

REVIEW

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Wnt signaling networks in autism spectrum disorder and intellectual disability

Vickie Kwan, Brianna K. Unda and Karun K. Singh*

Abstract

Background: Genetic factors play a major role in the risk for neurodevelopmental disorders such as autism spectrum disorders (ASDs) and intellectual disability (ID). The underlying genetic factors have become better understood in recent years due to advancements in next generation sequencing. These studies have uncovered a vast number of genes that are impacted by different types of mutations (e.g., de novo, missense, truncation, copy number variations).

Abstract: Given the large volume of genetic data, analyzing each gene on its own is not a feasible approach and will take years to complete, let alone attempt to use the information to develop novel therapeutics. To make sense of independent genomic data, one approach is to determine whether multiple risk genes function in common signaling pathways that identify signaling “hubs” where risk genes converge. This approach has led to multiple pathways being implicated, such as synaptic signaling, chromatin remodeling, alternative splicing, and protein translation, among many others. In this review, we analyze recent and historical evidence indicating that multiple risk genes, including genes denoted as high-confidence and likely causal, are part of the Wingless (Wnt signaling) pathway. In the brain, Wnt signaling is an evolutionarily conserved pathway that plays an instrumental role in developing neural circuits and adult brain function.

Conclusions: We will also review evidence that pharmacological therapies and genetic mouse models further identify abnormal Wnt signaling, particularly at the synapse, as being disrupted in ASDs and contributing to disease pathology.

Keywords: Autism spectrum disorders, ASD, Synapse, Wnt signaling, GSK3, Neurodevelopment, Signaling, Plasticity, Mutations, Neurotransmission, Neurogenesis, Neuronal migration

Background

The emerging genetic landscape of Wnt signaling in ASDs
ASDs and other psychiatric disorders may have heritability estimates greater than 90% [1], suggesting a strong genetic component to disease. With this background in mind, there has been an enormous advancement of new genetic technologies to discover risk-causing genes and loci. These developments paired with an increased ability to process large data sets have led to many new risk genes being discovered. The number of genes and chromosomal loci linked to ASDs is growing, making it difficult to determine which one(s) to study. This has inspired the field to determine if there are links between the genes and whether they converge into signaling

networks important for proper brain development. While the spectrum of ASDs is reflected by the multiple individual risk genes and loci, there is some common denominator between affected individuals, which strongly suggests that disruption of the core neurodevelopmental signaling pathways leads to disease symptoms. In this review, we will examine accumulating evidence for the involvement of Wnt signaling in developmental cognitive disorders. This includes emerging genetic data from large sequencing studies, clinically used medications, and mouse models. We will also present potential avenues for therapeutic approaches, and how Wnt signaling may be modulated for treatment of patient symptoms by leveraging clinical trial data from other fields.

* Correspondence: singhk2@mcmaster.ca

Department of Biochemistry and Biomedical Sciences, Stem Cell and Cancer Research Institute, McMaster University, Hamilton, Ontario L8S 4K1, Canada



Making sense of genetic findings

It is no surprise that the clinical heterogeneity of ASDs can be explained, at least in part, by the large number of genetic mutations found through next-generation sequencing. The number of mutations discovered ranges in the several hundreds, according to well-known sources such as the Simons Foundation Autism Research Initiative (SFARI). There is much difficulty in trying to understand the biological etiology of ASDs when so many genes are involved. One hypothesis is that the genetic lesions disrupt specific signaling pathways during discrete time points of brain development. For example, many of the initial genetic studies identified genes involved in synapse development and refinement. This was largely based on findings that multiple genes in syndromic forms of ASDs (e.g., Fragile X syndrome (*FMRI*), Rett syndrome (*MECP2*), Angelman syndrome (*UBE3A*), and genes that cause non-syndromic forms of ASDs (e.g., the Shank and neuroligin/neurexin family of proteins) have important roles during synapse development and refinement [2–8]. This suggests that the disruption of postnatal synaptic maturation could increase the risk for developing ASDs and related disorders. However, there has been accumulating evidence that other brain developmental milestones are also vulnerable, such as prenatal brain development (e.g., neurogenesis) [9], or postnatal development of non-neuronal cells (e.g., oligodendrocytes during myelination and microglia function) [10–13]. This is also supported by the implication of discrete cell types in the brain based on the identification of specific risk genes expressed in those cells (e.g., inhibitory neurons) [14–16]. In the current review, we take an alternative approach that is not in contrast to these hypotheses but examines whether there is convergence of multiple risk genes onto specific signaling pathways, which ultimately impact multiple cell types and/or developmental processes. We put forth the notion that by focusing on a specific pathway and dissecting which molecular players in that pathway are important for disease pathophysiology, it may offer an opportunity to identify key proteins to be pharmacologically targeted by drug therapies to treat these disorders.

