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Oligodendrocytes Development and Wnt Signaling Pathway

Shahid Hussain Soomro[1], Jifu Jie[2], Hui Fu[3,*]

[1]Wuhan University, School of Basic Medical Sciences, Department of Anatomy.

[2]Department of Anatomy, Health School of Bayinguoleng Mongolian Autonomous Prefecture, Korla, Xinjiang, China.

[3]Shenzhen Institute of Wuhan University, Shenzhen, china.

Abstract

Oligodendrocytes are specialized glial cell in central nervous system (CNS) responsible for the formation of myelin sheath around the axon. Oligodendrocyte proliferation and differentiation is regulated by Wnt signaling pathway, at various stages. However, different study groups have described controversial conclusions about the effect of Wnt on oligodendrocytes precursor cells (OPCs) development. Initially it has been proposed that Wnt pathway negatively regulates the OPCs proliferation and differentiation but recently some studies have described that Wnt promotes the differentiation of OPCs. After carefully reviewing the literature, we believe that Wnt play multiple roles in OPCs differentiation and its function is time (stage) and dose sensitive. Low to moderate activation of Wnt promotes OPC development, while too much or too low is inhibitory. Current evidences also suggested that in early developmental stages, Wnt inhibits the OPCs formation from neural progenitors and differentiation into immature oligodendrocytes. But in late stages Wnt plays promoting role in differentiation and maturation of oligodendrocytes. This review summarized the updated information regarding the critical role of Wnt signaling cascade in proliferation and differentiation of OPCs.

Corresponding author: Hui Fu, Shenzhen Institute of Wuhan University, Shenzhen, 518057, China. Email: hueyfu@hotmail.com

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Introduction

Oligodendrocytes (OLs) are specialized glial cell in central nervous system (CNS) responsible for the formation of myelin sheath around the axon which not only help in rapid conduction of electrical impulses but also provides metabolic and trophic support to underlying axon. Loss or damage to myelin sheath may result in various devastating neurological disorders including multiple sclerosis (MS), cerebral palsy and others [1-4]. Fortunately, the CNS has an excellent capacity to regenerate myelin sheath, in healthy individuals as well as in the early course of diseases [5]. However, during a prolonged disease course with recurrent attacks of demyelination, remyelination eventually fails leading to various demyelinating diseases [6-8]. It is therefore critical to understand the cellular and molecular mechanisms that regulate myelination in order to develop novel therapies to target remyelination [2,9-13]. In mammals, myelination process occurs during postnatal development [14, 15]. OLs development, from an oligodendrocyte precursor cell (OPC) to a mature myelinating OL, is controlled by a number of both inhibitory and inductive factors. Either failure of the mechanisms that promote myelination or the presences of strong inhibitory molecular signals suppress OPC differentiation and myelination. Important regulators of OL differentiation are electrical activity [16, 17], molecular signals derived from axons [18] and various extrinsic and intrinsic pathways. Among them Wnt signaling pathway is one of the critical pathways involved in the development of oligodendrocyte precursor cell. Wnt is one of the complex pathways with controversial role in the development of OLs. It affects many developmental stages of the OL lineage, with different effects. In this review we will discuss in detail about oligodendrocytes, Wnt (canonical) signaling pathway and its effect on OPCs development. This review will also highlight various targets of Wnt signaling pathway, which can be used or further investigated for the treatment of demyelinating diseases.

Functions of Oligodendrocytes

Oligodendrocytes are non-dividing cells, responsible for myelination in CNS. Mature oligodendrocytes form myelin sheath which provides critical insulation to facilitate axonal conduction by increasing the resistance and lowering the capacitance of the axonal membrane, resulting in faster conduction speed in myelinated axons than in unmyelinated axons of the same diameter [19]. The number of oligodendrocytes in any region of the CNS broadly depends upon, the number of OPCs migrating toward that region, the proliferative potential of the resident OPCs prior to differentiation and number of cells lost. All these factors ultimately affect the smooth and effective myelination process[20].

