

REST/NRSF TARGET GENES IN NEURONAL AND BETA CELLS: PATHOPHYSIOLOGICAL AND THERAPEUTIC PERSPECTIVES FOR DIABETES AND NEURODEGENERATIVE DISORDERS

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ABSTRACT

Pancreatic beta and neuronal cells share numerous similarities, including a key transcriptional mechanism of the differentiation programme. The mechanism involves the decrease or the extinction of the transcriptional repressor RE-1-silencing transcription factor (REST), also called neuron-restrictive silencer factor (NRSF), which leads to the expression of various genes encoding proteins required for mature beta and neuronal cell function. Abnormal expression and genetic variation in some of the REST/NRSF target genes have been reported in diabetes and neurodegenerative disorders, suggesting that common pathogenic mechanisms account for beta-cell decline and neuronal degeneration in the two diseases. In addition, some of the REST/NRSF target genes have been identified as potential therapeutic targets for improvement of beta-cell function in diabetes. This review sheds light on the neuronal and beta-cell REST/NRSF target genes that are potential future drug targets for the treatment of diabetes and neurodegeneration.

Keywords: Neuron, pancreatic beta cell, RE-1-silencing transcription factor (REST), neuron-restrictive silencer factor (NRSF), insulin, diabetes, Alzheimer's disease (AD), neurodegeneration.

INTRODUCTION

The link between diabetes mellitus and some forms of dementia, such as Alzheimer's disease (AD), has become irrefutable. Patients with Type 2 diabetes are more predisposed to the development of AD than individuals without diabetes.^{1,2} Conversely, AD patients have a higher chance of developing diabetes than the elderly without dementia.³ AD and diabetes are characterised by perturbed glucose metabolism in the brain and pancreas and increased cell death,³ leading to neuronal and pancreatic islet beta-cell dysfunction. These similar pathological features are supported by a large number of similarities between neuronal and beta cells. Indeed, despite a disparate embryonic origin, these two cell types are equipped with similar machineries involved in the secretory function and the control of apoptosis.⁴⁻⁷ These similar tasks are thought to occur during differentiation via

a transcriptional mechanism involving the RE-1-silencing transcription factor (REST) transcriptional repressor, otherwise known as neuron-restrictive silencer factor (NRSF). While REST/NRSF is widely expressed elsewhere in the body, the expression of REST/NRSF is extinguished in mature beta cells.^{4,6} Thus, the absence of REST/NRSF allows the expression of numerous genes playing a role in survival, metabolic, and secretory pathways of mature beta cells.^{4,6,8} Abundant expression of REST/NRSF target genes is also found in neuronal cells, although, unlike in beta cells, the expression of REST/NRSF is detectable.⁹ The present review provides insights into the role of REST/NRSF target genes in the regulation of survival, metabolic, and secretory pathways in beta and neuronal cells, as well as their contribution to neurological and metabolic disorders.

RE-1-SILENCING TRANSCRIPTION FACTOR/NEURON-RESTRICTIVE SILENCER FACTOR

REST/NRSF is a Gli-Krüppel-like zinc finger transcription factor.¹⁰ Although the expression level of REST/NRSF is highly variable, it is widely expressed in most tissues of adult mice. In adult rats and mice, the lowest level of REST/NRSF mRNA is detected in the central nervous system (CNS) and pancreas, whereas the highest expression of the factor is found in tissues including the thymus, placenta, uterus, and oocytes.^{4,10-12} REST/NRSF prevents or attenuates the transcription of its target genes. This is achieved by binding to a 21-bp RE-1 binding site/neuron-restrictive silencer element (NRSE) that is present in the regulatory regions.¹⁰ The NRSE sequence, localisation, and orientation vary within target genes.¹³ These differences may modulate promoter activity even if, in any case, repression is achieved.^{13,14}