Review

Convergent evidence for Wnt signaling

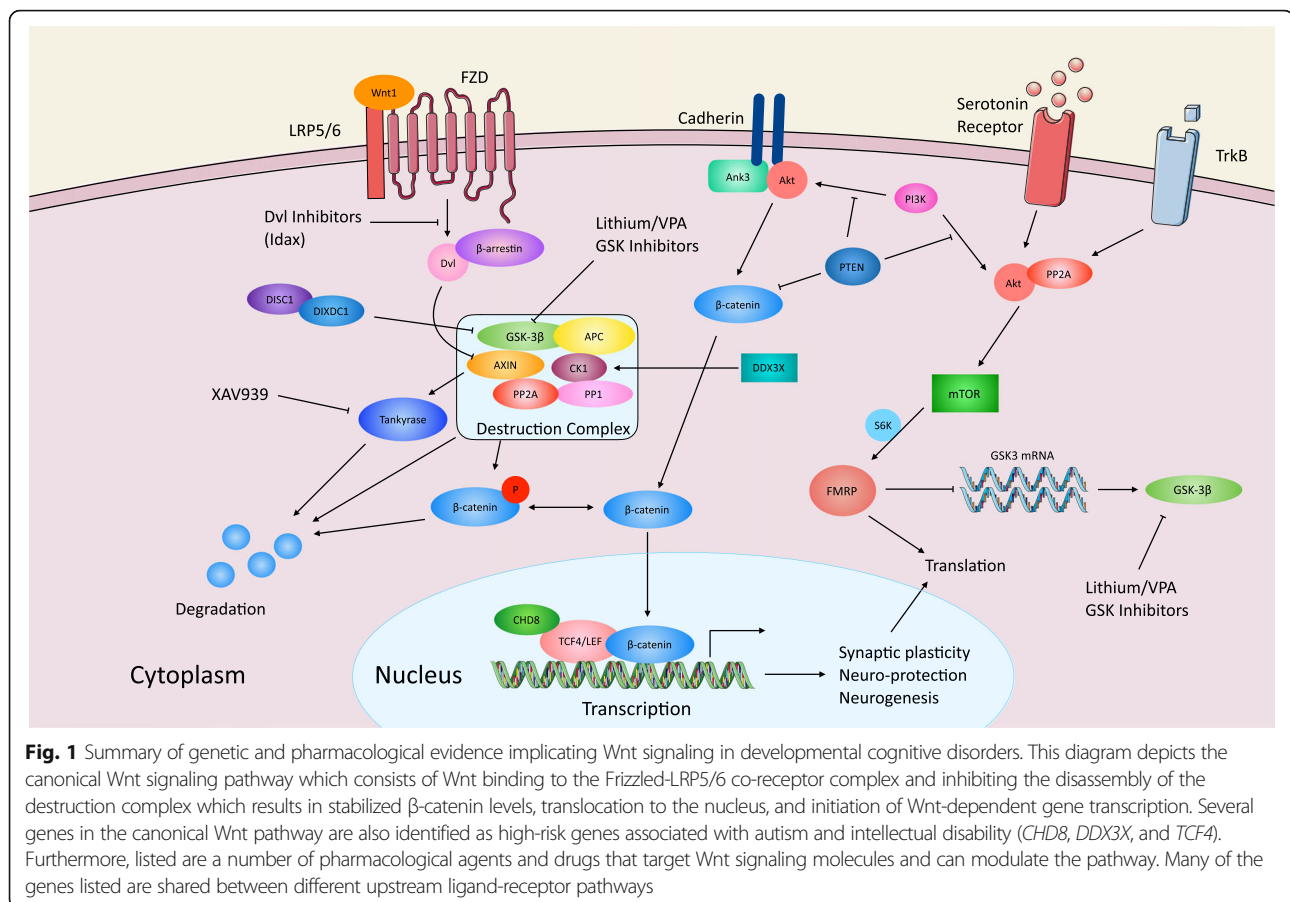
One pathway highlighted in the multitude of genetic studies is the Wingless (Wnt) signaling. This pathway is highly studied and conserved from lower to higher organisms, where it plays a variety of roles in almost all tissues. Broadly speaking, Wnt signaling in the brain can be divided into two main pathways: (i) “canonical” signaling that results in the stabilization of the protein β -catenin (encoded by *CTNNB1*), which upon stabilization, can exert functions at the plasma membrane or in the

