World Journal Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

Check for updates

The role of the Blood-Brain Barrier in cellular communication: A review

Adline Fernando [1], Ashraf Kadar Shahib [1], Ragini Raghu [1] and Mathangi Ganapathy [2,*]

[1] *Industrial Biotechnology, Department for Biotechnology, Anna University, Chennai 600025, India.*
[2] *Centre for Biotechnology, Anna University, Chennai 600025, India.*

World Journal of Biology Pharmacy and Health Sciences, 2023, 13(01), 362–381

Publication history: Received on 02 December 2022; revised on 19 January 2023; accepted on 21 January 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.13.1.0027

Abstract

The blood-brain barrier regulates the flow of ions, chemicals, and cells by acting as a conduit between blood and cerebral tissue. Additionally, it shields the brain against pathogen invasion and immune cell infiltration. It is composed of endothelial cells, pericytes, astrocytic end feet, perivascular macrophages, and microglial cells, which help in maintaining its integrity. There are various signaling pathways that are also involved in maintaining its integrity. The Wnt/β catenin, FZD4/FZD7, Hedgehog and TGF-β signaling pathways were evident to produce components or factors which stabilise the BBB. However, the NF-B and ERK signaling pathways caused the creation of MMPs, which increased the BBB's permeability. These functions are altered in pathological conditions like Alzheimer's disease, and Parkinson's disease which are also mentioned.

Keywords: Blood-brain Barrier; Signaling Pathways; Wnt; FDZ4/7; Hedgehog; TGF-β; ERK; NF-κB; Alzheimer's Disease; Parkinson's Disease; Neurodegeneration

1. Introduction

The blood-brain barrier regulates the flow of ions, chemicals, and cells when blood and neural tissue come into contact. It protects the brain from pathogen invasion and infiltrating immune cells. The BBB was first identified by German microbiologist Paul Ehrlich in 1885 [1], following the injection of dyes into the bloodstream. In comparison to the CNS, the peripheral tissues had substantially more dye accumulation. Further research using electron microscopy demonstrated that endothelial cells create the mammalian blood-brain barrier [2]. Numerous neuronal, vascular, and immunological cells are strongly linked to the brain endothelial cells, which aids in preserving the BBB's integrity.

2. Cells of BBB

Endothelial cells, perivascular macrophages, pericytes, astrocytic endfeet, and microglial cells make up the blood-brain barrier [3].

2.1. Endothelial Cells (ECs)

The inner layer of the blood vessels is composed of modified simple squamous epithelial cells originating from the mesodermal area. The continuous intercellular tight junctions (TJs), low rates of transcytosis, and lack of fenestrations (pores that permit the exchange of molecules between blood and tissue in peripheral ECs) that limit the movement of molecules make the ECs of the blood-brain barrier distinct from those of other tissues [4]. They are the most significant factor in the BBB's physical sealing.

* Corresponding author: Mathangi Ganapathy

2.2. Pericytes

The endothelial cell layer is periodically surrounded by cells called pericytes. Intimate contact between pericytes and endothelial cells is essential for the proper development of BBB and the brain's vasculature because the ratio of pericytes to endothelial cells in brain vessels is higher than that in peripheral arteries. Transforming growth factor (TGF), which binds to receptors on both cell types, is secreted by pericytes and ECs. Platelet-derived growth factor B (PDGFB), a different factor, is expressed in endothelial cells and affects pericytes. These and other components are used by the pericytes to influence the function of BBB. Interrupted communication between ECs and pericytes can cause channel development to be disrupted and increase barrier permeability [5].

2.3. Astrocytes

One of the main glial cell types, astrocytes, surrounds blood capillaries or brain processes. The extracellular matrix (ECM) proteins that are produced by the basal process end feet and contribute to the distinctive Basement membrane (BM) of the brain capillaries almost completely enshroud the capillary tube. After the BBB has been sealed, these cells start to appear in the brain postnatally **[5,6]**. Because of the biological connection that astrocytes offer between blood arteries and neurons, they can transmit signals that control blood flow in response to brain activity **[7,8]**. Controlling the contraction or dilation of the smooth muscle cells that surround capillaries and arterioles, respectively.

2.4. Immune cells

Immune cells from various types interact with CNS blood arteries and blood within the CNS. Microglial cells and perivascular macrophages make up the CNS cell population. Monocyte-derived cells called perivascular macrophages are found on the blood vessel's abluminal surface. They are created from blood-borne progenitor cells, which can pass across the BBB and can replenish themselves by 80% in just three months [9–11]. By phagocytosing cell debris, these cells serve as the initial line of defense for innate immunity. In the central nervous system (CNS), parenchymal immune cells called microglial cells participate in innate immunity, the regulation of wound healing, and neuronal growth [12,13]. They can also function in adaptive immunity as cells that deliver antigens. During embryonic development, these cells, which come from progenitor cells found in the yolk sac, enter the brain [14]. Several immune cell types in the blood, including neutrophils, T cells, and macrophages, interact and modify the BBB characteristics in response to an infection, injury, or disease [15,16].

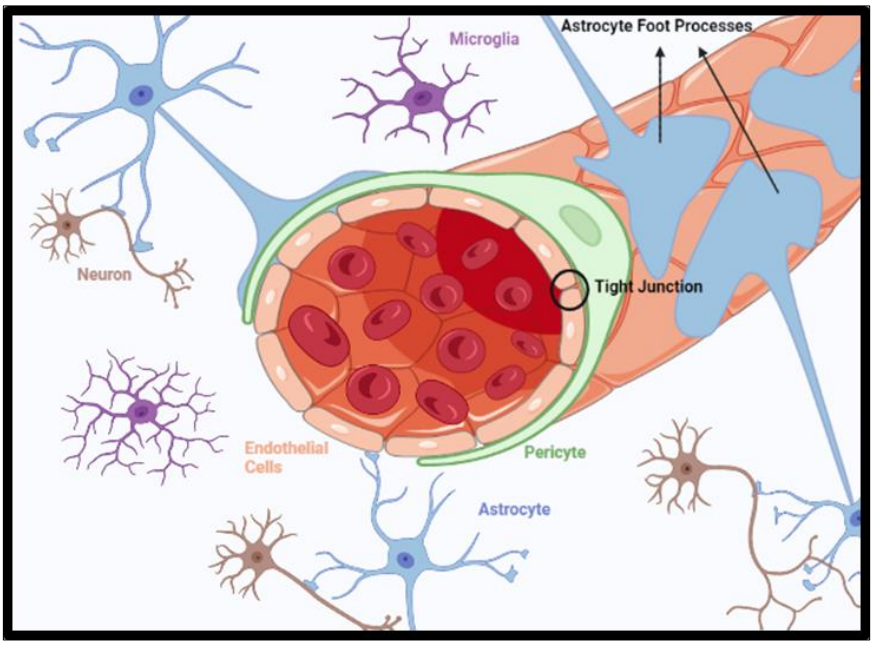

Figure 1 Neurovascular Unit (NVU). It encompasses the molecular and cellular elements that communicate at the point where the blood meets the central nervous system. The vascular basement membrane of the artery contains pericytes, which interact with the endothelial cells that make up the vessel walls. Both are covered by astrocyte processes collectively. The Neurovascular Unit is made up of the microglia, perivascular macrophages, and neurons that interact with astrocytic processes. (Figure adapted from [2])

3. Molecules of the BBB

3.1. Tight junctions (TJs)

The intricate tight connections between ECs, which, in contrast to simple tight junctions, offer a high electrical resistance (1800 cm2), carry out the barrier function [17]. By creating long, overlapping rows of occlusions between brain ECs, they greatly restrict the paracellular transit of macromolecules and polar substances into the central nervous system (CNS). This complex web of tightly knit connections is only present in the brain's capillaries. The three integral membrane proteins claudin, occludin, and junction adhesion molecules, as well as a variety of intracellular anchor molecules like Zonula occludins (ZO-1, ZO-2, and ZO-3), make up the TJs. [18].

3.2. Adherens junctions (AJs)

In order to create adhesive interactions between cells, adhesion junctions are made up of membrane proteins called cadherin that connect to the actin cytoskeleton through intermediary proteins called catenins. It is known that certain adherent junction and tight junction components interact, especially ZO-1 and catenins, which affects tight junction assembly [19].

4. Signaling pathways associated with the blood-brain barrier

4.1. Wnt /β-catenin signaling pathway

The Canonical wnt / wingless pathway is one of the major pathways regulating brain development acting via β catenin stabilization. It promotes catenin's nuclear translocation where it interacts with T cell factor (TCF) or lymphoid enhancer factor (Lef) transcription factors to control gene transcription [20, 21, 22]. β catenin interacts with cadherins in the adherens junction, where it plays a role in cell-cell adhesion [23]. When Wnt/beta-catenin signaling is genetically disrupted, it has been found to cause severe impairments in CNS-specific angiogenesis and BBB characteristics [24, 25, 26, 27]. Severe vascular abnormalities, such as capillary absence, thickening of the vascular plexus, and hemorrhagic malformed arteries, were present in the CNS of mice with a particular catenin mutation [24]. Additionally, the inactivation of catenin results in the up-regulation of plasmalemma vesicle-associated protein (PLVAP), which enhances transcellular vesicle trafficking and increases BBB permeability to plasma proteins, and the down-regulation of claudin-3, a paracellular component of TJ [25].

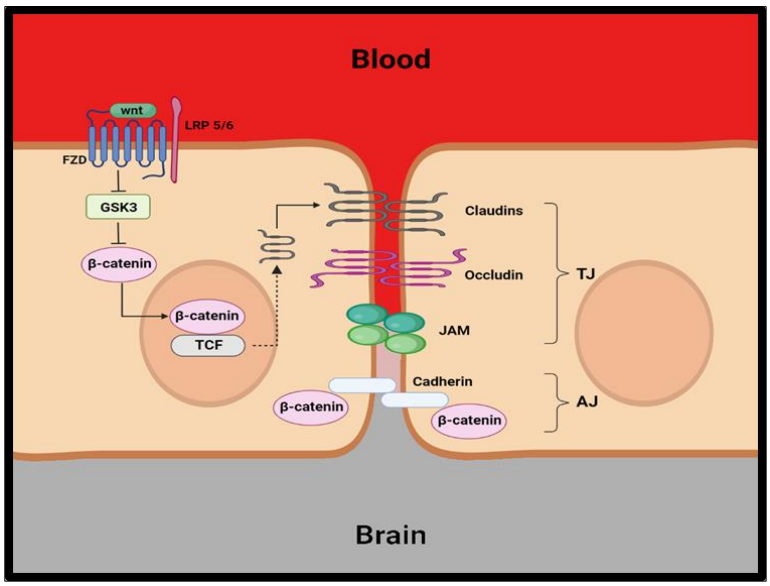

Figure 2 Wnt signaling and BBB. The main components of adherens junctions and tight junctions at the interface between ECs are illustrated. When the Wnt receptors FZD and LRP5/6 are activated, GSK3 is inhibited, stabilising beta-catenin so that it can enter the nucleus and activate the T cell-dependent transcription factor (TCF). This results in the direct or indirect activation of the cldn3 gene, which produces the claudin protein that strengthens the tight junctions. (Figure adapted from Paul Polakis et.al; www.jcb.org/cgi/doi/10.1083/jcb.200810040

Multiple sclerosis, AD, PD, and cancer have all been linked to BBB breakdown in terms of both its physical and functional features. [28]. since the TJ complexes are where the BBB's physical features are located, enhancing Wnt signaling can help treat neurodegenerative diseases by fortifying the TJ.

4.1.1. FZD4 and FZD7 signaling pathway

Frizzled signaling is carried out by frizzled proteins having a length of five hundred to seven hundred amino acids with linkers, hydrophobic domains, and link to Wnt/β-catenin signaling, which henceforth are composed of frizzled genes. Studies report that they were initially identified in fruit flies (Drosophila melanogaster), in an experiment that dealt with the polarity levels of epidermal cells **[29]**. These genes are responsible for various signaling pathways, they act as receptors for the well-known Wnt signaling and play a crucial role as receptors. There are majorly 10 frizzled genes in humans, respectively named FZD1 to FZD10 with each gene having a different identity percentage of amino acids **[29]**.