Oligodendrocytes Development

Oligodendrocytes are mature glial cells present in CNS derived from their precursor cells, commonly called as Oligodendrocyte precursor cells (OPCs). During the formation of CNS, OPCs are derived from neural stem cells. Around embryonic day (E12.5) OPCs are derived from pMN domain located at ventral midline of caudal portion of neural tube [21]. About 2 days later around E15, OPCs are also arises from dorsal spinal card. This is known as second wave of OPCs generation [22,23] Third wave also developed after birth from cerebral cortex which give rise that most of the population of OPCs present in adult brain [24,25].

The development of Oligodendrocytes lineage cells from their precursors to mature form is a complex process during which the cells exhibit morphological and biochemical changes. These diversities help to identify OLs lineage cells in various stages beneficial to adjust different targets for the treatment of demyelinating diseases. The development and maturation of oligodendrocytes require a series of highly-coordinated events that organise the proliferation and differentiation of the OPCs as well as the spatio-temporal regulation of myelination. After differentiation from neural stem cells, first recognized stage of oligodendrocytes lineage cells is OPCs. In this stage cells exhibit various markers including, Nestin, PSA-NCAM, PDGFRα and NG2. Among them, platelet-derived growth factor receptor α (PDGFRα) transcript is unique for oligodendrocytes at very early stages of development [26,27]. First signs of OPC maturation into oligodendrocytes and myelination can be observed around E17 and these processes continue after birth [28,29]. As OPCs start process of maturation, they lose their proliferative and migratory

capacity and their shape change to complex one [30]. Oligodendrocytes precursor cells when start differentiation, they express monoclonal antibody O4, and are termed pro-oligodendroblast [31]. With further development OPCs are differentiated in immature oligodendrocytes. In this stage oligodendrocytes express galactocerebroside (GalC) and 2′,3′-cyclic nucleotide 3′-phosphodihydrolase (CNPase). From this pre-myelinating immature stage oligodendrocytes are differentiated in to mature myelin forming oligodendrocytes where they express Myelin Basic Protein (MBP), ProteoLipid Protein (PLP), Myelin-Associated Glycoprotein (MAG), and Myelin/ Oligodendrocyte Glycoprotein, as well as other minor myelin proteins [32].

In the developmental myelination, OLs lineage cells are tightly regulated by various factors. These factors include growth factors, protein kinases, extracellular matrix, intracellular signaling cascade and soluble molecules. All these factors influence epigenetic modifications, transcriptional & translational regulation, and the actin cytoskeleton in oligodendrocytes [33-37]. Oligodendrocytes differentiation result from transcriptional changes in gene expression and is favoured by sonic hedgehog (Shh) (38, 39), thyroid hormone [38-41], IGF1(42, 43) and retinoic acid [44] and antagonized by mitogenic stimuli such as PDGF and FGF [40, 45-47], Wnt [48, 49], Notch [50, 51] and BMP4 [52-55]. The progression from OPCs to mature oligodendrocytes occurs in stages and is characterized by complex cytoskeletal organization [28] and progressive chromatin compaction [56, 57]. Various researchers have previously reported that changes of acetylation levels in nucleosomal histones, the basic unit of chromatin, are critical for oligodendrocyte differentiation in the developing brain and in repair after demyelination in adult mice [58-62]

Wnt Signaling Pathway

Wingless and integration site (Wnt) signaling cascade are a group of proteins, responsible for signals transmission from cell surface receptors to the nucleus where gene transcription carried out [63]. Wnt signaling is one of the fundamental mechanisms that direct cell proliferation, cell polarity and cell fate determination during embryonic development and tissue homeostasis [64]. Therefore mutations in the Wnt signaling pathway are often related to congenital diseases, carcinomas and other diseases [65].