nucleus and can act as a transcription factor that modulates the expression of target genes (Fig. 1); and (ii) “non-canonical” β -catenin-independent signaling [17]. Interestingly, many of the proteins in both signaling pathways localize to the synapse and play important functions in synaptic growth and maturation [18–23]. There are now multiple lines of evidence implicating this pathway in the etiology and pathophysiology of ASD and intellectual disability (ID). While the human genetic data is an important supporting factor, it is not the only one. There are a number of mouse genetic knockout (KO) models targeting Wnt signaling molecules, describing molecular, cellular, electrophysiological, and behavioral deficits that are consistent with ASD and ID. Furthermore, the genes involved in Wnt signaling are of significant clinical interest because there are a variety of approved drugs that either inhibit or stimulate this pathway.

Genetic evidence implicating Wnt signaling genes and support by cellular models

CHD8

The strongest single candidate gene for non-syndromic ASDs is chromodomain helicase DNA binding protein 8 (*CHD8*) [24–30]. There are multiple de novo, truncating, or missense mutations discovered in *CHD8* in individuals with ASDs [27–29, 31–34]. *CHD8* is found at active transcription sites with histone modifications H3K4me3 or H3K27ac, and it is thought to directly activate genes by binding near the transcriptional start site and promoting transcription factor activity or recruitment. It can also indirectly impact transcription by interacting with modified histone sites and other co-regulators to make chromatin more assessable [24, 34–36]. Interestingly, one of the major pathways regulated by *CHD8* is canonical Wnt signaling [37, 38]. Previous work characterized *CHD8* as a negative regulator of canonical Wnt signaling, which fits with the hypothesis that elevated canonical Wnt signaling activity causes excessive proliferation of embryonic neural progenitor cells (NPCs) in the brain and may in part explain the macrocephaly (“big brain”) phenotype observed in patients [27]. Furthermore, recent studies in human neural progenitors lacking one copy of *CHD8* support this notion, as it revealed many target genes controlled by *CHD8* that are involved in the regulation of spine head size [34, 39, 40]. However a recent study discovered that *CHD8* is in fact a positive regulator of Wnt/ β -catenin signaling NPCs, while simultaneously demonstrating that it negatively regulates the pathway in non-neuronal cell lines [41]. Given this unexpected finding, this suggests that *CHD8* regulates Wnt signaling in a cell-specific manner, and the possibility that some of the *CHD8* mutations may not be as simple as loss-of-function for Wnt signaling. Further work is



needed to clarify how *CHD8* regulates Wnt signaling in different cell types in the brain, and how patients with *CHD8* mutations acquire macrocephaly. It is also important to note that Wnt signaling is only one neurodevelopmental pathway regulated by *CHD8*, and recent studies have identified many others (e.g., chromatin remodeling). Therefore, future work needs to determine the precise mechanisms and time points during which *CHD8* regulates Wnt signaling during neurodevelopment. This is important to better comprehend how prenatal brain development could be compromised in individuals with *CHD8* mutations.