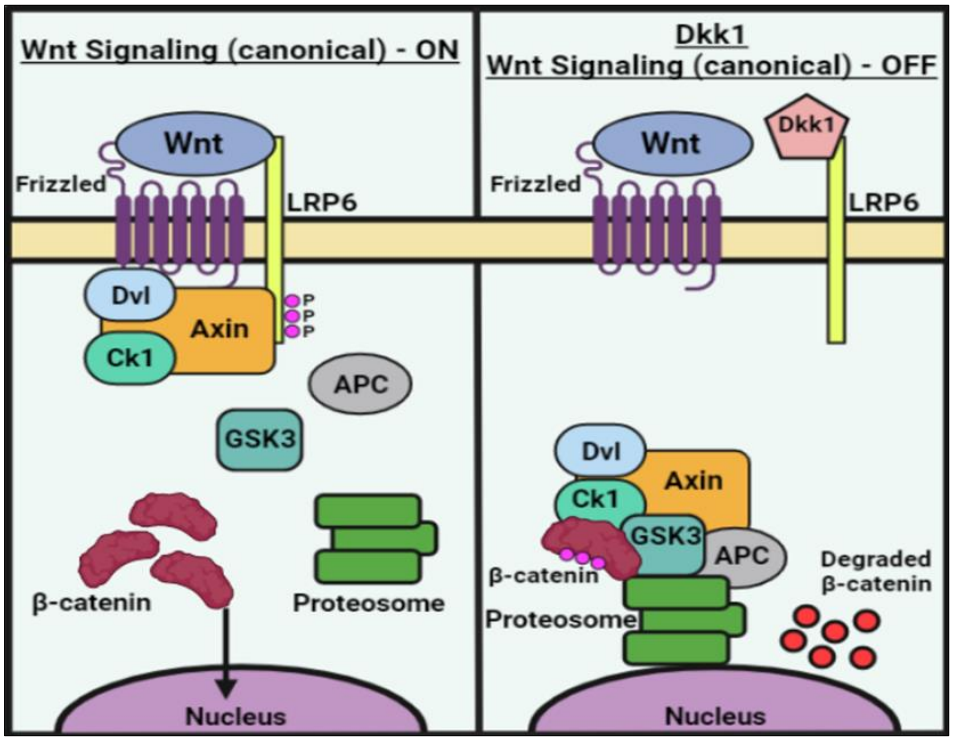

Figure 3 Canonical Wnt signaling facilitated by frizzled receptors. (a) Left side (Wnt signaling (canonical) – ON): The frizzled receptor along with the co-receptor LPR6 (Low-density lipoprotein related receptor 6) are both bound to Wnt, which in turn formulates combining of Axon with the previously phosphorylated LRP6, and also combining with Dvl(Dishevelled) and Ck1 (Casein kinase 1) resulting in the inhibition of GSK3 (Glycogen synthase kinase 3β), whose blocking results in the excess of beta-catenin in the cytoplasmic region, further translocating to the nucleus and henceforth stimulating gene expression. (b) Right side (Dkk1 Wnt signaling (canonical) – OFF): The Wnt antagonist Dkk1 (Dickkopf 1) on binding with the co-receptor LPR6, disables the function of Wnt of signaling through the canonical pathway and thereby inhibition of GSK3 since this function is lost, GSK3 performs phosphorylation of β-catenin and henceforth making it as a target for degrading by the proteasome. (Figure adapted from [30])

The main factor causing brain injury is blood-brain barrier malfunction or failure, several reports have proved this along with ICH. The permeability levels are henceforth increased which follows up to brain edema build-up of fluid around the brain regions resulting in an increase in pressure) which is vascular-derived. Frizzled family receptor 7 (FZD 7) is a major receptor located on the endothelial cell surface of the retinal vasculature, and are most important receptors of Wnt signaling [31]. Results and studies prove that the expression of FZD7 in the brains of humans and mice is evident. Its role is to control vascular permeability and the activation of endothelial cell signaling [32]. Evaluation through Evans blue extravasation of BBB permeability, the volume of hematoma cells measured at time intervals of 24 hours and 72 hours respectively, proved that the values had a considerable increase at 24 hours after the completion ICH, but the activation of the FZD 7 resulted in leakage of Evans blue in the region of the hemispheres, leading to dysfunctions in BBB [33].

In a similar function of FZD 7, the FZD 4 or Norrin signaling also tends to activate the Wnt pathway in the function of retinal vascular development and has a vital influence in assessing the gain or loss function of BBB. According to a study carried out in mice to calculate or estimate the dysfunction blood-brain barrier, where the covalent adducts of biotin which underwent intracardiac perfusion of Sulfo-NHS-biotin, were taken and stained [34]. The results proved that the deletion or removal of the FZD 4, in turn, led to the loss of integrity of blood brain barrier and therefore eradication of it is highly localised in the molecular layer [35].

4.1.2. Hedgehog signaling pathway

The hedgehog pathway (Hh) participates in neural guidance, embryonic morphogenesis, and angiogenesis [36,37]. It participates in vascular proliferation, development, and repairs adult tissues [38–40]. Sonic Hedgehog (Shh) signaling is predominantly involved in morphogenic CNS processes [41–43]. The Gli family of transcription factors then stimulates the target genes as a result of Smoothened's (Smo) activation when secreted Shh binds and inactivates the Patched-1 (Ptch-1) receptor [44]. Alvarez et al (2011).'s research suggests that perivascular astrocytes use the Hh pathway to connect with ECs in the blood-brain barrier because Ptch-1 and Smo were found on cultured BBB ECs but not on ECs and pericytes. Alvarez et al. (2011) also found that the mRNAs encoding occluding and claudin-5 were upregulated in response to Hh signaling. The deletion of Smo in ECs was associated with a considerable rise in the Blood Brain Barrier permeability to the endogenous blood proteins fibrinogen, immunoglobulins, apolipoprotein B, and postnatal day 19 (P19). Occludin, claudin-3, claudin-5, ZO1, and p120 expression significantly decreased along with the plasma protein leakage into the CNS, and laminin fragmentation and low laminin expression were shown to indicate a damaged basement membrane [45].

4.1.3. Transforming growth factor - beta signaling pathway

Transforming growth factor, a multifunctional cytokine, has a role in a number of cellular processes, including cell proliferation, differentiation, recognition, morphogenesis, wound healing, and death. Single-pass receptors are serine/threonine kinase receptors for TGF-beta. They are of two types – TGF-βRI and TGFβRII [46]. When a TGF-beta ligand attaches to and combines the type I and type II receptors on the cell surface, signaling is started [47].

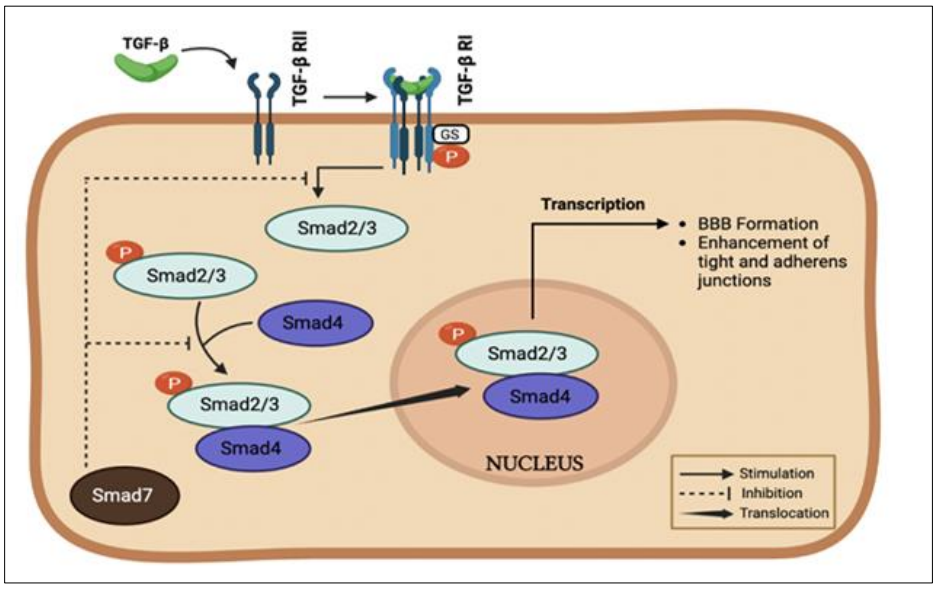

Figure 4 TGF-β signaling. An illustration of Smad signaling through TGF-β receptors and TGF-β. TGF-β binds to TGF-β receptor II, activating TGF-β receptor I as a result. Smad2/3 in the cytoplasm is phosphorylated as a result of this. Smad2/3 that have been activated bind to Smad4 in the cytoplasm before being mobilised and acting as a transcription factor in the nucleus. This causes a range of cell-type-dependent reactions that are crucial for a number of processes, including the creation of the BBB and the improvement of tight and adherent junctions (TJs and AJs). BBB degradation results from TGF-β pathway dysregulation. (Figure adapted from M Kandasamy et.al;http://www.aginganddisease.org/EN/10.14336/AD.2020.0222)

A receptor complex is formed when the type II receptor phosphorylates the type I receptor, which then phosphorylates the R-SMADs intracellularly. R-SMAD that has been phosphorylated joins forces with SMAD4 to go into the nucleus. It attaches to particular genes in the nucleus and controls a variety of cellular functions [48].

TGF-beta signaling impacts the formation and permeability of the blood-brain barrier via regulating adherens and tight junctions. In one experiment, it was discovered that brain pericytes continuously produce TGF-beta, inducing and upregulating blood-brain barrier activity. Thus, tight connections are improved as a result of the TGF-beta pathway being activated between brain pericytes and brain endothelial cells [49, 50].

Another report shows that SMAD4 stabilizes EC-pericyte interactions by regulation of the transcription of N-cadherin in association with Notch signal transduction and therefore disruption of Endothelial TGF-beta/SMAD4 signaling results in blood-brain barrier breakdown [51].

4.1.4. NF-κB signaling pathway

As a transcription factor that binds to the enhancer region and controls the production of the immunoglobulin κ light chain in B cells and plasma cells, NF-κB was first identified in 1986 [52]. Nearly all cells express NF-B, which controls a wide range of essential processes using a huge number of target genes. The key functions of many of the NF-κB target genes are cell division, cell survival control, and inflammation. [53] NF-κB is a complex made up of two separate subunits or two subunits that are different from one another. The most prevalent kind is a p50 and p65 heterodimer, which is present in almost all cell types. IκB proteins keep the inactive NF-κB dimer in the cytosol. The IκB proteins cover up a nuclear transition signal at the NF-κB complex, which isn't released until the IκK (IkappaB kinase) complex phosphorylates it, at which point the IκB is broken down. The classical pathway and the alternative signaling pathway are the two pathways through which NF-κB enters the nucleus and degrades IκB [54].

The NF-κB factor was discovered after inflammation in numerous BBB constituents, including the ECs and astrocytes. Blood-brain barrier permeability increases as a result of inflammatory processes.

NF-κB in Pericyte

Activation of NF-κB in the pericytes was observed to lead to degradation of the basal membrane by secretion of MMPs (MMP-9). Following that, the BBB opens [55].

NF-κB in ECs

Endothelial cell activation of NF-κB was found to result in the breakdown of tight junctions, which in turn increased the permeability of the EC layer [56].

NF-κB in Astrocytes

Deletion of IκBα was found to continuously activate NF-κB in astrocytes, resulting in inflammation in the brain and the breakdown of BBB.

4.1.5. ERK signaling pathway

The MAPK pathway, else known as the ERK pathway, is a combination of three major pathways which include the RAS - (constituent is a G protein), RAF, MEK, and ERK – (three protein kinases). The point of initiation of the pathway is when a ligand binds to RTK (receptor tyrosine kinase), further loss of enzymatic properties is due to mutations in the RAS and continues to be attached to GTP making the pathway active throughout. The subsequent simplified schematic diagram clearly explains the pathway [57].

