gated (HCN1) channels (McClelland et al., 2011). Similarly, upregulation of the chloride transporter KCC_2, whose function is indispensable for the neuronal maturation by shifting gamma-aminobutyric acid (GABA) from excitatory to inhibitory, is dependent on REST (Yeo et al., 2009).

Extensive neuronal depolarization by extracellular K^+ in *in vitro* cultures was shown to increase REST and downregulate known REST target genes, including BDNF and the transcription factor Neuronal PAS Domain protein 4 (NPAS4) (Bersten et al., 2014). Furthermore, pharmacological blockade of K^+-channels by 4-aminopyridine (4-AP) to induce neuronal hyperactivity, demonstrated a transient increase of REST mRNA and protein in excitatory neurons, followed by a decrease in action potential frequency. Increased REST levels, in turn, reduced expression of voltage-gated Na^+ channels (VGNa), thereby lowering the neuronal Na^+ current density. These findings indicate that REST has the potential to maintain neuronal activity by restoring physiological firing activity and preserving intrinsic homeostatic plasticity (Pozzi et al., 2013).

Npas4, a known REST target gene, is an activity-induced transcription factor restricted to the brain where it regulates the expression of inhibitory synaptic genes, thereby maintaining the homeostatic excitatory/inhibitory balance in neurons, which is required for contextual memory formation (Bersten et al., 2014). It is therefore likely that upregulated levels of REST during a perceived stressful event, can downregulate *Npas4*. Indeed, acute restraint and immobilisation of mice, which is both psychologically and physically stressful, has been shown to cause a reduction of *Npas4* in the hippocampus (Yun et al., 2010). It appears that NPAS4 functions primarily to scale down the level of network activity following neuronal excitation (Shan et al., 2018). Furthermore, aberrant increases in neuronal excitability have been observed following stress and are linked to AD and age-related memory impairments (Busche and Konnerth, 2015; Simkin et al., 2015). However, a direct link between REST and NPAS4 repression following stress has not yet been established (Sun and Lin, 2016).

In vitro, nuclear REST expression in hypothalamic neurons was reported to increase following pharmacological blockade of ionotropic glutamate receptors (CNQX, AMPAR antagonist and MK-801, NMDAR antagonist) (Singh-Taylor et al., 2018). The resulting increase in unbound glutamate could potentially contribute to the observed increase in REST. For example, a glutamate-mediated increase in REST was observed by Pozzi et al. (2013) following prolonged treatment of hippocampal neurons with 4-AP, a K^+-channel blocking agent known to cause a Ca^{2+}-dependent glutamate increase (Pozzi et al., 2013). Here, the increase in REST levels reduced expression of VGNa and consequently lowered the neuronal Na^+ current density, thereby maintaining homeostatic neuronal activity, restoring physiological neuronal firing rates and thus preserving integrative properties (Pozzi et al., 2013). Furthermore, studies using kainite, a glutamatergic agent, also revealed an upregulation of REST in hippocampal and cortical neurons *in vivo*, and in *ex vivo* brain slices (Calderone et al., 2003; McClelland et al., 2011; Spencer et al., 2006).

Interestingly, REST is known to repress glutamine synthetase expression upon GC-induced glutamate production (Abramovitz et al., 2008). This implies that REST is somehow activated by glutamate, which subsequently inhibits the production of glutamate through repression of glutamine synthetase, acting as a negative feedback mechanism. Accordingly, Korosi et al. (2010) reported an increase in hypothalamic neuronal REST following early-life stress. Here, increased levels of neuronal REST were accompanied by a reduction in excitatory synapses, a decline in miniature excitatory postsynaptic currents (mEPSC) onto CRH-neurons and a reduction in glutamate vesicular transporter vGlut2 (Korosi et al., 2010).

Many more genes involved in the regulation of neuronal excitability are controlled by REST-mediated transcriptional repression, including Ca^{2+} homeostasis (*Cadps, Calb1, Hpca, Cabp7* and *Camkv*), critical subunits of the NMDA and AMPA receptors (*Glun2b, Grin2a* and *Glur2*), postsynaptic density genes (*Psd95* and *Homer2*) and many more (*Glra2, Kcnc2, Lrp11, Kcnip2, Scn3b, Ntrk3* and *Hpca)* (Garcia-Manteiga et al., 2015; Johnson et al., 2007; McClelland et al., 2014). However, how these genes are regulated by REST following stress and their consequent impact on neuronal functioning is still unexplored terrain. In general, these studies indicate that REST is responsive to stress and, more importantly, can restore neuronal homeostasis.

