Review
Cracking the Code of Neuronal Cell Fate

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Abstract: Transcriptional regulation is fundamental to most biological processes and reverse-engineering programs can be used to decipher the underlying programs. In this review, we describe how genomics is offering a systems biology-based perspective of the intricate and temporally coordinated transcriptional programs that control neuronal apoptosis and survival. In addition to providing a new standpoint in human pathology focused on the regulatory program, cracking the code of neuronal cell fate may offer innovative therapeutic approaches focused on downstream targets and regulatory networks. Similar to computers, where faults often arise from a software bug, neuronal fate may critically depend on its transcription program. Thus, cracking the code of neuronal life or death may help finding a patch for neurodegeneration and cancer.

Keywords: apoptosis; neurotrophic factors; survival; transcriptional analysis; drug targets; drug repurposing; functional enrichment; regulatory network; neurological disease

1. Introduction

A central focus in neurobiology and neurology is the study of neuronal survival and apoptosis, two processes that guarantee the appropriate development of the central nervous system (CNS) and its homeostatic maintenance throughout adulthood. During development, in fact, the brain produces more neurons that will eventually survive, and the interplay of pro-apoptotic and pro-survival signal is essential for sculpting the nervous system. Following this developmental window, inappropriate activation of these mechanisms can contribute to the development of pathological conditions, such as brain tumors and neurodegenerative diseases [1–3].

Similar to computers, where faults often arise from malfunctioning software, neuronal fate critically depends on its programs. The ability of neuronal cells to promote or evade apoptotic cell death, in fact, does not depend by the expression or activity of a single gene/protein (hardware), but is regulated by a transcriptional program that is activated by different extracellular signals, including the absence or presence of neurotrophic factors (NFs) [4].

Although several studies have investigated the contribution of individual genes at the crossroad of apoptosis and survival signaling pathways, the complex and coordinated temporal transcriptional programs that orchestrate neuronal cell fate decisions remain mostly unknown. Thus "cracking" the code of neuronal life or death may not only provide new insights into the sophisticated cellular and molecular events underlying these processes but, more importantly, may help finding new treatment strategies for neuronal degeneration and cancer.

The advances in the field of omics technologies, together with the increase in knowledge and research of computational analysis and modeling of neuronal networks are now offering a systems biology-based approach to experimentally interrogate the complexity of transcriptional programs controlling neuronal apoptosis and survival and their malfunctions, offering a novel strategy to modulate these cell states. In this review, we will describe

how portraits of whole-genome expression analysis coupled to reverse engineering of regulatory networks are beginning to decode the complex transcriptional programs underlying neuronal cell fate and the implication of their perturbation in human pathology, which are paving the way to innovative therapeutic approaches focused on downstream targets and regulatory networks.

2. Systems Biology Approaches to Explore the Transcriptional Programs Underlying Neuronal Apoptosis and Survival

Neuronal turnover is not a static process and both survival and apoptosis rely on transcription. The condition for *de novo* gene expression and the activation of a "suicide" transcriptional program during neuronal apoptosis was postulated about four decades ago [5–9]. During the years, multiple genes or genetic pathways have been implicated in apoptosis; however, our inability to experimentally resolve and interrogate the full spectrum of genes operating in distinct temporal domains and their collective behavior has hampered the progress in this field and we had to wait the development of high-throughput technologies to begin its exploration from a system's biology perspective. The advent of omics technologies has, in fact, dramatically revolutionized the current understanding of the molecular mechanisms mediating neuronal survival and apoptosis and the transition between these two cellular states in a variety of experimental paradigms [10–16].

Despite *in vivo* studies better reproduce human pathology, neurons undergo apoptosis asynchronously and it is difficult to time the sequential transcriptional changes of different cell states. On the other hand, *in vitro* models, although somewhat artificial, allow the study of transcriptional changes in homogeneous neuronal populations undergoing synchronous cell states. Over the past decades, a large number of studies reported whole-genome expression analysis in multiple *in vitro* paradigms of neuronal apoptosis, including cerebellar granule neurons (CGNs), as well as cortical and hippocampal neurons, implying the existence of universal transcriptional mechanisms regulating neuronal cell death [9–21]. Among these experimental paradigms, CGNs represent, both *in vivo* and *in vitro*, the election model for examining the signal transduction mechanisms underlying neuronal apoptosis and survival [5,6,9,20,22–29]. CGNs are the most abundant type of neurons in the mammalian brain and can be cultured *in vitro* up to 98% homogeneity. *In vitro*, CGNs undergo rapid and synchronous apoptotic cell death within 24 h after removal of serum and lowering of extracellular potassium concentration from 25 to 5 mM [9,30]. This cell death paradigm presumably mimics the naturally occurring death of 20–30% of granule cells, which is essential for harmonizing their number with Purkinje cells between the third and fifth week postnatally, whereas its pathological counterpart causes an *in vivo* lesion model of deafferentation in adult rats cerebellar cortex [31,32]. Apoptosis of CGNs requires transcription and protein synthesis and the process becomes irreversible throughout the first 6 hours succeeding its induction. Before this "commitment point", apoptosis of CGNs can be rescued following the activation of specific signal transduction pathways or by the administration of NFs [9,30]. Over the past 20 years, our research groups and others have begun to explore the transcriptional changes during the pre-commitment phase of apoptosis and its rescue by different NFs [6,9,10,22,23,33–42]. Taken together, these studies highlighted that, although distinct NFs exert their survival effects by binding specific receptors and activating a plethora of intracellular second messengers, their signaling pathways share striking similarities and are propagated by common transcriptional cascades, suggesting the existence of a conserved transcriptional program at the intersection of apoptosis and survival.

Beside the evidence of a conserved transcriptional program, the key drivers of neuronal fate transitions remained enigmatic until we shifted our attention to transcriptional regulatory networks. In a recent work, we investigated the dynamic transcriptomic changes occurring during the early commitment phase (0.5 h, 1 h and 3 h) following CGNs apoptosis or their rescue by three different NFs (Pacap, Igf1 and SP). Overlapping these temporal transcriptome profiles, we identified a *core set* of genes (175 genes) exhibiting opposite mRNA

expression trends during neuronal apoptosis and NFs-mediated rescue (Figure 1) [43]. Of note, this *core set* included both rapid and delayed transcriptional changes in response to NFs rescue (Figure 1) [43]. In particular, *core set* genes encoding proteins involved in transcriptional activity, neuronal proliferation and differentiation, exhibited rapid and transient transcriptional activation, suggesting their primary role in the immediate response to NF-treatment (Figure 1) [43]. Among these were genes known for their contribution in the regulation of neuronal development and survival (i.e., *Pak4*, *Ntrk1*, *Twist2*, *Masp2*, *Hoxd9*, *Sstr2*, *Sstr3*, *Tep1*, *Tyrp1*) (Figure 1) [44,45,45–48]. The p21 activated kinase Pak4 plays a pivotal role in neuronal pathophysiology, promoting the activity of transcription factors involved in cell survival, such as Akt and Cepbp and, thus, contributing to a wide range of intracellular processes including cytoskeletal dynamics, neuronal development, axonal outgrowth and neuronal survival [49–51]. Down-regulated expression of *Pak4* has been associated with neurodegenerative disorders, including Amyotrophic Lateral Sclerosis and Parkinson's disease, and it has been proposed as a therapeutic target against cancer and neurodegeneration [52–55]. Nerve growth factor receptor Ntrk1 promotes neuronal survival, proliferation and differentiation in neuronal populations, representing a clinically relevant target in neurology [56–60]. On the other hand, we also observed that delayed early response *core set* genes were, instead, enriched in different cellular processes, including cell adhesion, cytoskeleton organization, metabolic processes and oxidative damage, supporting their role as secondary effectors of the transcriptional program governing neuronal fate decision (Figure 1) [43].
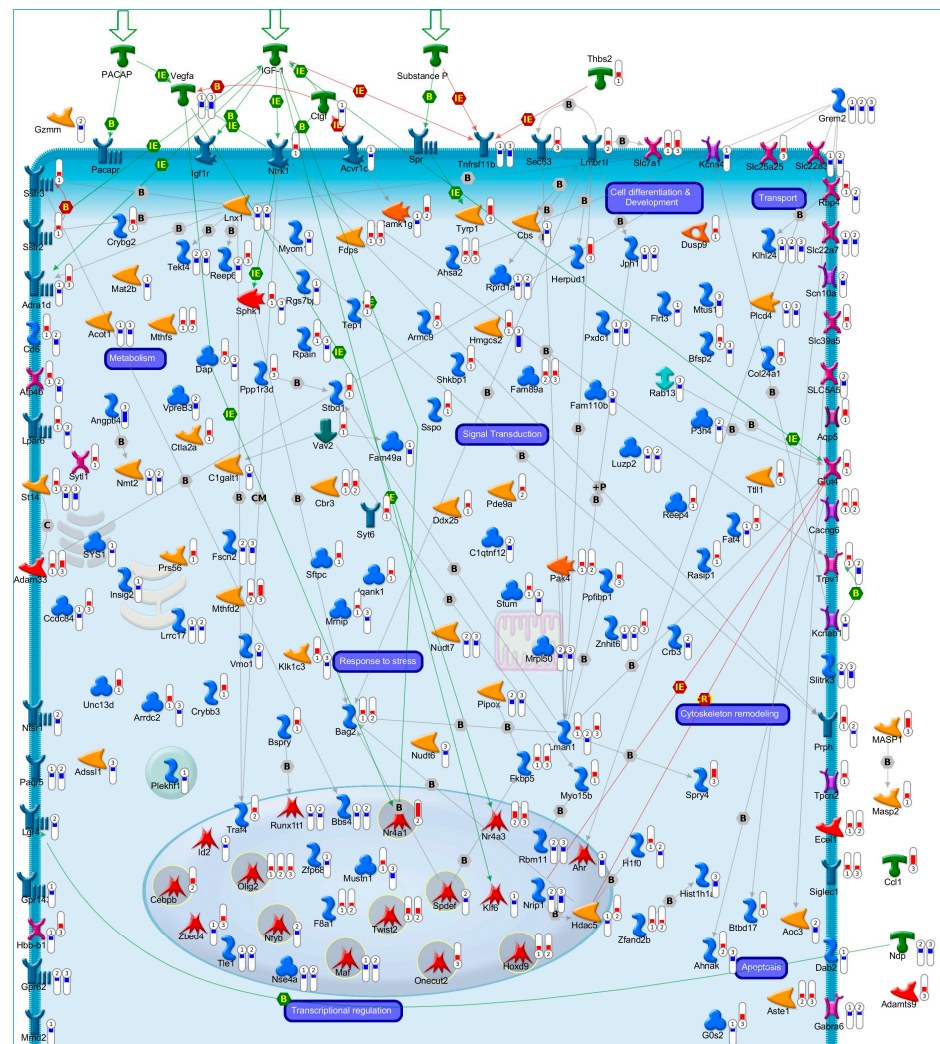

Figure 1. Transcriptional Profiles of Cell Fate Transitions Reveal Early Drivers of Neuronal Apoptosis

and Survival. In our recent work [43], we identified a *core set* of 175 genes exhibiting a significant opposite expression trend during the early commitment phase (0.5 h, 1 h and 3 h) of CGNs apoptosis or its rescue by three NFs (Pacap, Igf1 and SP). The illustrative map shows the biological function and sub-cellular localization of the encoded proteins of *core set* genes. Significant gene expression changes are shown with "thermometer-like" figures. Numbers indicate time points: ① 0.5 h, ② 1 h, and ③ 3 h following induction of CGNs apoptosis and rescue by NFs. For each time-point, the upward thermometers (red) indicate gene transcripts up-regulated by NFs treatment, while downward thermometers (blue) indicate genes down-regulated. The pathway map was created using MetaCore Pathway Map Creator tool (GeneGo). Further explanations are provided at https://portal.genego.com/legends/MetaCoreQuickReferenceGuide.pdf. (accessed on 14 February 2023).

Overall, these findings represent early portraits of the complex and coordinated temporal transcriptional programs underlying apoptosis and its rescue by NFs, further supporting the existence of a conserved transcriptional program governing neuronal life or death.