Types

Since last two decades, Wnt/β-catenin signaling has emerged an important pathway involved in many cellular processes. Wnt signaling pathway is of two types, canonical and non-canonical. Canonical Wnt signaling pathway plays essential roles in cell proliferation, migration, invasion and metastasis[66] while non-canonical Wnt pathway activates T cell related transcription to modulate cytoskeleton rearrangement, cell adhesion, migration and tissue separation[67]. Non-canonical Pathway again has been divided into two types, the planar cell polarity pathway and Wnt/Ca^{2+} pathway. In the planar cell polarity pathway, frizzled activates JNK and directs asymmetric cytoskeletal organization and coordinated polarization of cells within the plane of epithelial sheets. The Wnt/Ca^{2+} pathway leads to release of intracellular $Ca^{2+,}$ possibly via G-proteins. Elevated Ca^{2+} can activate the phosphatase calcineurin, which leads to dephosphorylation of the transcription factor NF-AT in the nucleus, where it causes the transcription of many genes. Role of canonical pathway in myelination and remyelination has been well investigated. Therefore in this review we mainly focused on canonical Wnt signaling pathway.

Canonical Wnt Signaling Pathway

In mammals, canonical Wnt signaling pathway consist of four components, Wnt ligands/proteins family (extracellular), frizzled receptors (located at surface membrane) along with low density lipoprotein receptor related protein-5 & 6 (LRP-5/6), β-catenin (cytoplasmic) and LEF/TCF transcription factors (intranuclear) [68]. Wnt pathway is activated by binding of Wnt ligand to surface receptors, seven-transmembrane domain Frizzled receptors (Fzd) and single-transmembrane domain co-receptor Lrp5/6[69]. This binding causes the degradation of "β-catenin destruction complex", which consists of adenomatous polyposis coli (APC), Axin, glycogen synthase kinase 3 β (Gsk3- β), and casein kinase 1 (CK1). β-catenin destruction complex degradation results in accumulation of β-catenin in the cytoplasm and starts entering into the nucleus where it binds to TCF4 and activates downstream gene e.g CyclinD, c-myc, CD44[70]. Finally this results in cell

proliferation, differentiation, metastasis, chemo-resistance and other biological effects. When Wnt is not activated, cytoplasmic β-catenin is degraded by β-catenin destruction complex. This degradation results from phosphorylation of β-catenin at amino terminal region by CK1 and GSK3-β. After phosphorylation β-catenin is recognized by β-Trcp, an E3 ubiquitin ligase subunit, followed by β-catenin ubiquitination and proteasomal degradation [71]. In the absence of β-catenin, Wnt target genes are repressed by the DNA-bound T cell factor/lymphoid enhancer factor (TCF/ LEF) family of proteins.

Wnt Components

Wnt ligands

Wnt ligands are conserved in all metazoan animals. Presence of 19 Wnts in mammals, indicate complexity and specificity of Wnt signaling pathway. Wnts are cysteine rich proteins of approximately 350-400 amino acids that contain an N-terminal signal peptide for secretion. Murine Wnt3a represents the first purified and biochemically characterized Wnt protein [72]. Wnt ligands represent secreted molecules, having extensive capacity for inhibiting differentiation of OPCs [20]. Fancy et al, identify changes in the expression of multiple Wnt ligands following the induction of demyelination. This further strength their role in remyelination process [48]. Identifying the cells responsible for secreting these ligands could broaden our understanding regarding demyelinated environment, which help in potential therapeutics development.

Wnt Receptors: Frizzled and LRP5/6

Wnt/β-catenin signaling pathway, for its function, required two distinct receptor families including, the Frizzled (Fz or Fzd) seven-pass transmembrane receptors (64) and the LDL receptor-related proteins 5 and 6 (LRP5 and LRP6) [71]. The mammalian genome contains 10 Fz genes, most of which have variable capacities to activate Wnt/β-catenin signaling when co-overexpressed with Wnt and LRP5/6 [73]. Among LRPs, LRP6 plays a more dominant role and is essential for embryogenesis whereas LRP5 is dispensable for embryogenesis but critical for adult bone homeostasis. Collectively LRP5 and LRP6 play critical role for the mouse gastrulation [71]. Activation of canonical and/or non-canonical pathway also depends upon the binding of Wnt ligand to receptor complement [63]. Fz function is involved in β-catenin and non-canonical pathways. The Fz-LRP5/6 co-receptor model describes that a Wnt-Fz binding capable of recruiting LRP5/6, thus activates the β-catenin pathway [71]. However some studies suggest that LRP6 antagonizes non-canonical Wnt signaling in vivo, possibly via competing for Wnt ligands [74] or an unknown mechanism [75]. Some other Wnt receptors also have been identified such as Ryk and ROR2, which usually have no/little function, but in some cases may antagonize, Wnt/β-catenin signaling [63].