3.3. REST and adult neurogenesis

There is a growing appreciation that the maintenance of adult neurogenesis plays an important role in neural plasticity and functioning (Gu et al., 2013). The exposure to various stressors is known to disrupt adult neurogenesis and to subsequently alter stress susceptibility, emotional and cognitive processes (Levone et al., 2015). REST is reportedly essential for the maintenance of the adult NSC pool (Mukherjee et al., 2016). Mice with a conditional knockout of REST showed a transient increase in adult neurogenesis caused by the premature exit of quiescent NSCs and a subsequent long-term decrease in adult neurogenesis (Gao et al., 2011). Early depletion of the neuronal stem cell pool is known to reduce adult neurogenesis and can thereby limit cognitive reserve. Furthermore, overstimulation of NSC differentiation was shown to interfere with memory retrieval in adult mice (Akers et al., 2014). Interestingly, chronic social defeat in adult C57Bl/6 mice was found to increase the levels of endogenous REST mRNA in adult-born DGCs. The stress-induced increase in neuronal REST was accompanied by a decrease in the number of adult-born DGCs, a decrease in initial dendritic branching and length, and an increase in the decay of synaptic N-methyl-D-aspartate receptor (NMDAR) mediated excitatory postsynaptic currents (EPSC). Furthermore, REST

accelerated the synaptic maturation of the few remaining adult-born DG neurons through a switch in synaptic NMDAR subunits from GluN2B to GluN2A. This NMDAR subunit switch promotes long-term potentiation (LTP) of synaptic transmission in mature dentate granule cells (Chen et al., 2015). These findings suggest that REST has a context-dependent role to maintain quiescence in NSCs, prevents premature differentiation and can ultimately protect against premature neuronal stem cell depletion.

3.4. REST and oxidative stress

The neurophysiological stress response is often accompanied by *de novo* synthesis of cytokines by CNS microglia, dopamine auto-oxidation and H_2O_2 generation, and by glutamatergic receptor activation which triggers profound Ca^{2+} influx, and all are known to increase the levels of ROS (Hayashi, 2015). REST has been widely implicated in the repression of ROS-induced genes and has even been shown to protect aged neurons from oxidative stress (Lu et al., 2014). Neuronal REST is upregulated following global ischaemia, kainic acid treatment and hypoxia (Calderone et al., 2003; McClelland et al., 2014). Following ischaemia, REST was found to transcriptionally repress a specific subset of genes involved in synaptic signalling (*9grin1*, *chrnb2*, *nefh*, *nfκb2*, *trpv1*, *chrm4*, *syt6*, *slc22a12/13* and *gria2*) (Noh et al., 2012). Furthermore, an upregulation of REST and its corepressor CoREST was observed in the hippocampus in ischaemia-vulnerable CA1 neurons, but not in resistant CA3 pyramidal neurons. However, upregulation of the C-terminal cofactor mSin3A was not observed (Noh et al., 2012). Likewise, increased nuclear REST localisation was observed in hypoxic neurons (Cavadas et al., 2016). REST recruitment following hypoxia was shown to supress *Synj1*, which encodes for an ATP-dependent protein involved in clathrin-mediated endocytosis, as well as other genes involved in cell proliferation (*Dlx5*, *Prkb* and *Met*), regulators of transcription factor activity *(Mycbp, Atf7ip, Tcf12, Lbx1, Mms19, Cdk19* and *Med12*), lipid biosynthesis (*Mboat2, Gpam, Pign, Agps* and *Acaca*), nucleic acids (*Parp4, Skiv2l2, Plrg1* and *Dhx37*) and genes involved in protein catabolism (*Fbxo18, Nedd4, Erlin2* and *Trip12*) (Cavadas et al., 2016). CK1 was identified as the upstream protein responsible for β-TrCP-dependent phosphorylation of REST, priming REST for ubiquitin-based proteasomal degradation under physiological conditions. The kinase was shown to decrease following global ischaemia causing increased REST levels in CA1 neurons (Kaneko et al., 2014).

