Is Autism a PIN1 Deficiency Syndrome? A Proposed Etiological Role for Glyphosate

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Abstract

Autism is a neurodevelopmental disorder whose prevalence has increased dramatically in the United States over the past two decades. It is characterized by stereotyped behaviors and impairments in social interaction and communication. In this paper, we present evidence that autism can be viewed as a PIN1 deficiency syndrome. PIN1 (Peptidylprolyl Cis/Trans Isomerase, NIMA-Interacting 1) is a peptidylprolyl cis/trans isomerase, and it has widespread influences in biological organisms. Broadly speaking, PIN1 deficiency is linked to many neurodegenerative diseases, whereas PIN1 overexpression is linked to cancer. Death associated protein kinase 1 (DAPK1) strongly inhibits PIN1, and the hormone melatonin inhibits DAPK1. Melatonin deficiency is strongly linked to autism. It has recently been shown that glyphosate exposure to rats inhibits melatonin synthesis due to increased glutamate release from glial cells and increased expression of metabotropic glutamate receptors. Glyphosate's inhibition of melatonin leads to a reduction in PIN1 availability in neurons. In this paper, we show that PIN1 deficiency can explain many of the unique morphological features of autism, including increased dendritic spine density, missing or thin corpus callosum and reduced bone density. We show how PIN1 deficiency disrupts the functioning of powerful high level signaling molecules, such as nuclear factor erythroid 2-related factor 2 (NRF2) and p53. Dysregulation of both of these proteins has been linked to autism. Severe depletion of glutathione in the brain resulting from chronic exposure to oxidative stressors and extracellular glutamate leads to oxidation of the cysteine residue in PIN1, inactivating the protein and further contributing to PIN1 deficiency. Impaired autophagy leads to increased sensitivity of neurons to ferroptosis. Finally, we consider evidence of the potential toxic effects of the mRNA SARS-CoV-2 vaccines in the light of metabolic defects in autism, and we propose that children with autism would be especially sensitive to damage from the vaccines.

Keywords

Autism, PIN1, glyphosate, apoptosis, mRNA vaccines, DAPK1, melatonin, glutathione, NRF2, p53.

Introduction

Autism is a neurodevelopmental disorder characterized mainly by impaired social interactions, repetitive behaviors, and limited verbal communications [1]. It is also associated with an increased risk to a host of emotional and psychological conditions, including depression, anxiety, gender dysphoria, schizophrenia, catatonia, and psychosis [2]. While genetics plays a role in autism risk, environmental exposures are likely driving the epidemic. Environmental toxicants induce inflammation, oxidative stress, and mitochondrial dysfunction in the brain, leading to neuropathology [3]. Environmental risk factors include air pollution, nutritional deficiencies, pesticides, toxic metal exposures, infection, and brain trauma [3-8].

Early diagnosis of autism has presented a significant challenge to clinicians for decades [9]. It is generally recognized that autism diagnoses can be divided into two categories: children diagnosed before age two (early-onset autism) and those diagnosed after age two (regressive autism). There is some evidence that children with regressive autism exhibit behaviors prior to regression that are predictive of it [10,11]. That said, another study showed that nearly half of the cases of regressive autism have no such discernible behaviors – the child regresses after a previously normal developmental phase [12].

Through the main body of this paper, we will describe in detail the mechanistic links we believe exist between glyphosate exposure and the myriad pathological changes found in the brain and other systems of children with autism. We will forego a discussion of the early vs regressive autism until near the end, where we will show how our exposure model of autism etiology can shed light on the mystery around autism's variable childhood age of onset.

The prevalence of autism has increased dramatically over the past two decades in the United States, strongly correlated with the dramatic rise in the use of glyphosate, the active ingredient in the herbicide Roundup, on core crops [13]. While correlation does not prove causation, there is now significant evidence that glyphosate causes neurodevelopmental problems, lending strength to the temporal correlations. In an epidemiological study, children who were born within 2000m of an agricultural source of glyphosate had a significantly increased risk to developing autism [14] While many other factors, both genetic and environmental, contribute to autism, we will show that glyphosate may be the most significant cause of the epidemic [13].

One of the known causes of autism is maternal immune activation (MIA) due to infection during pregnancy. Studies have shown that behavioral abnormalities in the offspring of rodents following MIA are characteristic of schizophrenia and autism [15]. Perturbations of the mother's gut microbiota during pregnancy can induce autism-like behaviors in mice [16]. Maternal glyphosate exposure at low doses has been shown to cause MIA in pregnant mice, associated with autism-like behaviors in the offspring, through increased expression of soluble epoxide hydrolase (sEH) [17]. Inflammation in the brain upregulates the expression of sEH, an enzyme that oxidizes polyunsaturated fatty acids (PUFAs) [15]. It has been proposed that prophylactic treatment to suppress the expression of sEH could be a beneficial treatment option for autism [17].

The human brain accounts for only 2% of the body mass but consumes 20% of the oxygen. It also has high amounts of PUFAs that are susceptible to oxidative damage through lipid peroxidation, leading to mitochondrial dysfunction [18]. Children naturally have low levels of glutathione, and glutathione deficiency is a common feature associated with autism, along with increased oxidative stress in the brain [19]. Several oxidative stress markers, such as lipid peroxides, malondialdehyde (MDA), protein carbonyls and 3-nitrotyrosine, are elevated in association with autism, and correlated with autism severity [20].

A study comparing children with autism against normal controls found a significant block in cystathionine formation associated with an accumulation of homocysteine and low levels of the essential antioxidant, glutathione. A low level of urinary methionine and S-adenosyl methionine (SAMe) indicates deficiencies in methylation pathways. A significant number of the children who were studied showed deficiencies in three B vitamins: B6 (pyridoxine), B9 (folate), and B12 (cobalamin) [21]. The conversion of homocysteine to cysteine in the transsulfuration pathway depends on pyridoxine as a cofactor [22]. The synthesis of methionine from cysteine depends on both folate and methylcobalamin [23]. Cultured neurons are protected from glutamate-induced neurotoxicity by administration of methylcobalamin, likely through membrane alteration by SAMe [24].

An impaired sulfation pathway was first recognized as a risk factor in autism in a paper published by Waring and Klovrza al. in 2000 [25]. Cystathionine β-synthase converts homocysteine to cystathionine, and this is the rate-limiting step of the transsulfuration pathway, ultimately producing sulfate and phosphoadenosine phosphosulfate (PAPS), the universal sulfate donor. Both ascorbate (vitamin C) and retinoic acid (vitamin A) are cofactors in this pathway, as shown in detail by McCully in 2011 [26]. Both ascorbate and retinoic acid have been shown to have therapeutic value in treating autism. In a study published in 2018, vitamin A deficiency was found in 78% of autistic children, and vitamin A supplementation improved autistic symptoms [27]. In a genetic mouse model of autism, retinoic acid treatment rescued social deficits [28]. In a valproate-induced mouse model of autism, prenatal exposure to ascorbate attenuated the effects of valproate on the autistic behaviors of the pups [29]. A paper published by Alvarez-Moya et al. in 2022 showed conclusively that glyphosate is genotoxic to erythrocytes of salamanders and tilapia, as well as human lymphocytes. They also showed that supplementation with ascorbate and resveratrol (an antioxidant) reduced glyphosate's genotoxic effects [30].

Children with autism commonly have sleep disorders and dysregulated circadian rhythms, suggesting disturbances in melatonin metabolism [31]. Melatonin is enzymatically degraded in the liver to 6-hydroxymelatonin and excreted in the urine as 6-sulfatoxymelatonin [32]. Several studies have shown that nocturnal levels of 6-sulfatoxymelatonin are significantly reduced in association with autism [33,34], likely due to impaired melatonin synthesis in the pineal gland. Melatonin is synthesized in the pineal gland from serotonin, through the addition of both an acetyl group and a methyl group. Serotonin is derived from the amino acid tryptophan, a product of the shikimate pathway in plants and microbes. Glyphosate's primary mechanism of toxicity in plants is believed to be its suppression of the shikimate pathway [35,36]. Therefore, glyphosate likely interferes with tryptophan synthesis by the gut microbes. Mice with a null mutation in the enzyme tryptophan hydroxylase (and therefore severely deficient in brain serotonin) displayed multiple characteristic features of autism [37]. S-adenosyl methionine is the source of the methyl group, so its deficiency would likely also lead to a deficiency in melatonin [38]. Importantly, glyphosate exposure to rats prenatally and perinatally caused a 43% reduction in serum melatonin levels measured after the rat pups had matured, likely through epigenetic effects [39].

A remarkable postmortem study showed disturbingly low levels of various cobalamin conjugates in autistic brains [40]. The authors measured levels of five different cobalamin species: hydroxycobalamin, methylcobalamin, adenosylcobalamin, cyanocobalamin, and glutathionylcobalamin. All of the conjugated cobalamins were significantly reduced in association with autism, particularly glutathionylcobalamin, which could be due in part to a deficiency in glutathione. Glutathionylcobalamin is an intermediate in the formation of methylcobalamin [41]. Methylcobalamin injections increase production of melatonin by the rat pineal gland, indicating a dependency on methylcobalamin to catalyze melatonin synthesis [42].

Proline is one of the 20 coding amino acids, and it has unique properties that play a powerful role in biology. Proline is the only coding amino acid that exists in two different isomers (cis- and trans-), which contain the exact same molecular formula but with different arrangements in space. Interestingly, proline can spontaneously switch back and forth between cis- and trans- isomers when it is embedded in a peptide sequence, although this happens infrequently. There is a class of enzymes called peptidylprolyl isomerases (PPIases) that catalyze the switch, and, when active, they can increase the rate of flipping from a cis- to a trans- isoform of proline by a factor of 1,000 [43].

PPIase NIMA-Interacting 1 (PIN1) is a member of the class of PPIases, and it has diverse roles in human development and the response to cellular stressors. It acts as a molecular switch by inducing conformational changes in the affected protein by isomerizing prolines [44]. Prolyl isomerization is involved in many cellular processes, including apoptosis, mitosis, cell signaling, ion channel gating, amyloidogenesis and neurodegeneration [45]. PIN1 regulates the function of several powerful signaling proteins, including catalytic activity, phosphorylation status, protein interactions, subcellular location and protein stability [46,47]. It plays a central role in phosphorylation pathways, which regulate many aspects of cellular activities in response to stressors, including the DNA damage response, antioxidant defenses, and programmed death. It is also in-

volved in the balance between excitatory and inhibitory neurotransmitter responses, and in the maturation of neurons during early life [48]. PIN1 is overexpressed in association with many cancers [49]. By contrast, it is under-expressed in association with many neurogenerative diseases [48].