REST/NRSF represses the expression of its targets via a mechanism involving chromatin modification and promoter methylation.¹⁵⁻¹⁸ REST/NRSF target genes have been identified, with the first set of target genes found by comparing the putative sequence targets from the GenBank database with a composite NRSE derived from a few identified REST/NRSF targets.¹⁹ The study led to the identification of 22 targets,¹⁹ although this list of targets has subsequently been extended. The combination of *in silico* searches with biochemical studies has led to the identification of 892 and 944 bona fide human and mouse NRSEs, respectively, among the thousands of putative targets found within each whole genome.²⁰ A comparative analysis of the NRSEs between species using a profile-based approach has refined the number of NRSE sites.¹² Thus, 895 NRSE sites conserved in human, mouse, rat, and dog (with an estimated false-positive rate of 3.4%) have been identified.¹² Other independent studies have used biochemical approaches to confirm the regulation of these targets by REST/NRSF.²¹

The regulation of NRSE-containing genes by REST/NRSF further varies within different cell types. REST/NRSF is expressed in human embryonic stem cells (ESCs) and ESC-derived neurons.²² Genome-wide data mining from ChIP-Seq datasets have identified 2,172 REST/NRSF targets in human ESCs, whereas 308 targets are found in ESC-derived neurons.²² These data suggest that the

binding of REST/NRSF to the NRSE relies on cell-dependent transcriptional cofactors and genomic and/or epigenomic context. Conversely, the precise number of REST/NRSF target genes expressed by cells in which REST/NRSF is absent or inactive (e.g. the pancreas and CNS) is unknown. This limitation results from the inadequacy of the technique used to immunoprecipitate REST/NRSF for ChIP-Seq analysis while the endogenous REST/NRSF is absent or almost undetectable. Nevertheless, the bioinformatics and biochemical analyses indicate that numerous targets are present in neuronal and beta cells, in which most of them share similar roles. The content below describes some of the targets and their implications in neuronal and beta cells.

REST/NRSF TARGET GENES ARE INVOLVED IN NEURONAL AND BETA-CELL DIFFERENTIATION

Evidence of a role for REST/NRSF target genes in neuronal cell differentiation comes from *in vitro* and *in vivo* studies in which the expression of REST/NRSF has been manipulated. REST/NRSF is expressed in neural stem cells (NSCs),²³ with the expression of the repressor required for repressing neuronal targets and for maintaining NSCs in an undifferentiated state.²³ Activation of REST/NRSF target genes via the introduction of dominant-positive REST/NRSF into NSCs is sufficient to promote neuronal differentiation. Conversely, abnormally elevated expression of REST/NRSF in NSCs may contribute to cerebellum-specific tumours by blocking neuronal differentiation.²³ Inactivation of REST/NRSF may reactivate differentiation and block the tumourigenic potential.²³ REST/NRSF expression is also abnormally elevated in medulloblastoma cells.²⁴ Countering the function of REST/NRSF de-represses the expression of neuronal genes and triggers apoptosis of the tumour cells.²⁴ REST/NRSF is highly expressed in ESCs,^{25,26} with a decrease in the level of REST/NRSF coinciding with the differentiation of these cells into mature neurons.^{25,26} Mutant animals with a conditional and CNS-specific knockout of REST/NRSF display an increase in neurogenesis.^{27,28} However, abnormal activation of REST/NRSF target genes outside neuronal cells perturbs embryo development and leads to early embryonic lethality.^{29,30} Suppression of REST/NRSF expression by genetic disruption of the gene in mice leads to forebrain malformation, disorganisation of the midbrain, and a widespread

apoptosis, which ultimately leads to death at embryonic day 11.5 (E11.5).^{29,30} Some key REST/NRSF targets involved in neuronal development have been identified and are listed in [Table 1](#).

Table 1: REST/NRSF target genes that control neuronal and islet cell differentiation.