Several reports have shown that the blood-brain barrier permeability level increase is highly related to the depletion of the TJs and AJs in the endothelial cells [58]. Blood-brain barrier hyperpermeability can be induced by the Extracellular signal-related kinase (ERK), the process is carried out by altering the compositions of the tight junctions [59], although the process is feasible, there is an alternative mechanism where two Matrix Metalloproteins namely MMP2 and MMP9 regulate the Blood-brain barrier permeability [60]. Another type of MMP, the MMP3 regulates blood-brain barrier permeability, and hence an experiment carried out in mice proves this with evidence of Evans blue extravasation [61].

Another report showcased the effects of the ERK pathway on the blood-brain barrier, showing reduced blood-brain barrier integrity when there occurs a condition of shortage or diminished supply of oxygen to the blood vessels. Inhibition of ERK resulted in the prevention of the above-mentioned dysfunction in BBB resulting in brain damage. A period of 8 hours of experimentation showed that the leakage of Evans blue was considerably reduced in the mice which were treated with ERK inhibitors, thus proving that the ERK activity inhibition reduces brain damage significantly during periods of shortage of oxygen [62].

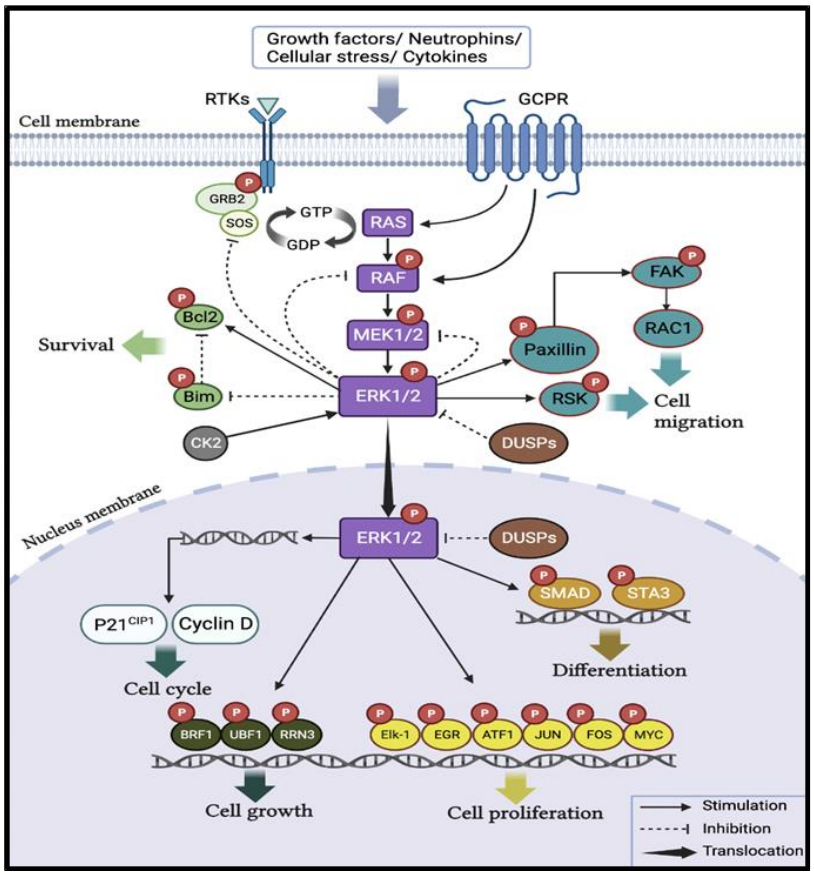

Figure 5 Schematic of the mechanism of ERK 1/2 pathway. This figure showcases the initial activation of Ras or Raf or MEK or ERK signaling run by phosphorylation of three tiers, the activated ERK 1/2 functions by phosphorylating various substrates in different parts of the cell. (Figure adapted from https://www.mdpi.com/1422-0067/23/3/1464)

5. Disorders

5.1. Alzheimer's disease

A degenerative neurological condition called Alzheimer's disease results in the destruction of brain cells. The most typical kind of dementia, it is marked by severe cognitive impairments, including memory loss, language decline, visuospatial deficits, and emotional issues. Neurofibrillary tangles (NFTs), amyloid plaques, neuroinflammation, and oxidative stress are some of the clinical indicators of AD. There is evidence that one of AD's most prevalent pathophysiologic features is the blood-brain barrier's malfunction and degradation **[63-66]**.

5.1.1. BBB dysfunction in AD

It has been discovered that BBB disruption can boost or speed up the process of amyloid production in addition to reducing the brain's capacity to remove Aβ [67–70].

The cleavage of the amyloid precursor protein (APP) in a certain order, first by β-secretase and then by γ-secretase, results in the formation of Aβ [71]. An overproduction of A may result from BBB malfunction activating β- and γ -secretase [67, 71]. Furthermore, deteriorated BBB performance also causes oxidative stress in the brain [72].

Recent research suggests that the pathophysiology of AD is not just excessive production and accumulation but also an inability to remove Aβ from the brain [65, 73]. The Aβ clearing process involves several BBB transporters. They include the RAGE (receptors for advanced glycation end products) [64,74,75], apolipoproteins [76], low-density lipoprotein receptor-related protein 1 (LRP-1) [77,78], efflux transporters ATP-binding cassette subfamily A member 1 (ABCA1), P-glycoprotein (P-gp) or ATP-binding cassette subfamily B member 1 (ABCB1), and breast cancer resistance protein (BCRP) [77,79,80].

5.1.2. Signaling pathways associated with Alzheimer's

Wnt signaling

The secreted glycoproteins known as Wnt ligands function as signaling molecules in a variety of cellular activities [81]. Additionally, Wnt ligands may alter the efficiency of inhibitory and excitatory synaptic transmission [82], and Wnt signaling activation promotes long-term potentiation while Wnt signaling inhibition inhibits it [83]. Wnt signaling dysregulation has also been linked to the pathophysiology of AD [84], and Wnt signaling activity guards against Aβ-induced synaptic dysfunction [85] and Aβ-dependent cytotoxic effects in hippocampal cultured neurons [86], it decreases Aβ deposition and spatial memory loss in APP/PS1 mice [87].

There is mounting evidence that the Wnt signaling pathway is crucial to the pathogenesis of Alzheimer's. The brains of several rodent AD models and the human brain with AD have both shown downregulation of Wnt signaling [88-92]. A study published by Vargas et al. suggests overexpression of Amyloid precursor protein and Presenilin 1 (APP/PS1) in an AD transgenic mouse model. An activator of non-canonical Wnt signaling that mimics the effects of Wnt-5a ligand or a potentiator of canonical Wnt signaling that requires activation of the signaling by endogenous Wnt-3a ligand bilaterally infused for a prolonged period of time improved memory in adult wildtype mice and rescued memory impairment in adult APP/PS1 mice, enhanced basal excitatory synaptic transmission in adult APP/PS1 [93]. Thus, these findings point to Wnt signaling stimulation as a potential Alzheimer's therapy. [94].

Hedgehog signaling

The sonic hedgehog pathway is best known for its role in development and in neurogenesis [95-100]. The canonical Shh signaling depends on primary cilia for signal transduction [97]. Armato et al. showed that Aβ1-42 reduces the length and frequency of primary cilia, which disrupts SHH signaling in NIH3T3 cells. When compared to controls, the hippocampus of APP23 mice and AD patients had higher levels of the SHH signal components SHH, SMO, GLI1, & GLI2, but PTCH1, PTCH2, and GLI3 had lower levels [101]. In NIH3T3 Shh-Light2 cells, which persistently produce the Gli-responsive luciferase construct, Vorobyeva et al experiments indicate a considerable decrease in Gli-mediated luciferase activity upon treatment with Aβ42 [102].

TGFβ Signaling

Many reports describe changes in TGFβ expression in AD Brains, serum, and CSF [103-109]. TGFβ1 isoform is expressed in the CNS as a result of CNS injury and may function as a protective and regenerative response [110]. TGFβ1 immunoreactivity is increased in or close to amyloid plaques [105,106] and around cerebral blood vessels [104,108,109]. TGFβ-1 mRNA levels in the brain vary from person to person but are considerably elevated in Alzheimer's brains than in controls [108,109]. In AD patients' brains, TGFβ2 immunostaining was likewise elevated in activated glia and degenerating neurons [105,110]. Amyloid-beta (Aβ) peptide deposition was shown to be enhanced by the co-expression of TGFβ by Wyss-Coray et al. [108]. According to this research, the TGFβ signaling pathway may be involved in the degenerative nature of AD. On the other hand, data also show that TGFβ signaling functions as a neurotrophic route and aids in the survival of neurons [111]. Additionally, it can improve Aβ clearance, decrease plaque deposition, and boost microglial phagocytosis in transgenic mice [109]. Additionally, it has been demonstrated that astrocyte-derived TGFβ protects synapses from amyloid-β oligomers (AβOs) in AD models [112].

NF-κB Signaling Pathway

There is accumulating evidence on the role of NF-κB in neurodegenerative diseases. The neurotoxic Aβ peptide, which builds up as plaques in Alzheimer's patients, has recently been shown to activate NF-κB in neuroblastoma cells [113] and cerebellar granule cells [114]. The production of reactive oxygen intermediates is necessary for this activation. The "receptor for advanced glycation end products" (RAGE) is also a receptor for Aβ, as Yan and colleagues discovered [115]. Nanomolar concentrations cause cytotoxicity when RAGE is expressed in COS cells. Patients with Alzheimer's disease were reported to have active NF-κB in this system in areas around early plaque stages [114].

ERK Signaling

The ERK signal transduction pathway, which may control mitochondrial dynamics in mitochondria generated from AD, is poorly understood. Increased oxidative stress, mitochondrial stress, and neural stress are all linked to activated MAP kinases ERK [116,117,118]. In α-synuclein-mediated alterations in mitochondrial dynamics, ERK activation is associated with enhanced mitochondrial fission and DLP1 translocation [119]. By reducing the levels of mitochondrial DLP1, the inhibition of ERK 1/ 2 activation restores mitochondrial morphology in AD. According to X.Gan et al., ERK activation brought on by oxidative stress increases DLP1 recruitment to mitochondria and causes excessive fission in

mitochondrial dynamics, which results in aberrant mitochondrial morphology like fragmentation [120]. Also, we infer from [120], that mitochondrial imbalance and dysfunction associated with AD depend on ERK, oxidative stress, & DLP1 transduction of signals.

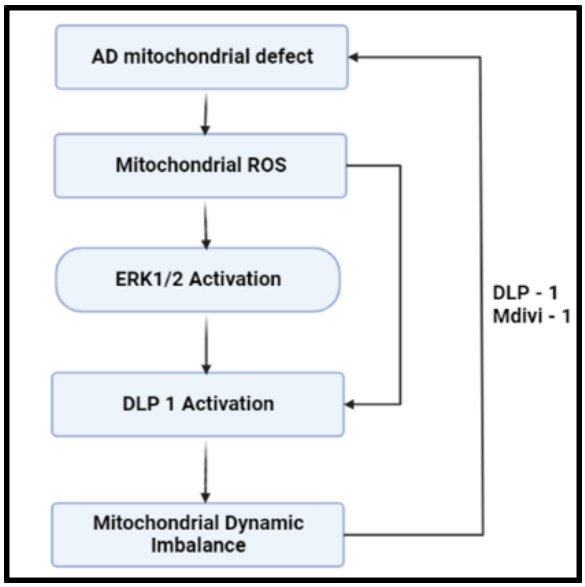

Figure 6 Defects in AD mitochondrial dysfunction cause increased mitochondrial ROS generation/accumulation, which activates the ERK signaling pathway. Directly or indirectly, ERK activation throws off the equilibrium of mitochondrial dynamics, alters the levels of DLP1 expression, and ultimately results in abnormal mitochondrial architecture and function. The modification in mitochondrial morphology and function related to AD mitochondrial degeneration is rescued by mdivi-1's inhibition of DLP1 expression levels. (Figure adapted from [120])

5.2. Parkinson's disease

Parkinson's disease (PD) is a complicated progressive neurological ailment that typically affects people over the age of 60. It is the second most frequent neuropathological ailment and the most common movement disorder. Parkinson's disease often manifests as both motor and non-motor symptoms at its onset. Some of the key clinical symptoms of Parkinson's disease are tremors, bradykinesia, postural instability, and stiffness. Lewy bodies, which are intracellular inclusion bodies, rich in α-synuclein, and the loss of the neurotransmitter dopamine in the substantia nigra pars compacta (SNpc) are characteristics of Parkinson's disease [121-124].