Wnt Antagonists & Agonists

Wnt/β-catenin signaling are antagonized or modulated by various secreted proteins. Among them sFRPs (secreted Frizzled related proteins), and WIF (Wnt inhibitory protein) bind to Wnt, while sFRPs also binds to Fz, and thereby act as Wnt antagonists for both β-catenin and non-canonical signalling[76].

Apart from these, Dickkopf (Dkk) and Wise/ SOST families also function as Wnt inhibitors. Dkk family proteins function as LRP5/6 ligands/antagonists, thus are considered specific inhibitors for canonical Wnt signaling pathway. Dkk1 inhibits Wnt signaling through LRP6 internalization/ degradation via transmembrane Kremen (Krm) proteins [77]. Some opponent studies argue that Dkk1 disturbed the Wnt-induced Fz-LRP6 complex formation and by this mechanism it act as inhibitor [78], while Krm plays a minor modulatory role in specific tissues [79]. Like Dkk1, SOST disrupt Wnt-induced Fz-LRP6 complex formation in vitro [80], and by this way it inhibits Wnt/ β-catenin signaling. Shisa family proteins are another wnt Inhibitors, which prevent Fz from reaching to cell surface, thus inhibit Wnt/β-catenin signaling autonomously [81]. Some other Wnt/ β-catenin signaling antagonists with multivalent activities have also been identified. IGFBP-4 (Insulin-like growth-factor binding protein-4) binds to both Fz and LRP6 and antagonizes Wnt/β-catenin signaling, further it also modulates IGF signaling [82].

Among the agonists, Norrin and R-spondin (Rspo) proteins are two distinct families, for Wnt/β-catenin signaling, have been identified. Norrin acts by binding to Fz4 and LRP5/6 during retinal vascularization [83]. Rspo proteins show synergy with

Wnt, Fz and LRP6 [84-87], and genetic interaction with LRP6 during embryogenesis [88]. Norrin and Rspo exhibit controversial mechanism of actions. Rspo binds to Fz and LRP6 both or individually, has been reported in some studies [86, 87] while another study reported that Rspo is a ligand for Krm and antagonized Dkk/Krm-mediated LRP6 internalization [73]. Review of literature revealed that Rspo activates Wnt/β-catenin by antagonizing LRP6 internalization. This looks less likely mechanism as Krm1/2 (causes LRP6 internalization with Dkk1) double knockout mice were viable and do not show mutant phenotype, further Rspo activated Wnt/β-catenin signaling in cells lacking both Krm genes [79,88]. Rspo genes are often co-expressed with and depend on Wnt for expression [84], and may represent a means of positive feedback that reinforces Wnt signaling.

β-catenin

β-catenin is essential component of Wnt signaling pathway, essential intracellular protein, encoded by CTNNB1 gene in human beings. Mutations (deletion or over expression) of β-catenin are associated with many cancers [89], cardiac and demyelination diseases.

In the case of Wnt "Off", β-catenin is phosphorylated and degraded. The scaffolding protein Axin uses separate domains to interact with GSK3, CK1α, and β-catenin and coordinates sequential phosphorylation of β-catenin at serine 45 by CK1α and then at threonine 41, serine 37 and serine 33 by GSK3 [90]. β-catenin phosphorylation at serine 33 and 37 creates a binding site for the E3 ubiquitin ligase β-Trcp, leading to β-catenin ubiquitination and degradation. Mutations of β catenin at and surrounding these serine and threonine residues are frequently found in cancers. But when Wnt is "On", β-catenin not phosphorylated, accumulated in cytoplasm, then enters into the nucleus, binds to TCF7l2 and causes genes transcription.