PIN1 has a very specific function, which is to switch a proline residue preceded by serine or threonine from the cis- to the trans- isomer. It is only active when the preceding serine or threonine is phosphorylated. Furthermore, enzymes that dephosphorylate the preceding residue, particularly protein phosphatase 2A (PP2A), are only active when the proline is in the trans- state [50]. Thus, removal of the phosphate anion depends upon PIN1's activity in maintaining the proline residue in the trans- configuration. This remarkably complex epigenetic effect has powerful influences on both the activity of the altered protein and its localization within the cell (e.g., nucleus or mitochondria). Protein phosphorylation is probably the most common post-translational modification in proteins, and 96% of the phosphorylations are applied to the (Ser/Thr)-Pro motif [51].

In this paper, we will develop the argument that autism can be characterized as a PIN1 deficiency syndrome. We will show that many of the neurodevelopmental defects and morphological features of autism are linked to PIN1 deficiency. We also argue that the disruptions in synaptic signaling linked to autism can be explained by PIN1 deficiency. Many of the genetic links to autism involve proteins that are regulated by PIN1. We provide substantial evidence from the research literature that glyphosate's mechanisms of toxicity can be expected to suppress PIN1 activity, either directly through cysteine oxidation by reactive oxygen species induced by glyphosate, or via suppression of melatonin synthesis, resulting in DAPK1 overexpression. This effect can explain its link to the autism epidemic. Finally, we hypothesize that autistic children are likely to be highly sensitive to the mRNA vaccines, as many of the toxic effects of the vaccine induce metabolic disruptions that are already ongoing in the autistic brain.

Glyphosate and Autism

Gut dysbiosis plays a role in many neurological diseases, including depression, Alzheimer's disease, Parkinson's disease, and autism [52]. There has been growing awareness recently regarding the complex interactions between the gut microbiome and the brain via the highly interconnected gut-brain axis, a bidirectional communication network [53]. Exposure to glyphosate reduces the abundance of a number of different acid-loving species that produce short chain fatty acids (SCFAs) from dietary fiber [54]. The SCFA butyrate delivered to the liver via the hepatic portal vein is detected by sensors in the liver, and a signal is conveyed to nerve centers in the brain via the vagus nerve which enhances sleep quality [55]. Sleep disorder is a prominent feature of autism [56]. As we mentioned earlier, melatonin deficiency caused by glyphosate likely also plays a role [39].

Butyrate induces the differentiation of immune cells into T-regulatory cells (Tregs), which control inflammation [51]. The prevalence of inflammatory bowel disease (IBD) has increased over time closely in step with the rise in glyphosate usage on core crops [57]. Glyphosate was one of the toxic chemicals identified as a contributor to IBD in a recent publication by Chen et al. [58]. Children with autism are at a significant increased risk to IBD, with an odds ratio (OR) of 1.66 ($p < 0.001$) [59].

Glyphosate exposure to rats for 35 days led to multiple disruptions in the gut. Glyphosate resulted in a decrease in the ratio of villus height to crypt depth in the duodenum and jejunum, a feature associated with celiac disease [60]. In this experiment, glyphosate also caused a decrease in glutathione levels and the activity of antioxidant enzymes, including glutathione peroxidase (Gpx). MDA content was also elevated, indicating PUFA peroxidation. The mRNA expression levels of several proteins associated with inflammation were increased, including interleukin-1β (IL-1β), IL-6, tumor necrosis factor- α (TNF-α), mitogen-activated protein kinase 3 (MAPK3), nuclear factor-ϰB (NF-ϰB,) and caspase-3. The relative abundance of *Firmicutes* and*Lactobacillus* species were reduced, while the abundance of several pathogenic species, mainly Fusobacteria strains, was increased [61]. In a study published in 2022, Fusobacteria were found to be more abundant in the gut of autistic children compared to normal controls [62].

Gluten intolerance is a prevalent feature of autistic children, and many parents have implemented a gluten-

free diet with the hope of healing their childrens' guts [63]. A remarkable case study involved a 5-year-old boy diagnosed with severe autism. Diagnosis of underlying celiac disease motivated implementation of a gluten-free diet along with various nutritional supplements. The child's gastrointestinal symptoms rapidly improved, and symptoms of autism abated. The authors suggested a malabsorption syndrome associated with central nervous system dysfunction [64]. Glyphosate is commonly used on wheat crops as a desiccant just before harvest, and this has resulted in high levels of glyphosate contamination in wheat-based foods [65]. Glyphosate usage on wheat has increased over time, in step with the rise in celiac disease [66].

Glyphosate has been linked to asthma in both human and animal studies. A study focused on the town of Monte Maíz in Córdoba, Argentina examined a possible relationship between glyphosate and asthma in the population there. This town was selected because it is situated in the middle of an agricultural region where glyphosate is heavily used on genetically modified corn and soy crops. Volatile grain dust from pulverized soy and corn grain husk is stored in huge silos in the town. Winds can easily disperse the dust into the surrounding area. Glyphosate and aminomethylphosphonic acid (AMPA) (a toxic breakdown product of glyphosate) were detected in 100% of the soil samples taken near the silos, and the levels of glyphosate and AMPA far exceeded the levels of any other pesticides. The asthma rates were significantly higher overall in the town compared to the rate in Argentina and were highest for those in close vicinity to the silos. The rate of asthma in the 18–45-year-old population living near the silos was more than double the national average [67]. In another study, mothers with asthma were 62% more likely to deliver an infant later diagnosed with autism [68].

In a study on farmers in North Carolina and Iowa, glyphosate, the most commonly used herbicide there, was significantly associated with both asthma and wheeze, whereas no association was found with the related herbicide glufosinate [69]. Exposure of mice to glyphosate-rich air samples induced IL-13 dependent pulmonary inflammation and induced the release of Th2 cytokines, a likely mechanism for increased asthma risk [70].

Glyphosate and Eosinophilic Esophagitis

Eosinophilic Esophagitis (EoE) is an emerging chronic immune-mediated disease that causes damage to the esophagus through excessive fibrosis, mediated by excessive infiltration of eosinophils into the esophagus and overexpression of IL-13. It currently affects one in 1000 people in the United States [71]. EoE was first identified in 1993, and its rate has been rising in prevalence over time since then. In an experiment designed to assess whether glyphosate could be causal in this alarming rise over time, mice were exposed to physiological levels of glyphosate in utero and throughout their lifespan. Chronic glyphosate treatment induced a 2-fold increase in esophageal eosinophils compared to baseline [71].

It is noteworthy that there are several other health conditions that have been found to co-occur with EoE, and it is likely that these correlations point to a common cause, namely glyphosate exposure. One of the strong comorbidities is autism, which is also comorbid with food allergies and gastrointestinal disturbances that co-occur with EoE. A study based in Virginia involving 266 children with a diagnosis of EoE found that 12.7% of them also had a diagnosis of autism [73]. This is much higher than the prevalence in the general population. A study based in Nevada found strong comorbidities between EoE and several different conditions, including gastroesophageal reflux disease (GERD) (3.69%), diseases of the gut (7.26%), asthma (13.4%) and pollen and food allergies (7%) [74]. Adults with autism were found to have a highly significant increased risk of GERD ($p = 0.0001$) [75]. We have already seen that glyphosate is a risk factor for asthma [67].

A study on 56 patients diagnosed with celiac disease found that six of them (10.7%) also had a diagnosis of EoE [76]. It has been hypothesized that glyphosate may be the primary cause of the rise in celiac disease in recent decades, which correlated strongly with the rise in the use of glyphosate on wheat as a desiccant [66]. Children with ASD are at a higher risk of gastrointestinal disorders and gluten intolerance, compared to the general population [77].

Glyphosate and Glutamate Neuroexcitotoxicity

Cattani et al. have demonstrated that maternal exposure of pregnant rats to glyphosate-based herbicide leads to glutamate neuroexcitotoxicity in the hippocampus of the offspring [78]. Exposure of pregnant female Wistar rats to the glyphosate-based herbicide Roundup at the no observed adverse effect level (NOAEL) for maternal toxicity, during pregnancy and lactation, led to significant neuroexcitotoxicity effects in the brains of the pups, due to excess extracellular glutamate [78]. Roundup reduced glutamate uptake from the synapse by astrocytes and increased the release of glutamate into the synaptic cleft by neurons in the hippocampus. Glyphosate suppressed the enzyme glutamine synthetase in astrocytes, impairing their ability to safely store glutamate as glutamine. Glyphosate also reduced the levels of glutathione and increased the levels of lipid peroxidation products [78]. Excess extracellular glutamate disrupts cystine (a cysteine dimer) uptake by cells via the Cystine/Glutamate Antiporter System xc-. This depletes the levels of glutathione, since cysteine is the rate-limiting substrate for glutathione synthesis [79].

In another study by Cattani et al., rats chronically exposed to low-dose glyphosate both prenatally and postnatally exhibited evidence of glutamate-related neurotoxicity at 60 days of age [80]. The exposed rats exhibited oxidative stress markers associated with depressive-like behavior. Astrocyte activation was suggested by elevated serum levels of the astrocytic protein S100B, a marker of astrocyte activation. S100B serum levels have been found to be elevated in association with autism [81]. A study on 40 patients suffering from poisoning by either glyphosate (23) or glufosinate [82] (17) found statistically significant correlations between serum levels of S100B and neurological complications [83].

Glyphosate exposure to goldfish (as Roundup) at low levels induced oxidative stress and suppressed the activities of superoxide dismutase (SOD), glutathione S-transferase (GST), glutathione reductase, and glucose-6-phosphate dehydrogenase in the tissues of the fish. SOD activities were reduced by 51 to 68% in the brain [84]. All these enzymes play important roles in reducing oxidative stress.

A comprehensive review paper with over 200 references detailed the toxic effects of glyphosate specifically on the nervous system. These authors wrote: "The results analyzed herein reflect the capacity of glyphosate to induce oxidative stress, neuroinflammation, and mitochondrial dysfunction, processes that lead to neuronal death by autophagia, necrosis, or apoptosis, as well as the appearance of behavioral and motor disorders." [85], p. 27.

Does Glyphosate Suppress PIN1 in Neurons?