5.2.1. BBB dysfunction in PD

Disruption of BBB has been linked to neurodegeneration in the SNpc in several animal studies. Because Parkinson's disease involves a secondary degree of BBB disruption, the cerebrovasculature is damaged downstream from the first insult, exacerbating the condition. The integrity of the striatal BBB was shown to be impaired with disruption in research utilizing the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) paradigm [127]. In addition, there was extensive transient albumin leakage, suggesting that the BBB paracellular pathway was disrupted [125-128]. In humans, a PET investigation on Parkinson's disease (PD) patients revealed a failure of the BBB transporter system. Gray et al. (2015) discovered a substantial increase in BBB permeability in the post-commissural putamen of Parkinson's disease patients in histological research [129]. Numerous studies using human and animal models of Parkinson's disease show a pathogenic link between BBB collapse and dopaminergic neuronal death. The processes behind dysfunction are yet unknown, despite clinical evidence and in vitro research indicating that disruption of the Blood-Brain Barrier is linked to neuronal cell death and neuroinflammation in Parkinson's disease [130-133].

5.2.2. Signaling pathways associated with PD

Wnt signaling

Dysregulated Wnt signaling is implicated in the development and progression of Parkinson's disease, according to an increasing body of experimental evidence. Parkinson's disease is brought on by a selective degeneration of mesencephalic dopaminergic (DA) neurons in the substantia nigra (SNc), which is regulated by canonical Wnt signaling. Studies have shown that Wnt1 expression increases the number of rat midbrain DA neurons in vitro and that Wnt1

deficiency impairs mesencephalon growth [134-136]. There are different hints that a population of astrocytes has been functionally activated. Reactive astrocytes are known for their active proliferation, morphological cell body expansion, and increased production of several neurotrophic factors, which are primarily distributed in the nigra and striatum of people with PD symptoms. In the MPTP model of PD, these reactive astrocytes and Wnt/β-catenin signaling showed a connection between nigrostriatal damage and healing [137]. Degeneration of DA neurons caused by the MPTP insult results in the regulation of Frizzled 1 and beta-catenin (Wnt signaling molecules), which in turn triggers the reactivation of the glial activation. The primary source of Wnt1 candidate cells is the active and reactive astrocytes found in the ventral midbrain. In primary mesencephalic astrocyte-neuron cultures, the Wnt/Fzd signaling inhibition with Dkk1 abolished the astrocyte-induced neuroprotection against the toxicity of MPP (+). The astrocyte-derived Wnt1 belonging to adult midbrain stem cells further boosted DA neurogenesis.

On the other hand, activation of Wnt/-catenin signaling in living organisms corrected the incapacity of DA neurons to recover and also prevented the absence of Wnt transcription in response to MPTP. This suggests that Wnt1 and MPTP-reactive astrocytes play a neuroprotective role in DA neuronal plasticity. Furthermore, it suggests that in the mature mammalian nervous system, Wnt signals might serve as the main mediators of neuron-glial communication. The frizzled-1/beta-catenin signaling pathway is a potential candidate in the regulatory circuit for DA neuron-astrocyte interaction in the ventral midbrain [138,139]. Additionally, the development of neurons and glia in neurospheres may be influenced by the activation or inhibition of Wnt/β-catenin signaling. Gliogenesis from neural stem cells was accelerated up by decreasing Wnt signaling. Long-term stimulation of the Wnt signaling pathway by Wnt-7a or GSK3 inhibitors led to a modest increase in the rate of assisted neuronal differentiation and decreased gliogenesis. Dkk1 overexpression and Wnt pathway inhibition, however, markedly increased gliogenesis.

Parkinson's disease treatment may significantly advance thanks to reactive astrocytes and microglia, according to a growing body of studies (PD) [140-142].

TGFβ- signaling

The major connecting link between Parkinson’s disease and TGF beta signaling are the family of neurotoxins profoundly known as α-synuclein (αSO). They perform by acting on the specialized fivefold glial cells called the astrocytes [143]. According to reports [144], patients with Parkinson's disease have much higher amounts of TGF beta in their brain and ventricular cerebro-spinal fluid (CSF) than healthy individuals.

The neurological and motor activities of nerves play a significant role in Parkinson's disease. TGF-beta deficit and the downstream gene Smad3 deficient contributed to the enhancement of these neurological and motor functions [145]. The major study [146] proved that TGF-beta signaling activation is responsible for the protection of neurons in the mice PD models.

The stimulation of the first counterpart by the neurotoxic-synuclein (SO) results in elevated levels of TGF-beta. This further stimulated and greatly enhanced the astrocytes' capacity for synaptogenesis. On the other hand, α-synuclein, which controls the loss of synapses, has a significant impact on mesenchymal nerve cells. TGF-beta therapy can treat this cause because it safeguards the mesenchymal neurons [147].

Hedgehog signaling

The Sonic Hedgehog protein (SHH) is a functional protein that is essential for the binding of patched receptors (Ptch). This pathway is primarily activated in cases of brain traumas and neurodegenerative illnesses like Parkinson's disease. They have a beneficial effect by shielding dopaminergic cells grown in culture from the poisonous MPP positive effect and restoring TH [tyrosine hydroxylase] positivity in living beings, which further enhances the nigrostriatal pathway [148].

A study [149] has demonstrated that the Parkinson's disease model will eventually have a higher or increased function of the motor neurons; this only happens as a result of overexpression of the Sonic Hedgehog signaling by reducing the loss of DA neurons and also stabilising and restoring the nigrostriatal pathway.

According to the most current study [150], behavioural deficits are reduced, microglial cell activation is inhibited, the body's inflammatory response is attenuated, and dopaminergic neurons are protected as a result of Sonic Hedgehog signaling through the PI3K/Akt pathway. This work was conducted in two stages: the first stage used a mouse model of PD caused by MPTP, and the second stage used a lab model of BV2 microglial cells treated with LPS.

NF-kB signaling

The NF-κB-mediated neuroinflammation plays a significant role in the aetiology of Parkinson's disease. The degradation of dopaminergic neurons in Parkinson's disease has been linked to alterations in NF-κB expression and nuclear translocation, according to a number of studies [151]. As a crucial regulator of various cellular events, Nuclear Factor-Kappa B has been implicated in multiple pathophysiological pathways linked with Parkinson's disease (PD), including mitochondrial dysfunction, inflammation, misfolded alpha-synuclein accumulation, and synaptic loss [152]. As previously stated, the NF- κB complex is made up of two subunits, the most prevalent of which are p50 and p65. It also contains Rel proteins like Rel-A, c-Rel, and RelB. The C-terminal Transcriptional Activation Domains (TADs) allows Rel proteins to increase the expression of target genes. According to Ghosh et al., Rel-A upregulation may at least partially contribute to the degeneration of dopaminergic neurons, as evidenced by the observation of elevated Rel-A subunit levels in glial cells and dopaminergic neurons of SN in PD patients. Rel-A suppression also prevented the loss of DA neurons in mice treated with MPTP [153]. In contrast, a long-term experiment revealed that mice lacking c-Rel developed -synuclein illness, which started in the olfactory bulb and advanced to the SN, followed by an increase in microglial activation and the associated motor symptoms. Following these alterations, oxidative/nitrosative stress and mitochondrial dysregulation occurred, revealing the neuroprotective effects of c-Rel [154-156].

ERK signaling

The Mitogen-Activated Protein (MAP) Kinase family is a subset in charge of intracellular signaling. They are in charge of a number of crucial eukaryotic activities, such as mitosis, cell division, cell death, and survival, among others [157]. The ERK 12 isomer is the most prevalent subgroup of the MAP kinase family. Major MAPK pathways known as ERK 1 and ERK2, are essential for cell differentiation, proliferation, survival, apoptosis, and other processes. Insulin and G protein-coupled receptors are activating agents that stimulate signal transmission by interacting with RTKs (Receptor with Tyrosine Kinase Activity) and GPCRs (G protein-coupled receptors). The ERK 12 signaling is essential for neuronal death in Parkinson's disease, which in turn is the driving force behind all neurodegenerative illnesses [158]. A study [159] on the CG4 cell line of the cells covering and further safeguarding nerve cells, particularly in the brain and spinal cord, established that the ERK 12 pathway inhibitor, PD98059, can be utilised to either tolerate or prevent hydrogen peroxide-induced cell death or apoptosis. Additionally, this inhibitor prevents the glial cells' production of nitric oxide, which causes the degeneration of neuronal cells [160]. Further, the inhibitor U0126 stated that striatal neuron death or damage induced by dopamine is also a causative result of the ERK ½ activation [161]. Some of the vital processes acting as a connective link between Parkinson's disease and ERK signaling include mitochondrial dysfunction, cell survival, apoptosis, oxidative stress, etc. [162].

6. Conclusion

The blood brain barrier is a vast field that still needs to be explored insignificantly. In this review paper, we have discussed the various cells involved in BBB functioning namely endothelial cells, pericytes, astrocytes, and immune cells, and further, molecular junctions such as tight junctions and Adheren junctions were also mentioned. The major plot of the review included the signaling pathways associated with BBB, starting from the Wnt/β-catenin signaling, followed by FZD4 and FZD7, Hedgehog, transforming growth factor (TGF) - Beta, NF - κβ, and finally ERK signaling. Each signaling pathway is explained in detail along with the metabolic working process with reference to various studies and research, and appropriate figures were given whenever required.

In addition to this, two major diseases that cause alterations in the Blood brain barrier (BBB) integrity were brought up into discussion - namely Alzheimer's and Parkinson's. The altered signaling pathways and BBB dysfunction were adequately mentioned in both disorders. To mention, the pathways that were altered in both Alzheimer's and Parkinson's encompassed Wnt signaling, Hedgehog, transforming growth factor (TGF) - Beta, NF – κβ, and ERK signaling pathways. Hence, even after discussing various aspects of BBB, it is still a mystery to humanity and copious research and projects are operational in order to bring light and clarity into this field.

Compliance with ethical standards

Acknowledgments

The authors wish to thank the Director, Centre for Biotechnology, Anna University for the infrastructure and support provided.

Authors contribution

Authors 1, 2 and 3 had equal participation in the concept and designing of this paper and in drafting it. Authors 2 and 4 were involved in the analysis and interpretation of data and also in the critical revision of the manuscript.

Disclosure of conflict of interest

The authors of this work declare they have no conflicts of interest.