3. Apoptosis/Survival Switch and Human Diseases: At the Crossroads between Cancer and Neurodegenerative Diseases

As previously mentioned, while elimination of superfluous neuronal cells is essential for normal brain development, dysfunctions in the mechanisms leading to neuronal apoptosis or survival may play a role in different brain pathological conditions, including ischemia, cancer, neurodegenerative and neuropsychiatric disorders. In particular, defects in apoptotic cell death may promote development of brain cancers, while a significant increase in neuronal loss is associated with various psychiatric and neurodegenerative diseases, supporting these conditions may be considered the flip sides of the same coin and may derive from perturbations of the same regulatory mechanisms [4,61–72]. In light of these premises, it appeared evident that investigating molecular mechanisms regulating neuronal cell death or survival can be fundamental to explore the pathogenesis underlying pathological conditions and drive the development of targeted therapies.

To better investigate this aspect, in our previous work, we evaluated the clinical relevance of *core set* genes involved with CGNs apoptosis and survival [43]. Disease enrichment analysis revealed the *core set* genes may be relevant in human pathology since genetic defects in most of them (121/175) have been associated with different human diseases (Figure 2A) [43]. Of particular interest is the significant association of a group of *core set* genes with cognitive/mental diseases (anxiety, attention deficit, schizophrenia, bipolar disorder, depressive syndrome and disruptive behavior disorders), supporting that a dysregulation of these apoptotic-related genes may contribute to the pathophysiology of these disorders (Figure 2A,B) [43,65,73–75]. Among these genes were key transcriptional regulators (e.g., *Ahr, Id2, Nr4a1, Nr4a3, Olig2, Zbed4*), sustaining previous evidence that several severe cognitive disorders are associated with alterations in transcriptional regulatory activity [76–78] (Figure 2B).

The potential contribution of *core set* genes in human pathology was further explored by directly matching the transcriptional changes of *core set* genes with disease-specific gene expression signatures included in the integrative Library of Integrated Network-Based Cellular Signatures (iLINCS, http://www.ilincs.org/ilincs/signatures/main) (accessed on 29 March 2023) [43]. This integrative web-based platform facilitates mining and re-analysis of user-submitted omics signatures in the context of a large collection of pre-computed disease signatures [79]. Our *in silico* analysis showed that *core set* expression patterns overlapped with transcriptional signatures associated with different human diseases, including various types of cancers and neurodegenerative disorders (Figure 2C), further supporting these two disease categories may derive from perturbations of the same regulatory mechanisms and can be considered the flip sides of the same coin [43]. Taken together, these data support the possibility that the early transcription changes associated with CGNs apoptosis and

survival may be conserved in other different cells, tissues and species, thus sustaining the existence of a universal program governing cellular life-and-death processes.
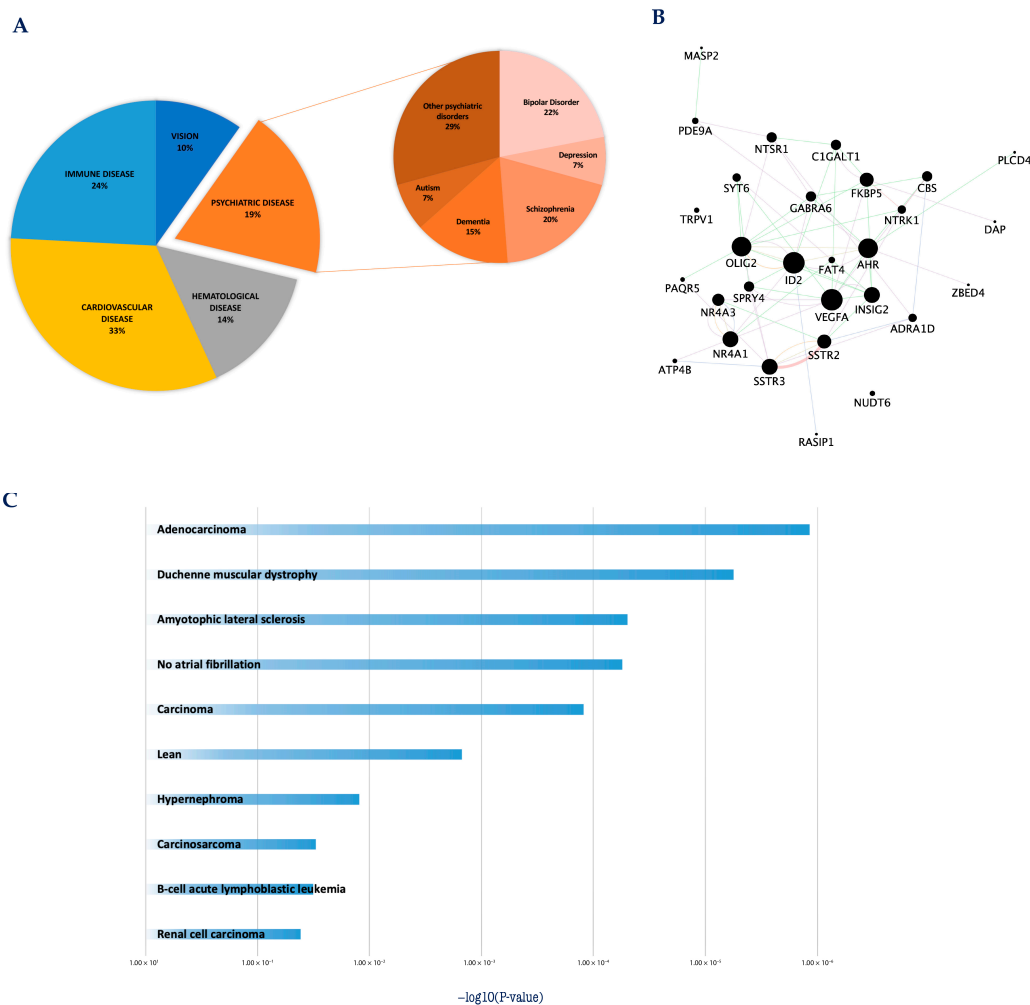
Figure 2. *Core set* genes are involved in the etio-pathogenesis of multiple cancer and neurological disorders. (**A**) Pie chart representation of *core set* genes implicated in human diseases. Disease enrichment analysis was performed with DAVID bioinformatics resources, including OMIM, KEGG DISEASE, and GAD catalogs. (**B**) The protein–protein interaction network of the 29 *core set* genes previously associated with cognitive/mental diseases. The network was built using the STRING website and visualized by Cytoscape (version: 3.8.2), by mapping the 'degree parameter' to node size. As the node size increased, the value of the connectivity degree of node genes increased. Differently colored 'edges' indicate the type of evidence supporting each interaction: dark purple: co-expression; light purple: physical interaction; light blue: co-localization; light green: shared protein domain; orange: predicted; grey: other. (**C**) Histogram of the most significantly enriched transcriptional signatures from iLINCS positively correlated with apoptotic CGN-related expression changes of *core set* genes. The significance of each disease related signature is represented by the enrichment scores value (−log10 (*p*-value)). For more details, please refer to the original work [43].

Given the implication of *core set* genes in human pathology, our findings open the possibility to identify new or already existent therapeutics that are able to modulate their activity. To this regard, we performed a transcriptional signature connectivity analysis in iLINCS to explore repurposing drugs that could revert the expression of the *core set* genes during neuronal apoptosis, representing putatively therapeutically useful candidates [43]. iLINCS, in fact, also includes a comprehensive large-scale drug perturbation databases containing transcriptomic profiles of dozens of cultivated cell lines treated with thousands

of chemical compounds serving as reference databases. By overlapping these drug per-
turbation signatures with the expression patterns of our apoptotic-related gene set, we
identified candidate repurposable drugs that may reverse apoptosis (Table 1) [43]. Of note,
almost all the perturbagens we have found are established neuroprotective entities [43].
Taken together, this evidence further supports the implication of the *core set* genes in human
pathology and highlight the utility of their perturbation as a therapeutical strategy.

Table 1. List of the most enriched "repurposable" drug candidates with a potential to reverse
apoptotic CGNs transcriptomic signature.

|	Perturbation	*p*-Value	Perturbation	*p*-Value
Inflammation & Immunologic disorders	Indomethacin	3.10×10^{-5}	Nystatin	3.24×10^{-5}
	Dipyrone	1.07×10^{-4}	Tranilast	3.41×10^{-5}
	Sulfanilamide	1.12×10^{-4}	Cyproheptadine	1.62×10^{-2}
	Rifabutin	2.34×10^{-4}	Rapamycin	1.66×10^{-6}
	Allopurinol	8.01×10^{-6}	Tacrolimus	5.22×10^{-5}
	Necrostatin	5.29×10^{-5}	Theophylline	3.80×10^{-5}
Cancer	Tozasertib	2.08×10^{-5}	Tyrphostin	1.54×10^{-15}
	L-Sulforaphane	1.00×10^{-4}	Tanespimycin	7.69×10^{-5}
Psychiatric disorders	Tianeptine	8.71×10^{-5}	Moclobemide	2.22×10^{-4}
	Amitriptyline	7.97×10^{-6}	Rolipram	2.15×10^{-4}
	Nortriptyline	8.62×10^{-6}	Azacyclonol	1.55×10^{-2}
	Bupropion	1.57×10^{-5}	Piracetam	4.11×10^{-5}
	Roflumilast	1.84×10^{-5}	Promazine hydrochloride	5.32×10^{-4}
	Citalopram	3.85×10^{-5}	Phenotiazine	1.09×10^{-4}
	Iproniazid	7.33×10^{-5}	Clozapine	1.35×10^{-4}
	Doxepin	1.94×10^{-4}	Diazepam	8.10×10^{-5}
Epilepsy	Lamotrigine	1.68×10^{-4}	Ethosuximide	1.07×10^{-4}
Cardiovascular diseases	Enaplapril	2.75×10^{-4}	Atorvastatin	1.03×10^{-6}
	Nifedipine	2.79×10^{-4}	Nicergoline	1.91×10^{-4}
Other	Monorden/Radicicol	6.94×10^{-3}	5-Nonyloxytryptamine	2.72×10^{-4}
	Purmorphamine	1.80×10^{-4}	Parthenolide	4.11×10^{-5}
	Pifithrin	2.95×10^{-30}		

4. Cracking the Transcriptional Regulatory Programs of Neuronal Cell Fate May Orient New Therapeutic Strategies

Until today, different therapeutic strategies aimed at controlling neuronal apoptosis
and survival have targeted the input (inducing signals) or output (executing machinery)
underlying mechanisms, which can be considered the cellular "hardware". Although many
of these therapeutic strategies have been validated, most of them remain in the preclinical
state because of lack of specificity and low efficacy [80]. An example is the use of NFs,
whose therapy potential is hampered by the difficulty in delivering these proteins to the
CNS and limiting their unwanted pleiotropic effects [81–87].

Similar to computers, where most of the problems commonly arise from buggy soft-
ware, our neurons may also deal with malfunctions in the transcription regulatory program.
Thus, cracking the code of neuronal fate may elicit novel pharmacological strategies, no
longer oriented to the cellular hardware but, rather, the nuclear transcriptional regulatory
mechanisms. Reconstruction of this cellular program by "reverse engineering" of gene
regulatory networks (GRNs) poses great opportunities in systems biology [88–97] and
allows to build accurate models of physiological and pathological processes, including
those implicated in neuronal fate and development [98–103]. The impact of using these
gene regulatory models to understand human diseases and find new treatments is pro-
found, since they may allow to identify disease driver genes and promising biomarkers
and therapeutic targets more efficiently and accurately [99,103–106].