Gene name	Beta cells and endocrine cells		Neurons		References
	Role	Targets	Role	Targets	
<i>Ascl1</i>	Endocrine differentiation	Neurogenin 3	Neurogenesis	Dlx2, Sox4, Ebf3, Gli3, Nf1b, NeuroD4, Ap3b2, Mcf2l, Nrnx3	12, 60, 61
<i>DLX6</i>	ND	ND	Differentiation of interneuron progenitors	Wnt5a	12, 62
<i>HNF4a</i>	Beta-cell replication	Ras/ERK signalling	Neural stem cell differentiation	Rho-GDP dissociation inhibitors	12, 63, 64
<i>LMX1A</i>	Beta-cell differentiation	Insulin	Dopamine-cell differentiation		12, 65, 66
<i>miR9</i>	Beta-cell terminal differentiation – differentiation of mesenchymal stem cells into beta cells	Onecut2	Neuronal fate	TLX, Foxg1, Gsh2, SIRT1	12, 65, 67, 68
<i>miR124</i>	Early pancreas development and beta-cell terminal differentiation	Foxa2	Neuronal fate	PTBP1, Sox9, SCP1, Ephrin-B1, JAG1, BAF53a, SP1	12, 65, 69, 70
<i>NeuroD1</i>	Endocrine differentiation and maintenance of differentiated phenotype of mature islet cells	PDX1, Pax4, Pax6, Nkx2.2, Nkx6.1, Hlxb9, insulin	Central nervous system and sensory nervous system development	Brn3d, IP3R, Ebf3	12, 65, 71, 72
<i>NeuroD2</i>	Endocrine lineage genes	Pax4, IAPP, glucokinase, somatostatin, tweety1	Neuronal differentiation	Zfhx1a	12, 73, 74
<i>NeuroD4</i>	ND	ND	Neuronal differentiation in the hindbrain	NOTCH ligands Dll1 and Dll3	12, 75
<i>Neurogenin3</i>	Endocrine lineage specification	NeuroD1, NeuroD2, NeuroD4	Differentiation of NPY, POMC, NPY, TH neurons	NeuroD1, Nhlh2	65, 76, 77
<i>Onecut1</i>	Early endocrine development	PDX-1, Onecut3	Retina development	Lim1, Prox1	12, 78, 79
<i>Pax2</i>	Size and number of islets	Glucagon	Mid and hindbrain development	Brn1, En2, Sef, Tapp1, <i>Ncrms</i>	12, 80, 81
<i>Pax4</i>	Endocrine lineage beta and delta-cell specification	Insulin, Glut2, Mafa	Retinal photoreceptor development	ND	12, 82, 83
<i>Sox2</i>	Pluripotent pancreatic stem cells	Oct-3/4, Nanog, FGF-4	Neurogenesis	Jag1, Gli3, Mycn	12, 84, 85

ND: not determined; REST: RE-1-silencing transcription factor; NRSF: neuron-restrictive silencer factor.

Similarly to neurons, REST/NRSF is present in pancreatic progenitors but is expressed at a very low level in the mature pancreas.^{12,31-33} However, the repressor is not detectable in various insulin-producing cell lines,^{4,6,34} suggesting that a decrease of REST/NRSF expression is required for endocrine cell differentiation.³² Several data support this hypothesis: firstly, suppression of REST/NRSF in mesenchymal stem cells contributes to the expression of beta-cell differentiation markers, including Neurogenin3 and NeuroD1, and programming into insulin-secreting cells;³⁵ secondly, forced expression of the repressor in progenitor cells reduces the number of endocrine-committed progenitors by E14.5 and ultimately diminishes the numbers of glucagon-positive and insulin-positive cells in E18.5 pancreas.³² This finding is in line with a report showing a Polycomb-mediated repressive methylation mark within the gene coding for REST/NRSF, which coincides with the activation of a core beta-cell de-repression programme.³³ The impact of REST/NRSF targets in beta cells has been further unveiled by beta-cell-specific overexpression of REST/NRSF in mice.⁸ These transgenic mice display reduced plasma insulin levels and develop glucose intolerance.⁸ Diminution of insulin production is associated with a reduced number of beta cells,⁸ with the decrease in insulin expression and beta cells possibly resulting from impaired beta-cell differentiation.⁸ Some pieces of evidence may confirm this hypothesis. Numerous REST/NRSF targets, transcription factors, and microRNAs are involved in beta-cell differentiation (Table 1). Interestingly, these genes are also involved in neuronal cell development and indicate that neurons and beta cells share a similar developmental programme.