DAPK1 is a stress-responsive calcium/calmodulin (Ca^{2+}/CaM) dependent serine/threonine (Ser/Thr) kinase and a mediator of pro-apoptotic cell death [86]. Among its many other functions, DAPK1 phosphorylates PIN1 on Ser71 in the catalytic active site. This phosphorylation fully inactivates PIN1 catalytic activity, as well as inhibiting its nuclear localization. DAPK1 is upregulated in the brains of patients with Alzheimer's disease, and its overexpression is implicated in Alzheimer's pathology [87]. Melatonin plays a central role in DAPK1 regulation. It binds to DAPK1 and promotes its ubiquitinization, resulting in its clearance through proteasomal degradation [87].

While melatonin is mainly viewed as a molecule that is produced by the pineal gland in the evening to promote sleep, it is also produced by many other cell types. In particular, microglia synthesize abundant melatonin which can transform them from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype. Melatonin synthesized by microglia in the cerebellum shortens the pro-inflammatory phase of activated microglia [88]. Melatonin has many beneficial protective effects on regulatory pathways. It significantly decreases DAPK1 expression in a post-transcriptional manner in neuronal cell lines and mouse primary cortical neurons [87]. Melatonin protects from ferroptosis via the Akt/NRF2/Gpx4 signaling pathway. The likely mechanism could be its suppression of DAPK1, which then allows PIN1 activation, and subsequently NRF2 activation through PIN1 binding, a topic we will return to later [89]. While melatonin increases the expression of NRF2, it also decreases the expression of the inflammatory markers TNF-α, IL-1β, IL-6 and inducible nitric oxide synthase (iNOS) [90].

Another way in which PIN1 can become suppressed is through insufficient levels of the antioxidant glutathione in the cell. When glutathione becomes depleted, PIN1 becomes oxidized by hydrogen peroxide, and this

inactivates it. The PIN1 active site contains an essential cysteine residue (Cys113), which is very sensitive to oxidation. Treatment of PIN1 with hydrogen peroxide results in the oxidation of Cys113 to sulfinic acid, and this reaction completely disables its isomerase activity [91]. This leads to impaired translocation of NRF2 and p53 to the nucleus, which shuts down their activation of a broad spectrum of enzymes that would normally promote antioxidant defenses and cell survival, respectively. We will have more to say about this in a later section.

We shall see in the next section that glyphosate's disturbance of glutamate signaling in the brain leads to severe deficiencies of glutathione in neurons.

Glutamate Neuroexcitotoxicity and Glutathione Depletion

Disturbances in the glutamatergic system are a common feature in autism, with imbalances in both the excitatory and inhibitory networks [92-94]. Glutamate is directly involved in brain development and synaptogenesis, and disrupted glutamatergic signaling is associated not only with autism, but also with epilepsy, schizophrenia, and depression [95]. In one study, children with autism and their family members had elevated levels of glutamate in the blood, along with reduced levels of glutamine [96].

Methylmercury, arsenic, lead, and paraquat exert a common toxic effect by inducing oxidative stress, mitochondrial damage, and depletion of glutathione [8]. The loss of glutathione is mediated in part through the accumulation of extracellular glutamate. Glutamate is the most important excitatory neurotransmitter in the brain, but in excess it becomes neurotoxic. Excessive activation of glutamate receptors leads to excessive calcium influx and activates a cell death cascade due to mitochondrial reactive oxygen species (ROS) [97].

A mechanism that results in glial cells releasing nonvesicular glutamate into the extrasynaptic space is a key factor in pathological glutamate signaling [98]. The cystine-glutamate antiporter system, xc- is the major route by which cysteine is taken up into cells (in its oxidized form as cystine) [97]. Extracellular glutamate is a competitive inhibitor of xc-, preventing uptake of cystine by the cell. Cysteine is the rate-limiting amino acid for glutathione synthesis. Thus, when extracellular glutamate accumulates following toxic exposures, glutathione becomes depleted [79]. N-acetyl cysteine (NAC) has found therapeutic value in treating autism, and this is likely due to the increased bioavailability of cysteine to support glutathione synthesis [99,100].

Glyphosate, Diabetes, Melatonin Deficiency and Autism

Acting as an endocrine disruptor, glyphosate can disrupt insulin signaling, leading to diabetes. Diabetes prevalence is rising in the United States in step with the rise in glyphosate usage on core crops [57]. Oral exposure of albino Wistar rats to glyphosate for 16 weeks was associated with a rise in fasting glucose and insulin, along with a drop in serum testosterone, and an increase in liver production of pro-inflammatory factors, including NF-$\varkappa$B, Il-6, Il-1β, and peroxisome proliferator-activated receptor-γ (PPAR-γ) [101]. Maternal diabetes during pregnancy is associated with increased risks for autism spectrum disorder and cognitive dysfunction in the offspring [102]. High circulating glucose levels interfere with pineal melatonin production, reducing melatonin levels in diabetic rats and type 1 diabetes patients [103]. Type 2 diabetic Goto-Kakizaki rats exhibit impaired melatonin synthesis, with increased inhibitory α-2-adrenoceptors, impaired 5-hydroxytryptophan formation, and reduced pineal gland protein content [104]. Thus, impaired melatonin supply to the fetus during pregnancy due to maternal diabetes could cause autism in the developing fetus via suppression of PIN1 signaling by DAPK1.

A Proposed Role for Glyphosate in Shared Pathway Disruptions in Autism, Alzheimer's Disease and Cancer

Perhaps surprisingly, autism and Alzheimer's disease overlap considerably in symptoms, genetics, and mechanisms, suggesting a similar underlying pathology [105]. PIN1 is normally expressed at very high levels in neurons, but it is inhibited in neurons in Alzheimer's disease via multiple mechanisms, including down-regulation, oxidation, phosphorylation and sequestration [106]. Just as autism rates over time are highly correlated with glyphosate usage on core crops, age-adjusted deaths due to Alzheimer's disease over time

had a correlation coefficient R of 0.917 with glyphosate usage on corn and soy crops in the United States, with a p-value of 2.2E-7 for the probability of a chance occurrence [57].

Also surprisingly, autism and cancer share common features involving mitochondrial dysfunction and dysregulated metabolic pathways, including p53, AKT, mTOR, WNT, NOTCH, and MAPK [107]. There is considerable overlap in the risk genes linked to both conditions [108]. Dysregulated ERK/MAPK signaling can lead to mitochondrial dysfunction upon toxic exposures in both neurons and tumor cells [109]. PIN1 overexpression is a well-known feature of tumor cells, where it facilitates mitosis, proliferation, and metastasis [110].

By contrast, we argue here that PIN1 is suppressed in neurons in association with autism, as is the case for many neurodegenerative diseases, especially Alzheimer's [111,112]. A neuron is a fully differentiated cell type that is intricately connected to large networks of other neurons. They do not have the option of dividing in the face of stressors. As a consequence, upon toxic exposures, their regulatory pathways have an opposite effect on PIN1 compared to cancer cells, and this drives them toward apoptotic signalling rather than inducing cellular proliferation following severe DNA damage. Oxidative stress can cause severe DNA damage [113]. Much of what is known about PIN1's function in cells was discovered through studies on cancer cells. In future sections we will reference this literature to help explain the many roles of PIN1 in biology.

Overexpressed mTOR Signaling Pathway: Autism is associated with increased dendritic spine density and reduced developmental spine pruning in neurons. These defects are correlated with overexpressed mTOR signaling and impaired autophagy. This potential for autophagy impairment would result in serious interference in the associated cell death mechanisms that can consequently lead to development of disease [114]. Designer mice have been created with constitutively expressed mTOR activity due to a defect in gene expression of proteins that inhibit mTOR. These mice exhibit autistic behaviors and have the same characteristic spine pruning defects in pyramidal neurons in the temporal lobe, along with impaired autophagy [115]. Microglia play an important role in synaptic pruning, as mice with deficient autophagy in microglia are impaired in synaptic pruning and exhibit behaviors characteristic of autism [116].

Ωντ/β-ςατενιν Σιγναλινγ Πατηωαψ: Several of the genes associated with autism converge in the regulation of the Wnt/β-catenin signaling pathway. Both gain and loss of function in this pathway contribute to abnormalities in embryonic brain development associated with autism [117]. Cultivated neurons exposed to glyphosate were impaired in differentiation and growth, eliciting shorter and unbranched axons, and developing less complex dendritic arbors compared to controls [118]. These features are characteristic of impaired neuronal maturation in autism [119]. In the glyphosate study, it was found that both the expression of Wnt5a and the activity of the serine/threonine kinase CaMKII were decreased [118]. Autophosphorylation of CaMKII increases its activity and prolongs the duration of its active state. A missense mutation in CaMKII that results in impaired autophosphorylation and more rapid turnover is associated with autism. When this mutation was introduced in mice, they displayed autistic-like behaviors [120]. Rat pups exposed to glyphosate in utero showed inhibition of the Wnt5a-CaMKII signaling pathway, associated with defects in motor activity and cognitive function [121].

The corpus callosum is the largest white matter tract in the brain, and it connects the two cerebral hemispheres together. Wnt5a-evoked CaMKII signaling instructs specific growth and guidance behaviors in the corpus callosum, controlling its development [122]. Intriguingly, the corpus callosum is thin and underdeveloped in PIN1 knockout mice [123]. Many neurodevelopmental disorders have been linked to malformation of the corpus callosum, including autism, ADHD, and schizophrenia [124]. BTBR mice, a well-established model for mouse autism, exhibit complete agenesis of the corpus callosum [125]. A large percentage of humans suffering from agenesis of the corpus callosum display many traits associated with autism, including deficits in communication and social skills and repetitive behaviors [126].

The DAPK1 regulatory function, which inhibits PIN1 activity, is central to CaMKII autophosphorylation of threonine at position 286 (Thr286), which is required for synaptic long-term potentiation (LTP) and

depression (LTD) [127,128]. Both LTP and LTD, which oppose each other, are involved in synaptic plasticity. The autophosphorylation of CaMKII results in the binding of the molecule to the N-methyl-D-aspartate (NMDA) receptor (NMDAR) subunit GluN2B and accumulation of CaMKII during LTP. DAPK1, through activating calcineurin (CaN), blocks CaMKII from binding to GluN2B by competitive inhibition. This creates a fine balance, regulated by Ca2+/CaM influx, which determines whether CaMKII will become attached to GluN2B (establishing LTP), or not (establishing LTD), a balance that is deregulated in autism. Specifically, DAPK1 overexpression, which we have argued can happen due to glyphosate's inhibition of melatonin synthesis, inhibits the accumulation of CaMKII in the synapse following LTP stimuli [128].