Recently, we applied a "reverse engineering" method to identify candidate upstream
regulators of early transcriptional changes observed following induction of CGNs apoptosis
and its rescue by NFs [43]. In particular, we performed an *in silico* analysis to predict
transcription factors (TFs) whose binding motifs are enriched in the promoter regions

of *core set* genes [43]. Our analysis revealed that temporally distinct modules of *core set* genes are regulated by the coordinated action of nine TFs (Hoxd9, Maf, Nr4a1, Cebpb, Olig2, Onecut2, Spdef, Twist2, Nfyb) that may act as upstream regulators of neuronal cell fate, converging apoptosis and survival-inducing signals in a highly interconnected and temporally ordered manner (Figure 3) [43]. In particular, these results showed a high degree of cross-regulation among the nine TFs as well as a common early (0.5 h and 1 h) and transient peak of transcription for the almost all TFs, with the exception of Onecut2 that was activated after 3 h following NF treatment (Figure 3). Of note, some of these transcription factors encode previously tested molecular/pharmacological targets and their exploitation may interfere with the early stages of the apoptotic/survival transcriptional program and represent novel therapeutic strategies [43]. In the following paragraphs, we will discuss these master regulators in light of their potential role as therapeutic targets for neurological disorders.
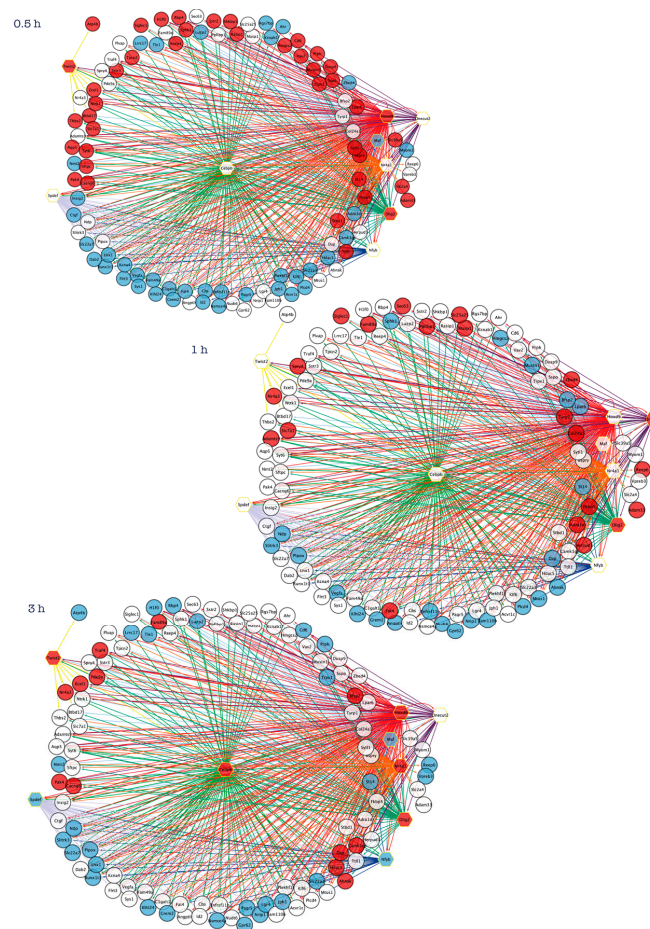
Figure 3. Reverse-engineering of transcriptional changes identifies key transcription factors at the intersection of neuronal apoptosis and survival. Inferring transcriptional gene regulatory networks of *core set* genes identify nine transcription factors (*Hoxd9*, *Maf*, *Nr4a1*, *Cebpb*, *Olig2*, *Onecut2*, *Spdef*, *Twist2*, *Nfyb*), which may act as upstream regulators of neuronal cell fate [43]. Transcription regulatory network analysis generated at each time point (0.5 h, 1 h, 3 h) following induction of apoptosis or rescue by NFs emphasizes how temporally distinct apoptosis and survival-inducing signals are orchestrated by the action of interconnected and temporally ordered TFs. Regulatory networks are visualized by Cytoscape and for each time-point the node color is consistent with the expression logFC of each gene: genes in blue are down-regulated by NFs treatment, while genes in red are up-regulated. Transcription factors are represented as hexagon nodes, while gene targets are represented as circle nodes. Regulons for each transcription factor are represented by different edge colors.

4.1. Homeobox D9 (Hoxd9)

Hoxd9 belongs to an evolutionarily conserved family of homeodomain-containing transcription factors that plays an important role during development of the central nervous system and continue to be expressed into adulthood [107–110]. Following their initial discovery, a substantial amount of information has been gained regarding the roles Hox genes play in various physiologic and pathologic processes, including brain cancer and neurological disorders, suggesting their molecular/pharmacological modulation as a potential strategy for therapies of complex human disorders [109,111,112]. The importance of *Hoxd9* as master regulator of neuronal cell fate is highlighted by its early transcriptional activation following NF-mediated rescue (Figures 1 and 3) [43]. In accordance with these results, previous studies have demonstrated that Hoxd9 regulates the expression of several genes involved in neuronal apoptosis, displaying increased expression in unfavorable brain tumors, whereas its loss of function causes defects in axonal targeting and reduction in neural cell numbers, suggesting its utility as a potential therapeutic target at the crossroads between neurodegeneration and cancer [111,113–115]. To this regard, siRNA-induced silencing of *Hoxd9* gene has been already employed to induce apoptosis in different types of brain tumors, including neuroblastoma [116,117].

4.2. Nuclear Receptor 4A1 (Nr4a1)

Nr4a orphan nuclear receptor are a family of transcription factors that are rapidly and strongly up-regulated in response to a diverse range of signals, including growth factors, cytokines, membrane depolarization, oxidative stress and excitotoxic insults to the central nervous system, which up-regulate neuroprotective genes and improve neuronal survival [118–121]. Nr4a sub-family members are categorized as early-response genes, are robustly induced in the CNS by pathological stimuli such as ischemia, seizures and focal brain injury and have pleiotropic physiological roles, including maintenance of neuronal integrity, regulation of the density and distribution of spines and synapses, suppression of apoptosis and induction of pro-survival genes [119,120,122]. Among the key components of this TF family is Nr4a1, whose gene expression levels were reverted (up-regulated) following NFs-induced rescue effects and that we found involved in the transcriptional regulation of a large number of *core set* genes, including other TFs (*Maf, Nfyb and Spdef*), implicated in system development, regulation of apoptotic process, chemotaxis and metabolic process (Figures 1 and 3) [43]. In particular, as an immediate-early gene, Nr4a1 modulates cell fate by controlling mitochondrial functions and synaptic activity in response to a variety of stressors and sensory stimuli [123,124]. Notably, a marked decrease of Nr4a1 was associated with a variety of neurological conditions, including Alzheimer's and Parkinson's diseases, and its pharmacological activation exerts neuroprotective, anti-inflammatory and pro-survival effects, proposing Nr4a1 as a potential therapeutic target for multiple neurological disorders [120,122,123,125–134]. Within this context, previous studies have provided evidence for the implication of nuclear receptors (i.e., Nr4a1 and Nr4a3) in schizophrenia and bipolar disorders, demonstrating that down-regulated expression levels or sequence variations correlate with increased susceptibility to these cognitive disorders (Figure 2) [126,127,135,136].

4.3. Musculoaponeurotic Fibrosarcoma (Maf)

Maf (also known as c-Maf or v-Maf) is a member of a large group of b-Zip proteins that form a complex regulatory network, acting either as transcriptional activators or repressors of multiple cellular genes involved in immune response, apoptosis as well as neuronal outgrowth, maintenance and differentiation [19,109,122]. Despite little is known about the specific role of Maf in neuronal apoptosis and degeneration, recent reports suggest that over-expression of this gene can cause cell death probably through a p53-mediated signaling [122,137]. In agreement with these results, we found an early and transient peak of transcription for *Maf* following induction of CGNs apoptosis, while its expression decreased following treatment with NFs (Figures 1 and 3) [43]. As other oxidative stress

reactive proteins, Maf has been implicated in various neurological disorders, including Alzheimer's and Parkinson's diseases, and its role is emerging as a novel target in the treatment of these disorders [138–140].

4.4. CCAAT Enhancer Binding Protein Beta (Cebpb)

Cebpb encodes a basic-leucine zipper transcription factor that plays pivotal roles in development and synaptic plasticity of the nervous system, regulating the expression of genes involved in cell differentiation, neuronal development, immune response, neuronal apoptosis and metabolism [141–146]. In accordance with our study showing a transient activation of *Cebpb* during NFs-mediated rescue from apoptosis [43], previous studies demonstrated that up-regulation of this TF in rat primary cortical and cerebellar neuronal cultures plays neuroprotective and antiapoptotic effects, while its reduced neuronal levels may represent a pathogenic factor in neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, supporting the potential of Cebpb as a pharmacological target in brain injury and neurodegenerative disorders (Figures 1 and 3) [141,147–152].

4.5. Oligodendrocyte Transcription Factor2 (Olig2)

Among the enriched TFs in up-regulated core set genes, we identified the basic-helix-loop-helix (bHLH) transcription factor Olig2 that plays a key role in directing cell fate choices, promoting cell proliferation and controlling CNS development [43,153,154]. Several studies, in fact, have demonstrated that activation of Olig2 in response to different NFs (e.g., FGF, GDNF and PDGF) exerts protective and pro-survival effects in multiple neuronal types [155–158]. According with these findings, we observed an increased expression of Olig2 during CGNs rescue by Pacap, Igf1 and SP (Figures 1 and 3) [43]. Despite the role elicited by Olig2 in the adult cerebral cortex under pathological conditions is not yet known, its reduced expression seems to switch cell fate from differentiation to death, contributing to the development of psychiatric disorders and acute/chronic neurodegenerative diseases, including Alzheimer's disease and Amyotrophic Lateral Sclerosis, while its increased expression has been associated with different brain tumors, supporting its potential utility as therapeutic target for the treatment of both cancer and neurodegeneration [159–171]. Of note, several evidence showed that Olig2 deficiency as well as the presence of rare genetic polymorphisms in this gene (i.e., rs1059004) may represent risk factors for cognitive disorders and schizophrenia, through an effect on neuroanatomical connectivity (Figure 2) [159,164,172–176].

4.6. One Cut Homeobox 2 (Onecut2)

Onecut2 encodes a member of a family of transcription factors that function as transcriptional activators controlling cell differentiation and survival, as well as oxidative defense signaling, and that have only been recently proposed as regulators of neuronal differentiation [177–184]. Showing a consistent increased expression of this TF in CGNs during NF-mediated rescue, our results support the importance of Onecut2 for neuronal survival (Figures 1 and 3) [43]. Although the expression of this factor is dysregulated in different types of tumors or following hypoxic insult to neurons, future studies are needed to further investigate the utility of Onecut2 as a target for brain tumors or neurodevelopmental disorders.

4.7. SAM Pointed Domain Containing ETS Transcription Factor (Spdef)

Spdef is an ETS (E26 transformation-specific) transcription factor, highly expressed in the prostate but also expressed in the brain and liver, where it regulates cellular differentiation, proliferation, cell-cycle control and apoptosis [185]. We observed an increased expression of *Spdef* throughout the time-course of CGNs apoptosis and its down-regulation following NFs treatment (Figures 1 and 3) [43]. This evidence supports previous studies proposing its role as a tumor suppressor in various types of cancers [186,187]. In addition, altered expression of SPDEF has been found in Alzheimer's disease patients and animal models, while a recent association was found between blood-based Spdef methylation and stress

response, altered dopaminergic neurotransmission and increased vulnerability to substance abuse, suggesting its role as a biomarker for these pathological conditions [188–191].

4.8. Nuclear Transcription Factor Y Subunit Beta (Nfyb)

According to our recent findings showing increased expression of Nfyb during CGNs apoptosis [43], previous works demonstrated that its induction promotes neuronal apoptosis via the proapoptotic protein Bim and the activation of the p53 signaling pathway (Figures 1 and 3) [192–194]. Nfyb regulates transcription of several genes that are related to cell cycle and its alterations contribute to neurodegeneration and apoptosis [195,196].

4.9. Twist Family BHLH Transcription Factor 2 (Twist2)

Twist2 is a highly conserved member of the Twist subfamily of basic Helix-Loop-Helix (bHLH) transcription factors that have been implicated in the transcriptional regulation of developmental programs in multiple cell lineages, and that are known to play important roles in cell migration, inflammation, protection of cells from apoptosis, and cellular response to oxidative stress [197–199]. According with the anti-apoptotic, anti-oxidative and anti-inflammatory effects of this TF, we observed its increased expression following NF-induced neuronal apoptotic rescue (Figures 1 and 3) [43]. From a clinical point of view, Twist2 is upregulated in a variety of cancers, including glioma and neuroblastoma [181]. In addition, Twist2 dysfunctions are associated with human pathological conditions characterized by oxidative stress-induced neuronal death, supporting its potential role as therapeutical target for cancer and neurological diseases [199,200,200–203].

5. Conclusions

In this review, we highlighted how whole-genome gene expression analysis coupled to reverse engineering of gene regulatory networks are beginning to decode the complex transcriptional programs underlying neuronal apoptosis and survival [43]. This new experimental approach may foster an innovative pharmacology no longer oriented to influence the cellular hardware but focused on its regulatory transcriptional program.