Some research groups have found that the increase in neuronal REST caused ischaemia-induced neuronal death through suppression of the GluR2 promotor and subsequent AMPAR Ca^{2+} permeability (Calderone et al., 2003; McClelland et al., 2014). However, upregulation of REST is not necessarily harmful and could be regarded as a protective mechanism. For example, enhanced REST expression was observed upon 4AP (K^+ channel inhibitor) in hippocampal neurons. Here, the increase in REST levels reduced expression of VGNa and consequently lowered the neuronal Na^+ current density, thereby maintaining homeostatic neuronal activity, restoring physiological neuronal firing rates and thus preserving integrative properties (Pozzi et al., 2013). Overall, these studies indicate that REST is responsive to oxidative stress and, more importantly, has the ability to restore neuronal homeostasis.

3.5. REST and ageing

Ageing is one of the most challenging public health issues that countries around the world face nowadays. With a vast growth in the aged population, researchers, clinicians and social support services are searching for initiatives and interventions with the potential to promote successful ageing. Here, pathological ageing can be defined as the decline or loss of functional properties at cellular, tissue and organ level. In other words, the inability to maintain homeostasis yields a decreased adaptability to internal and external stressors and an increased vulnerability to disease, cognitive frailty and even mortality. On the other hand, healthy ageing can be considered as the ability to maintain homeostasis through dynamic reorganisation of the balance in responses to intrinsic and extrinsic stressors (Fedarko, 2011).

REST gained recognition as a protective factor in healthy ageing when Lu et al. (2014) discovered that the protein was profoundly elevated in the neurons of healthy aged individuals, whilst REST was markedly reduced in the neurons of patients with mild cognitive impairment (MCI) and AD (Lu et al., 2014). Furthermore, they found a positive correlation between nuclear REST levels and cognitive function in the human brain. The increased REST expression levels observed in healthy patients, seemed to protect them from neuronal apoptosis, amyloid-β toxicity and oxidative stress (Lu et al., 2014). REST levels were shown to progressively increase in hippocampal and cortical nuclei of healthy aging humans, leading to the upregulation of protective genes (*Bcl2*, *Sod1* and *Foxo1*) and to the downregulation of genes related to neuronal degeneration (*Mapk11, Fas, Fadd, Tradd, Bax, Bid, Daxx, Puma* and *Cycs*). In contrast, neuronal REST protein appeared to translocate to the cytoplasm to be degraded by autophagosomes in AD and MCI patients. Taken together, neuronal REST represses genes promoting neuronal cell death, inflammation, AD pathology and protects neurons from oxidative stress and amyloid-β toxicity in the ageing human brain (Lu et al., 2014).

Furthermore, REST cellular localisation was examined in the dopaminergic neurons of healthy, middle-aged (47–61 years old) and aged (72–81 years) controls. In the middle-aged cases, neuronal REST expression was only observed in the cytosol, whilst in the elderly individuals neuronal REST expression was observed in both the cytosol and nucleus (Kawamura et al., 2019). These findings led to the assumption that neuronal nuclear REST expression and entry might be dependent on senescence stimuli within the aged human brain (Kawamura et al., 2019). However, this would not explain why nuclear REST translocation in AD and PD neurons is unsuccessful. The answer might lie in the presence of aggregation-prone proteins with the propensity to sequester REST in the cytosol and prevent nuclear translocation. Indeed, REST sequestration in Lewy and pale bodies and autophagosome-mediated degradation is observed in PD and AD, both diseases in which nuclear REST translocation is unsuccessful (Kawamura et al., 2019; Lu et al., 2014). Furthermore, Meyer et al. (2019) recently proposed that the failed nuclear translocation of REST is caused by disease-related disruption of the nuclear lamina, using induced pluripotent stem cells (iPSCs) derived from patients with sporadic AD (Meyer et al., 2019).

These findings strongly suggest that REST has the ability to maintain neuronal homeostasis during healthy ageing, as loss of the transcriptional repressor from the neuronal nucleus is observed in various neuropathological disorders. However, many questions remain regarding REST expression levels in the ageing field, e.g. can modulation of REST protect against brain ageing?