Wnt/β-catenin signaling increases both mRNA expression and protein synthesis of the cell adhesion molecule neuroligin-3, which in turn is essential for the maturation of synapses. Genetic mutations in neuroligin-3 are associated with autism [129]. β-catenin is a major substrate for PIN1 in neural progenitor cells. The developing brain of PIN1 knockout mice shows reduced expression of β-catenin during differentiation, leading to significantly fewer upper layer neurons in the motor cortex [130].

Τηε Ιντεγριν β1/ΦΑΚ/ΣΡ˜ Σιγναλινγ Πατηωαψ: Tetraspanin 7 (TSPAN7) is a master regulator of morphological changes that take place during cell differentiation through cytoskeleton remodeling [131]. Focal adhesion kinase (FAK) is a tyrosine kinase that regulates cellular adhesion, motility, proliferation, and survival, and it interacts with TSPAN7 through the Integrin β1/FAK/SRC signaling pathway. FAK plays an important role in neural migration, dendritic morphology, axonal branching, and synapse formation, all of which are dysregulated in autism [132]. Activation and autophosphorylation of FAK promote neurite formation in neurons [133]. TSPAN7 knockout rats exhibit autism-like behaviors, and this has been linked to impairments in this pathway, which is critical for neurite outgrowth [134].

One of the major pathogenic features of autism is reduced cell migration. Lymphoblasts share features with neurons, and it has been discovered that growing them in culture can serve a useful role to identify systemic pathologies in pathways linked to specific diseases. The protein expression level of FAK is significantly decreased in autistic lymphoblasts, and this was associated with increased adhesion properties and decreased migration, attributed to impaired FAK function in the lymphoblasts [132]. PIN1 isomerizes two prolines in FAK adjacent to Ser-910 and Ser-571, and this leads to dephosphorylation of FAK Tyr-397 [110]. PIN1 isomerization is required to recruit the phosphatase to FAK. Dephosphorylation of FAK at Tyr397 inhibits FAK kinase activity, promoting the disassembly of focal adhesion and enhancing tumor cell metastasis [135]. Experimentally, FAK Tyr-397 dephosphorylation causes cells to round up and lose their attachment to focal adhesions, promoting cellular migration [136]. Thus, low expression of PIN1 would explain the pathology observed in autism, because it leads to suppression of FAK Tyr-397 dephosphorylation. Autistic neurons have reduced migratory capabilities due to increased adhesion complexes that lead to migratory defects, a process in which PIN1 inactivation and DAPK1 over-activation are major participators. This defect interferes with the maturation process of neurons in the brain during neurodevelopment.

Glyphosate, FAK and Anoikis

The motif Arginine-Glycine-Aspartate (RGD), expressed in integrin ligands, is the recognition site for integrin binding to these ligands, and it regulates cell-cell and cell-extracellular matrix (ECM) interactions. Short synthetic peptides that contain the RGD sequence promote cell adhesion when adhered onto a surface, by binding to integrins in the cell membrane, and inhibit it through a decoy phenomenon when presented to cells in solution [137]. It has been proposed and demonstrated experimentally that glyphosate has biomimetic features that cause it to disrupt cellular adhesion properties in unpredictable ways. Glyphosate can mimic an RGD binding site, and, as a consequence, glyphosate adsorbed on the surface of a cell enhances cellular adhesion. By contrast, glyphosate in solution can act as a decoy to interfere with focal adhesion. These authors hypothesized that the interference of glyphosate in solution with cellular adhesion processes could trigger anoikis [138]. Anoikis ("homelessness" in Greek) is a form of apoptosis that is induced by disrupted cell–ECM interactions [139].

Inappropriate cell-substrate contact triggers anoikis [140]. FAK gene silencing has been shown to promote

anoikis in adenocarcinoma cells [140]. This is consistent with the idea that neuronal cell death by anoikis would be a feature of autism, given that FAK signaling is reduced in association with autism [134]. Thus, downregulation of FAK/SRC signaling in autism due to decreased FAK activity is expected to lead to enhanced apoptosis by anoikis in the brains of autistic individuals [132,141].

PIN1, PSD-95, the Synapse, and Glyphosate

Postsynaptic density protein-95 (PSD-95) is a major regulator of synaptic maturation. It interacts with NMDA receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, stabilizing and trafficking them to the postsynaptic membrane. PSD-95 is involved in glutamatergic transmission, synaptic plasticity, and dendritic spine morphogenesis during neurodevelopment. PSD-95 null mice have learning and memory deficits and impaired socialization, associated with increased NMDAR expression [142]. There is now overwhelming evidence that PSD-95 disruption is associated with the cognitive and learning deficits that are characteristic of autism and schizophrenia [143,144].

Glyphosate exposure in rats has been shown to affect synaptic function. Studies have demonstrated that glyphosate exposure leads to a decrease in dendritic complexity, synaptic spine formation and maturation, and synapse formation in hippocampal neurons. Glyphosate downregulates the expression of synaptic proteins such as synapsin-1, PSD-95, and CaMKII, and decreases PSD-95 clustering in the hippocampus. These changes in synaptic assembly and protein expression likely contribute to the impairment of cognitive function and neuronal connectivity in rats exposed to glyphosate [145].

PSD-95 is a membrane-associated guanylate kinase, and it is the main scaffolding protein at excitatory postsynaptic densities (PSDs). It plays a major role in regulating synaptic strength and plasticity. PSD-95 anchors NMDA receptors (NMDARs) in the PSD, thus increasing their numbers. Phosphorylated PSD-95 recruits PIN1 to the synapse, and PIN1 controls the synaptic content of NMDARs via PSD-95 prolyl-isomerization. PSD-95 has six potential PIN1 consensus motifs between the PDZ2 and PDZ3 domains, and binding of PIN1 following phosphorylation of the preceding serine/threonine greatly influences its behavior [146].

Specifically, prolyl-isomerization following phosphorylation decreases the ability of PSD-95 to complex with NMDARs, leading to a downregulation of NMDAR-mediated synaptic transmission, and this is associated with a decrease in dendritic spine density. Thus, PIN1 deficiency would be expected to result in *upregulated* NMDAR expression and *increased* dendritic spine density. Indeed, PIN1 null mice have an increase in spine density [146], a feature that is commonly associated with autism [147]. Upregulation of NMDARs at neuronal synapses, along with increased glutamine synthetase expression in astrocytes, has been linked to autism in a mouse model [148]. NMDAR expression was upregulated in the brain in another mouse model of autism, and the NMDAR antagonist memantine was used to treat their autistic-like behaviors [149]. Memantine has also been proposed to have therapeutic value to treat autism in humans [150].

The term synaptopathy is used to describe brain disorders associated with synaptic dysfunction. *DLG4* is the gene that encodes PSD-95.*DLG4* -related synaptopathy refers to a group of neurodevelopmental disorders associated with variants in the *DLG4* gene. Many of the variants are de novo loss-of-function mutations, which may disrupt binding to PIN1. These disorders are characterized by a broad range of symptoms including global developmental delay, intellectual disability, autism spectrum disorder, attention deficit-hyperactivity disorder, and synaptic dysfunction [151].

DAPK1's role in apoptosis and the related molecular regulations of cancer pathways and neuronal damage

DAPK1 is among the proteins positively regulating cell death by apoptosis and thus working to prevent cancer metastases. We have already seen that glyphosate suppresses melatonin synthesis, and that melatonin plays a critical role in suppressing DAPK1 activity [39,87]. DAPK1 is a potent modulator of PIN1 activity and their molecular interactions are significantly implicated in the development of tau-associated pathology [104], in the amyloid β-related pathology of Alzheimer's disease (AD) [152] and in the disablement of neuronal

network restoration following neural traumas [153]. Therefore, as DAPK1 directly inhibits PIN1 function [86], it is important to revisit DAPK1 regulatory aspects of activation and/or deactivation that relate to the DAPK1 tertiary structure. These regulatory activities affect the molecular activity of PIN1 and other important molecules implicated in neurodegeneration and cancer.

DAPK1 has a multi-domain structural organization that enables it to perform a wide range of functions, succinctly described in a study by P Singh et al. [86]. What is outstanding about this molecule, and a feature that differentiates it from other kinases, is that DAPK1 does not require an extra phosphorylation event in its catalytic domain to become activated. Near the DAPK1 catalytic kinase domain, there is an autoregulatory Ca^{2+}/CaM domain that serves as a pseudo-substrate for the catalytic domain, and when CaM is not bound to that region, the function of DAPK1 is auto-inhibited. It is for this reason that the catalytic domain of DAPK1 is unique compared to other kinases.

Adjacent to the peptide-to-peptide region in the catalytic domain, there is a protruding positively charged comb region that allows for numerous regulatory properties of DAPK1, including the regulation of apoptosis [154]. However, it is the extra-catalytic domain molecular interactions that are important for DAPK1's activity, degradation and cellular localization. Next to the CaM autoregulatory domain (which inhibits the catalytic domain of DAPK1 in the absence of CaM), lies an ankyrin repeat rich domain, which is responsible for many of the protein's interactions. This ankyrin repeat rich domain determines DAPK1's ubiquitination status and subsequent proteasomal degradation.

DAPK1, Anoikis and Synapses: In the absence of the ankyrin repeats, DAPK1 localizes from actin filaments to focal adhesions, and this relates to tropomyosin regulation by DAPK1 phosphorylation and facilitation of cancer cell death. This function of DAPK1 is very important as it regulates the phenomenon called anoikis that prevents cancer. Anoikis is a distinct cell-death process similar to apoptosis, and it reflects the capacity that normal cells have to migrate and stay alive; whereas, when DAPK1 is activated in cancer cells that attach to soft surfaces, anoikis is initiated and these cells die, thus restricting their migration and metastatic potential [155,156]. Anoikis is a safeguard mechanism that lets healthy cells remain alive and functional, whereas it kills abnormal neural cells that have pathological adherence junctions during embryonic development.

