Misregulation of Wnt Signaling Pathways

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Wnt signaling pathways constitute a group of signal transduction pathways that direct many physiological processes, such as development, growth, and differentiation. Dysregulation of these pathways is thus associated with many pathological processes, including neurodegenerative diseases, metabolic disorders, and cancer. At the same time, alterations are observed in plasma membrane compositions, lipid organizations, and ordered membrane domains in brain and metabolic diseases that are associated with Wnt signaling pathway activation.

Keywords: Wnt signaling pathway ; plasma membrane ; ordered domain ; lipid raft ; Alzheimer's disease ; Parkinson's disease ; Schizophrenia ; diabetes ; obesity ; nonalcoholic fatty liver disease ; nonalcoholic steatohepatitis

1. Introduction

Wnt signaling pathways are highly conserved in the animal kingdom, based on their components and functional roles in the regulation of development, tissue homeostasis, and regeneration [1][2][3][4][5][6][7][8]. Thus, it is not surprising that changes in Wnt pathway components and modulators—including loss or gain of function—play a role in many pathologies associated with growth, development, and cancer. Although major pathway components have been characterized in detail, misregulation of Wnt signaling within the context of human diseases is extremely complex, and remains only partially understood. Understanding of this underlying complexity will enable the identification of novel therapeutic targets for many diseases associated with the Wnt pathway [9][10][11].

The plasma membrane plays a fundamental role in the regulation of cell signaling. Regulation occurs through the surface receptors, modulators, and associated lipids that actively control the transmission of molecular signals from the outside to the inside and activate downstream signaling events. The plasma membrane consists of nanodomains—the so-called ordered membrane domains or lipid rafts that are defined as dynamic assemblies of various saturated lipids, sterols, glycosphingolipids, and glycosyl-phosphatidylinositol (GPI)-anchored proteins [12][13][14]. These domains influence membrane fluidity and receptor trafficking, thereby playing a key role in the functioning of receptors, protein sorting, and regulation of receptor-mediated signaling [15][16][17][18]. These nanodomains have been revealed to be altered in various diseases, including cancer, neurological and neurodegenerative diseases, and metabolic diseases [19][20][21]. Changes in the composition and organization of membrane proteins and lipids also play an important role in Wnt pathway activation and, thus, in the pathology of pathway-associated diseases [22][23]. Considering that the membrane proteins account for over 60% of the targets of all FDA-approved small-molecule drugs, it is critical to characterize Wnt pathway components that act across the plasma membrane as potential therapeutic targets [9][22][24][25]. Here, we review the abnormal regulation of the Wnt signaling pathway in brain and metabolic disorders. In particular, we address how plasma membrane components of Wnt pathways and membrane domain organization are affected in Alzheimer's disease (AD), Parkinson's disease (PD), Schizophrenia (SZ), diabetes, obesity, nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH).

2. Wnt Signaling Pathways

Wnt signaling is an evolutionarily conserved signaling pathway that controls a wide range of biological responses, including proliferation, differentiation, preservation of the stem cell pool, control of lineage-specific tissue differentiation during embryogenesis, and maintenance of adult tissue homeostasis [3][4][5]. The Wnt pathway is divided into two main groups—i.e., β-catenin-dependent (canonical) and β-catenin-independent (non-canonical)—which can be further divided into the planar cell polarity (PCP) and the Wnt/Ca 2+ pathways (**Figure 1**). The canonical Wnt cascade is inactive in the absence of Wnt ligands, and this leads to phosphorylation of β-catenin by a cytoplasmic multiprotein complex that contains the kinases glycogen synthase kinase 3β (Gsk3β) and casein kinase 1a (Ck1a), the scaffold protein Axin, and adenomatous polyposis coli (Apc) [26][27]. This phosphorylation targets cytoplasmic β-catenin for degradation by the ubiquitin–proteasome system. Canonical Wnt signaling is activated by binding of Wnt ligands to the membrane receptor