REST/NRSF TARGET GENES ARE INVOLVED IN NEURONAL AND BETA-CELL SECRETORY FUNCTION

The very low expression and absence of REST/NRSF in mature neuronal and beta cells, respectively, underlines a role for the target genes in the specialised secretory function of these two cell types. One of the earliest identified REST/NRSF target genes was the regulator of synaptic transmission synapsin I.³⁶⁻³⁸ In neurons, synapsin I is localised to the surface of small synaptic vesicles.³⁹ Synapsin I interacts with Rab3a and the cytoskeleton, and thereby tethers vesicles in a storage pool away from presynaptic release

sites.⁴⁰ Besides small synaptic vesicles, neuronal cells have dense-core vesicles (DCVs) filled with neuropeptides, neurotrophic factors, and other modulatory substances.⁴¹ The DCVs secrete their contents from synaptic and extrasynaptic regions of axons and dendrites in response to calcium influx. Secretion by DCVs requires the soluble N-ethylmaleimide-sensitive-factor attachment protein receptor (SNARE) proteins, including the t-SNAREs, synaptosomal-associated protein 25 (SNAP25), syntaxin 1a, and the v-SNARE vesicle-associated membrane protein 2 (VAMP2).⁴¹ SNAP25 and syntaxin 1a are REST/NRSF target genes.¹² In PC12 cells and astrocytes in which REST/NRSF is highly expressed, the expression of SNAP25 and syntaxin 1 is almost undetectable.⁴² Inactivation of REST/NRSF de-represses the expression of the two secretory machinery proteins and allows regulated DCV exocytosis.⁴² Some of the REST/NRSF target genes controlling neuronal secretion are listed in Table 2. Many of these genes play a crucial role in the regulation of glucose-induced insulin secretion. Downregulation of their expression by overexpression of REST/NRSF in beta cells hampers insulin secretion.^{8,34}

REST/NRSF TARGET GENES ARE INVOLVED IN SURVIVAL AND DEATH OF NEURONAL AND PANCREATIC BETA CELLS

There is growing evidence indicating that REST/NRSF confers either protection or death in neuronal and beta cells. The expression of REST/NRSF is detectable in the rat hippocampal CA1 pyramidal neurons,⁴³ and the level of expression increases and promotes apoptosis in response to ischaemia insults.⁴³ REST/NRSF is also expressed in the neurons of the prefrontal cortex,⁹ but, unlike hippocampal CA1 neurons, the expression of the repressor is protective against pro-apoptotic stimuli, stress, and neurodegenerative disorders such as AD.⁹ The level of REST/NRSF expression increases during normal ageing,⁹ with the rise in REST/NRSF expression associated with a reduction in expression of many pro-apoptotic targets.⁹ However, the expression of REST/NRSF decreases in the prefrontal cortex of AD patients compared with healthy and age-matched individuals.⁹

The neuronal destruction in AD has been associated with an increase in the pro-apoptotic targets⁹ (Table 3), which underlines a role for REST/NRSF in the molecular pathogenesis of AD.⁹

Table 2: REST/NRSF target genes that control neuronal and beta-cell secretion.

Gene name	Beta cells	Neurons	References
	Role	Role	
<i>Cplx 1 and 2</i>	Docking and regulation of vesicles/ membrane fusion	Docking and regulation of vesicles/ membrane fusion	8, 86
<i>Cx36</i>	Gap junction in lipid raft domains of beta-cell membrane, exchange of cationic molecules, gene expression	Electrical activity	87, 88
<i>GRIN1</i>	Inhibits glucose-induced insulin secretion	Adrenaline and dopamine release	12, 59, 89
<i>MAPK8IP1</i>	Regulation of the glucose transporter Glut2 expression	Regulation of the motor cargo and vesicles transport	6, 9
<i>miR9</i>	Regulates granuphilin and insulin exocytosis	Regulates vesicle transport by MAP1B, BK	67, 90
<i>miR29a, miR29b</i>	Regulates expression of MCT1 and Onecut2	Regulates expression of MCT1 and Onecut2	12, 67
<i>Onecut2</i>	Regulates granuphilin gene expression	ND	90
<i>Snap25</i>	Fusion of insulin-containing vesicles	Fusion of clear and dense-core vesicles	8, 12, 42
<i>Syt2</i>	Binds calcium and regulates glucose- stimulated insulin secretion in a cell line	Calcium sensor for rapid neurotransmitter release	12, 91
<i>Syt4</i>	Regulates glucose-induced insulin secretion	Regulates calcium-dependent exocytosis	12, 91
<i>Syt6</i>	ND	Fusion of synaptic vesicles	12, 92
<i>Syt7</i>	Binds calcium and regulates glucose- stimulated insulin secretion	Calcium sensor for rapid neurotransmitter release	12, 91
<i>Syt14</i>	ND	ND	12
<i>Syn1</i>	Not required for glucose-induced insulin secretion in islets	Neurotransmitter release	12, 93
<i>Syn3</i>	ND	Neurotransmitter release	12, 94