DAPK1's ankyrin repeat sequence is essential for its protein-to-protein communication, as is the case for many other ankyrin repeat proteins [157]. For DAPK1, the ankyrin repeat domain mainly functions to provide control of its amounts in cells, regulated via ubiquitination and proteasomal degradation of the protein [158]. The DAPK1 ankyrin repeats react strongly with DAPK interacting protein-1 (DIP-1), targeting the proteasomal degradation of DAPK1. Thus, whether or not DAPK1 will exert apoptosis survival signaling in normal cells depends on the expression and interactions of its ankyrin repeat domain with DIP-1. When DIP-1 is expressed, it forms a strong complex with DAPK1 and DAPK1 suffers from DIP-1's ubiquitination in the complex and it is thereby tagged for proteasomal degradation [158]. However, when the DAPK1 ankyrin repeat domain is deleted, DAPK1 relocalizes from actin cytoskeleton microfilaments to adhesion complexes where it exerts cell death by anoikis of migrating cancer cells [156].

DAPK1 is strongly involved in neuronal cell death and the development of neurodegeneration [159]. Furthermore, anoikis is considered as a key pathogenic factor for glaucoma, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD) [160,161]. Therefore, whether the anoikis mechanism of cell death will appear in a certain type of cell ultimately depends on the functionality of the ankyrin repeat domain of DAPK1.

Although research on the relationship between anoikis and prion disease is sparse, there is growing evidence for a role for anoikis in prion disease pathogenesis. The prion protein modulates epithelial to mesenchymal cell transition [162], and anoikis crosstalk with epithelial-mesenchymal transition in resisting cancer metastasis is substantial [163]. Moreover, the prion protein is upregulated in many cancers [164]. Therefore, a potential DAPK1 upregulation and re-localization from microfilaments to adhesion complexes may underly both neurodegenerative and prion disease pathology.

Figure 1 provides a graphical representation of these complex processes relating disturbed expression of PIN1 and DAPK1 to disease.

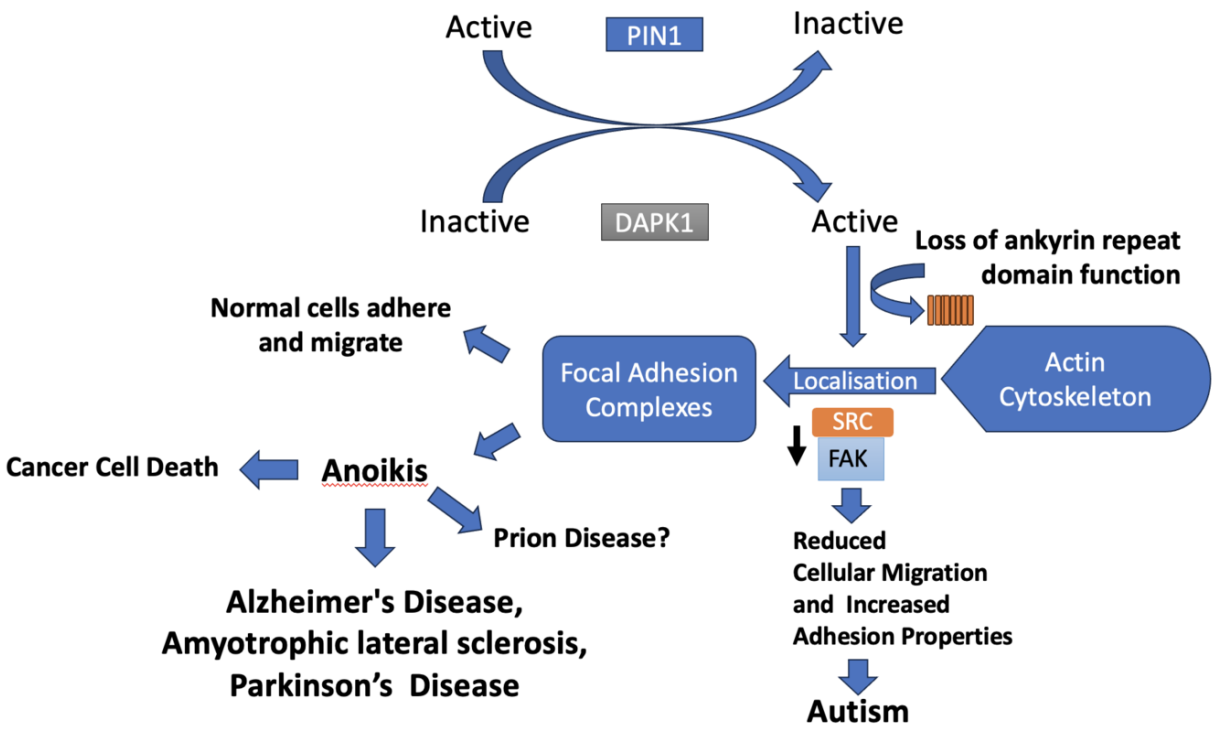

Figure 1: PIN1 deactivation/DAPK1 activation. When DAPK1 deactivates PIN1 and loses function of its ankyrin repeat domain (ARD), it travels from the cytoskeleton to focal adhesion complexes. Through this sub-localization of DAPK1, Src normally catalyzes its phosphorylation for focal complex assembly to occur. In autism, due to low expression of FAK and loss of PIN1 activation, Src function predominates to assembly of matrix adhesion catalysis and impairs cellular migration. Reduced cellular migration is an impairment regularly seen in autism. Furthermore, increased cell adhesion complex assembly contributes to normal cell adhesion and migration and cancer cell death. On the other hand, anoikis initiated by DAPK1 localisation to focal adhesion complexes is a causative factor for neurodegenerative disease pathogenesis and a probable contributing factor for prion disease and autism.

Preservation of homeostasis in adhesion complex formation has a significant role in the prevention of neurodegeneration, as it maintains the normal functions of neuronal synapses [165]. On a molecular level, normal synaptic behavior is attributed to synaptic cell adhesion molecule (CAM) pathways where the scaffolding SH3 ankyrin repeat domain 3 (SHANK3) proteins are the protagonists [166]. Dysregulation in these CAM pathways involving neuroligins and neurexins, that regulate cellular adhesions of synapses, are associated with the pathology of autism spectrum disorders (ASDs) [167]. Multiple studies have shown that many of the genes that are mutated in association with autism involve proteins that play a critical role in cellular pathways associated with the synapse. These genes encode scaffolding proteins, adhesion molecules, and proteins involved in synaptic transmission and plasticity. This observation has suggested that synaptic dysfunction may be a core feature of autism [168]. DAPK1 is highly enriched in the synaptic dendritic spines, where it plays an important regulatory role in synaptic plasticity [169]. Furthermore, PIN1 localizes at postsynaptic sites and, in particular, at the lipid rafts of dendrites and postsynaptic density (PSD) areas which cohere to the postsynaptic membrane and maintain synaptic plasticity [170,171].

The loss of PIN1 activity, as found in the brain cortical tissues of AD patients, results in a decrease in SHANK protein levels and the alteration of ubiquitin-related modifications of PSD proteins. Structural abnormalities of the synapses of AD patients are a consequence. Moreover, the loss of PIN1 activity due to oxidative stress makes neurons more susceptible to the toxicity of amyloid-βfibrils, and this results in the inhibition of NMDA receptor stimulation (and therefore reduced synaptic plasticity), as well as enhancement of NMDA associated degeneration of synapses [171]. Constitutionally, the loss of PIN1 activity and a concurrent operational activity of DAPK1 localised also at synaptic adhesion complexes of glutamate NMDA receptors would provide a deregulated response of the otherwise naturally occurring neuronal cell death by apoptosis [172]. In cases where the extracellular matrix and the adhesion of cells fail to be properly regulated, anoikis-induced cell death, including for neurons, occurs [173]. These mechanisms can feasibly explain many of the abnormal neural plasticity features encountered in autistic individuals [168,173].

DAPK1 Regulatory Mechanisms and Protein Interactions: DAPK1 has a profoundly complex regulatory mechanism involving phosphorylation and dephosphorylation, and it interacts with many other important proteins to alter their function in various ways. These other proteins include not only PIN1, but also many biologically important proteins whose disruption is linked to autism, including PP2A [174], ERK//MAPK [175,176], and p53 [177], among others. One of the final determinants of whether DAPK1 will be activated or not relies on the phosphorylation of the serine 308 residue, which is located in the Ras of complex (ROC) protein domain of the molecule, adjacent to the ankyrin repeat domain. The ROC domain modulates its kinase activity. ROC is a conserved domain of the ROCO multidomain family of proteins, making DAPK1 a member of this family. ROC domains are implicated in the development of neurodegenerative diseases, including Alzheimer's disease (AD) [178]. When the ROC domain of DAPK1 interacts with a GTPase, the subsequent conversion of GTP to GDP phosphorylates Ser-308 and inactivates the protein [86,177]. Nevertheless, this makes the activation of DAPK1 subject to other ROCO protein kinase activations and regulations [178]. In contrast, when the same Ser-308 becomes dephosphorylated by the activity of protein phosphatase 2A (PP2A), an important protein for cell signaling and growth mostly characterized as a tumor suppressor, DAPK1 becomes activated [86,178,179] The PP2A-DAPK1 interaction and activation via Ser-308 dephosphorylation in the ROC subdomain is essential for many DAPK1 functions, including apoptosis, regulation of autophagy and cellular proliferation and development, and these are especially important cellular events for halting cancer progression [180].

The ROC amino acid sequence of DAPK1, starting from residue 667, is directly followed by the C terminal of ROC (COR) subdomain consisting of the ROC-COR domain of DAPK1. This domain is then followed by the Death Domain (DD), which is highly important for the molecule's functions [86]. The ROC-COR and DD domains of DAPK1 are highly significant for regulation of PIN1 activity [181]. The 637–1423 sequence of DAPK1 efficiently binds to PIN1. This suggests that the DAPK1 cytoskeleton-binding domain, ranging from 637–847, which involves the ROC subdomain, is highly likely involved with the binding of PIN1.

The peptide-to-peptide interactions between DAPK1 and PIN1 cause the de-activation of PIN1's isomerase activity by direct phosphorylation of Ser71 in Pin1. Although, at first glance the phosphorylation of Ser71 seems to be a phenomenally minor molecular event, its biological and medical consequences are of high impact for the survival of the cell [86,180,181]. The destabilization and thus inhibition of cyclin D1 by DAPK1 is mediated by an additional functional insufficiency of PIN1. The relevant experiments by TH Lee et al. are ominous [181]. When DAPK1 is expressed in its wild form, PIN1 deactivation causes a cyclin D1 destabilization and reduction in Cyclin D1 promoter activation. Incapacitation of Cyclin D1 in the cells relates to severe deregulation of cell cycle progression, amplification of cancerous molecular events during cell cycling [182], and moreover, to the insufficiency of neural cell proliferation and control that leads to autism [183]. Cyclin D1 levels are significantly reduced in various tissues of PIN1 NULL mice [184].