Author Contributions: Conceptualization, writing—original draft preparation, G.M. and S.C.; review and editing, G.M., V.L.C., M.G., V.D. and S.C.; supervision, SC. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Mattson, M.P. Apoptosis in neurodegenerative disorders. *Nat. Rev. Mol. Cell Biol.* **2000**, *1*, 120–129. [CrossRef]
2. Datta, A.; Sarmah, D.; Mounica, L.; Kaur, H.; Kesharwani, R.; Verma, G.; Veeresh, P.; Kotian, V.; Kalia, K.; Borah, A.; et al. Cell Death Pathways in Ischemic Stroke and Targeted Pharmacotherapy. *Transl. Stroke Res.* **2020**, *11*, 1185–1202. [CrossRef] [PubMed]
3. Erekat, N.S. Apoptosis and its therapeutic implications in neurodegenerative diseases. *Clin. Anat.* **2022**, *35*, 65–78. [CrossRef] [PubMed]
4. Mattson, M.P. Neuronal Life-and-Death Signaling, Apoptosis, and Neurodegenerative Disorders. *Antioxid. Redox Signal.* **2006**, *8*, 1997–2006. [CrossRef] [PubMed]
5. Yoshida, K.; Yamada, M.; Nishio, C.; Konishi, A.; Hatanaka, H. SNRK, a member of the SNF1 family, is related to low K(+)-induced apoptosis of cultured rat cerebellar granule neurons. *Brain Res.* **2000**, *873*, 274–282. [CrossRef]

6. Galli, C.; Meucci, O.; Scorziello, A.; Werge, T.M.; Calissano, P.; Schettini, G. Apoptosis in cerebellar granule cells is blocked by high KCl, forskolin, and IGF-1 through distinct mechanisms of action: The involvement of intracellular calcium and RNA synthesis. *J. Neurosci.* **1995**, *15*, 1172–1179. [CrossRef] [PubMed]

7. Garcia-Valenzulela, E.; Gorczyca, W.; Darzynkiewicz, Z.; Sharma, S.C. Apoptosis in adult retinal ganglion cells after axotomy. *J. Neurobiol.* **1994**, *25*, 431–438. [CrossRef]

8. Martin, D.P.; Schmidt, R.E.; DiStefano, P.S.; Lowry, O.H.; Carter, J.G.; Johnson, E.M. Inhibitors of protein synthesis and RNA synthesis prevent neuronal death caused by nerve growth factor deprivation. *J. Cell Biol.* **1988**, *106*, 829–844. [CrossRef]

9. D'Mello, S.R.; Galli, C.; Ciotti, T.; Calissano, P. Induction of apoptosis in cerebellar granule neurons by low potassium: Inhibition of death by insulin-like growth factor I and cAMP. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 10989. [CrossRef]

10. Cavallaro, S. Cracking the code of neuronal apoptosis and survival. *Cell Death Dis.* **2015**, *6*, e1963. [CrossRef]

11. Cavallaro, S. Neuronal apoptosis revealed by genomic analysis: Integrating gene expression profiles with functional information. *Neuroinformatics* **2007**, *5*, 115–126. [CrossRef] [PubMed]

12. Cavallaro, S.; Calissano, P. A Genomic Approach to Investigate Neuronal Apoptosis. *Curr. Alzheimer Res.* **2006**, *3*, 285–296. [CrossRef] [PubMed]

13. Cavallaro, S.; D'Agata, V.; Alessi, E.; Coffa, S.; Alkon, D.L.; Manickam, P.; Ciotti, M.T.; Possenti, R.; Bonini, P.; Marlier, L.; et al. Gene expression profiles of apoptotic neurons. *Genomics* **2004**, *84*, 485–496. [CrossRef] [PubMed]

14. Paratore, S.; Parenti, R.; Torrisi, A.; Copani, A.; Cicirata, F.; Cavallaro, S. Genomic profiling of cortical neurons following exposure to β-amyloid. *Genomics* **2006**, *88*, 468–479. [CrossRef] [PubMed]

15. Hetmańczyk-Sawicka, K.; Iwanicka-Nowicka, R.; Fogtman, A.; Cieśla, J.; Włodarski, P.; Żyżyńska-Granica, B.; Filocamo, M.; Dardis, A.; Peruzzo, P.; Bednarska-Makaruk, M.; et al. Changes in global gene expression indicate disordered autophagy, apoptosis and inflammatory processes and downregulation of cytoskeletal signalling and neuronal development in patients with Niemann–Pick C disease. *Neurogenetics* **2020**, *21*, 105–119. [CrossRef]

16. Ułamek-Kozioł, M.; Czuczwar, S.J.; Kocki, J.; Januszewski, S.; Bogucki, J.; Bogucka-Kocka, A.; Pluta, R. Dysregulation of Autophagy, Mitophagy, and Apoptosis Genes in the CA3 Region of the Hippocampus in the Ischemic Model of Alzheimer's Disease in the Rat. *J. Alzheimer's Dis.* **2019**, *72*, 1279–1286. [CrossRef]

17. Calissano, P.; Matrone, C.; Amadoro, G. Apoptosis and in vitro Alzheimer's disease neuronal models. *Commun. Integr. Biol.* **2009**, *2*, 163–169. [CrossRef]

18. Parenti, R.; Paratore, S.; Torrisi, A.; Cavallaro, S. A natural antisense transcript against Rad18, specifically expressed in neurons and upregulated during β-amyloid-induced apoptosis. *Eur. J. Neurosci.* **2007**, *26*, 2444–2457. [CrossRef]

19. Estus, S.; Tucker, H.M.; Van Rooyen, C.; Wright, S.; Brigham, E.F.; Wogulis, M.; Rydel, R.E. Aggregated Amyloid-β Protein Induces Cortical Neuronal Apoptosis and Concomitant "Apoptotic" Pattern of Gene Induction. *J. Neurosci.* **1997**, *17*, 7736. [CrossRef]

20. Lossi, L.; Gambino, G. Apoptosis of the cerebellar neurons. *Histol. Histopathol.* **2008**, *23*, 367–380. [CrossRef]

21. Jung, C.G.; Uhm, K.O.; Miura, Y.; Hosono, T.; Horike, H.; Khanna, K.K.; Kim, M.J.; Michikawa, M. Beta-amyloid increases the expression level of ATBF1 responsible for death in cultured cortical neurons. *Mol. Neurodegener.* **2011**, *6*, 47. [CrossRef] [PubMed]

22. Maino, B.; Ciotti, M.T.; Calissano, P.; Cavallaro, S. Transcriptional analysis of apoptotic cerebellar granule neurons following rescue by gastric inhibitory polypeptide. *Int. J. Mol. Sci.* **2014**, *15*, 5596–5622. [CrossRef] [PubMed]

23. Maino, B.; D'Agata, V.; Severini, C.; Ciotti, M.T.; Calissano, P.; Copani, A.; Chang, Y.C.; Delisi, C.; Cavallaro, S. Igf1 and pacap rescue cerebellar granule neurons from apoptosis via a common transcriptional program. *Cell Death Discov.* **2015**, *1*, 15029. [CrossRef] [PubMed]

24. Yan, G.-M.; Paul, S.M. Cultured Cerebellar Granule Neurons as a Model of Neuronal Apoptosis. *Apoptosis Tech. Protoc.* **1997**, 47–66. [CrossRef]

25. Chiang, L.W.; Grenier, J.M.; Ettwiller, L.; Jenkins, L.P.; Ficenec, D.; Martin, J.; Jin, F.; DiStefano, P.S.; Wood, A. An orchestrated gene expression component of neuronal programmed cell death revealed by cDNA array analysis. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 2814–2819. [CrossRef]

26. Austdal, L.P.E.; Mathisen, G.H.; Løberg, E.M.; Paulsen, R.E. Calcium-induced apoptosis of developing cerebellar granule neurons depends causally on NGFI-B. *Int. J. Dev. Neurosci.* **2016**, *55*, 82–90. [CrossRef]

27. Fernández-Suárez, D.; Krapacher, F.A.; Andersson, A.; Ibáñez, C.F.; Kisiswa, L. MAG induces apoptosis in cerebellar granule neurons through p75NTR demarcating granule layer/white matter boundary. *Cell Death Dis.* **2019**, *10*, 1–15. [CrossRef]

28. De Luca, A.; Weller, M.; Fontana, A. TGF-β-Induced Apoptosis of Cerebellar Granule Neurons Is Prevented by Depolarization. *J. Neurosci.* **1996**, *16*, 4174. [CrossRef]

29. Padmanabhan, J.; Park, D.S.; Greene, L.A.; Shelanski, M.L. Role of Cell Cycle Regulatory Proteins in Cerebellar Granule Neuron Apoptosis. *J. Neurosci.* **1999**, *19*, 8747–8756. [CrossRef]

30. Contestabile, A. Cerebellar granule cells as a model to study mechanisms of neuronal apoptosis or survival in vivo and in vitro. *Cerebellum* **2002**, *1*, 41–55. [CrossRef]

31. Williams, R.W.; Herrup, K. The Control of Neuron Number. *Annu. Rev.* **2003**, *11*, 423–453. [CrossRef] [PubMed]

32. Borsello, T.; Di Luzio, A.; Ciotti, M.T.; Calissano, P.; Galli, C. Granule neuron DNA damage following deafferentation in adult rats cerebellar cortex: A lesion model. *Neuroscience* **1999**, *95*, 163–171. [CrossRef] [PubMed]

33. Maino, B.; Spampinato, A.G.; Severini, C.; Petrella, C.; Ciotti, M.T.; D'Agata, V.; Calissano, P.; Cavallaro, S. The trophic effect of nerve growth factor in primary cultures of rat hippocampal neurons is associated to an anti-inflammatory and immunosuppressive transcriptional program. *J. Cell. Physiol.* **2018**, *233*, 7178–7187. [CrossRef]

34. Pattarawarapan, M.; Burgess, K. Molecular basis of neurotrophin-receptor interactions. *J. Med. Chem.* **2003**, *46*, 5277–5291. [CrossRef]

35. Cavallaro, S.; Copani, A.; D'Agata, V.; Musco, S.; Petralia, S.; Ventra, C.; Stivala, F.; Travali, S.; Canonico, P.L. Pituitary adenylate cyclase activating polypeptide prevents apoptosis in cultured cerebellar granule neurons. *Mol. Pharmacol.* **1996**, *50*, 60–66. [PubMed]

36. Amadoro, G.; Pieri, M.; Ciotti, M.T.; Carunchio, I.; Canu, N.; Calissano, P.; Zona, C.; Severini, C. Substance P provides neuroprotection in cerebellar granule cells through Akt and MAPK/Erk activation: Evidence for the involvement of the delayed rectifier potassium current. *Neuropharmacology* **2007**, *52*, 1366–1377. [CrossRef] [PubMed]

37. Vaudry, D.; Gonzalez, B.J.; Basille, M.; Pamantung, T.F.; Fontaine, M.; Fournier, A.; Vaudry, H. The neuroprotective effect of pituitary adenylate cyclase-activating polypeptide on cerebellar granule cells is mediated through inhibition of the CED3-related cysteine protease caspase-3/CPP32. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 13390–13395. [CrossRef]

38. Linseman, D.A.; Phelps, R.A.; Bouchard, R.J.; Le, S.S.; Laessig, T.A.; McClure, M.L.; Heidenreich, K.A. Insulin-Like Growth Factor-I Blocks Bcl-2 Interacting Mediator of Cell Death (Bim) Induction and Intrinsic Death Signaling in Cerebellar Granule Neurons. *J. Neurosci.* **2002**, *22*, 9287–9297. [CrossRef]

39. Gleichmann, M.; Weller, M.; Schulz, J.B. Insulin-like growth factor-1-mediated protection from neuronal apoptosis is linked to phosphorylation of the pro-apoptotic protein BAD but not to inhibition of cytochrome c translocation in rat cerebellar neurons. *Neurosci. Lett.* **2000**, *282*, 69–72. [CrossRef]

40. Paratore, S.; Teresa Ciotti, M.; Basille, M.; Vaudry, D.; Gentile, A.; Parenti, R.; Calissano, P.; Cavallaro, S. Gastric inhibitory polypeptide and its receptor are expressed in the central nervous system and support neuronal survival. *Cent. Nerv. Syst. Agents Med. Chem.* **2011**, *11*, 210–222. [CrossRef]

41. Seaborn, T.; Masmoudi-Kouli, O.; Fournier, A.; Vaudry, H.; Vaudry, D. Protective effects of pituitary adenylate cyclase-activating polypeptide (PACAP) against apoptosis. *Curr. Pharm. Des.* **2011**, *17*, 204–214. [CrossRef] [PubMed]

42. Schulz, J.B.; Weller, M.; Klockgether, T. Potassium Deprivation-Induced Apoptosis of Cerebellar Granule Neurons: A Sequential Requirement for New mRNA and Protein Synthesis, ICE-Like Protease Activity, and Reactive Oxygen Species. *J. Neurosci.* **1996**, *16*, 4696–4706. [CrossRef] [PubMed]