ND: not determined; REST: RE-1-silencing transcription factor; NRSF: neuron-restrictive silencer factor.

Table 3: REST/NRSF target genes that control neuronal and beta-cell apoptosis rate.

Gene name	Beta cells	Neurons	References
	Role	Role	
<i>BAX</i>	Apoptosis	Apoptosis	9, 12, 95
<i>BBC3</i>	Apoptosis	Apoptosis	9, 12, 96
<i>BID</i>	Apoptosis	Apoptosis	9, 12, 97
<i>Cx36</i>	Survival	Apoptosis	87, 88
<i>FADD</i>	Apoptosis	Apoptosis	9, 98
<i>FAS</i>	Apoptosis	Apoptosis	9, 99
<i>MAPK8IP1</i>	Survival	Survival/Apoptosis	9, 100
<i>MAPK10</i>	Survival	Apoptosis	52, 56, 101
<i>MAPK11</i>	Survival	Apoptosis	9, 102
<i>MAPK12</i>	ND	Apoptosis	9
<i>miR-29a</i>	Apoptosis	Survival	12, 103
<i>TRADD</i>	Apoptosis	Apoptosis	9, 98

ND: not determined; REST: RE-1-silencing transcription factor; NRSF: neuron-restrictive silencer factor.

Therefore, within different brain regions and neuronal subtypes, REST/NRSF is capable of triggering opposite cellular outcomes upon exposure to stressful stimuli. This observation suggests that REST/NRSF target genes are differentially expressed within neuronal subtypes via a mechanism that is independent of REST/NRSF. A lack of balance between the levels of pro-apoptotic and pro-survival REST/NRSF target genes may account for either the protection or apoptosis of neurons. Another mechanism through which REST/NRSF may direct cell outcome is dependent on its subcellular localisation: although REST/NRSF is a nuclear transcription factor, the repressor is found in the cytosol of striatal and cortical neurons.⁴⁴ The cytosolic localisation of REST/NRSF relies on huntingtin, which interacts with and thereby sequesters the repressor within the cytosol.⁴⁴ In Huntington's disease (HD), mutant huntingtin dissociates from REST/NRSF and leads to the repressor's nuclear translocation and neuronal dysfunction via a decrease in the transcription of brain-derived neurotrophic factor.⁴⁴

In pancreatic beta cells, the absence of REST/NRSF is required for survival:⁴⁵ the decrease in the number of beta cells caused by increased apoptosis in transgenic mice with beta-cell-specific overexpression of REST/NRSF argues in favour of this statement.⁴⁵ The expression of targets involved in the survival of beta cells is greatly reduced within the islets of the mutant animals, suggesting that the majority of REST/NRSF targets expressed in beta cells are required for beta-cell survival. These targets include the gap junction protein connexin 36 and some components of the mitogen-activated protein kinase pathways, such as MAPK8IP1 (islet brain 1), MAPK10 (JNK3), and MAPK11 (p38a) (Table 3); it is noteworthy that these same targets have been described as leading to apoptosis in neuronal cells. This underlines a possible divergence in the mechanisms orchestrating the survival and apoptosis signals in neuronal and beta cells.