Frizzled (Fzd) and the co-receptor low-density lipoprotein-receptor-related protein (Lrp) 5/6. Formation of the Wnt–receptor complex leads to the recruitment of the core components of the destruction complex to the cell surface, phosphorylation of the cytoplasmic tail of Lrp6 by Gsk3β and Ck1α, and stabilization of β-catenin in the cytoplasm and its nuclear translocation. In the nucleus, β-catenin interacts with the T-cell factor/lymphoid enhancer factor (Tcf/Lef) family of transcription factors, and regulates the expression of target genes [28][29]. The PCP pathway was originally described in the fruit fly Drosophila melanogaster , and controls coordinated, uniformly polarized cellular behavior in a wide variety of cells [30]. In mammals, PCP regulates key developmental processes ranging from neural tube closure to determination of left– right (L–R) asymmetry, and demonstrates essential roles in vertebrate development [31]. In the PCP pathway, the non-canonical Wnt ligands interact with the receptor Fzd and co-receptors (receptor tyrosine kinase-like orphan receptor (Ror)/receptor tyrosine kinase-related tyrosine kinase (Ryk)/protein tyrosine kinase 7 (Ptk7)). These interactions regulate the small GTPase molecules Rho, Rac, and Cdc42, and activate the kinases c-Jun N-terminal kinase (Jnk), the mitogen-activated protein kinase (MAPK) pathways, and Rho/Rho-associated coiled-coil-containing protein kinase (Rock) to control cell polarization and migration [32][33][34]. In the Wnt/Ca 2+ pathway, intracellular Ca 2+ is activated by the binding of Wnt to Fzd and coupling between Fzds and G proteins. This further activates protein kinase C (PKC), calcium/calmodulin-dependent protein kinase type II (CaMKII), and nuclear factor of activated T cells (NFAT), and regulates cell movement, cell fate, and cell migration as well as suppressing the canonical Wnt pathway (**Figure 1**) [33][34][35].

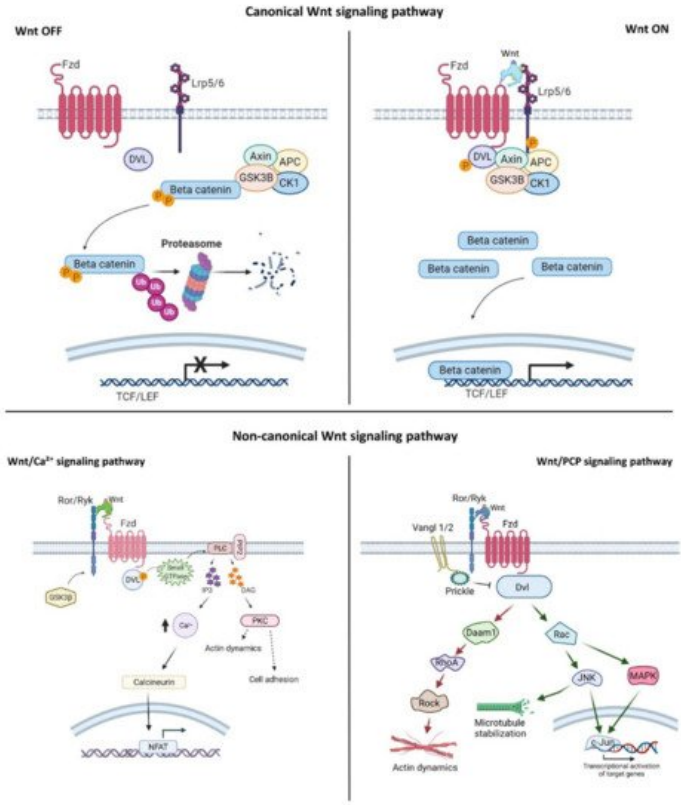

Figure 1. Wnt signaling pathway activation. The canonical Wnt signaling pathway: In the Wnt-off state, Gsk3β, and Apc phosphorylate β-catenin and degrade it by ubiquitination. In the Wnt-on state, the canonical Wnt binds to Fzd receptors and Lrp5/6 co-receptors. This interaction recruits Dvl and Axin to the Wnt–receptor complex, and causes stabilization of β-catenin in the cytosol. Next, β-catenin is translocated into the nucleus, where it binds to the Tcf/Lef regions and activates Wnt target genes. Non-canonical Wnt signaling pathways: In the calcium pathway, binding of non-canonical Wnt ligands to Ror-Ryk-Fzd recruits Dvl which, in turn, binds to small GTPase to further activate phospholipase C (PLC). In the PCP pathway, non-canonical Wnt ligands bind to the Ror/Ryk-Fzd receptor complex, recruiting Dvl to the plasma membrane and activating Rac and Daam1. Next, target genes are transcriptionally activated through JNK and MAPK. Created with BioRender.com.