Furthermore, the ankyrin repeat, the ROC-COR and the DD domains of DAPK1 are subject to other molecular modifications that influence the molecule's pluripotent functions. When the tyrosine at positions 491/492 of the ankyrin repeat domain of DAPK1 is phosphorylated by the proto-oncogene tyrosine-protein kinase Src (from sarcoma), this deactivates DAPK1 from performing essential anti-cancer intra-molecular

interactions. The Src mediated deactivation of DAPK1 produces a crucial loss of DAPK1-induced anti-cellular migration and proliferation functions, and it is surely not coincidental that DAPK1 inactivation by Src is found in situations of tumor metastasis and progression [185].

However, as described above, DAPK1 over-activation and therefore PIN1 deactivation may be leading factors that contribute to autism brain pathology by enhanced anoikis (apoptosis) events. FAK plays an essential role in neuronal migration, neurite growth, pruning, and synapse formation in the developing brain [186,187]. It has been proposed that pathological detachment of progenitor cells during neurogenesis induces anoikis as a defense mechanism to protect from teratogenic insults [188]. This aligns with the observation that both glyphosate and glyphosate-based herbicides produce teratogenic effects on Xenopus laevis embryos and chicken embryos [189]. Plausibly, autistic neurons, by having a reduced activity of FAK and therefore FAK/SRC signaling, are defective in their migratory properties and therefore are prone to enhanced cell death by anoikis during embryonic development.

Another major molecular event for DAPK1 is the phosphorylation of Ser735 located in the ROC-COR domain and the subsequent molecular interactions with extracellular signal regulated kinase (ERK). The DAPK1 docking sequence that serves as a substrate for ERK lies within the DAPK1 DD [190]. The simultaneous induction of DAPK1 catalytic activity via the activation of ERK promotes cellular death mechanisms including neuronal apoptosis [191]. Moreover, interacting DAPK1 and ERK mechanisms are involved in malignancy development and autism [108]. Finally, the DD of DAPK1 has a strong influence towards cancer progression, as it is a direct modulator of p53 and a potent stimulator of the TNF-α/Fas pathway resulting in apoptosis [159]. DAPK1 phosphorylates p53 at Ser23 by direct binding of DD at the p53 DNA binding domain. Phosphorylation of p53 Ser23 by DAPK1 induces the transcriptional activation of BAX, whereas in the cytoplasm it induces mitochondrial associated necrosis and apoptosis, as indicated in studies on neurons [191-194]. Moreover, an indirect regulation of p53 by DAPK1 is through DAPK1's direct binding to MDM2 and its phosphorylation at Thr-419. This phosphorylation promotes MDM2 ubiquitination and proteasomal degradation, liberates p53 from MDM2, and promotes p53 expression. The antitumorigenic associations of MDM2 downregulation and indirect upregulation of p53 by DAPK1 are of considerable contemporary interest in breast cancer research [195].

PIN1's Crucial Role for P53 Expression and Activation

The tumor suppressor p53 and the proto-oncogene Bcl-2 were two of the earliest identified cancer-related genes [195]. p53 is a global transcription factor that maintains the integrity of the cell under stressful conditions through its activation of expression of many proteins involving cell cycle arrest and DNA repair as part of the DNA stress response. p53 in the cytoplasm also plays an important role in safeguarding the mitochondria from DNA damage [196]. PIN1 deficiency results in defective p53 transactivation [197,198], and p53 transactivation is reduced in association with autism [199]. Knocking down of p53 in mice significantly promotes repetitive behavior and reduces sociability, clear signs of autism [177,197].

In addition to its role in DNA protection from toxic exposures, p53 is important in hippocampal neurons for learning and memory. Lee et al. wrote in their abstract: "Altogether, our study suggests p53 as an activity-dependent transcription factor that mediates the surface expression of AMPAR, permits hippocampal synaptic plasticity, represses autism-like behavior, and promotes hippocampus-dependent learning and memory" [177]. A study published in 2023 demonstrated that glyphosate activates microglia via toll-like 4 receptor (TLR4) and triggers cellular stress, resulting in impaired hippocampal plasticity and learning [200].

Under quiescent conditions, p53 remains bound to MDM2, an E3 ubiquitin ligase that promotes its constant proteasomal degradation, maintaining the protein at low levels. Upon stress activation, p53's localization to the nucleus depends upon binding to PIN1. Genotoxic exposures induce the phosphorylation and activation of p53 on its Ser/Thr-Pro motifs, and this allows PIN1 to isomerize critical proline residues in p53. PIN1 in turn stimulates the DNA-binding activity and transactivation functions of p53. PIN1-deficient cells are defective in p53 activation, and this results in impaired checkpoint control in response to DNA damage [198].

Lack of PIN1 also leads to increased destabilization of p53 by its inhibitor, MDM2. Thr81-Pro82 is a

crucial site for PIN1 to promote checkpoint kinase 2- (Chk2)-dependent phosphorylation of p53 on Ser20. This serine phosphorylation modification stimulates the dissociation of p53 from MDM2, protecting it from ubiquitination and degradation [198,201].

p53 still induces cell death when it is impaired in its ability to localize to the nucleus. When PIN1 levels are low under stressful conditions, p53 accumulates in the cytoplasm, where it can induce death by apoptosis or necrosis [202,203]. p53 interacts in the cytoplasm with Bcl-2, the founding member of the Bcl-2 family of proteins that regulate cell death, to suppress its anti-apoptotic activity, thus sensitizing the cell to apoptosis via permeabilization of mitochondria [195]. This extranuclear influence of p53 has been coined as transcription-independent p53-induced apoptosis (TIPA) [204]. p53 can also inhibit cystine uptake, leading to ferroptosis due to glutathione depletion [205]. Cytoplasmic, but not nuclear, p53 suppresses macroautophagy, through activation of the mTOR pathway [206,207]. We will return to this topic in a later section since it pertains to autism.

Palmitate is the most common saturated fatty acid in food, but it can lead to lipotoxicity and apoptosis in exposed cells. p53 provides some protection against palmitate-induced apoptosis through its activation of gene expression of DNA-protective proteins. However, this depends upon its ability to translocate to the nucleus, which in turn depends upon PIN1. Experimentally, cell lines from p53-/- mice were significantly more sensitive to apoptosis through excessive ROS in response to excess palmitate exposure [208].

PIN1's Crucial Role in NRF2 Expression and Activation

Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that plays a crucial role in cellular defense mechanisms, particularly in response to oxidative stress, by transactivating a large number of genes associated with the stress response, including antioxidant, anti-inflammatory, and detoxification proteins [209]. NRF2 activation leads to increased synthesis of the potent antioxidant glutathione. The activation of NRF2 typically involves its translocation to the nucleus, where it binds to antioxidant response elements (AREs) in the promoters of target genes, initiating their transcription [210].

In a review study published in 2021, collectively involving 87 studies with 4928 children with autism and 4181 controls, it was reported that the levels of reduced glutathione, total glutathione, methionine, cysteine, folate, vitamin D and cobalamin were consistently significantly reduced in children with ASD compared to the controls [211]. In a post-mortem study, glutathione synthase expression was significantly decreased in frontal cortex brain tissue from seven autism subjects compared to 8 controls. NRF2 gene expression was also decreased in the frontal cortex, and this downregulation corresponded to a decrease in the abundance of methylcobalamin and total cobalamin, as well as S-adenosylmethionine (SAMe) [212].

Kelch-like ECH-associated protein 1 (KEAP1) is a ubiquitin ligase that senses oxidative stress and tightly regulates the activity of NRF2. Under normoxic conditions, NRF2 is bound to KEAP1, and this binding keeps it in the cytoplasm and prevents it from entering the nucleus. Also, intracellular levels of NRF2 are kept low because proteasomal degradation (ubiquitination) of NRF2 persists when it is tied up in a KEAP1/NRF2 complex [213]. However, under elevated intracellular levels of ROS, the cysteine residues of KEAP1 sensor domains become oxidized, and this triggers conformational alterations of the KEAP1 tertiary structure, which results in the release of NRF2 from the protein complex. This renders NRF2 free to enter the nucleus and proceed with its antioxidant and cytoprotective activities by inducing the expression of the NRF2-ARE related gene targets [214].

Paradoxically, acute oxidative stress can suppress NRF2 protein synthesis, through the global inhibition of protein synthesis [215]. Supraphysiologic levels of stress can even induce misfolding of both KEAP1 and NRF2, a maladaptive event that impairs protein function. Treatment of both yeast and mammalian cells with hydrogen peroxide results in the formation of misfolded protein inclusions, dose dependently [214].

PIN1 stabilizes NRF2 by competing with KEAP1 for NRF2 binding [216]. Furthermore, the common heat shock protein HSP90α is a molecular chaperone that is essential for transport of NRF2 to the nucleus, but this also critically depends on PIN1. Prolyl isomerization of NRF2 by PIN1 allows importin α5 to associate

with the Hsp90α-PIN1-NRF2 complex. A dynein motor system transports this complex along microtubules toward the nuclear pore complex, achieving the import of NRF2 into the nucleus, as illustrated in Figure 2 [217]. The BTBR (Black and Tan BRachyury) mouse strain is a commonly used mouse model of autism [218]. Sulforaphane is a natural molecule derived from cruciferous vegetables, and it has been shown to activate NRF2 [219]. BTBR mice treated with sulforaphane had reduced repetitive behaviors and improved socialization. Glutathione peroxidase and glutathione reductase activity were increased in both the periphery and the brain of these mice. Oxidative stress parameters such as the NF-ϰB transcription factor and lipid peroxides were reduced in their neutrophils [220]. This implies that impaired NRF2 transactivation due to insufficient PIN1 is a feature of autism.