References

[1] Ehrlich P (1885) Das Sauerstoffbedürfnis des Organismus. In: Eine Farbenanalytische Studie, Hirschwald, Berlin. https://doi.org/10.1016/B978-0-08-009054-2.50039-0

[2] Marie Blanchette, Richard Daneman; Formation and maintenance of the BBB. https://doi.org/10.1016/j.mod.2015.07.007

[3] Development of the blood-brain barrier; Werner Risau and Hartwig Wolburg. https://doi.org/10.1016/0166-2236(90)90043-A

[4] Development, maintenance and disruption of the blood-brain barrier Birgit Obermeier, Richard Daneman & Richard M Ransohoff. https://doi.org/10.1038/nm.3407

[5] Daneman R, Zhou L, Kebede AA, Barres BA (2010) Pericytes are required for blood-brain barrier integrity during embryogenesis. Nature 468:562–566. https://doi.org/10.1038/nature09513

[6] Yang Y, Higashimori H, Morel L. 2013. Developmental maturation of astrocytes and pathogenesis of neurodevelopmental disorders. J. Neurode Discord 5:22. https://doi.org/10.1186/1866-1955-5-22

[7] Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. 2010. Glial and neuronal control of brain blood flow. Nature 468: 232–243. https://doi.org/10.1038/nature09613

[8] Gordon GR, Howarth C, MacVicar BA. 2011. Bidirectional control of arteriole diameter by astrocytes. Exp Physiol 96: 393–399. https://doi.org/10.1113/expphysiol.2010.053132

[9] Unger ER, Sung JH, Manivel JC, Chenggis ML, Blazar BR, Krivit W. 1993. Male donor-derived cells in the brains of female sex-mismatched bone marrow transplant recipients: A Y-chromosome specific in situ hybridization study. J Neuropathol Exp Neurol 52: 460–470. https://doi.org/10.1097/00005072-199309000-00004

[10] Vass K, Hickey WF, Schmidt RE, Lassmann H. 1993. Bone marrow-derived elements in the peripheral nervous system. An immunohistochemical and ultrastructural investigation in chimeric rats. Lab Invest 69: 275–282. PMID: 8377470. Bone marrow-derived elements in the peripheral nervous system. An immunohistochemical and ultrastructural investigation in chimeric rats - PubMed (nih.gov)

[11] Williams K, Alvarez X, Lackner AA. 2001. Central nervous system perivascular cells are immunoregulatory cells that connect the CNS with the peripheral immune system. Glia 36: 156–164. https://doi.org/10.1002/glia.1105

[12] Streit WJ, Conde JR, Fendrick SE, Flanary BE, Mariani CL. 2005. Role of microglia in the central nervous system's immune response. Neurol Res 27: 685–691. https://doi.org/10.1179/016164105x49463a

[13] Ajami B, Bennett JL, Krieger C, Tetzlaff W, Rossi FM. 2007. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. Nat Neurosci 10: 1538–1543. https://doi.org/10.1038/nn2014

[14] Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, Mehler MF, Conway SJ, Ng LG, Stanley ER, et al. 2010. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 330: 841–845. https://doi.org/10.1126/science.1194637

[15] Persidsky Y, Ghorpade A, Rasmussen J, Limoges J, Liu XJ, Stins M, Fiala M, Way D, Kim KS, Witte MH, et al. 1999. Microglial and astrocyte chemokines regulate monocyte migration through the blood–brain barrier in human immunodeficiency virus-1 encephalitis. Am J Pathol 155: 1599–1611. https://doi.org/10.1016/s0002-9440(10)65476-4

[16] Hudson LC, Bragg DC, Tompkins MB, Meeker RB. 2005. Astrocytes and microglia differentially regulate trafficking of lymphocyte subsets across brain endothelial cells. Brain Res 1058: 148–160. https://doi.org/10.1016/j.brainres.2005.07.071

[17] Electrical resistance across the blood-brain barrier in anaesthetized rats: a developmental study**.** A M Butt,H C Jones,N J Abbott. https://doi.org/10.1113/jphysiol.1990.sp018243

[18] Structure, Function and regulation of the Blood-Brain Barrier Tight junction in central nervous system disorders Jeffrey J. Lochhead, Junzhi Yang, Patrick T. Ronaldson and Thomas P. Davis. https://doi.org/10.3389/fphys.2020.00914

[19] Matter, K., Balda, M.S., 2003. signaling to and from tight junctions. Nat. Rev., Mol. Cell Biol. 4, 225 – 236. https://doi.org/10.1038/nrm1055

[20] Moon, R.T. 2005. Wnt/beta-catenin pathway. Sci. STKE. https://doi.org/10.1126/stke.2712005cm1

[21] Britta Engelhardt & Stefan Liebner; Novel insights into the development and maintenance of the blood-brain barrier (2014).Novel insights into the development and maintenance of the blood–brain barrier | SpringerLink

[22] Marie Blanchette & Richard Daneman; Formation and maintenance of the BBB (2015).https://doi.org/10.1016/j.mod.2015.07.007

[23] Brembeck , F.H. , M. Rosario , and W. Birchmeier . 2006. Balancing cell adhesion and Wnt signaling, the key role of beta-catenin. Curr. Opin. Genet. Dev. 16: 51 – 59. https://doi.org/10.1016/j.gde.2005.12.007

[24] Daneman,R., Agalliu, D., Zhou, L., Kuhnert, F., Kuo, C.J., Barres, B.A., 2009.Wnt/beta-catenin signaling is required for CNS, but not non-CNS, angiogenesis. Proc. Natl. acad. Sci. U.S.A. 641-646. https://doi.org/10.1073/pnas.0805165106

[25] Liebner, S., M. Corada , T. Bangsow , J. Babbage , A. Taddei , C.J. Czupalla , M. Reis , A. Felici , H. Wolburg , M. Fruttiger , et al . 2008. Wnt/b-catenin signaling controls the development of the blood-brain barrier. J. Cell Biol. 183: 409 – 417. https://doi.org/10.1083/jcb.200806024

[26] Stenman. J.M., Rajagopal. J., Carroll, T.J., Ishibashi, M., McMahon, J., McMahon, A.P., 2008; Canonical wnt signaling regulates organ-specific assembly and differentiation of CNS vasculature. Science 1247-1250. https://doi.org/10.1126/science.1164594

[27] Wang Y, Rattner A, Zhou Y, Williams J, Smallwood PM, Nathans J (2012) Norrin/Frizzled4 signaling in retinal vascular development and blood brain barrier plasticity. Cell 151:1332–1344 Zolkovic 2008. https://doi.org/10.1016/j.cell.2012.10.042

[28] Zlokovic, B.V. 2008. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 57: 1. https://doi.org/10.1016/j.neuron.2008.01.003

[29] Huang, Hui-Chuan, and Peter S. Klein. “The Frizzled Family: Receptors for Multiple Signal Transduction Pathways.” Genome Biology, vol. 5, no. 7, 2004, pp. 234–234, https://doi.org/10.1186/gb-2004-5-7-234

[30] Purro, Silvia A., et al. “Dysfunction of Wnt Signaling and Synaptic Disassembly in Neurodegenerative Diseases.” Journal of Molecular Cell Biology, vol. 6, no. 1, 2014, pp. 75–80, https://doi.org/10.1093/jmcb/mjt049

[31] Peghaire, Claire, et al. “Fzd7 (Frizzled-7) Expressed by Endothelial Cells Controls Blood Vessel Formation Through Wnt/β-Catenin Canonical Signaling.” Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 36, no. 12, 2016, pp. 2369–80, https://doi.org/10.1161/ATVBAHA.116.307926

[32] Ferreira Tojais, Nancy, et al. “Frizzled7 Controls Vascular Permeability through the Wnt-Canonical Pathway and Cross-Talk with Endothelial Cell Junction Complexes.” Cardiovascular Research, vol. 103, no. 2, 2014, pp. 291–303, https://doi.org/10.1093/cvr/cvu133

[33] He, Wei, et al. “Activation of Frizzled-7 Attenuates Blood–brain Barrier Disruption through Dvl/β-catenin/WISP1 Signaling Pathway after Intracerebral Hemorrhage in Mice.” Fluids and Barriers of the CNS, vol. 18, no. 1, 2021, pp. 44–44, https://doi.org/10.1186/s12987-021-00278-9

[34] Wang, Yanshu, et al. “Norrin/Frizzled4 Signaling in Retinal Vascular Development and Blood Brain Barrier Plasticity.” Cell, vol. 151, no. 6, 2012, pp. 1332–44, https://doi.org/10.1016/j.cell.2012.10.042

[35] Ye, Xin, et al. “The Norrin/Frizzled4 Signaling Pathway in Retinal Vascular Development and Disease.” Trends in Molecular Medicine, vol. 16, no. 9, 2010, pp. 417–25, https://doi.org/10.1016/j.molmed.2010.07.003

[36] Marc Fuccillo, Alexandra L. Joyner and Gord Fishell. Morphogen to mitogen: the multiple roles of hedgehog signaling in vertebrate neural development, Volume 7 (2006). http://dx.doi.org/10.1038/nrn1990

[37] T. Nagase, M. Nagase, M. Machida, T. Fujita; Hedgehog Signaling in Vascular Development Angiogenesis 11, 71 (2008). https://doi.org/10.1007/s10456-008-9105-5

[38] Shigeru Kanda, Yasushi Mochizuki, Takashi Suematsu, Yasuyoshi Miyata, Koichiro Nomata, Hiroshi Kanetake. Sonic hedgehog induces capillary morphogenesis by endothelial cells though phosphoinositide 3-kinase. 2003 Mar 7;278(10):8244-9. https://doi.org/10.1074/jbc.M210635200

[39] E. Hochman, A. Castiel, J. Jacob-Hirsch, N. Amariglio, S. Izraeli; Molecular pathways regulating pro-migratory effects of Hedgehog signaling; J. Biol. Chem. 281, 33860 (2006). https://doi.org/10.1074/jbc.m605905200

[40] N. Byrd, L. Grabel. Hedgehog signaling in murine vasculogenesis and angiogenesis. Trends Cardiovasc. Med. 14, 308 (2004). https://doi.org/10.1016/j.tcm.2004.09.003

[41] C. Chiang et al., Cyclopia and defective axial patterning in mice lacking sonic hedgehog gene function. Nature 383, 407 (1996). doi: 10.1038/383407a0. Cyclopia and defective axial patterning in mice lacking Sonic hedgehog gene function | Nature

[42] J. Briscoe, J. Ericson. Specification of neuronal fates in the ventral neural tube Curr. Opin. Neurobiol. 11, 43 (2001). doi: 10.1016/s0959-4388(00)00172-0. https://doi.org/10.1016/S0959-4388(00)00172-0

[43] J. Briscoe, J. Ericson. The specification of neuronal identity by graded sonic hedgehog signaling. Semin. Cell Dev. Biol. 10, 353 (1999). doi: 10.1006/scdb.1999.0295. https://doi.org/10.1006/scdb.1999.0295

[44] T. Østerlund, P. Kogerman; Hedgehog signaling; how to get from Smo to Ci and Gli; Trends Cell Biol. 16, 176 (2006). Sci-Hub | Hedgehog signaling: how to get from Smo to Ci and Gli. Trends in Cell Biology, 16(4), 176–180 | 10.1016/j.tcb.2006.02.004

[45] Jorge Ivan Alvarez et al.,The Hedgehog Pathway Promotes Blood-Brain Barrier Integrity and CNS Immune Quiescence, Science 334, 1727 (2011); https://doi.org/10.1126/science.1206936

[46] J. Massague´, TGF-beta signal transduction, Annu. Rev. Biochem. 67 (1998) 753 – 791. https://doi.org/10.1146/annurev.biochem.67.1.753

[47] Shi Y, Massagué J. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. Cell. 2003 Jun 13;113(6):685-700. DOI: https://doi.org/10.1016/s0092-8674(03)00432-x . PMID: 12809600.

[48] Xi Q, Wang Z, Zaromytidou AI, Zhang XH, Chow-Tsang LF, Liu JX, Kim H, Barlas A, Manova-Todorova K, Kaartinen V, Studer L, Mark W, Patel DJ, Massagué J. A poised chromatin platform for TGF-β access to master regulators. Cell. 2011 Dec 23;147(7):1511-24. DOI: https://doi.org/10.1016/j.cell.2011.11.032 . PMID: 22196728; PMCID: PMC3582033.

[49] Zhang Y, Yang X. The Roles of TGF-β Signaling in Cerebrovascular Diseases. Front Cell Dev Biol. 2020 Sep 18;8:567682. doi: https://doi.org/10.3389/fcell.2020.567682 . PMID: 33072751; PMCID: PMC7530326.

[50] Dohgu S, Takata F, Yamauchi A, Nakagawa S, Egawa T, Naito M, Tsuruo T, Sawada Y, Niwa M, Kataoka Y. Brain pericytes contribute to the induction and up-regulation of blood-brain barrier functions through transforming growth factor-beta production. Brain Res. 2005 Mar 21;1038(2):208-15. DOI: https://doi.org/10.1016/j.brainres.2005.01.027 . PMID: 15757636.

[51] Li F, Lan Y, Wang Y, Wang J, Yang G, Meng F, Han H, Meng A, Wang Y, Yang X. Endothelial Smad4 maintains cerebrovascular integrity by activating N-cadherin through cooperation with Notch. Dev Cell. 2011 Mar 15;20(3):291-302. DOI: https://doi.org/10.1016/j.devcel.2011.01.011 . PMID: 21397841.