CTNNB1 (β -catenin)

β -catenin is a central player in the canonical Wnt signaling pathway and works with co-factors to initiate Wnt-dependent gene transcription (Fig. 1). It has directly been implicated in ASDs due to the identification of de novo mutations in the *CTNNB1* gene in patients with ASD using exome sequencing [25, 28, 29, 42]. Given the core nature of this gene in canonical Wnt signaling, this strongly places aberrations in Wnt signaling as one of the main networks in ASD pathogenesis. Network analysis from gene expression data also indicates that β -

catenin exists in a protein network, including *CHD8* and other ASD or ID associated genes [25]. The relationship between Wnt signaling and chromatin remodeling factors demonstrates that proper interplay between these pathways is important for appropriate levels of canonical Wnt-dependent gene transcription. *CHD8* regulates β -catenin-mediated canonical Wnt signaling, which could occur by *CHD8* directly by binding to β -catenin or indirectly by inhibiting the recruitment of co-factors required for transcription at promoter sequences. Future work will need to determine precisely which neural progenitor sub-populations are most sensitive to disruptions in canonical Wnt/ β -catenin signaling during prenatal brain development. For example, previous studies indicated that global stabilization of β -catenin in the cortex, which elevates canonical Wnt signaling, leads to brain overgrowth due to increased cycling neural progenitor cells and production of neurons [43]. In contrast, deletion of β -catenin from parvalbumin-expressing inhibitory neurons leads to ASD-like defects in neuronal activation and behavior, such as social interaction and object recognition impairments [44].

β -catenin also functions in pathways other than canonical Wnt signaling, such as cell adhesion at the

plasma membrane. β -catenin interacts with cadherins to regulate dendritic spine growth and synaptic competition during the process of postnatal period of dendritic pruning [45]. A recent study identified that dominant mutations in *CTNNB1* from ID patients when expressed in mice have a reduced affinity for membrane-associated cadherins [46]. This is associated with a decrease in cadherin interaction and decreased intrahemispheric connections, with deficits in dendritic branching, long-term potentiation, and cognitive function [46]. Therefore, it is possible that mutations in β -catenin could lead to aberrant Wnt signaling developmentally, concurrent with disruption of plasma membrane signaling at synaptic sites, both leading to disrupted gene transcription programs and abnormal synaptic plasticity. Furthermore, both of these pathogenic events would increase disease risk. In this regard, these pathways are also likely connected given that β -catenin signaling at the membrane impacts nuclear Wnt-dependent transcription [47].

PTEN

Another high-risk autism candidate gene that has roles in Wnt signaling is *PTEN* due to the discovery of numerous individuals with mutations [29, 48–50]. *PTEN* has multiple functions but is best known for its role as a negative regulator of the PI3K-Akt-mTOR pathway. Individuals with heterozygous mutations in *PTEN* are also at risk for macrocephaly, indicating that *PTEN* regulates brain size, which is thought to be an impact on certain individuals with ASD [51–59]. Multiple mouse models of *Pten* have further strengthened the notion that it is an important regulator of different neural circuits associated with ASDs and cognition. For example, an early study identified that global *Pten* +/- mice have impairments in social interaction behaviors [52]. Knocking out *Pten* in the cerebellar Purkinje cells led to impaired sociability, repetitive behavior, and deficits in motor learning. Additionally, knocking out *Pten* in a subset of cortical excitatory neurons results in profound synaptic signaling changes [60], while ASD-associated *Pten* alleles expressed in inhibitory neurons cause excitatory/inhibitory imbalances [54]. Interestingly, *PTEN* has recently been identified to function with β -catenin to regulate normal brain growth, implicating *PTEN* in Wnt signaling. It was discovered that β -catenin signaling is elevated in a mouse model of *Pten* (*Pten* +/-), and a heterozygous mutation in *β -catenin* suppresses the excessive cortical brain growth in *Pten* +/- mice [53]. This indicates that multiple ASD risk factors likely converge upon neural progenitor proliferation during embryonic brain development, potentially through regulation of canonical Wnt signaling.