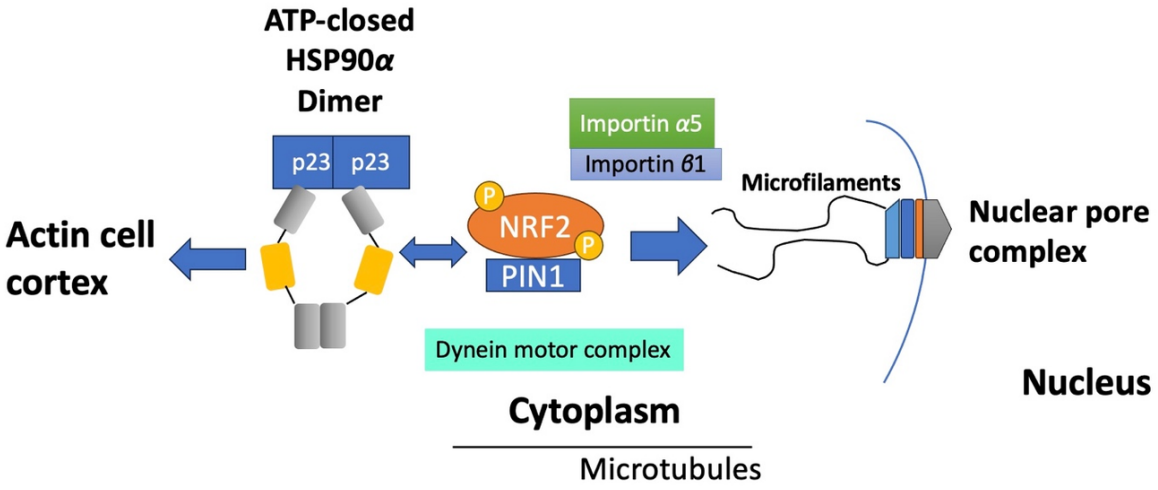

Figure 2: NRF2-PIN1 interaction. NRF2 remains inactive in the cytoplasm under stress-free conditions, bound to KEAP1. Under conditions of oxidative stress, PIN1 plays an essential role in the activation of NRF2. Upon NRF2 stabilization by PIN1, it can influence cellular policy in two distinct ways, depending on its localization in the cell. Interaction with the dynein motor complex and HSP90α localizes the complex to the actin cell cortex. On the other hand, when the NRF2/PIN1 complex interacts with importin α5 and importin β1, it enters the nucleus via the nuclear pore complex, and activates many genes associated with antioxidant defenses. Impaired NRF2 transactivation due to insufficient PIN1 is a feature of autism.

The FoxO Transcription Factors, Autophagy and mTOR

The set of forkhead box (FoxO) transcription factors play an essential role in neurodevelopment. FoxO3 enters the nucleus and activates the gene expression of a set of proteins involved in diverse cellular processes, including proliferation and autophagy [221,222]. Conditional deletion of FoxO1, FoxO3 and FoxO4 strongly impairs autophagy in developing neurons in the hippocampus [223]. Furthermore, FoxO deficiency leads to altered dendritic morphology and increased spine density in mouse hippocampal neurons [223].

The PI3K/Akt/mTOR pathway involves complex feedback loops that regulate the balance between anabolic and catabolic activities via two critical branches, mTORC1 and mTORC2. mTOR signaling is disrupted in association with autism [224]. Both the FoxO transcription factors and mTORC1 are downstream effectors of Akt. FoxO expression suppresses mTORC1 and increases activation of the PI3K/Akt/mTORC2 pathway [225]. Insufficient FoxO expression leads to impaired autophagy, while at the same time promoting proliferation and differentiation through increased activation of mTORC1. Impaired autophagy is a common feature found in association with autism [226]. Autophagy is essential for synaptic pruning, which is impaired in autism [115].

PIN1 plays an essential role in facilitating the translocation of FoxO3 to the nucleus to effect activation of its target proteins [227]. Thus, PIN1 deficiency leads to impaired autophagy due to inactivation of FoxO3. The mTORC1 pathway activates the transcription factor NRF2, while at the same time inhibiting autophagy [228].

The degradation and clearance of damaged molecules in a cell are achieved mainly through macroautophagy and the ubiquitin proteasome [229]. mTORC1 is a well-established inhibitor of macroautophagy. It not only inhibits the induction of autophagy by phosphorylating the core proteins involved in initiation, but also targets each subsequent step of the autophagy process [230].

The rates of hearing loss, both moderate and severe, among autistic children are much higher than the rates in the general population [231]. Overactive mTORC1 in the cochlea is one of the critical causes of age-related hearing loss [232]. Studies on mice revealed that Rapamycin, a potent inhibitor of mTORC1 [233], along with N-acetylcysteine supplementation, could rescue cochlear hair cells from injury due to oxidative stress. PIN1 protects hair cells from senescence by inhibiting the PI3K/Akt/mTOR pathway [234]. Juglone is a drug that is known to reduce expression of PIN1. Treatment of mice with hydrogen peroxide and juglone induced ROS-related phosphorylation of p53. This resulted in damage to the cochlea and hearing loss due to cellular senescence [234].

Altered dopamine signaling has been implicated as a contributing factor in autism, and this could be due to impaired autophagy [235]. Chronic lack of autophagy enhances evoked dopamine release from dopaminergic neurons [236].

PIN1 and Epilepsy

There is a high rate of co-occurrence between autism and epilepsy, and many genetic defects are linked to both conditions [238,239]. Glyphosate has been shown to cause seizures in round worms, and this likely occurred through its action as a GABA-A receptor antagonist [240].

Recent studies reveal the role of PIN1 in the pathological development of a range of neurodegenerative diseases, which also includes a significant influence in the pathology of epilepsy. During epileptic seizures, an abnormal electrophysiology persists in the brain [241]. On the molecular level, the deregulation of synaptic transmissions is considered as a major contributing factor for epileptic seizures [242]. The balance of PIN1 isomerase activity would therefore be of importance for epilepsy, since it regulates the excitatory glutamate, N-methyl-D-aspartic acid (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and the inhibitory gamma-aminobutyric acid (GABA) and glycine receptors. All these receptors are deregulated during epilepsy, as described in the Y Chen et al. study [243].

The acquisition of epileptic seizures in association with PIN1 deficiency has been observed in both animals and humans with impaired PIN1 function, suggesting that the expression of PIN1 can inhibit the symptoms of epilepsy [244]. PIN1 null mice have significantly increased susceptibility to seizures and develop age-dependent spontaneous epilepsy [245]. Recent studies in animals show that PIN1 deficiency increases the susceptibility to epileptic seizures upon chemical stimuli. Moreover, in humans with epilepsy, PIN1 is significantly downregulated whereas AMPA receptors are overactive. PIN1 deficient mice have a significantly increased risk to seizures, and humans with epilepsy have increased phosphorylation of CaMKII and increased levels of AMPA receptors in the neocortex. PIN1 knockout increases the number of AMPA receptors through hyperphosphorylation of CaMKII [245]. In animal experiments, CaMKII hyperphosphorylation is reversed by the restoration of PIN1 expression in the prefrontal cortex of their brains [245]. Social impairments in animal models of autism can be ameliorated by antagonists of the AMPA receptors [246]. These studies suggest that PIN1 upregulation can restore proper neural network function and cortical synaptic organization in epilepsy.

Autism, Asthma and the Regulation of PIN1

As already described in earlier sections, activated DAPK1, in synergy with p53, promotes the transcriptional activation of BAX, a condition that results in neuronal cell apoptosis and death [191]. Neural apoptotic cell

death mediated by BAX also implies that PIN1 will be deactivated by DAPK1 in neurons [86]. Similarly, in eosinophils, apoptosis is prevented by activated PIN1 in the nucleus, and, by contrast, apoptosis is magnified by the inhibition of PIN1 [247]. Eosinophils are short-lived cells and, in common with neurons, are highly differentiated and unable to divide. The activation of BAX in eosinophils is also crucial for their mitochondrial mediated apoptotic signaling, in order to prevent the emergence of long-lived eosinophils that induce inflammation and asthma [248]. The DAPK1-activation-PIN1-inhibition mediated expression of BAX, which is important for the control of overwhelming eosinophil migration and continued activation of long-lived eosinophils, constitutes a primary pathologic factor in asthma [249].

Although an earlier meta-analysis study had failed to prove a direct relationship between asthma and autism [250], there are serious immune defects and comorbidities in autistic individuals that imply a predisposition to asthma in autistic individuals [251]. Moreover, a recent research investigation indicates that genetic relationships exist between autism and asthma [252].

The study of L Guglielmi et al. [253] provides a fine description of autism spectrum disorder (ASD) associated pathogenesis linked to potassium (K^+) channelopathies. Briefly, in ASD there is a dysfunction of several K(+) channel types, often with a genetic link, and these contribute to the repetitive behavior and social and communication impairments encountered in autism. In the dendrites of pyramidal neurons, there are numerous transient A-type potassium ion channels that regulate action potential depolarizations and abnormal excitatory events [254]. Kv4.2 is one of these crucial potassium channel hippocampal proteins that controls neuronal plasticity and holds a central role in learning and memory acquisition [255]. Quite importantly, the functioning of Kv4.2 depends on the activity of PIN1. When PIN1 becomes activated, it binds dynamically to the Thr-607 phosphorylated form of Kv4.2, leading to the isomerization of the proline involved at the related pSer/Thr-Pro motif. This causes the dissociation of Kv4.2 from its dipeptidyl peptidase 6 (DPP6) subunit, inhibiting the Kv4.2 function for protection from excess neuron excitability through depolarization [256]. The isomerization induced by PIN1 in Kv4.2 is important for proper neuronal and cognitive function [256].

Furthermore, in contrast to PIN1-mediated neuron over-excitability due to the loss of Kv4.2 function, other studies that relate to Alzheimer's disease (AD) indicate that mutations in the synaptic scaffolding protein, SHANK3, which associates with autism [257], render the loss of PIN1 activity important for the regulation of synaptic plasticity in AD [171]. Given the aforementioned evidence, justifiable scientific grounds suggest a common PIN1-mediated pathogenic mechanism associated with both asthma and neurological defects encountered in ASD. PIN1 is significantly implicated in other studies of the pathogenesis of asthma by inducing eosinophilic inflammation through the upregulation of TGF-β1 [258]. In this concept, the mode of induction or inhibition of apoptosis by the DAPK1–PIN1 interactive regulation becomes important for the onset of both asthma and neurologic defects in autism [86,191].

The SARS-CoV-2 mRNA Vaccines: Will They Increase Autism Rates?