43. Morello, G.; Villari, A.; Spampinato, A.G.; La Cognata, V.; Guarnaccia, M.; Gentile, G.; Ciotti, M.T.; Calissano, P.; D'agata, V.; Severini, C.; et al. Transcriptional profiles of cell fate transitions reveal early drivers of neuronal apoptosis and survival. *Cells* **2021**, *10*, 3238. [CrossRef] [PubMed]

44. Gao, Y.; Liu, L.; Zhang, Z.; Qin, C.; Yang, B.; Ke, Y. TYRP1 Protects Against the Apoptosis and Oxidative Stress of Retinal Ganglion Cells by Binding to PMEL. *Ocul. Immunol. Inflamm.* **2022**. [CrossRef]

45. Mercurio, D.; Oggioni, M.; Fumagalli, S.; Lynch, N.J.; Roscher, S.; Minuta, D.; Perego, C.; Ippati, S.; Wallis, R.; Schwaeble, W.J.; et al. Targeted deletions of complement lectin pathway genes improve outcome in traumatic brain injury, with MASP-2 playing a major role. *Acta Neuropathol. Commun.* **2020**, *8*, 174. [CrossRef] [PubMed]

46. Gangwani, K.; Snigdha, K.; Kango-Singh, M. Tep1 Regulates Yki Activity in Neural Stem Cells in Drosophila Glioma Model. *Front. Cell Dev. Biol.* **2020**, *8*, 306. [CrossRef] [PubMed]

47. Srikant, C.B. Cell Cycle Dependent Induction of Apoptosis by Somatostatin Analog SMS 201-995 in AtT-20 Mouse Pituitary Cells. *Biochem. Biophys. Res. Commun.* **1995**, *209*, 400–406. [CrossRef]

48. Stumm, R.K.; Zhou, C.; Schulz, S.; Endres, M.; Kronenberg, G.; Allen, J.P.; Tulipano, G.; Höllt, V. Somatostatin Receptor 2 Is Activated in Cortical Neurons and Contributes to Neurodegeneration after Focal Ischemia. *J. Neurosci.* **2004**, *24*, 11404. [CrossRef]

49. Yu, X.; Huang, C.; Liu, J.; Shi, X.; Li, X. The significance of PAK4 in signaling and clinicopathology: A review. *Open Life Sci.* **2022**, *17*, 586–598. [CrossRef]

50. Civiero, L.; Greggio, E. PAKs in the brain: Function and dysfunction. *Biochim. Biophys. Acta Mol. Basis Dis.* **2018**, *1864*, 444–453. [CrossRef]

51. Gnesutta, N.; Qu, J.; Minden, A. The Serine/Threonine Kinase PAK4 Prevents Caspase Activation and Protects Cells from Apoptosis. *J. Biol. Chem.* **2001**, *276*, 14414–14419. [CrossRef] [PubMed]

52. Cong, C.; Liang, W.; Zhang, C.; Wang, Y.; Yang, Y.; Wang, X.; Wang, S.; Huo, D.; Wang, H.; Wang, D.; et al. PAK4 suppresses motor neuron degeneration in hSOD1G93A-linked amyotrophic lateral sclerosis cell and rat models. *Cell Prolif.* **2021**, *54*. [CrossRef] [PubMed]

53. Pütz, S.M.; Kram, J.; Rauh, E.; Kaiser, S.; Toews, R.; Lueningschroer-Wang, Y.; Rieger, D.; Raabe, T. Loss of p21-activated kinase Mbt/PAK4 causes Parkinson-like phenotypes in Drosophila. *Dis. Model. Mech.* **2021**, *14*, dmm047811. [CrossRef] [PubMed]

54. Won, S.Y.; Park, M.H.; You, S.T.; Choi, S.W.; Kim, H.K.; McLean, C.; Bae, S.C.; Kim, S.R.; Jin, B.K.; Lee, K.H.; et al. Nigral dopaminergic PAK4 prevents neurodegeneration in rat models of Parkinson's disease. *Sci. Transl. Med.* **2016**, *8*, 367ra170. [CrossRef] [PubMed]

55. Won, S.Y.; Park, J.J.; Shin, E.Y.; Kim, E.G. PAK4 signaling in health and disease: Defining the PAK4–CREB axis. *Exp. Mol. Med.* **2019**, *51*, 1–9. [CrossRef] [PubMed]

56. Arévalo, J.C.; Waite, J.; Rajagopal, R.; Beyna, M.; Chen, Z.Y.; Lee, F.S.; Chao, M.V. Cell Survival through Trk Neurotrophin Receptors Is Differentially Regulated by Ubiquitination. *Neuron* **2006**, *50*, 549–559. [CrossRef]

57. Majdan, M.; Walsh, G.S.; Aloyz, R.; Miller, F.D. TrkA mediates developmental sympathetic neuron survival in vivo by silencing an ongoing p75NTR-mediated death signal. *J. Cell Biol.* **2001**, *155*, 1275. [CrossRef] [PubMed]

58. Culmsee, C.; Gerling, N.; Lehmann, M.; Nikolova-Karakashian, M.; Prehn, J.H.M.; Mattson, M.P.; Krieglstein, J. Nerve growth factor survival signaling in cultured hippocampal neurons is mediated through TrkA and requires the common neurotrophin receptor p75. *Neuroscience* **2002**, *115*, 1089–1108. [CrossRef]

59. Zhou, Y.; Lu, T.J.; Xiong, Z.Q. NGF-dependent retrograde signaling: Survival versus death. *Cell Res.* **2009**, *19*, 525–526. [CrossRef]

60. Zhang, Y.Z.; Moheban, D.B.; Conway, B.R.; Bhattacharyya, A.; Segal, R.A. Cell surface Trk receptors mediate NGF-induced survival while internalized receptors regulate NGF-induced differentiation. *J. Neurosci.* **2000**, *20*, 5671–5678. [CrossRef]

61. Moujalled, D.; Strasser, A.; Liddell, J.R. Molecular mechanisms of cell death in neurological diseases. *Cell Death Differ.* **2021**, *28*, 2029–2044. [CrossRef] [PubMed]

62. Wolozin, B.; Behl, C. Mechanisms of neurodegenerative disorders: Part 2: Control of cell death. *Arch. Neurol.* **2000**, *57*, 801–804. [CrossRef] [PubMed]

63. Cui, J.; Zhao, S.; Li, Y.; Zhang, D.; Wang, B.; Xie, J.; Wang, J. Regulated cell death: Discovery, features and implications for neurodegenerative diseases. *Cell Commun. Signal.* **2021**, *19*, 1–29. [CrossRef]

64. Tatton, W.G.; Olanow, C.W. Apoptosis in neurodegenerative diseases: The role of mitochondria. *Biochim. Biophys. Acta* **1999**, *1410*, 195–213. [CrossRef] [PubMed]

65. Uribe, E.; Wix, R. Neuronal migration, apoptosis and bipolar disorder. *Rev. Psiquiatr. Salud Ment.* **2012**, *5*, 127–133. [CrossRef]

66. Karlović, D. Apoptosis—The potential pathophysiological mechanism in mood disorders modifiable by lithium salts. *Biochem. Med.* **2008**, *18*, 291–310. [CrossRef]

67. Margolis, R.L.; Chuang, D.M.; Post, R.M. Programmed cell death: Implications for neuropsychiatric disorders. *Biol. Psychiatry* **1994**, *35*, 946–956. [CrossRef]

68. Andreone, B.J.; Larhammar, M.; Lewcock, J.W. Cell Death and Neurodegeneration. *Cold Spring Harb. Perspect. Biol.* **2020**, *12*, a036434. [CrossRef]

69. Chi, H.; Chang, H.Y.; Sang, T.K. Neuronal Cell Death Mechanisms in Major Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2018**, *19*, 3082. [CrossRef]

70. Yuan, J.; Yankner, B.A. Apoptosis in the nervous system. *Nature* **2000**, *407*, 802–809. [CrossRef]

71. Gorman, A.M. Neuronal cell death in neurodegenerative diseases: Recurring themes around protein handling. *J. Cell. Mol. Med.* **2008**, *12*, 2263–2280. [CrossRef] [PubMed]

72. D'Mello, S.R.; Chin, P.C. Treating neurodegenerative conditions through the understanding of neuronal apoptosis. *Curr. Drug Targets CNS Neurol. Disord.* **2005**, *4*, 3–23. [CrossRef] [PubMed]

73. Parul; Mishra, A.; Singh, S.; Singh, S.; Tiwari, V.; Chaturvedi, S.; Wahajuddin, M.; Palit, G.; Shukla, S. Chronic unpredictable stress negatively regulates hippocampal neurogenesis and promote anxious depression-like behavior via upregulating apoptosis and inflammatory signals in adult rats. *Brain Res. Bull.* **2021**, *172*, 164–179. [CrossRef]

74. Bachis, A.; Cruz, M.I.; Nosheny, R.L.; Mocchetti, I. Chronic Unpredictable Stress Promotes Neuronal Apoptosis in the Cerebral Cortex. *Neurosci. Lett.* **2008**, *442*, 104. [CrossRef] [PubMed]

75. Jarskog, L.F.; Glantz, L.A.; Gilmore, J.H.; Lieberman, J.A. Apoptotic mechanisms in the pathophysiology of schizophrenia. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2005**, *29*, 846–858. [CrossRef] [PubMed]

76. Wang, Y.; Huang, A.; Gan, L.; Bao, Y.; Zhu, W.; Hu, Y.; Ma, L.; Wei, S.; Lan, Y. Screening of Potential Genes and Transcription Factors of Postoperative Cognitive Dysfunction via Bioinformatics Methods. *Med. Sci. Monit.* **2018**, *24*, 503. [CrossRef]

77. Santos-Terra, J.; Deckmann, I.; Fontes-Dutra, M.; Schwingel, G.B.; Bambini-Junior, V.; Gottfried, C. Transcription factors in neurodevelopmental and associated psychiatric disorders: A potential convergence for genetic and environmental risk factors. *Int. J. Dev. Neurosci.* **2021**, *81*, 545–578. [CrossRef]

78. Johnston, M.V.; Alemi, L.; Harum, K.H. Learning, Memory, and Transcription Factors. *Pediatr. Res.* **2003**, *53*, 369–374. [CrossRef]

79. Stathias, V.; Turner, J.; Koleti, A.; Vidovic, D.; Cooper, D.; Fazel-Najafabadi, M.; Pilarczyk, M.; Terryn, R.; Chung, C.; Umeano, A.; et al. LINCS Data Portal 2.0: Next generation access point for perturbation-response signatures. *Nucleic Acids Res.* **2020**, *48*, D431–D439. [CrossRef]

80. Fischer, U.; Schulze-Osthoff, K. Apoptosis-based therapies and drug targets. *Cell Death Differ.* **2005**, *12* (Suppl. 1), 942–961. [CrossRef]

81. Razavi, S.; Nazem, G.; Mardani, M.; Esfandiari, E.; Salehi, H.; Esfahani, S.H.Z. Neurotrophic factors and their effects in the treatment of multiple sclerosis. *Adv. Biomed. Res.* **2015**, *4*, 53. [CrossRef] [PubMed]

82. Bondarenko, O.; Saarma, M. Neurotrophic Factors in Parkinson's Disease: Clinical Trials, Open Challenges and Nanoparticle-Mediated Delivery to the Brain. *Front. Cell. Neurosci.* **2021**, *15*, 178. [CrossRef] [PubMed]

83. Chen, J.; Shehadah, A.; Pal, A.; Zacharek, A.; Cui, X.; Cui, Y.; Roberts, C.; Lu, M.; Zeitlin, A.; Hariri, R.; et al. Neurotrophic Factor BDNF, Physiological Functions and Therapeutic Potential in Depression, Neurodegeneration and Brain Cancer. *Int. J. Mol. Sci.* **2020**, *21*, 7777. [CrossRef]

84. Padmakumar, S.; Taha, M.S.; Kadakia, E.; Bleier, B.S.; Amiji, M.M. Delivery of neurotrophic factors in the treatment of age-related chronic neurodegenerative diseases. *Expert Opin. Drug Deliv.* **2020**, *17*, 323–340. [CrossRef]

85. Chmielarz, P.; Saarma, M. Neurotrophic factors for disease-modifying treatments of Parkinson's disease: Gaps between basic science and clinical studies. *Pharmacol. Rep.* **2020**, *72*, 1195–1217. [CrossRef]

86. Alfonsetti, M.; D'Angelo, M.; Castelli, V. Neurotrophic factor-based pharmacological approaches in neurological disorders. *Neural Regen. Res.* **2023**, *18*, 1220–1228. [CrossRef]

87. Reagents for Therapeutic Targets of Neurodegenerative Diseases: Get Quote, RFQ, Price or Buy. Available online: https://www.news-medical.net/Reagents-for-therapeutic-targets-of-neurodegenerative-diseases (accessed on 9 February 2023).