TCF7L2 (TCF4)

Recent studies have identified mutations in *CTNNB1* within individuals with developmental delay and ID who do not have an ASD [46, 61, 62]. Additional support comes from another ASD exome sequencing study that identified de novo loss of function variants in *TCF7L2* (transcription factor 7-like 2 (T-cell specific, HMG-box)) [63, 64], which also goes by the name *TCF4*, and is confused with transcription factor 4 (TCF4) as they share the same symbol. Importantly, *TCF7L2* is a key player in canonical Wnt signaling as it helps to initiate gene transcriptional response when Wnt ligands bind their receptors on the membrane, and the signal is transduced to the nucleus (Fig. 1). These genetic studies directly implicate de novo missense variants in *TCF4* in ASD, suggesting that perturbations to the core canonical signaling complex play a pathogenic role. However, the role of *TCF4* in brain development and which time points and cell types it regulates is not well known and needs to be identified in future studies.

DDX3X

A recent study identified de novo mutations in *DEAD-box helicase 3, X-linked (DDX3X)* in a population of unexplained ID [65]. *DDX3X* was identified as a regulator of the Wnt- β -catenin network, via regulation of the kinase activity of CK1 ϵ , to promote phosphorylation of Dvl, both critical factors in canonical Wnt signaling (Fig. 1). Moreover, in model systems testing the Wnt pathway, *DDX3X* was found to be required for Wnt- β -catenin signaling in mammalian cells through loss of function studies [66]. Therefore, in addition to ASD, Wnt- β -catenin signaling may be disrupted in generalized ID and developmental disorders (DD), further demonstrating the importance of this pathway in proper neurodevelopment. However, a critical question that remains is how do mutations in Wnt signaling molecules give rise to different phenotypes, such as ASD versus ID/DD? This insight would provide tremendous clinical utility, as it will allow caregivers and clinicians to plan therapies according to the future outcome.

Animal models support the involvement of Wnt signaling

Mouse models provide support for Wnt signaling as a clinically relevant pathway for developmental cognitive disorders. First, modeling of high-risk (i.e., causative) ASD genes, for example using gene knockouts (KO), offer the opportunity to determine the neural circuits and brain regions responsible for causing ASD-like behavior. Second, interrogation of other genes in the same pathway, which are not directly involved in ASD from human genetic studies, offers the opportunity to further support that pathway in ASD pathophysiology. For example, while no ASD-specific genetic mutations

have been identified in the *disheveled* genes (*Dvl 1, 2 and 3*), *Dvl1* or *Dvl1/3* KO mice display adult social and repetitive behavioral abnormalities, which are the core features of ASD symptoms [67–69]. This type of example lends further evidence that perturbation of the core Wnt signaling transduction molecules like *Dvl1/3* can result in ASD-like abnormalities even though they are not directly implicated in human genetic studies.

In addition to *Dvl1/3*, recent studies have highlighted that conditional or complete KO mouse models of other genes involved in Wnt signaling support the pathway being involved in ASD-like phenotypes. One of the best-studied genes is *glycogen synthase kinase 3* (*GSK3*) α and β , which is a negative regulator of canonical Wnt signaling and also plays important roles directly at the synapse (Fig. 1). It is well-established that the inhibition of *GSK3* using lithium or specific inhibitors (e.g., CHIR 99021) causes an increase in activation of the canonical transcriptional pathway of Wnt signaling [70]. *Gsk-3 β* heterozygous (+/-) mice display behaviors that resemble wild type (WT) mice treated with lithium, a drug that is used to treat bipolar disorder [71], demonstrating that disruption of Wnt signaling leads to behavioral abnormalities. Furthermore, forebrain-specific deletion of *Gsk-3 β* in excitatory neurons leads to anxiolytic and pro-social effects [72], suggesting that *GSK-3 β* plays important roles in normal behavior. The most convincing evidence that *GSK3* and Wnt signaling may be involved in developmental cognitive disorders is its role in Fragile X syndrome (FXS), which is the most commonly inherited form of intellectual disability and is linked to ASDs [73, 74]. Fragile X Mental Retardation Protein (FMRP) KO mice, which is a FXS model, has been shown to possess a dysregulation of *GSK3 β* activity. Specifically, *GSK-3 β* protein and its activity is pathogenically elevated in FXS models [75, 76], and pharmacological correction of this enhanced activity using lithium or *GSK3* inhibitors in mice rescues neurobehavioral and brain morphological abnormalities [77–82]. Furthermore, studies investigating FXS mice demonstrated that Wnt signaling is also disrupted [83, 84]. Of course, *GSK-3 β* has many downstream signaling targets, one of which is the Wnt signaling pathway; demonstrating that modulation of *GSK-3 β* activity can have therapeutic effects beyond the treatment of bipolar disorder.