Wnt pathways are fine-tuned by a number of positive and negative regulators that can affect the ligand–receptor complex interactions at the plasma membrane, cytoplasmic events, or nuclear control of transcription [22][36][37][38][39][40][41][42][43]. The plasma membrane plays key roles in protection of the cell from its surroundings, providing a stable environment inside the cell, management of molecular transport, and cell–cell communication. Embodying numerous receptors and lipids that take part in cell signaling, the plasma membrane is critical for the reception of signals and their transmission through a series of molecular switches to internal signaling pathways. The activity of the canonical Wnt signaling pathway is also dependent on the membrane components that tightly regulate the interaction of ligands with their (co)receptors in

the specialized membrane nanodomains, i.e., the ordered membrane domains or lipid rafts (**Figure 2**). The ordered domains are necessary not only for the proper interaction of the canonical Wnt ligand with its (co)receptors, phosphorylation of Lrp6, endocytosis of receptor complexes, and downstream canonical signaling activity, but also for the regulation of non-canonical Wnt signaling activity [15][42][44][45]. The roles of the ordered membrane domains in the activation of Wnt pathways have been reviewed in detail previously [22]. Here, we focus on the involvement of Wnt–receptor complex components and ordered membrane domains or lipid rafts in certain brain disorders and metabolic diseases.

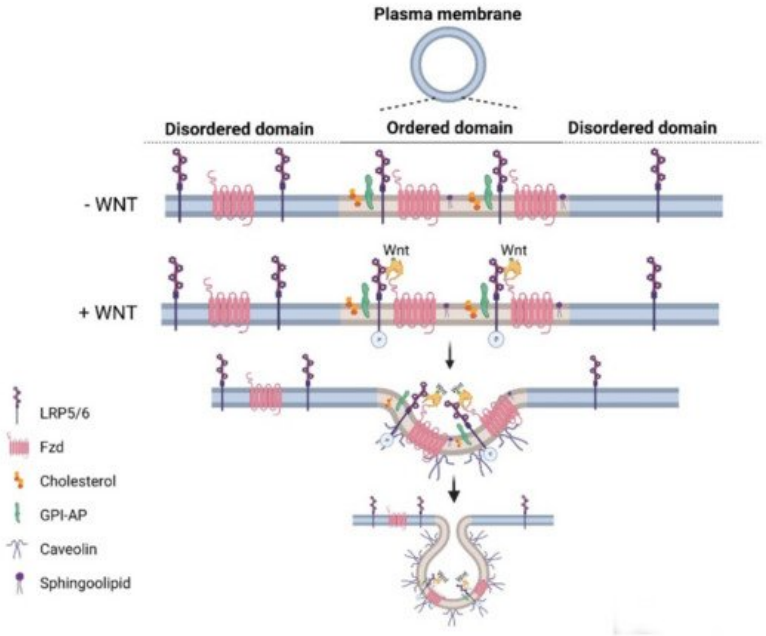

Figure 2. Canonical Wnt signaling activity is controlled by components of the plasma membrane. In general, the ordered domains are enriched in cholesterol, glycolipids, and caveolin. The ordered domains are necessary for the binding of the canonical Wnt ligand to its (co)receptors, Lrp5/6 phosphorylation, receptor endocytosis, and signaling activity. Created with BioRender.com.

3. Wnt Signaling Pathway in Metabolic Diseases

Wnt signaling is a major regulator of the development and growth of various tissues and organs involved in bodily metabolism, relating it with a range of metabolic diseases including diabetes, obesity, NAFLD, and NASH, which will be discussed here.

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, which begins with isolated steatosis and advances to nonalcoholic steatohepatitis (NASH), steatofibrosis, and cirrhosis.

3.1. Diabetes and Obesity

Several in vitro and in vivo studies have shown that the components of the Wnt signaling pathway are involved in β-cell proliferation, insulin secretion, and lipid metabolism [46][47][48]. Moreover, Wnt/β-catenin is linked to the long-term complications of type 2 diabetes mellitus (T2DM) and nephropathy [49][50]. T2DM is the most common type of metabolic disease [51]. The findings of recent genome-wide association studies in humans have identified *TCF7L2*/*TCF4* as a susceptibility gene for T2DM, and associated various *TCF7L* polymorphisms with a significantly higher risk of developing T2DM [52][53][54]. Secreted Wnt6 contributes to diabetes-associated centrosome amplification by activating the canonical pathway via the Fzd4 receptor [55]. Wnt signaling inhibition using Dkk1 significantly decreased neovascularization in diabetic rats as compared to untreated diabetic rats [56]. Furthermore, mutations in the Wnt signaling pathway's components have been reported in patients with proliferative diabetic retinopathy—an advanced eye disease seen in diabetic people [56]. The Wnt signaling proteins Fzd4, TSPAN12, NDP, Lrp5, Lrp6, and β-catenin were also elevated in diabetic retinopathy in humans and animal models [56][57].