4. REST-modulating treatments

As discussed, REST has an important role in maintaining neuronal homeostasis following internal and external insults, through the regulation of neuronal hyperexcitability, maintenance of the adult stem cell pool and adaptation of synaptic signalling. Furthermore, REST appears to be a critical modulator of the neuroendocrine stress response. Whilst its involvement in regulating physiological stress responses is still being explored, increased levels of nuclear neuronal REST appear to be mostly beneficial in the ageing population. However, to add to the controversy surrounding the protective properties of REST, various therapies that dampen REST activity were found to be neuroprotective, especially following ischaemia (Calderone et al., 2003). Most ischaemia-related studies report that REST knockdown either using shRNA, lentiviral-mediated dnREST delivery, or decoy antisense oligodeoxynucleotides (ODNs) prevented ischaemia-induced

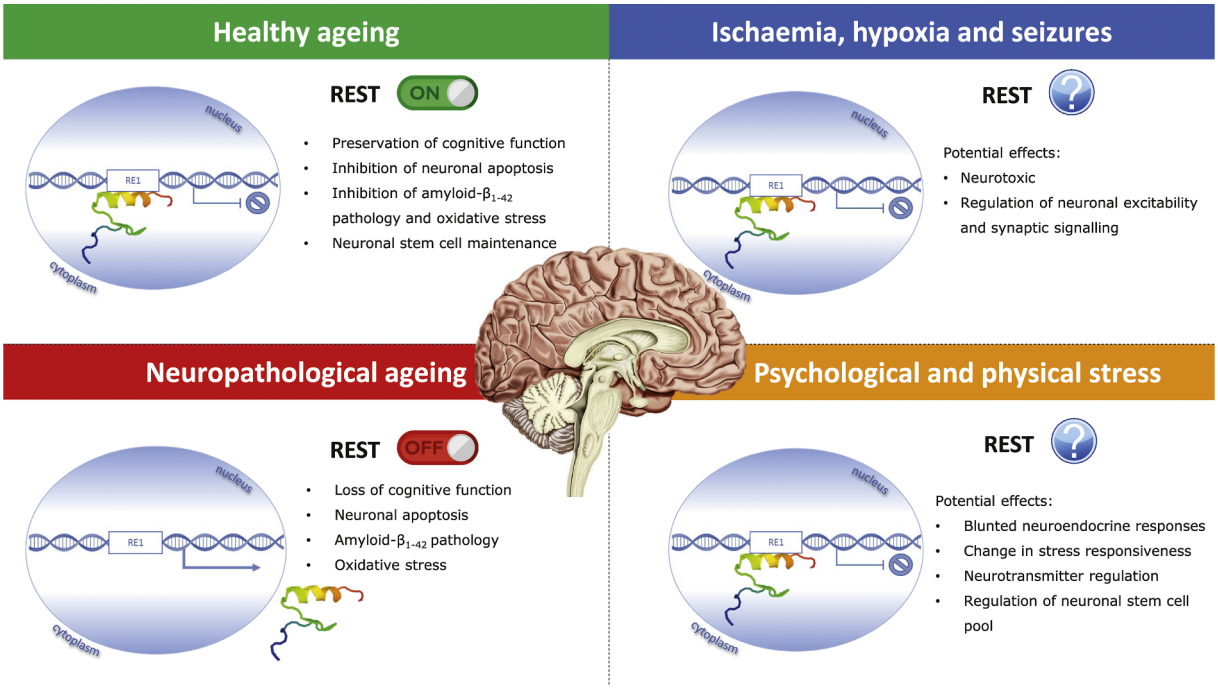

Fig. 5. An overview of our current understanding of REST's ability to modulate neurophysiological responses toward stressful insults. REST has the ability to modulate the neurophysiological stress response through epigenetic repression of neuronal genes. The genes targeted are dependent on the context and regulate functions such as synaptic plasticity and excitability, maintenance of the adult stem cell pool, and the neuroendocrine stress response. However, regulation of REST is complex and its activity is strongly dependent on a variety of factors, including the stimulus and cell-type, its cellular localisation, the splice variants present and their chromatin binding affinities, cooperation with other transcriptional co-factors, and the accessibility of its target genes. Currently, experimental data suggests that nuclear translocation of REST during healthy ageing is beneficial and may inhibit neuronal apoptosis, amyloid-$\beta_{1\text{-}42}$ pathology and oxidative stress. Correspondingly, loss of nuclear REST is associated with neuropathological ageing and neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. Following ischaemia, hypoxia and epileptic seizures, however, REST's effects are less clear. Whilst REST is thought to contribute to neurotoxicity following ischaemia, hypoxia and seizures, it has also been reported that REST can promote neurophysiological homeostasis through the regulation of neuronal excitability and synaptic signalling. Similarly, REST responds to psychological and physical stressors, but its downstream effects, including modulation of the neuroendocrine response and regulation of the neuronal adult stem cell pool, currently remain unknown.

neuronal death, improved associated memory deficits or prevented epigenetic modification of REST target genes (Calderone et al., 2003; Hwang et al., 2014; Noh et al., 2012; Patterson et al., 2017). Again in contrast, REST-directed miRNA therapy was also suggested to play a crucial role in the discovery of therapy for prion-related neuropathologies, as overexpression of REST in primary cortical neurons alleviated prion disease-induced oxidative stress and mitochondrial damage in neurons (Shah et al., 2018; Song et al., 2017).