Another well-studied gene in relation to ASD and psychiatric disorders is *disrupted in schizophrenia 1* (*DISC1*). While the genetic evidence linking *DISC1* to developmental cognitive disorders is not strong, the multiple cellular and mouse models of *Disc1* perturbation has led to important findings linking Wnt signaling to abnormal neurodevelopment. For example, a landmark study initially described *DISC1* as an inhibitor of *GSK-3 β* , similar to the actions of lithium, demonstrating

that *DISC1* positively regulates canonical Wnt signaling [85], which has been followed up by other studies [86–89]. Several follow-up studies on multiple mouse models of *Disc1* demonstrate that *DISC1* perturbation causes significant neurodevelopmental phenotypes, including cognitive defects and psychiatric-like behavioral manifestations [90–94].

There are other known regulators of Wnt signaling that when disrupted leads to neurocognitive and neurodevelopmental phenotypes. A recent example is *AnkyrinG* (*Ank3*), which was found to possess a genome-wide significant signal in bipolar disorder [95, 96]. *Ank3* is a scaffolding protein that localizes to the nodes of Ranvier in mature neurons, important for the formation and maintenance of the axon initial segment [95]. It has also been shown to regulate glutamatergic synapse structure and function through modulation of AMPAR-mediated synaptic transmission and maintenance of dendritic spine morphology [97]. Interestingly, *Ank3* is a negative regulator of canonical Wnt signaling during embryonic neurogenesis in the mouse brain and functionally interacts with *DISC1* to regulate this process [46]. *Ank3* heterozygous mice possess behavioral phenotypes such as reduced anxiety and increased motivation for reward, which can be corrected by modulating Wnt signaling through *GSK-3 β* [98], demonstrating the clinical involvement of this pathway. In addition to *Ank3*, other recently characterized genes in mice also support a role for Wnt signaling in neurodevelopmental disorders. DIX domain containing 1 (*DIXDC1*) is a positive regulator of Wnt signaling and neurogenesis through binding to *DISC1* [99] and a *Dixdc1* KO mouse displayed behaviors associated with neuropsychiatric disorders such as abnormal startle reflex and reduced social interaction [100]. The behavioral phenotypes displayed by these mice could be rescued through lithium or *GSK3* inhibitor treatment [101, 102].

There are three other Wnt signaling-related genes that have been characterized in mice that lend further support to the involvement of Wnt signaling in developmental cognitive disorders (see Fig. 1). The first is *adenomatous polyposis coli* (*APC*), which is a critical component of the destruction complex in the canonical Wnt pathway and is important for neural plasticity, learning, and memory in mice. A conditional *Apc* KO mouse showed increased synaptic spine density, elevated frequency of miniature excitatory postsynaptic potentials (mEPSPs), enhanced long-term potentiation (LTP), and ASD-like behaviors (e.g., repetitive behaviors and reduced social interest) [103]. Second, analysis of a *Prickle2* mouse model demonstrates its importance in ASD-related neural circuits and behavior [104, 105]. *Prickle2* is a postsynaptic protein that interacts with PSD-95 and is part of the non-canonical Wnt signaling