88. Saint-André, V. Computational biology approaches for mapping transcriptional regulatory networks. *Comput. Struct. Biotechnol. J.* **2021**, *19*, 4884–4895. [CrossRef] [PubMed]

89. Zak, D.E.; Gonye, G.E.; Schwaber, J.S.; Doyle, F.J. Importance of Input Perturbations and Stochastic Gene Expression in the Reverse Engineering of Genetic Regulatory Networks: Insights from an Identifiability Analysis of an In silico Network. *Genome Res.* **2003**, *13*, 2396–2405. [CrossRef]

90. Zoppoli, P.; Morganella, S.; Ceccarelli, M. TimeDelay-ARACNE: Reverse engineering of gene networks from time-course data by an information theoretic approach. *BMC Bioinform.* **2010**, *11*, 1–5. [CrossRef]

91. Stolovitzky, G.; Monroe, D.; Califano, A. Dialogue on reverse-engineering assessment and methods: The DREAM of high-throughput pathway inference. *Ann. N. Y. Acad. Sci.* **2007**, *1115*, 1–22. [CrossRef]

92. van der Sande, M.; Frölich, S.; van Heeringen, S.J. Computational approaches to understand transcription regulation in development. *Biochem. Soc. Trans.* **2023**, *51*, 1–12. [CrossRef] [PubMed]

93. Ashworth, J.; Wurtmann, E.J.; Baliga, N.S. Reverse engineering systems models of regulation: Discovery, prediction and mechanisms. *Curr. Opin. Biotechnol.* **2012**, *23*, 598. [CrossRef] [PubMed]

94. De Bastiani, M.A.; Pfaffenseller, B.; Klamt, F. Master regulators connectivity map: A transcription factors-centered approach to drug repositioning. *Front. Pharmacol.* **2018**, *9*, 697. [CrossRef] [PubMed]

95. Carré, C.; Mas, A.; Krouk, G. Reverse engineering highlights potential principles of large gene regulatory network design and learning. *NPJ Syst. Biol. Appl.* **2017**, *3*, 17. [CrossRef]

96. Perkel, J.M. Smart software untangles gene regulation in cells. *Nature* **2022**, *609*, 428–431. [CrossRef]

97. Villaverde, A.F.; Banga, J.R. Reverse engineering and identification in systems biology: Strategies, perspectives and challenges. *J. R. Soc. Interface* **2014**, *11*, 20130505. [CrossRef]

98. Vohradsky, J. Neural model of the genetic network. *J. Biol. Chem.* **2001**, *276*, 36168–36173. [CrossRef]

99. De Cegli, R.; Iacobacci, S.; Flore, G.; Gambardella, G.; Mao, L.; Cutillo, L.; Lauria, M.; Klose, J.; Illingworth, E.; Banfi, S.; et al. Reverse engineering a mouse embryonic stem cell-specific transcriptional network reveals a new modulator of neuronal differentiation. *Nucleic Acids Res.* **2013**, *41*, 711–726. [CrossRef]

100. Acquaah-Mensah, G.K.; Taylor, R.C. Brain in situ hybridization maps as a source for reverse-engineering transcriptional regulatory networks: Alzheimer's disease insights. *Gene* **2016**, *586*, 77–86. [CrossRef]

101. Petrovskiy, E.D.; Saik, O.V.; Tiys, E.S.; Lavrik, I.N.; Kolchanov, N.A.; Ivanisenko, V.A. Prediction of tissue-specific effects of gene knockout on apoptosis in different anatomical structures of human brain. *BMC Genom.* **2015**, *16*, S3. [CrossRef]

102. Cheng, Y.; Yin, Y.; Zhang, A.; Bernstein, A.M.; Kawaguchi, R.; Gao, K.; Potter, K.; Gilbert, H.Y.; Ao, Y.; Ou, J.; et al. Transcription factor network analysis identifies REST/NRSF as an intrinsic regulator of CNS regeneration in mice. *Nat. Commun.* **2022**, *13*, 4418. [CrossRef]

103. Lefebvre, C.; Rieckhof, G.; Califano, A. Reverse-engineering human regulatory networks. *Wiley Interdiscip. Rev. Syst. Biol. Med.* **2012**, *4*, 311. [CrossRef] [PubMed]

104. Carro, M.S.; Lim, W.K.; Alvarez, M.J.; Bollo, R.J.; Zhao, X.; Snyder, E.Y.; Sulman, E.P.; Anne, S.L.; Doetsch, F.; Colman, H.; et al. The transcriptional network for mesenchymal transformation of brain tumours. *Nature* **2010**, *463*, 318–325. [CrossRef]

105. Dusonchet, J.; Li, H.; Guillily, M.; Liu, M.; Stafa, K.; Derada Troletti, C.; Boon, J.Y.; Saha, S.; Glauser, L.; Mamais, A.; et al. A Parkinson's disease gene regulatory network identifies the signaling protein RGS2 as a modulator of LRRK2 activity and neuronal toxicity. *Hum. Mol. Genet.* **2014**, *23*, 4887–4905. [CrossRef] [PubMed]

106. Łastowska, M.; Al-Afghani, H.; Al-Balool, H.H.; Sheth, H.; Mercer, E.; Coxhead, J.M.; Redfern, C.P.F.; Peters, H.; Burt, A.D.; Santibanez-Koref, M.; et al. Identification of a neuronal transcription factor network involved in medulloblastoma development. *Acta Neuropathol. Commun.* **2014**, *2*, 35. [CrossRef]

107. Fromental-Ramain, C.; Warot, X.; Lakkaraju, S.; Favier, B.; Haack, H.; Birling, C.; Dierich, A.; Dolle, P.; Chambon, P. Specific and redundant functions of the paralogous Hoxa-9 and Hoxd-9 genes in forelimb and axial skeleton patterning. *Development* **1996**, *122*, 461–472. [CrossRef] [PubMed]

108. Domsch, K.; Papagiannouli, F.; Lohmann, I. The HOX-Apoptosis Regulatory Interplay in Development and Disease. *Curr. Top. Dev. Biol.* **2015**, *114*, 121–158. [CrossRef]

109. Bhatlekar, S.; Fields, J.Z.; Boman, B.M. Role of HOX genes in stem cell differentiation and cancer. *Stem Cells Int.* **2018**, *2018*. [CrossRef]

110. Briscoe, J.; Wilkinson, D.G. Establishing neuronal circuitry: Hox genes make the connection. *Genes Dev.* **2004**, *18*, 1643–1648. [CrossRef]

111. Gonçalves, C.S.; Le Boiteux, E.; Arnaud, P.; Costa, B.M. HOX gene cluster (de)regulation in brain: From neurodevelopment to malignant glial tumours. *Cell. Mol. Life Sci.* **2020**, *77*, 3797–3821. [CrossRef]

112. Finch, N.A.; Wang, X.; Baker, M.C.; Heckman, M.G.; Gendron, T.F.; Bieniek, K.F.; Wuu, J.; Dejesus-Hernandez, M.; Brown, P.H.; Chew, J.; et al. Abnormal expression of homeobox genes and transthyretin in C9ORF72 expansion carriers. *Neurol. Genet.* **2017**, *3*, e161. [CrossRef]

113. Goodman, F.R.; Majewski, F.; Collins, A.L.; Scambler, P.J. A 117-kb microdeletion removing HOXD9-HOXD13 and EVX2 causes synpolydactyly. *Am. J. Hum. Genet.* **2002**, *70*, 547–555. [CrossRef]

114. Sneha, N.P.; Dharshini, S.A.P.; Taguchi, Y.H.; Gromiha, M.M. Integrative Meta-Analysis of Huntington's Disease Transcriptome Landscape. *Genes* **2022**, *13*, 2385. [CrossRef]

115. Kocak, H.; Ackermann, S.; Hero, B.; Kahlert, Y.; Oberthuer, A.; Juraeva, D.; Roels, F.; Theissen, J.; Westermann, F.; Deubzer, H.; et al. Hox-C9 activates the intrinsic pathway of apoptosis and is associated with spontaneous regression in neuroblastoma. *Cell Death Dis.* **2013**, *4*, e586. [CrossRef]

116. Zhu, H.; Dai, W.; Li, J.; Xiang, L.; Wu, X.; Tang, W.; Chen, Y.; Yang, Q.; Liu, M.; Xiao, Y.; et al. HOXD9 promotes the growth, invasion and metastasis of gastric cancer cells by transcriptional activation of RUFY3. *J. Exp. Clin. Cancer Res.* **2019**, *38*, 412. [CrossRef]

117. Tabuse, M.; Ohta, S.; Ohashi, Y.; Fukaya, R.; Misawa, A.; Yoshida, K.; Kawase, T.; Saya, H.; Thirant, C.; Chneiweiss, H.; et al. Functional analysis of HOXD9 in human gliomas and glioma cancer stem cells. *Mol. Cancer* **2011**, *10*, 60. [CrossRef]

118. Kuert, P.A.; Hartenstein, V.; Bello, B.C.; Lovick, J.K.; Reichert, H. Neuroblast lineage identification and lineage-specific Hox gene action during postembryonic development of the subesophageal ganglion in the Drosophila central brain. *Dev. Biol.* **2014**, *390*, 102–115. [CrossRef]

119. Volakakis, N.; Kadkhodaei, B.; Joodmardi, E.; Wallis, K.; Panman, L.; Silvaggi, J.; Spiegelman, B.M.; Perlmann, T. NR4A orphan nuclear receptors as mediators of CREB-dependent neuroprotection. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 12317–12322. [CrossRef]

120. Ly, L.L.; Yoshida, H.; Yamaguchi, M. Nuclear transcription factor Y and its roles in cellular processes related to human disease. *Am. J. Cancer Res.* **2013**, *3*, 339–346.

121. Herring, J.A.; Elison, W.S.; Tessem, J.S. Function of Nr4a Orphan Nuclear Receptors in Proliferation, Apoptosis and Fuel Utilization Across Tissues. *Cells* **2019**, *8*, 1373. [CrossRef]

122. Hale, T.K.; Myers, C.; Maitra, R.; Kolzau, T.; Nishizawa, M.; Braithwaite, A.W. Maf transcriptionally activates the mouse p53 promoter and causes a p53- dependent cell death. *J. Biol. Chem.* **2000**, *275*, 17991–17999. [CrossRef]

123. Jeanneteau, F.; Barrè, C.; Vos, M.; De Vries, C.J.M.; Rouillard, X.; Levesque, D.; Dromard, Y.; Moisan, M.-P.; Duric, V.; Franklin, T.C.; et al. The Stress-Induced Transcription Factor NR4A1 Adjusts Mitochondrial Function and Synapse Number in Prefrontal Cortex. *J. Neurosci.* **2018**, *38*, 1335–1350. [CrossRef]

124. Chen, Y.; Wang, Y.; Ertürk, A.; Kallop, D.; Jiang, Z.; Weimer, R.M.; Kaminker, J.; Sheng, M. Activity-induced Nr4a1 regulates spine density and distribution pattern of excitatory synapses in pyramidal neurons. *Neuron* **2014**, *83*, 431–443. [CrossRef]

125. Jakaria, M.; Haque, M.E.; Cho, D.-Y.; Azam, S.; Kim, I.-S.; Choi, D.-K. Molecular Insights into NR4A2(Nurr1): An Emerging Target for Neuroprotective Therapy Against Neuroinflammation and Neuronal Cell Death. *Mol. Neurobiol.* **2019**, *56*, 5799–5814. [CrossRef]

126. Corley, S.M.; Tsai, S.Y.; Wilkins, M.R.; Weickert, C.S. Transcriptomic analysis shows decreased cortical expression of nr4a1, nr4a2 and rxrb in schizophrenia and provides evidence for nuclear receptor dysregulation. *PLoS ONE* **2016**, *11*, e0166944. [CrossRef]

127. Tsai, S.-Y.; Catts, V.S.; Fullerton, J.M.; Corley, S.M.; Fillman, S.G.; Weickert, C.S. Nuclear Receptors and Neuroinflammation in Schizophrenia. *Mol. Neuropsychiatry* **2017**, *3*, 181–191. [CrossRef]

128. Xiao, G.; Sun, T.; Songming, C.; Cao, Y. NR4A1 enhances neural survival following oxygen and glucose deprivation: An in vitro study. *J. Neurol. Sci.* **2013**, *330*, 78–84. [CrossRef]