[52] Sen R, Baltimore D: Multiple nuclear factors interact with the immunoglobulin enhancer sequences. Cell. 1986, 46: 705-716. https://doi.org/10.1016/0092-8674(86)90346-6

[53] May MJ, Ghosh S: Signal transduction through NF-kappa B. Immunol Today. 1998, 19: 80-88. https://doi.org/10.1016/S0167-5699(97)01197-3

[54] Wenzel J, Schwaninger M. The blood–brain barrier and its regulation by NF-κB. e-Neuroforum [Internet]. 2016 Jun 2;7(2):23–30. Available from: https://doi.org/10.1007/s13295-016-0022-6

[55] Bell RD,WinklerEA, SinghI, Sagare AP,Deane R,Wu Z, Holtzman DM, Betsholtz C, Armulik A, Sallstrom J, Berk BC, Zlokovic BV (2012) Apolipoprotein e controls cerebrovascular integrityvia cyclophilin a. Nature485:512–516. https://doi.org/10.1038/nature11087

[56] Aveleira CA, Lin CM, Abcouwer SF, Ambrósio AF, Antonetti DA. TNF-α signals through PKCζ/NF-κB to alter the tight junction complex and increase retinal endothelial cell permeability. Diabetes. 2010 Nov;59(11):2872-82. Doi: https://doi.org/10.2337/db09-1606 Epub 2010 Aug 6. PMID: 20693346; PMCID: PMC2963546.

[57] McCain, Jack. "The MAPK (ERK) Pathway: Investigational Combinations for the Treatment of BRAF- Mutated Metastatic Melanoma." P&T (Lawrenceville, N.J.), vol. 38, no. 2, 2013, pp. 96–108. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3628180/

[58] Tian, Jijing, et al. “Brain Infection by Hepatitis E Virus Probably via Damage of the Blood-Brain Barrier Due to Alterations of Tight Junction Proteins.” Frontiers in Cellular and Infection Microbiology, vol. 9, 2019, pp. 52–52, https://doi.org/10.3389/fcimb.2019.00052

[59] Wang, Li-Feng, et al. “Activation of VEGF/Flk-1-ERK Pathway Induced Blood–Brain Barrier Injury After Microwave Exposure.” Molecular Neurobiology, vol. 52, no. 1, 2014, pp. 478–91, https://doi.org/10.1007/s12035-014-8848-9

[60] Zhu, Hongyan, et al. “TLR2 Ligand Pam3CSK4 Regulates MMP-2/9 Expression by MAPK/NF-κB Signaling Pathways in Primary Brain Microvascular Endothelial Cells.” Neurochemical Research, vol. 43, no. 10, 2018, pp. 1897–904, https://doi.org/10.1007/s11064-018-2607-7

[61] Zhang, Qin, et al. “Increase in Blood-Brain Barrier (BBB) Permeability Is Regulated by MMP3 via the ERK Signaling Pathway.” Oxidative Medicine and Cellular Longevity, vol. 2021, 2021, pp. 6655122–14, https://doi.org/10.1155/2021/6655122

[62] Chen, Wei, et al. “Phosphorylation of Astrocytic Connexin43 by ERK1/2 Impairs Blood-Brain Barrier in Acute Cerebral Ischemia.” Cell & Bioscience, vol. 7, no. 1, 2017, pp. 43–43, https://doi.org/10.1186/s13578-017-0170-6

[63] Zenaro E, Piacentino G, Constantin G (2017) The blood-brain barrier in Alzheimer’s disease. Neurobiol Dis 107, 548 41-56. https://doi.org/10.1016/j.nbd.2016.07.007

[64] Yamazaki Y, Kanekiyo T (2017) Blood-brain barrier dysfunction and the pathogenesis of Alzheimer’s disease. Int J Mol Sci 18, E1965. https://doi.org/10.3390/ijms18091965

[65] Miners JS, Schulz I, Love S (2017) Differing associations between Abeta accumulation, hypoperfusion, blood-brain barrier dysfunction and loss of PDGFRB pericyte marker in the precuneus and parietal white matter in Alzheimer’s disease. J Cereb Blood Flow Metab 38, 103-115. https://doi.org/10.1177%2F0271678X17690761

[66] Tarasoff-Conway JM, Carare RO, Osorio RS, Glodzik L, Butler T, Fieremans E, Axel L, Rusinek H, Nicholson C, Zlokovic BV, Frangione B, Blennow K, Menard J, Zetterberg H, Wisniewski T, de Leon MJ (2016) Clearance systems in the brain–implications for Alzheimer disease. Nat Rev Neurol 12, 248. https://doi.org/10.1038/nrneurol.2016.36

[67] Zhang GS, Tian Y, Huang JY, Tao RR, Liao MH, Lu YM, Ye WF, Wang R, Fukunaga K, Lou YJ, Han F (2013) The gamma-secretase blocker DAPT reduces the permeability of the blood-brain barrier by decreasing the ubiquitination and degradation of occludin during permanent brain ischemia. CNS Neurosci Ther 19, 53-60. https://doi.org/10.1111%2Fcns.12032

[68] Griffin JM, Kho D, Graham ES, Nicholson LF, O’Carroll 691 SJ (2016) Statins inhibit fibrillary beta-amyloid-induced inflammation in a model of the human blood-brain barrier. PLoS One 11, e0157483. https://doi.org/10.1371/journal.pone.0157483

[69] Wang H, Chen F, Du YF, Long Y, Reed MN, Hu M, Suppiramaniam V, Hong H, Tang SS (2018) Targeted inhibition of RAGE reduces amyloid-beta influx across the blood-brain barrier and improves cognitive deficits in db/db mice. Neuropharmacology 131, 143-153. https://doi.org/10.1016/j.neuropharm.2017.12.026

[70] Janelidze S, Hertze J, Nagga K, Nilsson K, Nilsson C, Wennstrom M, van Westen D, Blennow K, Zetterberg H, Hansson O (2017) Increased blood-brain barrier permeability is associated with dementia and diabetes but not amyloid pathology or APOE genotype. Neurobiol Aging 51, 104-112. https://doi.org/10.1016%2Fj.neurobiolaging.2016.11.017

[71] Atwal JK, Chen Y, Chiu C, Mortensen DL, Meilandt WJ, Liu Y, Heise CE, Hoyte K, Luk W, Lu Y, Peng K, Wu P, Rouge L, Zhang Y, Lazarus RA, Scearce-Levie K, Wang W, Wu Y, Tessier-Lavigne M, Watts RJ (2011) A therapeutic antibody targeting BACE1 inhibits amyloid-beta production in vivo. Sci Transl Med 3, 84ra43. https://doi.org/10.1126/scitranslmed.3002254

[72] Cai Z, Zhao B, Ratka A (2011) Oxidative stress and beta-amyloid protein in Alzheimer’s disease. Neuromolecular Med 13, 223-250. https://doi.org/10.1007/s12017-011-8155-9

[73] Xiang Y, Bu XL, Liu YH, Zhu C, Shen LL, Jiao SS, Zhu 727 XY, Giunta B, Tan J, Song WH, Zhou HD, Zhou XF, Wang YJ (2015) Physiological amyloid-beta clearance in the periphery and its therapeutic potential for Alzheimer’s disease. Acta Neuropathol 130, 487-499. https://doi.org/10.1007/s00401-015-1477-1

[74] Giri R, Selvaraj S, Miller CA, Hofman F, Yan SD, Stern D, Zlokovic BV, Kalra VK (2002) Effect of endothelial cell polarity on beta-amyloid-induced migration of monocytes across normal and AD endothelium. Am J Physiol Cell Physiol 283, C895-904. https://doi.org/10.1152/ajpcell.00293.2001

[75] Wan W, Chen H, Li Y (2014) The potential mechanisms of Abeta-receptor for advanced glycation end-products interaction disrupting tight junctions of the blood-brain barrier in Alzheimer's disease. Int J Neurosci 124, 75-81. http://dx.doi.org/10.3109/00207454.2013.825258

[76] Bell RD, Sagare AP, Friedman AE, Bedi GS, Holtzman 750 DM, Deane R, Zlokovic BV (2007) Transport pathways for clearance of human Alzheimer's amyloid beta-peptide and apolipoproteins E and J in the mouse central nervous system. J Cereb Blood Flow Metab 27, 909-918. https://doi.org/10.1038/sj.jcbfm.9600419

[77] Ueno M, Nakagawa T, Wu B, Onodera M, Huang CL, Kusaka T, Araki N, Sakamoto H (2010) Transporters in the brain endothelial barrier. Curr Med Chem 17, 1125-1138. 757. https://doi.org/10.2174/092986710790827816

[78] Kanekiyo T, Bu G (2014) The low-density lipoprotein receptor-related protein 1 and amyloid-beta clearance in Alzheimer's disease. Front Aging Neurosci 6, 93. http://dx.doi.org/10.3389/fnagi.2014.00093

[79] Zhang, W., Xiong, H., Callaghan, D., Liu, H., Jones, A., Pei, K., Fatehi, D., Brunette, E., & Stanimirovic, D. (2013). Blood-brain barrier transport of amyloid beta peptides in efflux pump knock-out animals evaluated by in vivo optical imaging. *Fluids and barriers of the CNS*, *10*(1), 13. https://doi.org/10.1186/2045-8118-10-13.

[80] Do TM, Noel-Hudson MS, Ribes S, Besengez C, Smirnova M, Cisternino S, Buyse M, Calon F, Chimini G, Chacun H, Scherrmann JM, Farinotti R, Bourasset F (2012) ABCG2- and ABCG4-mediated efflux of amyloid-beta peptide 1-40 at the mouse blood-brain barrier. J Alzheimers Dis 30, 770 155-166. https://doi.org/10.3233/jad-2012-112189

[81] Ciani L, Salinas PC. WNTs in the vertebrate nervous system: from patterning to neuronal connectivity. Nat Rev Neurosci 2005; 6: 351-62. https://doi.org/10.1038/nrn1665

[82] Park M, Shen K. WNTs in synapse formation and neuronal circuitry. EMBO J 2012; 31: 2697-704. https://doi.org/10.1038/emboj.2012.145

[83] Cerpa W, Gambrill A, Inestrosa NC, Barria A. Regulation of NMDA receptor synaptic transmission by Wnt signaling. J Neurosci 2011; 31: 9466-71. https://doi.org/10.1523/jneurosci.6311-10.2011

[84] Boonen RA, van Tijn P, Zivkovic D. Wnt signaling in Alzheimer's disease: up or down, that is the question. Ageing Res Rev 2009; 8: 71-82. https://doi.org/10.1016/j.arr.2008.11.003

[85] Shruster A, Eldar-Finkelman H, Melamed E, Offen D. Wnt signaling pathway overcomes the disruption of neuronal differentiation of neural progenitor cells induced by oligomeric amyloid beta-peptide. J Neurochem 2011; 116: 522-9. https://doi.org/10.1111/j.1471-4159.2010.07131.x

[86] Alvarez AR, Godoy JA, Mullendorff K, et al. Wnt-3a overcomes beta-amyloid toxicity in rat hippocampal neurons. Exp Cell Res 2004; 297: 186-96. https://doi.org/10.1016/j.yexcr.2004.02.028

[87] Toledo EM, Inestrosa NC. Activation of Wnt signaling by lithium and rosiglitazone reduced spatial memory impairment and neurodegeneration in brains of an APPswe/PSEN1DeltaE9 mouse model of Alzheimer's disease. Mol Psychiatry 2010; 15: 272-85. https://doi.org/10.1038/mp.2009.72

[88] Folke J, et al. , 2019. Impaired Wnt signaling in the prefrontal cortex of Alzheimer's disease. Mol. Neurobiol 56, 873–891. https://doi.org/10.1007/s12035-018-1103-z

[89] Riise J, et al. , 2015. Aberrant Wnt signaling pathway in medial temporal lobe structures of Alzheimer's disease. J. Neural Transm. (Vienna) 122, 1303–1318. https://doi.org/10.1007/s00702-015-1375-7