pathway [106]. The *Prickle2* KO mouse has previously been shown to be more sensitive to seizures and also shows reduced dendrite branching, synapse number, and postsynaptic density (PSD) size, as well as behavioral abnormalities (learning abnormalities, altered social interaction, and behavioral inflexibility). Although the involvement of *Prickle2* implicates non-canonical Wnt signaling, the phenotypes associated with the KO mouse demonstrate that multiple aspects of Wnt signaling (canonical and non-canonical) are important for the establishment of neural circuits that are disrupted in ASD. While the studies on APC and *Prickle2* do not directly implicate abnormal Wnt signaling, we speculate that these mice would have alterations in this pathway due to the importance of these molecules in Wnt signaling in neural cells. Third, a recent study identified that rare missense variants in the *Wnt1* gene discovered in ASD patients show abnormal activation of the Wnt signaling pathway, providing evidence that subtle changes to the coding sequence of Wnt signaling molecules alter biological signaling [107]. Together, these studies indicate that when analyzed using animal models, members of the Wnt signaling pathway, which have no link to disease from human genetic studies, demonstrate how disruption of this core signaling pathway in the brain results in developmental phenotypes consistent with human disease.

Targeting Wnt signaling in ASD/ID mouse models

In addition to animal models, there are two specific drug-induced models that implicate Wnt signaling. The first is valproic acid (VPA), which is thought to increase the risk for ASD through exposure to a pregnant woman during prenatal development [108]. The administration of VPA to pregnant mice has long been used as a model of ASD, as the offspring of these mice develop ASD-like deficits in brain structure, neuronal signaling, and behavior [109]. VPA has many targets, but one of its better characterized effects is the stimulation of the canonical Wnt signaling pathway through modulation of histone deacetylase and GSK3 [110–114], demonstrating that abnormal Wnt signaling likely plays an important role in the pathogenicity of VPA. A second model that was recently developed and more specifically implicates Wnt signaling is exposure of pregnant mice to the compound, XAV939, which is a tankyrase inhibitor, resulting in enhanced canonical Wnt signaling [115]. This leads to the expansion of the intermediate progenitor cell population in the developing cerebral cortex. The result of exposure to XAV939 is an overpopulation of neurons in the cortex, which disrupts the development and function of dendrites and dendritic spines of excitatory neurons and alters the distribution of interneurons. These mice exhibit ASD-like behavioral abnormalities, implicating that

changes to canonical Wnt signaling during prenatal brain development can have a profound impact on brain size and function. These results suggest a causal relationship between abnormal modulation of Wnt signaling during neurodevelopment and autism-like features [115].

Hope for ASD treatment using Wnt signaling modulators?

There is only one FDA approved for ASDs, which is used to treat irritability associated with ASDs (risperidone, an antipsychotic medication), demonstrating the urgent need to find new medications. Many of the medications used are “off-label” (e.g., antidepressants, anti-convulsants, stimulants, and anti-anxiety medications) and do not treat the core symptoms, and can have very strong side effects. While these medications have multiple modes of molecular action, interestingly, many impact Wnt signaling. For example, haloperidol (typical antipsychotic medication) is known to inhibit dopamine receptors, thereby increasing GSK3 β inhibition through Akt activation [116], which impacts downstream canonical Wnt signaling [117, 118]. Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine), which are used to treat depression, potentially by increasing hippocampal neurogenesis in mice, have been shown to antagonize canonical Wnt signaling, which causes a reduction in expression of the serotonin transporter (SERT) in serotonergic raphe neurons through miR-16 [119, 120]. Additionally, lithium is a well-known treatment for bipolar disorder, and one of its main activities is inhibition of GSK-3 β , which positively stimulates the canonical Wnt pathway [121–123]. Stimulants such as Methylphenidate (e.g., Ritalin) can function as a negative regulator of the canonical pathway by activating GSK-3 β [124, 125]. In this regard, various GSK-3 β inhibitors have been used to rescue neurogenesis defects in mouse models of psychiatric disorders and ASD, which also stimulate canonical Wnt signaling pathways [69]. Taken together, while it is important to be cautious of the multiple mechanisms of action of all of the classes of medications discussed here, it is intriguing to find that all of them either directly or indirectly impact canonical Wnt signaling in the brain to some degree. This suggests that abnormal Wnt signaling likely plays a core role in the disease pathogenesis of developmental cognitive disorders, and restoring normal levels of this pathway with medications could be an option for treatment.