129. Rouillard, C.; Baillargeon, J.; Paquet, B.; St-Hilaire, M.; Maheux, J.; Lévesque, C.; Darlix, N.; Majeur, S.; Lévesque, D. Genetic disruption of the nuclear receptor Nur77 (Nr4a1) in rat reduces dopamine cell loss and L-Dopa-induced dyskinesia in experimental Parkinson's disease. *Exp. Neurol.* **2018**, *304*, 143–153. [CrossRef]

130. Zhao, L.G.; Tang, Y.; Tan, J.Z.; Wang, J.W.; Chen, G.J.; Zhu, B.L. The effect of NR4A1 on APP metabolism and tau phosphorylation. *Genes Dis.* **2018**, *5*, 342–348. [CrossRef]

131. Bao, X.J.; Wang, G.C.; Zuo, F.X.; Li, X.Y.; Wu, J.; Chen, G.; Dou, W.C.; Guo, Y.; Shen, Q.; Wang, R.Z. Transcriptome profiling of the subventricular zone and dentate gyrus in an animal model of Parkinson's disease. *Int. J. Mol. Med.* **2017**, *40*, 771–783. [CrossRef]

132. Chatterjee, S.; Walsh, E.N.; Yan, A.L.; Giese, K.P.; Safe, S.; Abel, T. Pharmacological activation of Nr4a rescues age-associated memory decline. *Neurobiol. Aging* **2020**, *85*, 140–144. [CrossRef] [PubMed]

133. Munoz-Tello, P.; Lin, H.; Khan, P.; de Vera, I.M.; Kamenecka, T.; Kojetin, D. Assessment of NR4A Ligands that Directly Bind and Modulate the Orphan Nuclear Receptor Nurr1. *bioRxiv* **2020**. [CrossRef] [PubMed]

134. Bridi, M.S.; Hawk, J.D.; Chatterjee, S.; Safe, S.; Abel, T. Pharmacological Activators of the NR4A Nuclear Receptors Enhance LTP in a CREB/CBP-Dependent Manner. *Nat. Publ. Gr.* **2016**, *42*, 1243–1253. [CrossRef] [PubMed]

135. Ruiz-Sánchez, E.; Jiménez-Genchi, J.; Alcántara-Flores, Y.M.; Castañeda-González, C.J.; Aviña-Cervantes, C.L.; Yescas, P.; del Socorro González-Valadez, M.; Martínez-Rodríguez, N.; Ríos-Ortiz, A.; González-González, M.; et al. Working memory deficits in schizophrenia are associated with the rs34884856 variant and expression levels of the NR4A2 gene in a sample Mexican population: A case control study. *BMC Psychiatry* **2021**, *21*, 86. [CrossRef] [PubMed]

136. Novak, G.; Zai, C.C.; Mirkhani, M.; Shaikh, S.; Vincent, J.B.; Meltzer, H.; Lieberman, J.A.; Strauss, J.; Lévesque, D.; Kennedy, J.L.; et al. Replicated association of the NR4A3 gene with smoking behaviour in schizophrenia and in bipolar disorder. *Genes Brain Behav.* **2010**, *9*, 910–917. [CrossRef] [PubMed]

137. Muto, A.; Tashiro, S.; Tsuchiya, H.; Kume, A.; Kanno, M.; Ito, E.; Yamamoto, M.; Igarashi, K. Activation of Maf/AP-1 repressor Bach2 by oxidative stress promotes apoptosis and its interaction with promyelocytic leukemia nuclear bodies. *J. Biol. Chem.* **2002**, *277*, 20724–20733. [CrossRef]

138. Peng, S.; Lalani, S.; Leavenworth, J.W.; Ho, I.C.; Pauza, M.E. c-Maf interacts with c-Myb to down-regulate Bcl-2 expression and increase apoptosis in peripheral CD4 cells. *Eur. J. Immunol.* **2007**, *37*, 2868–2880. [CrossRef]

139. Katsuoka, F.; Motohashi, H.; Tamagawa, Y.; Kure, S.; Igarashi, K.; Engel, J.D.; Yamamoto, M. Small Maf compound mutants display central nervous system neuronal degeneration, aberrant transcription, and Bach protein mislocalization coincident with myoclonus and abnormal startle response. *Mol. Cell. Biol.* **2003**, *23*, 1163–1174. [CrossRef]

140. Jiang, Q.; Mao, H.; He, G.; Mao, X. Targeting the oncogenic transcription factor c-Maf for the treatment of multiple myeloma. *Cancer Lett.* **2022**, *543*, 215791. [CrossRef]

141. Balamurugan, K.; Sterneck, E. The Many Faces of C/EBPδ and their Relevance for Inflammation and Cancer. *Int. J. Biol. Sci.* **2013**, *9*, 917–933. [CrossRef]

142. Pulido-Salgado, M.; Vidal-Taboada, J.M.; Saura, J. C/EBPβ and C/EBPδ transcription factors: Basic biology and roles in the CNS. *Prog. Neurobiol.* **2015**, *132*, 1–33. [CrossRef] [PubMed]

143. Kfoury, N.; Kapatos, G. Identification of neuronal target genes for CCAAT/Enhancer Binding Proteins. *Mol. Cell. Neurosci.* **2009**, *40*, 313–327. [CrossRef] [PubMed]

144. Cortes-Canteli, M.; Aguilar-Morante, D.; Sanz-SanCristobal, M.; Megias, D.; Santos, A.; Perez-Castillo, A. Role of C/EBPβ transcription factor in adult hippocampal neurogenesis. *PLoS ONE* **2011**, *6*, e24842. [CrossRef] [PubMed]

145. Meir, O.; Dvash, E.; Werman, A.; Rubinstein, M. C/EBP-β regulates endoplasmic reticulum stress-triggered cell death in mouse and human models. *PLoS ONE* **2010**, *5*, e9516. [CrossRef]

146. Moore, F.; Santin, I.; Nogueira, T.C.; Gurzov, E.N.; Marselli, L.; Marchetti, P.; Eizirik, D.L. The transcription factor C/EBP delta has anti-apoptotic and anti-inflammatory roles in pancreatic beta cells. *PLoS ONE* **2012**, *7*, e31062. [CrossRef]

147. Cortes-Canteli, M.; Luna-Medina, R.; Sanz-SanCristobal, M.; Alvarez-Barrientos, A.; Santos, A.; Perez-Castillo, A. CCAAT/enhancer binding protein β deficiency provides cerebral protection following excitotoxic injury. *J. Cell Sci.* **2008**, *121*, 1224–1234. [CrossRef]

148. Wang, Z.H.; Gong, K.; Liu, X.; Zhang, Z.; Sun, X.; Wei, Z.Z.; Yu, S.P.; Manfredsson, F.P.; Sandoval, I.M.; Johnson, P.F.; et al. C/EBPβ regulates delta-secretase expression and mediates pathogenesis in mouse models of Alzheimer's disease. *Nat. Commun.* **2018**, *9*, 1784. [CrossRef]

149. Ramberg, V.; Tracy, L.M.; Samuelsson, M.; Nilsson, L.N.G.; Iverfeldt, K. The CCAAT/enhancer binding protein (C/EBP) δ is differently regulated by fibrillar and oligomeric forms of the Alzheimer amyloid-β peptide. *J. Neuroinflamm.* **2011**, *8*, 34. [CrossRef]

150. Nadeau, S.; Hein, P.; Fernandes, K.J.L.; Peterson, A.C.; Miller, F.D. A transcriptional role for C/EBP β in the neuronal response to axonal injury. *Mol. Cell. Neurosci.* **2005**, *29*, 525–535. [CrossRef]

151. Chen, C.M.; Wu, C.T.; Chiang, C.K.; Liao, B.W.; Liu, S.H. C/EBP Homologous Protein (CHOP) Deficiency Aggravates Hippocampal Cell Apoptosis and Impairs Memory Performance. *PLoS ONE* **2012**, *7*, e40801. [CrossRef]

152. Nashine, S.; Liu, Y.; Kim, B.J.; Clark, A.F.; Pang, I.H. Role of C/EBP Homologous Protein in Retinal Ganglion Cell Death After Ischemia/Reperfusion Injury. *Invest. Ophthalmol. Vis. Sci.* **2015**, *56*, 221–231. [CrossRef] [PubMed]

153. Seto, Y.; Ishiwata, S.; Hoshino, M. Characterization of Olig2 expression during cerebellar development. *Gene Expr. Patterns* **2014**, *15*, 1–7. [CrossRef]

154. Gaber, Z.B.; Novitch, B.G. All the embryo's a stage, and Olig2 in its time plays many parts. *Neuron* **2011**, *69*, 833–835. [CrossRef] [PubMed]

155. Esain, V.; Postlethwait, J.H.; Charnay, P.; Ghislain, J. FGF-receptor signalling controls neural cell diversity in the zebrafish hindbrain by regulating olig2 and sox9. *Development* **2010**, *137*, 33–42. [CrossRef] [PubMed]

156. Cui, Q.L.; Fragoso, G.; Miron, V.E.; Darlington, P.J.; Mushynski, W.E.; Antel, J.; Almazan, G. Response of human oligodendrocyte progenitors to growth factors and axon signals. *J. Neuropathol. Exp. Neurol.* **2010**, *69*, 930–944. [CrossRef]

157. Allahdadi, K.J.; De Santana, T.A.; Santos, G.C.; Azevedo, C.M.H.; Mota, R.A.; Nonaka, C.K.; Silva, D.N.; Valim, C.X.R.; Figueira, C.P.; Dos Santos, W.L.C.; et al. IGF-1 overexpression improves mesenchymal stem cell survival and promotes neurological recovery after spinal cord injury. *Stem Cell Res. Ther.* **2019**, *10*, 146. [CrossRef] [PubMed]

158. Furusho, M.; Kaga, Y.; Ishii, A.; Hébert, J.M.; Bansal, R. Fibroblast Growth Factor Signaling Is Required for the Generation of Oligodendrocyte Progenitors from the Embryonic Forebrain. *J. Neurosci.* **2011**, *31*, 5055–5066. [CrossRef]

159. Sims, R.; Hollingworth, P.; Moskvina, V.; Dowzell, K.; O'Donovan, M.C.; Powell, J.; Lovestone, S.; Brayne, C.; Rubinsztein, D.; Owen, M.J.; et al. Evidence that variation in the oligodendrocyte lineage transcription factor 2 (OLIG2) gene is associated with psychosis in Alzheimer's disease. *Neurosci. Lett.* **2009**, *461*, 54–59. [CrossRef]

160. Komatsu, H.; Takeuchi, H.; Kikuchi, Y.; Ono, C.; Yu, Z.; Iizuka, K.; Takano, Y.; Kakuto, Y.; Funakoshi, S.; Ono, T.; et al. Ethnicity-Dependent Effects of Schizophrenia Risk Variants of the OLIG2 Gene on OLIG2 Transcription and White Matter Integrity. *Schizophr. Bull.* **2020**, *46*, 1619–1628. [CrossRef]

161. Gouvêa-Junqueira, D.; Falvella, A.C.B.; Antunes, A.S.L.M.; Seabra, G.; Brandão-Teles, C.; Martins-de-Souza, D.; Crunfli, F. Novel Treatment Strategies Targeting Myelin and Oligodendrocyte Dysfunction in Schizophrenia. *Front. Psychiatry* **2020**, *11*, 379. [CrossRef]

162. Tsigelny, I.F.; Mukthavaram, R.; Kouznetsova, V.L.; Chao, Y.; Babic, I.; Nurmemmedov, E.; Pastorino, S.; Jiang, P.; Calligaris, D.; Agar, N.; et al. Multiple spatially related pharmacophores define small molecule inhibitors of OLIG2 in glioblastoma. *Oncotarget* **2015**, *8*, 22370–22384. [CrossRef] [PubMed]

163. Alton, G.; Kesari, S. Novel small molecule inhibitors of the OLIG2 transcription factor: Promising new therapeutics for glioblastoma. *Future Oncol.* **2016**, *12*, 1001–1004. [CrossRef]

164. Chen, X.; Wang, F.; Gan, J.; Zhang, Z.; Liang, X.; Li, T.; Huang, N.; Zhao, X.; Mei, F.; Xiao, L. Myelin Deficits Caused by Olig2 Deficiency Lead to Cognitive Dysfunction and Increase Vulnerability to Social Withdrawal in Adult Mice. *Neurosci. Bull.* **2020**, *36*, 419–426. [CrossRef] [PubMed]