Most of these strategies, however, are limited by the rapid degradation of the decoy modulators and unwanted side-effects. Recently, Paonessa et al. (2016) developed an optogenetic strategy to modulate REST expression. They created two photo-switchable chimeras to target the REST-interacting sequence of the corepressor mSin3a (PAH1) or the active domain of REST-interacting LIM domain protein (RILP/PRICKLE1). REST physiology was controlled by altering assembly of the corepressor complex and by REST binding to the DNA. The effects of the optogenetic approach are reversible, can be fine-tuned long-term, and interfere with REST function without affecting its expression (Paonessa et al., 2016). Furthermore, activation of the cAMP responsive pathway using 8-Br-cAMP was shown to cause a temporal downregulation of REST (Kreouzis et al., 2018). Potentially, this mechanism is modulated by SP1, as SP1 is a transcriptional regulator of REST (Ravache et al., 2010; Zhang et al., 2007). It is known that protein kinase A (PKA) activation tags SP1 for degradation following 8-Br-cAMP mediated phosphorylation of SP1. Therefore, inhibition of the cAMP pathway could serve as a potential way of enhancing REST activity (Kreouzis et al., 2018).

Interestingly, neuron-derived exosomes (NDEs) in plasma were found to accurately predict neuronal REST levels, which may act as a biomarker for the prediction and staging of MCI and AD (Winston et al., 2016). Similarly, Ashton et al. (2017) recently identified REST protein levels in neuronally-derived microvesicles in the blood as a biomarker for cognitive decline and AD. REST protein levels in the blood were found to be psychologically-modifiable through a mindfulness-based stress reduction intervention, which led to an increase in blood REST levels and a reduction in anxiety and depression (Ashton et al., 2017).

5. Conclusion

As the key regulator of epigenetic neuronal gene expression, REST determines which genes are targeted in response to stress. The protein was found to orchestrate experience-dependent neuronal plasticity and synaptic remodelling to fine-tune neuronal gene expression that shapes neuronal homeostasis following stressful experiences. Overall, it appears that REST is highly responsive towards internal and external stressors in the young and ageing neuron. However, the exact downstream effects remain to be elucidated. As REST function is strongly dependent on the stimulus and cell-type, in addition to its cellular localisation, the splice variants present and their chromatin binding affinities, its cooperation with other transcription factors and co-factors, and the accessibility of its target genes; more research is needed to fully contextualise the involvement of REST in mediating neurophysiological stress responses (Bruce et al., 2004; Chen and Miller, 2018; Mortazavi et al., 2006; Satoh et al., 2013; Yu et al., 2011; Zhao et al., 2017; Zheng et al., 2009).

For now, we know that REST has the ability to regulate the neurophysiological response towards stressful stimuli through various mechanisms. REST can regulate the neuroendocrine stress response

through its ability to repress *Crh*, *5htr1a*, *Tph2* and *Bdnf,* amongst other genes. Furthermore, REST has a context-dependent role to maintain quiescence of NSCs in the adult stem cell pool, can prevent premature stem cell differentiation and can protect against premature NSC depletion. REST was also found to regulate neuronal excitability, through the modulation of Ca^{2+} homeostasis and ion channel activity. In general, these studies indicate that REST is responsive to intrinsic and extrinsic stressors and, more importantly, can restore neuronal homeostasis. Furthermore, whilst REST nuclear translocation was shown to maintain neuronal homeostasis during healthy ageing, loss of the transcriptional repressor from the neuronal nucleus is observed in various neuropathological disorders, preventing the protein from exerting its epigenetic protective function (Fig. 5).

Therefore, modulation of neuronal REST could be a promising therapeutic strategy to promote neuronal homeostasis and adaptation following stressful insults, especially in the ageing population. However, many issues regarding the role of REST's various splice variants, the downstream implication of REST's associated cofactors, and the importance of the stimulus for REST nuclear translocation remain. Addressing these obstacles will help to elucidate the intricate characteristics of neuronal REST expression and downstream gene regulation in the young and ageing brain.

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Competing interests statement

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