The US Centers for Disease Control are now recommending that the SARS-CoV-2 mRNA vaccine be administered to children as young as six months of age, and also to pregnant women [259]. We believe there is reason to be concerned that this policy may lead to increases in the prevalence of autism both in vaccinated infants and in the offspring of vaccinated pregnant women. It has become very clear that the SARS-CoV-2 spike protein is extremely toxic, and it may be the primary cause of observed severe vaccine side effects following mRNA vaccination. The spike protein itself is likely a major cause of myocarditis following vaccination, as circulating spike protein, both free and antibody-bound, was found in subjects who developed myocarditis after the vaccine, but not in the control subjects [260]. A study on 28 cases of fatal myocarditis immediately following mRNA vaccination for SARS-CoV-2 established that all 28 deaths were most likely linked to the vaccine [261]. The spike protein is predicted to cause neuroinflammation and neurodegenerative disease, in part through its prion-like properties [262,263].

The lipid nanoparticles in the vaccine are designed so as to protect the mRNA from degradation, and, furthermore, the mRNA itself has been engineered to resist enzymatic breakdown through the substitution of

methylpseudouridine for all of the uridine residues [264]. The synthetic cationic lipids assure that the mRNA will be released from the endosome, escaping lysosomal degradation, and then be persistently translated into spike protein. While mRNA normally degrades within a few hours, vaccine spike antigen and mRNA can persist for up to eight weeks in lymph node germinal centers [265].

The nanoparticles can breach the blood brain barrier, and the mRNA nanoparticles can be phagocytized by microglia in the brain and then translated into spike protein, stimulating a massive immune response. This causes upregulation of TNF-α, IL-1β, and IL-6, stimulating ROS production and neuroinflammation. Neuroinflammation in turn provokes astrocytes to release excessive glutamate into the synapse, overstimulating the NMDARs and causing neuroexcitotoxicity [266]. This leads to a reduction in BDNF signaling and impaired neuroplasticity, as is seen in schizophrenia and autism [267]. As we have seen, extracellular glutamate interferes with cystine uptake in neurons, leading to glutathione deficiency. A recent review paper has proposed that glutathione deficiency may be at the core of COVID-19 pathophysiology [268]. Glyphosate's ability to deplete glutathione would therefore likely lead to more severe outcomes from COVID-19 and/or more severe adverse reactions to the mRNA vaccines.

A seminal study by Erdogan et al. on rat pups found strong evidence that the mRNA vaccines cause autism-like symptoms in rats. Pregnant rat dams were exposed to a full adult dose of the BNT162b2 vaccine, and the offspring were carefully evaluated for behavioral issues and motor performance, as well as monitoring for any changes in brain chemistry. Exposed male rat pups, but not female pups, exhibited pronounced autism-like behaviors, including repetitive behaviors, impaired social interaction, as well as impaired coordination and agility. Notably, the exposed male offspring were found to have statistically significant decreased expression of BDNF and WNT ($p < 0.01$) and significantly increased expression of mTOR ($p < 0.01$) [269].

BDNF is an important player in WNT signaling, and its expression has been shown to be essential for synapse maturation in the hippocampus mediated by neuroligin [270]. Downregulation of BDNF leads to decreased levels of Bcl2 through impaired Akt signaling, with a resulting increase in apoptosis in neurons, a mechanism that has been proposed as potentially being responsible for the pathogenesis of autism [271]. We have already seen that WNT signaling is decreased following exposure to glyphosate, making these injections synergistically toxic with glyphosate [118]. Overexpression of mTOR has been linked to increased spine density in excitatory synapses in autism [272]. As we have already stated, an overactive mTOR pathway impairs microglial autophagy, resulting in decreased clearance of unproductive synapses [116].

In the Erdogan et al. study, post-mortem analyses showed that exposed male pups also had significantly fewer neurons in specialized regions of the hippocampus compared to male pups of the unvaccinated mothers, as well as lower counts of Purkinje cells in the cerebellum [269].

While the rat dams in this experiment was exposed to a much higher dose of the vaccine than would be appropriate given their weight, it is also the case that the rat ACE2 receptor has a much reduced capacity to facilitate uptake of the spike protein compared to the human ACE2 receptor, making rats far less susceptible to SARS-CoV-2 [273].

We have shown that children with autism have impairments in melatonin synthesis, and that glyphosate exposure reduces melatonin levels in rats [39]. It has been proposed that melatonin supplementation can be therapeutic in treating long COVID, through its anti-inflammatory, antioxidant and immune enhancing properties [274]. A study on mice humanized to express the human ACE2 protein and exposed to SARS-CoV-2 found that melatonin therapy inhibited SARS-CoV-2 brain entry and protected brain endothelial cells from damage. They showed that melatonin inhibits virus-induced damage of cerebral small vessels, diminishes brain inflammation, and decreases viral load in the brain. This result suggests that melatonin deficiency, such as is seen in autism and induced by glyphosate, would lead to increased risk to severe COVID as well as vaccine adverse reactions.

At the beginning of this paper, we noted the standard categorization of autism onset as "early," typically onset prior to age 2; and "regressive," with onset after age 2. We cited studies that have shown that over 50% of regressive cases of autism displayed subtle-yet-perceivable sensory and/or behavioral abnormalities prior

to regression, i.e. during the "normal" developmental months. We propose here that the risk of developing the sensory and behavioral changes characteristic of autism – along with the concurrent pathophysiology described in this paper - lies on a continuum. Differing levels of*in utero* , neonatal, and postnatal glyphosate exposure, against a background of other risk factors, helps explain this chronological gradient of autism symptom onset.

We strongly suggest that glyphosate may be playing a significant (and possibly central) role in contributing to the autistic phenotype. Current CDC recommendation regarding COVID-19 vaccination is that infants should be vaccinated beginning at 6 months of age [275] Furthermore, prenatal and postnatal exposure to the constituents of COVID-19 mRNA vaccines via maternal, neonatal and early-postnatal periods is potentially an additional strong push toward that same phenotype for the reasons we have explained above. For children manifesting as regressive autism, we are concerned that mRNA vaccination may contribute the spark of neuroinflammation that is the tipping point for an infant with excessive prior exposure to glyphosate and/or other environmental factors, particularly when combined with risk genes. In this regard, we agree with the letter published by Mawson (2019) regarding the finding of increased autism following MMR vaccination: "Many factors, including receiving the MMR vaccine and other vaccines, may be combining with as-yet unidentified host and environmental factors to cause [autism]." [276]. We believe this paper makes a compelling case that one of those environmental factors has now been identified.

Conclusion

The incidence of autism has increased dramatically over the past two decades. While its causal factors are most certainly multifactorial (toxicants, genetics, nutrient deficiencies, etc.), there are numerous cellular and biochemical pathologies that are shared by virtually all individuals with the condition. This paper has focused on what we believe to be a prime suspect as a causal environmental factor, glyphosate exposure. We have itemized several biochemical and histological pathologies associated with autism throughout this paper. We weave into this narrative a review of the literature to show substantial evidence that exposure to glyphosate has also been associated with the same pathologies found in individuals with autism. We also highlight a unique role for melatonin in protecting against development of those same neurological pathologies, and review evidence that glyphosate exposure also suppresses melatonin production.

Another prominent focus of this paper is on what we believe to be the most important pathways through which glyphosate, melatonin suppression, glutamate neuroexcitotoxicity and potentially other causal factors lead to the phenotype of autism, namely suppression of cellular isomerase PIN1 activity. Its suppression, whether by glyphosate exposure, melatonin deficiency, DAPK1 activation, glutathione deficiency, oxidative stress, or other causes, is the first domino to fall, initiating a long series of downstream events that result in all the underlying pathological changes we have catalogued as associated with autism. Because of both the direct and indirect role PIN1 plays in so many cellular regulatory pathways and processes, its loss of activity has catastrophic consequences leading to autism pathology. This becomes perhaps most explicitly manifest in the developing neurological system of infants and children, making them most vulnerable to the pathological changes PIN1 suppression induces. Figure 3 provides a graphical representation of the processes we have identified in this paper leading to autism in children.

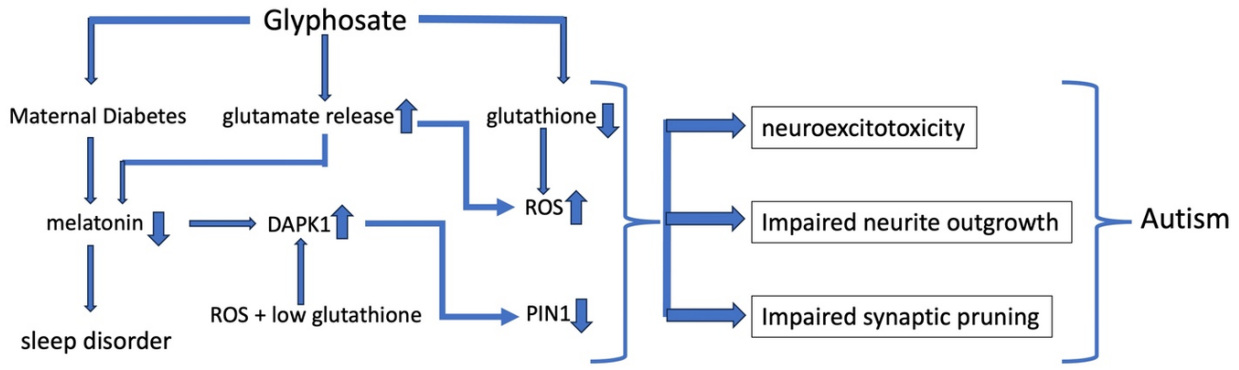

Figure 3: The complex processes by which glyphosate damages the infant brain, leading to impaired neurodevelopment and autism spectrum disorder. PIN1 plays a central role in the pathology. Glyphosate plausibly induces severe depletion in glutathione levels in the brain via its induction of oxidative stress and its disruption of melatonin synthesis in the brain. Increased ROS and elevated expression of DAPK1 both contribute to the loss of PIN1 activity. These three features - low glutathione, oxidative stress, and reduced PIN1 activity – disrupt brain development, resulting in the characteristic morphological and behavioral features of autism.

We end our review with a note of caution about mRNA vaccinations in general, but especially for children, and for autistic children most directly. We have called attention to the established pathways whereby the mRNA and associated LNPs can migrate to the brain and induce neuroinflammation, creating many of those same pathological imbalances we previously showed to be associated with autism.

Given the ominous rise in the incidence of autism now happening around the globe, we believe it is imperative that distribution and use of glyphosate, and administration of COVID-19 mRNA-LNP vaccinations to pregnant women and infants be halted immediately, while the mechanisms behind their potential connection to autism – and possibly a wide range of other diseases – can be definitively ruled out through additional detailed research.

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