Due to the potential functions of the Wnt/β-catenin signaling pathway on bone development and remodeling, its dysregulation in T2DM makes patients more susceptible to bone complications. Sclerostin, which antagonizes the Wnt/β-catenin pathway by binding to Lrp5/6, is a small protein expressed by the *SOST gene* in osteocytes, and was found to be expressed at higher levels in T2DM subjects than in controls [58][59]. Interestingly, T2DM patients had lower levels of bone

turnover markers and β-catenin, which are negatively correlated with sclerostin, suggesting that sclerostin prevents bone turnover by suppressing the canonical Wnt signaling pathway [58].

Vascular calcification is one of the most common complications in patients with T2DM. miR-128-3p accelerates cardiovascular calcification and insulin resistance in T2DM rats by targeting the pancreatic islet endocrine cell marker ISL-1 and activation of the Wnt pathway [60]. Upregulation of miR-128-3p enhanced the expression of Wnt1, β-catenin, and GSK-3β at the transcriptional level, and also increased phosphorylation of β-catenin and GSK-3β [60]. The Wnt/β-catenin pathway has been shown to be activated by another microRNA—miR-27a—which suppresses the Wnt antagonist Sfrp1 and activates Wnt/β-catenin signaling to promote the occurrence of renal fibrosis in diabetic nephropathy [61]. These findings collectively reveal the Wnt signaling pathway as a promising target for the treatment of T2DM and associated diseases.

The Wnt/β-catenin signaling pathway plays a vital role in adipose tissue lipogenesis and adipocyte metabolism—particularly under obesogenic conditions [62][63]. A cohort study involving 1004 people with atherosclerosis found that expression of Wnt5a was elevated in adipose tissue, with a concomitant increase in its receptors Fzd2 and Fzd5 in the human arterial wall and in vascular oxidative stress due to activation of NADPH oxidases [64]. Mice homozygous for the Lgr4 mutation, which acts as the receptor for the Wnt agonist R-spondins (Rspos) to enhance canonical Wnt signaling, showed reduced adiposity and resisted obesity [65]. These mice exhibited a parallel increase in energy expenditure of brown-like adipocytes in white adipose tissue, counteracting obesity. Moreover, a functional low-frequency missense variant of Lgr4 has been associated with an increased risk of obesity [65]. Adiponectin is an adipose-tissue-derived adipokine, and its levels are reduced during obesity [66][67]. AdipoRon, a small-molecule adiponectin receptor agonist, suppresses Rspo1-mediated canonical Wnt signaling [68]. By decreasing the free cholesterol levels at the plasma membrane, redirecting the cholesterol into the lysosomes, and reducing membrane rigidity, AdipoRon modulates the membrane order and inhibits Wnt signaling [68]. Therefore, it is likely that obese individuals, with low levels of circulating adiponectin, will exhibit increased plasma membrane rigidity and elevated Wnt signaling activity.

3.2. Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH)

The liver has critical functions in the control of metabolic pathways such as glucose metabolism and fatty acid metabolism [69]. The Wnt signaling pathways regulate fatty acid metabolism, and epigenetic activation of the canonical Wnt signaling pathway has been associated with a fat metabolism disorder called NAFLD [70]. NAFLD, defined as a range of conditions caused by the accumulation of fat in the liver, is one of the most common causes of chronic liver disease, which begins with steatosis, advances into NASH, and further progresses to end-stage liver diseases such as fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) [71]. The molecular mechanisms of NAFLD are poorly defined. Loss-of-function studies in the Wnt co-receptor Lrp6 have been associated with NAFLD. Mice homozygous for the $Lrp6^{R611C}$ mutation exhibit both steatohepatitis and steatofibrosis features associated with NAFLD [72]. Impaired Wnt signaling in the homozygote $Lrp6^{R611C}$ mice was efficiently remedied by administration of Wnt3a. Lrp6 knockdown also stimulated the non-canonical Wnt proteins RhoA (Ras homolog family member A) and ROCK2 (Rho-associated protein kinase), as well as their phosphorylated forms. Thus, the Lrp6 and non-canonical Wnt pathways are likely to be important therapeutic targets against NAFLD and NASH. The role of Lrp6 has also been evaluated in another study, where miR-21 was found to inhibit Lrp6 expression and Wnt β-catenin signaling activity, and enhanced the expression of critical lipid metabolic enzymes [73]. These results strongly suggest that targeting the Wnt β-catenin pathway at the plasma membrane can be an efficient therapeutic strategy against NAFLD and NASH.