[90] Tapia-Rojas C, Inestrosa NC, 2018. Wnt signaling loss accelerates the appearance of neuropathological hallmarks of Alzheimer's disease in J20-APP transgenic and wild-type mice. J. Neurochem 144, 443–465. https://doi.org/10.1111/jnc.14278

[91] Vargas JY, et al. , 2015. WASP-1, a canonical Wnt signaling potentiator, rescues hippocampal synaptic impairments induced by Abeta oligomers. Exp. Neurol 264, 14–25. https://doi.org/10.1016/j.expneurol.2014.11.005

[92] Bayod S, et al. , 2015. Downregulation of canonical Wnt signaling in hippocampus of SAMP8 mice. Neurobiol. Aging 36, 720–729. https://doi.org/10.1016/j.neurobiolaging.2014.09.017

[93] Vargas JY, Fuenzalida M, Inestrosa NC. In vivo activation of Wnt signaling pathway enhances cognitive function of adult mice and reverses cognitive deficits in an Alzheimer's disease model. J Neurosci 2014; 34: 2191-2202. https://doi.org/10.1523/jneurosci.0862-13.2014

[94] Jia L, et al. , 2019. Restoring Wnt/beta-catenin signaling is a promising therapeutic strategy for Alzheimer's disease. Mol. Brain 12, 104. https://doi.org/10.1186/s13041-019-0525-5

[95] Lee JJ, von Kessler DP, Parks S, Beachy PA. Secretion and localized transcription suggest a role in positional signaling for products of the segmentation gene hedgehog. Cell. 1992;71(1):33–50. https://doi.org/10.1016/0092-8674(92)90264-d

[96] Echelard Y, Epstein DJ, St-Jacques B, Shen L, Mohler J, McMahon JA, McMahon AP. Sonic hedgehog, a member of a family of putative signaling molecules, is implicated in the regulation of CNS polarity. Cell. 1993;75(7):1417–30. https://doi.org/10.1016/0092-8674(93)90627-3

[97] Varjosalo M, Taipale J. Hedgehog: functions and mechanisms. Genes Dev. 2008;22(18):2454–72. https://doi.org/10.1101/gad.1693608

[98] Breunig JJ, Sarkisian MR, Arellano JI, Morozov YM, Ayoub AE, Sojitra S, Wang B, Flavell RA, Rakic P, Town T. Primary cilia regulate hippocampal neurogenesis by mediating Sonic hedgehog signaling. Proc Natl Acad Sci USA. 2008;105(35):13127–32. https://doi.org/10.1073/pnas.0804558105

[99] Ihrie PA, Shah JK, Harwell CC, Levine JH, Guinto CD, Lezamera M, Kriegstein AP, Alvarez-Buylla A. Persistent Sonic hedgehog signaling in adult brain determines neural stem cell positional identity. Neuron. 2011;71(2):250–62. https://doi.org/10.1016/j.neuron.2011.05.018

[100] Alvarez-Buylla A, Ihrie RA. Sonic hedgehog signaling in the postnatal brain. Semin Cell Dev Biol. 2014;33:105–11. https://doi.org/10.1016/j.semcdb.2014.05.008

[101] He P, et al. , 2014. Deficiency of patched 1-induced Gli1 signal transduction results in astrogenesis in Swedish mutated APP transgenic mice. Hum. Mol. Genet 23, 6512–6527. https://doi.org/10.1093/hmg/ddu370.

[102] Anna G. Vorobyeva and Aleister J. Saunders. Amyloid-β interrupts canonical Sonic hedgehog signaling by distorting primary cilia structure. Vorobyeva and Saunders Cilia (2018) 7:5 https://doi.org/10.1186/s13630-018-0059-y

[103] Luterman JD, Haroutunian V, Yemul S, Ho L, Purohit D, Aisen PS. Cytokine gene expression as a function of the clinical progression of Alzheimer disease dementia. Arch Neurol 2000: 1153–60 (2000). https://doi.org/10.1001/ARCHNEUR.57.8.1153

[104] Grammas P, Ovase R. Cerebrovascular transforming growth factorb contributes to inflammation in the Alzheimer's disease brain. Am J Pathol 160: 1583–7 (2002). https://doi.org/10.1016/s0002-9440(10)61105-4

[105] Peress NS, Perillo E. Differential expression of TGF-beta 1, 2 and 3 isotypes in Alzheimer's disease: a comparative immunohistochemical study with cerebral infarction, aged human and mouse control brains. J Neuropathol Exp Neurol 54: 802-11 (1995). https://doi.org/10.1097/00005072-199511000-00007

[106] van der Wal EA, Gómez-Pinilla F, Cotman CW. Transforming growth factor-b1 is in plaques in Alzheimer and Down pathologies. Neuroreport 4: 69–72 (1993). https://doi.org/10.1097/00001756-199301000-00018

[107] Tarkowski E, Issa R, Sjogren M, Wallin A, Blennow K, Tarkowski A, Kumar P. Increased intrathecal levels of the angiogenic factors VEGF and TGF-beta in Alzheimer's disease and vascular dementia. Neurobiol Aging 23: 237-43 (2002). https://doi.org/10.1016/S0197-4580%2801%2900285-8

[108] Wyss-Coray T, Masliah E, Mallory M, McConlogue L, JohnsonWood K, Lin C, et al. Amyloidogenic role of cytokine TGF-b1 in transgenic mice and Alzheimer's disease. Nature 389: 603–6 (1997). https://doi.org/10.1038/39321

[109] Wyss-Coray T, Lin C, Yan F, Yu G, Rohde M, McConlogue L, et al. TGF-b1 promotes microglial amyloid-b clearance and reduces plaque burden in transgenic mice. Nat Med 7: 614–8 (2001). https://doi.org/10.1038/87945

[110] Finch CE, Laping NJ, Morgan TE, Nichols NR, Pasinetti GM. TGF-b1 is an organizer of responses to neurodegeneration. J Cell Biochem 53: 314–22 (1993). https://doi.org/10.1002/jcb.240530408

[111] Wyss-Coray T, 2006. Tgf-Beta pathway as a potential target in neurodegeneration and Alzheimer's. Curr. Alzheimer Res 3, 191–195. https://doi.org/10.2174/156720506777632916

[112] Diniz LP, et al. , 2017. Astrocyte transforming growth factor beta 1 protects synapses against abeta oligomers in Alzheimer's disease model. J. Neurosci 37, 6797–6809. https://doi.org/10.1523/jneurosci.3351-16.2017

[113] Behl, C. et al. Hydrogen peroxide mediates amyloid beta protein toxicity (1994). Cell 77, 817–827. https://doi.org/10.1016/0092-8674(94)90131-7

[114] Kaltschmidt, B. et al. Transcription factor NF-kappaB is activated in primary neurons by amyloid beta peptides and in neurons surrounding early plaques from patients with Alzheimer disease (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 2642–2647. https://doi.org/10.1073/pnas.94.6.2642

[115] Yan, S.D. et al. RAGE and amyloid-β peptide neurotoxicity in Alzheimer's disease (1996). Nature 382, 685–691. https://doi.org/10.1038/382685a0

[116] O. Arancio, H.P. Zhang, X. Chen, C. Lin, F. Trinchese, D. Puzzo, S. Liu, A. Hegde, S.F. Yan, A. Stern, J.S. Luddy, L.F. Lue, D.G. Walker, A. Roher, M. Buttini, L. Mucke, W. Li, A.M. Schmidt, M. Kindy, P.A. Hyslop, D.M. Stern, S.S.Du. Yan, RAGE potentiates Abeta-induced perturbation of neuronal function in transgenic mice, Embo J. 23 (2004) 4096–4105. https://doi.org/10.1038/sj.emboj.7600415

[117] X.B. Dong, C.T. Yang, D.D. Zheng, L.Q. Mo, X.Y. Wang, A.P. Lan, F. Hu, P.X. Chen, J.Q. Feng, M.F. Zhang, X.X. Liao, Inhibition of ROS-activated ERK1/2 pathway contributes to the protection of H2S against chemical hypoxia-induced injury in H9c2 cells, Mol. Cell. Biochem. 362 (2012) 149–157. https://doi.org/10.1007/s11010-011-1137-2

[118] A. Rasola, M. Sciacovelli, F. Chiara, B. Pantic, W.S. Brusilow, P. Bernardi. Activation of mitochondrial ERK protects cancer cells from death through inhibition of the permeability transition, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 726–731. https://doi.org/10.1073/pnas.0912742107

[119] Y.X. Gui, X.Y. Wang, W.Y. Kang, Y.J. Zhang, Y. Zhang, Y. Zhou, T.J. Quinn, J. Liu, S.D. Chen, Extracellular signal-regulated kinase is involved in alpha-synuclein-induced mitochondrial dynamic disorders by regulating dynamin-like protein 1, Neurobiol. Aging 33 (2012) 2841–2854. https://doi.org/10.1016/j.neurobiolaging.2012.02.001

[120] Xueqi Gan, Shengbin Huang, Long Wu, Yongfu Wang, Gang Hu, Guangyue Li, Hongju Zhang, Haiyang Yu, Russell Howard Swerdlow, John Xi Chen, Shirley ShiDu Yan. Inhibition of ERK-DLP1 signaling and mitochondrial division alleviates mitochondrial dysfunction in Alzheimer's disease cybrid cell. Biochimica et Biophysica Acta 1842 (2014) 220–231. https://doi.org/10.1016/j.bbadis.2013.11.009

[121] Váradi C. Clinical Features of Parkinson's Disease: The Evolution of Critical Symptoms. Biology (Basel). 2020 May 19;9(5):103. https://doi.org/10.3390/biology9050103 PMID: 32438686; PMCID: PMC7285080.

[122] Dexter DT, Jenner P. Parkinson disease: from pathology to molecular disease mechanisms. Free Radic Biol Med. 2013 Sep;62:132-144. https://doi.org/10.1016/j.freeradbiomed.2013.01.018. Epub 2013 Feb 4. PMID: 23380027.

[123] Mhyre TR, Boyd JT, Hamill RW, Maguire-Zeiss KA. Parkinson's disease. Subcell Biochem. 2012;65:389-455. https://doi.org/10.1007/978-94-007-5416-4_16. PMID: 23225012; PMCID: PMC4372387.

[124] Desai BS, Monahan AJ, Carvey PM, Hendey B. Blood-brain barrier pathology in Alzheimer's and Parkinson's disease: implications for drug therapy. Cell Transplant. 2007;16(3):285-99. https://doi.org/10.3727/000000007783464731. PMID: 17503739.

[125] Obermeier B, Daneman R, Ransohoff RM. Development, maintenance and disruption of the blood-brain barrier. Nat Med. 2013 Dec;19(12):1584-96. https://doi.org/10.1038/nm.3407. Epub 2013 Dec 5. PMID: 24309662; PMCID: PMC4080800.

[126] Gray MT, Woulfe JM. Striatal blood-brain barrier permeability in Parkinson's disease. J Cereb Blood Flow Metab. 2015 May;35(5):747-50. doi: 10.1038/jcbfm.2015.32. Epub 2015 Mar 11. PMID: 25757748; PMCID: PMC4420870.

[127] Pan Y, Nicolazzo JA. Impact of aging, Alzheimer's disease and Parkinson's disease on the blood-brain barrier transport of therapeutics. Adv Drug Deliv Rev. 2018 Oct;135:62-74. https://doi.org/10.1016/j.addr.2018.04.009. Epub 2018 Apr 14. PMID: 29665383.

[128] Zlokovic BV. The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron. 2008 Jan 24;57(2):178-201. https://doi.org/10.1016/j.neuron.2008.01.003. PMID: 18215617.

[129] Kortekaas R, Leenders KL, van Oostrom JC, Vaalburg W, Bart J, Willemsen AT, Hendrikse NH. Blood-brain barrier dysfunction in parkinsonian midbrain in vivo. Ann Neurol. 2005 Feb;57(2):176-9. https://doi.org/10.1002/ana.20369. PMID: 15668963.

[130] Al-Bachari S, Naish JH, Parker GJM, Emsley HCA, Parkes LM. Blood-Brain Barrier Leakage Is Increased in Parkinson's Disease. Front Physiol. 2020 Dec 22;11:593026. https://doi.org/10.3389/fphys.2020.593026. PMID: 33414722; PMCID: PMC7784911.