CONCLUSION AND PERSPECTIVE

The identification of REST/NRSF target genes has unveiled the striking similarities between neuronal and islet beta cells in numerous processes, including development and cellular function. These targets can therefore be considered as common markers for neuronal and beta-cell differentiation from stem cells. Some of the targets are also instrumental in

regulating key apoptotic and survival signalling pathways in neuronal and beta cells. These genes can contribute to neuronal and beta-cell death in AD and diabetes. The pathogenesis of the two diseases is multifactorial and includes a genetic component. The REST/NRSF target genes are candidates for mutations associated with the development of diabetes and AD, as illustrated by MAPK8IP1. Some individuals who are carriers of a loss-of-function mutation found within the coding region of *MAPK8IP1* develop a rare and monogenic form of diabetes.⁴⁶ Conversely, a gain-of-function mutation within the promoter region of the same gene has been associated with AD.⁴⁷

Accumulation of MAPK8IP1 has been found within beta-amyloid deposits in degenerated neurons,⁴⁸ suggesting a role for this protein and other REST/NRSF targets in neuronal degeneration caused by amyloid deposits. The increase in MAPK8IP1 content within the neurons of AD patients may be the consequence of an increased mRNA level caused by a reduction in REST/NRSF expression.⁹ The restoration of REST/NRSF expression or the blocking of its key apoptotic target genes may be a therapeutic target for combating neurodegeneration in AD. Similar to neurons in AD, pancreatic islets of diabetic patients are characterised by deposition of amyloid aggregates, which may contribute to islet beta-cell decline and therefore aggravation of diabetes over time.^{48,49} In both diabetes and AD, amyloid deposits result from complexes of amyloid oligomers that include beta amyloids.^{48,50} Some REST/NRSF targets may account for the formation of beta amyloid and deposits. These targets include MAPK8IP1, MAPK10, and the γ -secretase component presenilin 1.^{12,48,50-52} In beta cells, amyloid aggregation can be blocked by the glucagon-like peptide 1 receptor agonist exenatide.⁵³ The use of GLP-1 mimetics has been shown to protect beta cells against apoptosis induced by a large number of stimuli, including cytokines.^{54,55} The mechanism through which these GLP-1 mimetics achieve cytoprotective effects in beta-cells implicates the anti-apoptotic REST/NRSF target genes MAPK8IP1 and MAPK10.^{54,56} It is possible that the effect of GLP-1 mimetics on amyloid aggregation relies on these two REST/NRSF targets and therapeutic strategies able to promote the expression of both targets may be valuable for improving functional beta-cell viability in diabetes.

There are some diseases, however, in which the decline of cells is associated with an increase in

REST/NRSF activity and the subsequent decrease of its targets. This is exemplified by HD, in which the nuclear activity of REST/NRSF contributes to neuronal dysfunction and death. This suggests that inhibition of the repressor activity could be a therapeutic strategy in some cases. In this respect, the identification of a benzimidazole-5-carboxamide derivative (X5050) that promotes the degradation of REST/NRSF and, consequently, the induction of its targets within human NSCs could be promising.⁵⁷ Other methods of inducing expression of REST/NRSF target genes could involve microRNAs (miRNAs). Expression of REST/NRSF target genes has been monitored in mice with beta-cell-specific knockout of the key ribonuclease for biogenesis of miRNAs, Dicer1.⁵¹ Additional strategies for stimulating the expression of REST/NRSF target genes may consist of triggering alternative splicing isoforms of REST/NRSF. The gene encoding REST/NRSF gives rise to several alternative mRNAs,⁵⁸ and one of these produces the dominant-positive REST4, which antagonises the activity of the full-length gene

product.⁵⁸ A mechanism involving the neural-specific Ser/Arg repeat-related protein of 100 kDa transcriptional activator has been identified as leading to the induction of REST4 expression.⁵⁸ Activation of this mechanism could be a promising strategy for blocking the repressor activity of REST/NRSF in diseases such as HD.

The identification of REST/NRSF target genes may enable the discovery of novel drug targets that will slow the progression of diabetes by improving insulin secretion and/or by preventing beta-cell destruction. The proof-of-concept has recently been validated for the NMDA receptor. GRIN1 is a subunit of the NMDA glutamate receptor complex that negatively regulates insulin secretion.⁵⁹ Antagonising the NMDA receptor improves glucose-induced insulin secretion and glucose tolerance in individuals with Type 2 diabetes.⁵⁹ If the REST/NRSF targets have similar roles in neurons and beta cells then there will be good reason to believe that the therapeutic strategy would be useful in the treatment of both diabetes and neurodegenerative disorders such as AD.

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