Compositions of phospholipid fatty acids have been found to alter in the cell membranes of patients with T2DM, obesity, metabolic syndrome, or NAFLD [74][75][76][77]. The risk factors in NAFLD and NASH cause remodeling of the plasma membranes by changing their physicochemical properties. For example, co-exposure to the environmental contaminant benzo[a]pyrene and the hepatotoxicant ethanol triggered a general membrane order with higher lipid raft clustering in the plasma membrane of liver cells, and induced in vivo hepatotoxicity via membrane remodeling [78]. Moreover CD36—a scavenger receptor responsible for lipid accumulation and progression of metabolic dysfunction—localized more at the plasma membrane of hepatocytes in mice and humans with NASH [79]. Strikingly, inhibition of the palmitoylation of CD36 protected the mice from NASH by reducing the hydrophobicity of CD36 and reducing its localization at the membrane of hepatocytes [79][80]. Expression of Toll-like receptor 4 (TLR4), which is also involved in the pathogenesis of NASH, was found to be higher in the ordered membrane domains in NASH patients, and the TLR4 antagonist sparstolonin B attenuated TLR4 trafficking to these domains, as well as early liver inflammation in a murine model of NASH [81][82][83]. Co-expression of Fzd9 and Wnt3a with TLR4 in neuronal or glial cells as a response to inflammatory stimuli supports the idea that TLR4 trafficking in ordered membrane domains might also be controlled by Wnt signaling in fatty liver diseases [84][85]. Glucagon-like peptide 1 receptor (GLP-1R) likewise localizes in lipid raft/caveolae microdomains of the plasma

membranes in liver samples of patients with NASH, and is transcriptionally activated by the canonical Wnt signaling pathway [86][87][88]. The Wnt/β-catenin pathway has also been shown to promote the activation of Nod-like receptor protein 3 (NLRP3) inflammasomes [89]. Strikingly, the activation of NLRP3 inflammasomes contributed to NAFLD and NASH, and they were further enhanced by palmitic acid in hepatic stellate cells [90].

Cholesterol appears to be another major actor that plays a role in the development of NASH. Dysregulation of hepatic cholesterol homeostasis causes accumulation of hepatic free cholesterol (FC) and oxidized low-density lipoprotein (oxLDL) in NAFLD and NASH [91][92][93]. The phytochemical curcumin suppressed expression of lectin-like oxLDL receptor-1 (LOX-1) via interruption of canonical Wnt signaling in hepatic stellate cells, which are the main effector cells of NASH-associated hepatic fibrogenesis [94]. Given the stimulatory role of Wnt signaling in cholesterol endocytosis/flux and the production of lipid droplets, and the importance of cholesterol in Wnt–receptor complex formation, further studies in NASH will unravel the potential role of Wnt signaling activation at the plasma membrane in the induction of hepatic FC levels [15][91][95].

4. Conclusions

The Wnt signaling pathways are essential for many cellular events that take place in development, homeostasis, and regeneration. Being the initiator of Wnt–receptor complex formation that activates the signaling pathway, the plasma membrane plays an essential role in the regulation of Wnt signaling. Signaling initiation and regulation strongly depend on the content and organization of the membrane. In pathological processes, including brain disorders and metabolic diseases, changes occur in the composition of membrane lipids and proteins. While the Wnt signaling pathway has been relatively better characterized in AD and PD with respect to the content and organization of the plasma membrane domains, there exists limited knowledge concerning this issue in SZ. Therefore, further studies are required in order to clarify the role of the Wnt signaling pathway in SZ in the context of plasma membrane organization. Understanding the molecular mechanism of the Wnt signaling pathway in the context of plasma membrane organization will contribute to the development of new therapeutic strategies for the diseases in which the Wnt signaling pathway is dysregulated.

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