Many times the medications tested in pilot clinical trials for neurological disorders are failed drugs from cancer trials. There are many drugs developed and tested as modulators of Wnt signaling in the cancer field that could potentially be repurposed for developmental cognitive disorders. In cases where a reduction in Wnt signaling is thought to underlie the pathology of the disorder, usage of compounds that elevated canonical

Wnt signaling could be applied. An example of this is GSK-3 β inhibitors that have failed in cancer trials but may be effective for ASDs and ID (e.g., Tideglusig, ClinicalTrials.gov identifier: NCT02586935). In cases where elevated Wnt signaling is thought to contribute to disease pathology, there are many potential options to inhibit canonical Wnt signaling using chemicals (Fig. 1) that inhibit the interaction between β -catenin and its targets (e.g., inhibiting β -catenin interaction with the TCF factors), disheveled inhibitors (through targeting of the PDZ domain which generally inhibit the Frizzled–PDZ interaction), and tankyrase inhibitors (e.g., XAV939, which induces the stabilization of axin by inhibiting the poly (ADP)-ribosylating enzymes tankyrase 1 and tankyrase 2) [126]. These candidate compounds may be of clinical use in cases where it is thought that the genetic risk factor for ASD or ID causes elevated canonical Wnt signaling (e.g., potentially some individuals with CHD8 mutations); however, even if these drugs made it to the clinic, they would likely have to be delivered in utero, since embryonic brain development is most affected by such genetic mutations, posing ethical issues for pre-diagnosis therapies.

Conclusions

The goal towards better understanding and treating developmental cognitive disorders is a difficult road and will require a multifaceted research and clinical approach to be successful. In this review, we present evidence that one such signaling pathway that may be central to disease pathogenesis and treatment is the Wnt signaling network. Ongoing and future genetic studies will need to determine the strength of association of this pathway with disease; however, given the medications and drugs that target this pathway currently available, this presents an opportunity for new clinical trials in the near future.

Abbreviations

ANK3: AnkyrinG; APC: Adenomatous polyposis coli; ASD: Autism spectrum disorder; BP: Bipolar disorder; CHD8: Chromatin-helicase-DNA-binding protein 8; CIHR: Chiron; CTNNB1: (β -catenin); DDX3X: DEAD-box helicase 3, X-linked; DISC1: Disrupted in schizophrenia 1; DIXDC1: Dix domain containing 1; DVL: Disheveled; FDA: Food and drug administration; FMR1: Fragile X mental retardation 1; FMRP: Fragile X mental retardation protein; FXS: Fragile X syndrome; GSK: Glycogen synthase kinase; ID: Intellectual disability; KO: Knockout; LTP: Long-term potentiation; MECP2: Methyl CpG binding protein 2; miniature excitatory postsynaptic potentials; mEPSPs: Miniature excitatory postsynaptic potentials; NDD: Neurodevelopmental disorders; Prickle2: Prickle planar cell polarity protein 2; PSD: Postsynaptic density; PTEN: Phosphatase and tensin homolog; SERT: Serotonin transporter; SFARI: Simons Foundation Autism Research Initiative; SSRI: Selective serotonin reuptake inhibitor; UBE3A: Ubiquitin-protein ligase E3A; VPA: Valproic acid; Wnt: Wingless; WT: Wild type

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Authors' contributions

The topics of discussion were generated by KKS and VK, and BU assisted KKS in writing the manuscript. VK designed the figures with KKS. All authors read and approved the final manuscript.

Competing interests

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Consent for publication

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