165. Johns, T.; Greenall, S.; Chen, S.; Stewart, R.; Alton, G.; Kesari, S. DDIS-19. CT-179: An Inhibitor of The Olig2 Transcription Factor with Potent Anti-Tumour Activity In Brain Cancer. *Neuro. Oncol.* **2018**, *20*, vi73. [CrossRef]

166. Wegener, A.; Deboux, C.; Bachelin, C.; Frah, M.; Kerninon, C.; Seilhean, D.; Weider, M.; Wegner, M.; Nait-Oumesmar, B. Gain of Olig2 function in oligodendrocyte progenitors promotes remyelination. *Brain* **2015**, *138*, 120–135. [CrossRef]

167. Szu, J.; Wojcinski, A.; Jiang, P.; Kesari, S. Impact of the Olig Family on Neurodevelopmental Disorders. *Front. Neurosci.* **2021**, *15*, 332. [CrossRef] [PubMed]

168. Uchida, Y. Molecular mechanisms of regeneration in Alzheimer's disease brain. *Geriatr. Gerontol. Int.* **2010**, *10*, S158–S168. [CrossRef]

169. Stewart, S.E.; Platko, J.; Fagerness, J.; Birns, J.; Jenike, E.; Smoller, J.W.; Perlis, R.; Leboyer, M.; Delorme, R.; Chabane, N.; et al. A genetic family-based association study of OLIG2 in obsessive-compulsive disorder. *Arch. Gen. Psychiatry* **2007**, *64*, 209–215. [CrossRef]

170. Satoh, J.-I.; Asahina, N.; Kitano, S.; Kino, Y. A Comprehensive Profile of ChIP-Seq-Based Olig2 Target Genes in Motor Neuron Progenitor Cells Suggests the Possible Involvement of Olig2 in the Pathogenesis of Amyotrophic Lateral Sclerosis. *J. Cent. Nerv. Syst. Dis.* **2015**, *7*, JCNSD.S23210. [CrossRef]

171. Tan, B.T.; Yu, J.; Yin, Y.; Jia, G.W.; Jiang, W.; Yu, L.H. The Olig family affects central nervous system development and disease. *Neural Regen. Res.* **2014**, *9*, 329–336. [CrossRef]

172. Zhou, B.; Zhu, Z.; Ransom, B.R.; Tong, X. Oligodendrocyte lineage cells and depression. *Mol. Psychiatry* **2020**, *26*, 103–117. [CrossRef] [PubMed]

173. Raabe, F.J.; Galinski, S.; Papiol, S.; Falkai, P.G.; Schmitt, A.; Rossner, M.J. Studying and modulating schizophrenia-associated dysfunctions of oligodendrocytes with patient-specific cell systems. *NPJ Schizophr.* **2018**, *4*, 23. [CrossRef] [PubMed]

174. Fessel, J. Formulating treatment of major psychiatric disorders: Algorithm targets the dominantly affected brain cell-types. *Discov. Ment. Health* **2023**, *3*, 3. [CrossRef]

175. Cai, S.; Lv, Y.; Huang, K.; Zhang, W.; Kang, Y.; Huang, L.; Wang, J. Association of rs1059004 polymorphism in the OLIG2 locus with whole-brain functional connectivity in first-episode schizophrenia. *Behav. Brain Res.* **2020**, *379*, 112392. [CrossRef] [PubMed]

176. Valdés-Tovar, M.; Rodríguez-Ramírez, A.M.; Rodríguez-Cárdenas, L.; Sotelo-Ramírez, C.E.; Camarena, B.; Sanabrais-Jiménez, M.A.; Solís-Chagoyán, H.; Argueta, J.; López-Riquelme, G.O. Insights into myelin dysfunction in schizophrenia and bipolar disorder. *World J. Psychiatry* **2022**, *12*, 264. [CrossRef]

177. Van Der Raadt, J.; Van Gestel, S.H.C.; Kasri, N.N.; Albers, C.A. ONECUT transcription factors induce neuronal characteristics and remodel chromatin accessibility. *Nucleic Acids Res.* **2019**, *47*, 5587–5602. [CrossRef]

178. Patel, T.; Hammelman, J.; Closser, M.; Gifford, D.K.; Wichterle, H. General and cell-type-specific aspects of the motor neuron maturation transcriptional program. *bioRxiv* **2021**. [CrossRef]

179. Hahn, O.; Foltz, A.G.; Atkins, M.; Kedir, B.; Moran-Losada, P.; Guldner, I.H.; Munson, C.; Kern, F.; Pálovics, R.; Lu, N.; et al. A spatiotemporal map of the aging mouse brain reveals white matter tracts as vulnerable foci. *bioRxiv* **2022**. [CrossRef]

180. Chakrabarty, K.; Von Oerthel, L.; Hellemons, A.; Clotman, F.; Espana, A.; Koerkamp, M.G.; Holstege, F.C.P.; Pasterkamp, R.J.; Smidt, M.P. Genome wide expression profiling of the mesodiencephalic region identifies novel factors involved in early and late dopaminergic development. *Biol. Open* **2012**, *1*, 693–704. [CrossRef]

181. Toch, M.; Harris, A.; Schakman, O.; Kondratskaya, E.; Boulland, J.L.; Dauguet, N.; Debrulle, S.; Baudouin, C.; Hidalgo-Figueroa, M.; Gow, A.; et al. Onecut-dependent Nkx6.2 transcription factor expression is required for proper formation and activity of spinal locomotor circuits. *Sci. Rep.* **2020**, *10*, 996. [CrossRef]

182. Ulmke, P.A.; Sakib, M.S.; Ditte, P.; Sokpor, G.; Kerimoglu, C.; Pham, L.; Xie, Y.; Mao, X.; Rosenbusch, J.; Teichmann, U.; et al. Molecular Profiling Reveals Involvement of ESCO2 in Intermediate Progenitor Cell Maintenance in the Developing Mouse Cortex. *Stem Cell Rep.* **2021**, *16*, 968–984. [CrossRef]

183. Francius, C.; Clotman, F. Dynamic expression of the Onecut transcription factors HNF-6, OC-2 and OC-3 during spinal motor neuron development. *Neuroscience* **2010**, *165*, 116–129. [CrossRef] [PubMed]

184. Bhatnagar, S.; Chertkow, H.; Schipper, H.M.; Yuan, Z.; Shetty, V.; Jenkins, S.; Jones, T.; Wang, E. Increased microRNA-34c abundance in Alzheimer's disease circulating blood plasma. *Front. Mol. Neurosci.* **2014**, *7*, 2. [CrossRef] [PubMed]

185. Hin, N.; Newman, M.; Kaslin, J.; Douek, A.M.; Lumsden, A.; Nik, S.H.M.; Dong, Y.; Zhou, X.F.; Manucat-Tan, N.B.; Ludington, A.; et al. Accelerated brain aging towards transcriptional inversion in a zebrafish model of the K115fs mutation of human PSEN2. *PLoS ONE* **2020**, *15*, e0227258. [CrossRef]

186. Cai, Y.; Wang, M.; Cui, Y.; Tan, Z.; Jiang, Y. Differential Expression Profile of lncRNA in Glioma Cells and the Effect of lncRNA NKX3-1 on Glioma Cells Through Fem1b/SPDEF Pathway. *Front. Oncol.* **2021**, *11*, 2734. [CrossRef] [PubMed]

187. Ducker, C.; Shaw, P.E. Ubiquitin-Mediated Control of ETS Transcription Factors: Roles in Cancer and Development. *Int. J. Mol. Sci.* **2021**, *22*, 5119. [CrossRef] [PubMed]

188. Kong, W.; Mou, X.; Deng, J.; Di, B.; Zhong, R.; Wang, S.; Yang, Y.; Zeng, W. Differences of immune disorders between Alzheimer's disease and breast cancer based on transcriptional regulation. *PLoS ONE* **2017**, *12*, e0180337. [CrossRef]

189. Tansey, K.E.; Cameron, D.; Hill, M.J. Genetic risk for Alzheimer's disease is concentrated in specific macrophage and microglial transcriptional networks. *Genome Med.* **2018**, *10*, 14. [CrossRef]

190. Arefin, A.S.; Mathieson, L.; Johnstone, D.; Berretta, R.; Moscato, P. Unveiling Clusters of RNA Transcript Pairs Associated with Markers of Alzheimer's Disease Progression. *PLoS ONE* **2012**, *7*, e45535. [CrossRef]

191. Tay, N.; Macare, C.; Liu, Y.; Ruggeri, B.; Jia, T.; Chu, C.; Biondo, F.; Ing, A.; Luo, Q.; Sarkysian, D.; et al. Allele-specific methylation of SpDEF: A novel moderator of psychosocial stress and substance abuse. *Am. J. Psychiatry* **2019**, *176*, 146–155. [CrossRef]

192. Hughes, R.; Kristiansen, M.; Lassot, I.; Desagher, S.; Mantovani, R.; Ham, J. NF-Y is essential for expression of the proapoptotic bim gene in sympathetic neurons. *Cell Death Differ.* **2010**, *18*, 937–947. [CrossRef] [PubMed]

193. Gatta, R.; Dolfini, D.; Mantovani, R. NF-Y joins E2Fs, p53 and other stress transcription factors at the apoptosis table. *Cell Death Dis.* **2011**, *2*, e162. [CrossRef] [PubMed]

194. Gurtner, A.; Fuschi, P.; Martelli, F.; Manni, I.; Artuso, S.; Simonte, G.; Ambrosino, V.; Antonini, A.; Folgiero, V.; Falcioni, R.; et al. Transcription factor NF-Y induces apoptosis in cells expressing wild-type p53 through E2F1 upregulation and p53 activation. *Cancer Res.* **2010**, *70*, 9711–9720. [CrossRef]

195. Olajide, O.J.; Suvanto, M.E.; Chapman, C.A. Molecular mechanisms of neurodegeneration in the entorhinal cortex that underlie its selective vulnerability during the pathogenesis of Alzheimer's disease. *Biol. Open* **2021**, *10*, bio056796. [CrossRef]

196. Yamanaka, T.; Tosaki, A.; Kurosawa, M.; Matsumoto, G.; Koike, M.; Uchiyama, Y.; Maity, S.N.; Shimogori, T.; Hattori, N.; Nukina, N. NF-Y inactivation causes atypical neurodegeneration characterized by ubiquitin and p62 accumulation and endoplasmic reticulum disorganization. *Nat. Commun.* **2014**, *5*, 3354. [CrossRef] [PubMed]

197. Franco, H.L.; Casasnovas, J.; Rodríguez-Medina, J.R.; Cadilla, C.L. Redundant or separate entities?—Roles of Twist1 and Twist2 as molecular switches during gene transcription. *Nucleic Acids Res.* **2011**, *39*, 1177–1186. [CrossRef]

198. Twist Is a Potential Oncogene That Inhibits Apoptosis. Available online: http://genesdev.cshlp.org/content/13/17/2207 (accessed on 9 February 2023).

199. Puisieux, A.; Valsesia-Wittmann, S.; Ansieau, S. A twist for survival and cancer progression. *Br. J. Cancer* **2005**, *94*, 13–17. [CrossRef] [PubMed]

200. Floc'h, N.; Kolodziejski, J.; Akkari, L.; Simonin, Y.; Ansieau, S.; Puisieux, A.; Hibner, U.; Lassus, P. Modulation of Oxidative Stress by Twist Oncoproteins. *PLoS ONE* **2013**, *8*, e72490. [CrossRef]

201. Jembrek, M.J.; Oršolić, N.; Mandić, L.; Sadžak, A.; Šegota, S. Anti-Oxidative, Anti-Inflammatory and Anti-Apoptotic Effects of Flavonols: Targeting Nrf2, NF-κB and p53 Pathways in Neurodegeneration. *Antioxidants* **2021**, *10*, 1628. [CrossRef]

202. Pan, Y.; Zhu, Y.; Yang, W.; Tycksen, E.; Liu, S.; Palucki, J.; Zhu, L.; Sasaki, Y.; Sharma, M.K.; Kim, A.H.; et al. The role of Twist1 in mutant huntingtin-induced transcriptional alterations and neurotoxicity. *J. Biol. Chem.* **2018**, *293*, 11850–11866. [CrossRef]

203. Yang, W.; Xiang, Y.; Liao, M.J.; Wu, P.F.; Yang, L.; Huang, G.H.; Shi, B.Z.; Yi, L.; Lv, S.Q. Presenilin1 inhibits glioblastoma cell invasiveness via promoting Sortilin cleavage. *Cell Commun. Signal.* **2021**, *19*, 1112. [CrossRef] [PubMed]