[131] Rite I, Machado A, Cano J, Venero JL. Blood-brain barrier disruption induces in vivo degeneration of nigral dopaminergic neurons. J Neurochem. 2007 Jun;101(6):1567-82. https://doi.org/10.1111/j.1471-4159.2007.04567.x. Epub 2007 Apr 16. PMID: 17437543.

[132] Gray MT, Woulfe JM. Striatal blood-brain barrier permeability in Parkinson's disease. J Cereb Blood Flow Metab. 2015 May;35(5):747-50. https://doi.org/10.1038/jcbfm.2015.32. Epub 2015 Mar 11. PMID: 25757748; PMCID: PMC4420870.

[133] Lu M, Hu G. Targeting metabolic inflammation in Parkinson's disease: implications for prospective therapeutic strategies. Clin Exp Pharmacol Physiol. 2012 Jun;39(6):577-85. https://doi.org/10.1111/j.1440-1681.2011.05650.x. PMID: 22126374.

[134] Thomas KR, Capecchi MR. Targeted disruption of the murine int-1 proto-oncogene resulting in severe abnormalities in midbrain and cerebellar development. Nature. 1990 Aug 30;346(6287):847-50. doi: https://doi.org/10.1038/346847a0 . PMID: 2202907

[135] Castelo-Branco G, Wagner J, Rodriguez FJ, Kele J, Sousa K, Rawal N, Pasolli HA, Fuchs E, Kitajewski J, Arenas E. Differential regulation of midbrain dopaminergic neuron development by Wnt-1, Wnt-3a, and Wnt-5a. Proc Natl Acad Sci U S A. 2003 Oct 28;100(22):12747-52. https://doi.org/10.1073/pnas.1534900100 . Epub 2003 Oct 13. Erratum in: Proc Natl Acad Sci U S A. 2004 Nov 16;101(46):16390. PMID: 14557550; PMCID: PMC240689.

[136] Dai TL, Zhang C, Peng F, Niu XY, Hu L, Zhang Q, Huang Y, Chen L, Zhang L, Zhu W, Ding YQ, Song NN, Liao M. Depletion of canonical Wnt signaling components has a neuroprotective effect on midbrain dopaminergic neurons in an MPTP-induced mouse model of Parkinson's disease. Exp Ther Med. 2014 Aug;8(2):384-390. https://doi.org/10.3892/etm.2014.1745 . Epub 2014 May 28. PMID: 25009587; PMCID: PMC4079420.

[137] L'Episcopo, F., Tirolo, C., Testa, N., Caniglia, S., Morale, M. C., Cossetti, C., D'Adamo, P., Zardini, E., Andreoni, L., Ihekwaba, A. E., Serra, P. A., Franciotta, D., Martino, G., Pluchino, S., & Marchetti, B. (2011). Reactive astrocytes and Wnt/β-catenin signaling link nigrostriatal injury to repair in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson's disease. *Neurobiology of disease*, *41*(2), 508–527. https://doi.org/10.1016/j.nbd.2010.10.023.

[138] Chen, L. (2013). Roles of Wnt/β-Catenin Signaling in Controlling the Dopaminergic Neuronal Cell Commitment of Midbrain and Therapeutic Application for Parkinson's Disease. In (Ed.), Trends in Cell Signaling Pathways in Neuronal Fate Decision. IntechOpen. https://doi.org/10.5772/53282

[139] L'episcopo F, Serapide MF, Tirolo C, Testa N, Caniglia S, Morale MC, Pluchino S, Marchetti B. A Wnt1 regulated Frizzled-1/β-Catenin signaling pathway as a candidate regulatory circuit controlling mesencephalic dopaminergic neuron-astrocyte crosstalk: Therapeutical relevance for neuron survival and neuroprotection. Mol Neurodegener. 2011 Jul 13;6:49. https://doi.org/10.1186/1750-1326-6-49. PMID: 21752258; PMCID: PMC3162575.

[140] Kunke D, Bryja V, Mygland L, Arenas E, Krauss S. Inhibition of canonical Wnt signaling promotes gliogenesis in P0-NSCs. Biochem Biophys Res Commun. 2009 Sep 4;386(4):628-33. https://doi.org/10.1016/j.bbrc.2009.06.084. Epub 2009 Jun 21. PMID: 19545542.

[141] L' Episcopo F, Tirolo C, Testa N, Caniglia S, Morale MC, Marchetti B. Glia as a turning point in the therapeutic strategy of Parkinson's disease. CNS Neurol Disord Drug Targets. 2010 Jul;9(3):349-72. https://doi.org/10.2174/18715271079129263. PMID: 20438439.

[142] Chen LW, Yung KL, Chan YS. Reactive astrocytes as potential manipulation targets in novel cell replacement therapy of Parkinson's disease. Curr Drug Targets. 2005 Nov;6(7):821-33. https://doi.org/10.2174/138945005774574506. PMID: 16305461

[143] Diniz, Luan Pereira, et al. "Astrocyte Transforming Growth Factor Beta 1 Protects Synapses Against Aβ Oligomers in Alzheimer's Disease Model." The Journal of Neuroscience, vol. 37, no. 28, 2017, pp. 6797–809, https://doi.org/10.1523/JNEUROSCI.3351-16.2017

[144] Mogi, M., Harada, M., Kondo, T., Narabayashi, H., Riederer, P., & Nagatsu, T. (1995). Transforming growth factor-beta 1 levels are elevated in the striatum and in ventricular cerebrospinal fluid in Parkinson's disease. *Neuroscience letters*, *193*(2), 129–132. https://doi.org/10.1016/0304-3940(95)11686-q.

[145] Giráldez-Pérez, Rosa, et al. "Models of α-Synuclein Aggregation in Parkinson's Disease." Acta Neuropathologica Communications, vol. 2, no. 1, 2014, pp. 176–176, https://doi.org/10.1186/s40478-014-0176-9

[146] Chen, Xiao, et al. "TGF-B1 Neuroprotection via Inhibition of Microglial Activation in a Rat Model of Parkinson's Disease." Journal of Neuroimmune Pharmacology, vol. 12, no. 3, 2017, pp. 433–46, https://doi.org/10.1007/s11481-017-9732-y

[147] Ma, Rong, et al. "Primary Cilia and Ciliary Signaling Pathways in Aging and Age-Related Brain Disorders." Neurobiology of Disease, vol. 163, 2022, pp. 105607–105607, https://doi.org/10.1016/j.nbd.2021.105607

[148] Dass, B., et al. "Behavioural and Immunohistochemical Changes Following Supranigral Administration of Sonic Hedgehog in 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine-Treated Common Marmosets." Neuroscience, vol. 114, no. 1, 2002, pp. 99–109, https://doi.org/10.1016/S0306-4522(02)00214-2

[149] Zhang, Yi, et al. "Lentivirus-Mediated Delivery of Sonic Hedgehog into the Striatum Stimulates Neuroregeneration in a Rat Model of Parkinson Disease." Neurological Sciences, vol. 35, no. 12, 2014, pp. 1931–40, https://doi.org/10.1007/s10072-014-1866-6

[150] Shao, Shuai, et al. "Activation of Sonic Hedgehog Signal by Purmorphamine, in a Mouse Model of Parkinson's Disease, Protects Dopaminergic Neurons and Attenuates Inflammatory Response by Mediating PI3K/AKt Signaling Pathway." Molecular Medicine Reports, vol. 16, no. 2, 2017, pp. 1269–77, https://doi.org/10.3892/mmr.2017.6751

[151] Panet H, Barzilai A, Daily D, Melamed E, Offen D. Activation of nuclear transcription factor kappa B (NF-kappaB) is essential for dopamine-induced apoptosis in PC12 cells. J Neurochem. 2001 Apr;77(2):391-8. https://doi.org/10.1046/j.1471-4159.2001.00213.x. PMID: 11299301.

[152] Dolatshahi M, Ranjbar Hameghavandi MH, Sabahi M, Rostamkhani S. Nuclear factor-kappa B (NF-κB) in pathophysiology of Parkinson disease: Diverse patterns and mechanisms contributing to neurodegeneration. Eur J Neurosci. 2021 Apr 21. https://doi.org/0.1111/ejn.15242. Epub ahead of print. PMID: 33884689.

[153] Ghosh A, Roy A, Liu X, Kordower JH, Mufson EJ, Hartley DM, Ghosh S, Mosley RL, Gendelman HE, Pahan K. Selective inhibition of NF-kappaB activation prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease. Proc Natl Acad Sci U S A. 2007 Nov 20;104(47):18754-9. https://doi.org/10.1073/pnas.0704908104. Epub 2007 Nov 13. PMID: 18000063; PMCID: PMC2141849.

[154] Baiguera C, Alghisi M, Pinna A, Bellucci A, De Luca MA, Frau L, Morelli M, Ingrassia R, Benarese M, Porrini V, Pellitteri M, Bertini G, Fabene PF, Sigala S, Spillantini MG, Liou HC, Spano PF, Pizzi M. Late-onset Parkinsonism in NFκB/c-Rel-deficient mice. Brain. 2012 Sep;135(Pt 9):2750-65. https://doi.org/10.1093/brain/aws193. Epub 2012 Aug 21. PMID: 22915735; PMCID: PMC3437025.

[155] Parrella E, Bellucci A, Porrini V, Benarese M, Lanzillotta A, Faustini G, Longhena F, Abate G, Uberti D, Pizzi M. NF-κB/c-Rel deficiency causes Parkinson's disease-like prodromal symptoms and progressive pathology in mice. Transl Neurodegener. 2019 May 21;8:16. https://doi.org/10.1186/s40035-019-0154-z. PMID: 31139367; PMCID: PMC6530198.

[156] Singh SS, Rai SN, Birla H, Zahra W, Rathore AS, Singh SP. NF-κB-Mediated Neuroinflammation in Parkinson's Disease and Potential Therapeutic Effect of Polyphenols. Neurotox Res. 2020 Mar;37(3):491-507. https://doi.org/10.1007/s12640-019-00147-2. Epub 2019 Dec 10. PMID: 31823227.

[157] Plotnikov, Alexander, et al. "The MAPK Cascades: Signaling Components, Nuclear Roles and Mechanisms of Nuclear Translocation." Biochimica et Biophysica Acta. Molecular Cell Research, vol. 1813, no. 9, 2011, pp. 1619–33, https://doi.org/10.1016/j.bbamcr.2010.12.012

[158] Cheung, E. C., & Slack, R. S. (2004). Emerging role for ERK as a key regulator of neuronal apoptosis. *Science's STKE : signal transduction knowledge environment*, *2004*(251), PE45. https://doi.org/10.1126/stke.2512004pe45

[159] BHAT, N. R., and PEISHENG ZHANG. "Hydrogen Peroxide Activation of Multiple Mitogen-Activated Protein Kinases in an Oligodendrocyte Cell Line : Role of Extracellular Signal-Regulated Kinase in Hydrogen Peroxide-Induced Cell Death." Journal of Neurochemistry, vol. 72, no. 1, 1999, pp. 112–19, https://doi.org/10.1046/j.1471-4159.1999.0720112.x

[160] TENG, LESHENG, et al. "Involvement of the ERK Pathway in the Protective Effects of Glycyrrhizic Acid Against the MPP+-Induced Apoptosis of Dopaminergic Neuronal Cells." International Journal of Molecular Medicine, vol. 34, no. 3, 2014, pp. 742–48, https://doi.org/10.3892/ijmm.2014.1830

[161] Chen, Jun, et al. "Dopamine Promotes Striatal Neuronal Apoptotic Death via ERK Signaling Cascades." The European Journal of Neuroscience, Received 30 April 2008, revised 6 November 2008, accepted 20 November 2008, vol. 29, no. 2, 2009, pp. 287–306, https://doi.org/10.1111/j.1460-9568.2008.06590.x

[162] Bohush, Anastasiia, et al. "Role of Mitogen Activated Protein Kinase Signaling in Parkinson's Disease." International Journal of Molecular Sciences, vol. 19, no. 10, 2018, p. 2973–, https://doi.org/10.3390/ijms19102973