TCF/LEF

The TCF/LEF family transcription factors mostly bind to β-catenin and cause genes regulation [91,92]. TCF represses gene expression by interacting with the repressor Groucho (TLE1 in human), which promotes histone deacetylation and chromatin compaction. β-catenin stabilization and nuclear accumulation leads TCF/β-catenin complex formation, which displace Groucho [93] and recruits other co-activators for gene activation. In mammalian, four TCF/LEF family genes are present including, LEF1, TCF1, TCF3 and TCF4. Alternative splicing and promoter usage produce a large number of TCF variants with distinct properties [91,92]. TCF proteins are HMG (high mobility group) DNA-binding factors, bind to a DNA consensus sequence known as Wnt responsive element (WRE). A genome-wide analysis in colon carcinoma suggested that TCF4/β-catenin target genes have multiple WREs, most of which are located at large distances from transcription start sites [94]. Some TCF1 and TCF4 splicing variants have another DNA-binding domain called C-clamp, which recognizes an additional GC element downstream of the typical WRE, allowing different sets of target genes regulation [95].

TCF1 and TCF4 act as both repressors and activators, LEF1 usually acts as activator whereas TCF3 mostly exhibits repressor function but sometimes behaves as activator as well [91, 92]. TCF/β-catenin induced transcription is mostly regulated by three strategies including, (i) Alternative promoter usage in TCF-1 and LEF-1 genes produces dnTCF-1/dnLEF-1, which lack the amino-terminal β-catenin-binding domain and thus act as the endogenous dominant negative TCF/ LEF [91,92]. (ii) dnTCF-1, antagonizes TCF-4 in stem cell renewal, thus causes tumor suppression [49]. Chibby and ICAT (Nuclear antagonists) bind to β-catenin and disrupt β-catenin/ TCF and β-catenin/co-activator interactions, thus promote β-catenin nuclear export [96,97]. Apart from these antagonists, KLF4 also acts as inhibitor and prevents β-catenin transcriptional activation, critical for tumor suppression [98].

TCF/LEF can undergo post-translational modifications including phosphorylation, acetylation, sumoylation, and ubiquitination/degradation [91,92]. These modifications result in activation or suppression of downstream genes. TCF-3 phosphorylation by CK1 and LEF-1 phosphorylation by CK2 enhances their binding to β-catenin and diminishes LEF-1 binding to Groucho/TLE, whereas LEF-1 and TCF-4 phosphorylation by NLK (Nemo-like kinase) leads to deceased LEF/TCF/β-catenin complex binding to DNA and their degradation. LEF-1 and TCF-4 sumoylation represses LEF-1 activity by targeting it to nuclear bodies but enhances

TCF-4/β-catenin transcription. These modifications of TCF/LEF proteins may result in their paradoxal role.

Self-Regulation of Wnt Signaling Pathway

Wnt/β-catenin signaling regulates proliferation, fate specification and differentiation in different developmental stages and various adult tissues homeostasis. Therefore Wnt target genes show diversity [99] and cell- and context-specificity [64]. Wnt signaling components including Fz, LRP6, Axin2, TCF/LEF, Dkk1, and Rspo, are often regulated positively or negatively by TCF/β-catenin [64,84,100,101]. Wnt induction of Axin2, Dkk1, Naked and suppression of Fz and LRP6 constitute negative feedback loops that suppressed Wnt signaling [64]. Contrary, Wnt induction of Rspo and TCF/LEF genes constitute positive feedback and reinforce Wnt signaling [102,103]. These various Wnt pathway self-regulatory loops are mostly utilized in a cell-specific manner, providing further complexity in the control of amplitude and duration of Wnt responses.

Wnt Signaling and Diseases

Wnt/β-catenin signaling pathway plays a critical role in development and homeostasis. Therefore, there is no surprise that its mutations would be associated with many hereditary disorders, demyelinating diseases, carcinomas and other diseases (Table 1). These mutations involve various Wnt ligands, agonists and antagonists, and affect on Wnt regulation of human development leading to various disease processes. For example, RSPO1 mutations result in XX sex reversal [104], a condition having similar features to patients with WNT4 mutations [105]. FZ4 or LRP5 mutations are associated with familial exudative vitreo-retinopathy (FEVR) [106], manifested by defective retinal vascularization [83]. LRP5 loss-of-function mutations has been identified in patients with osteoporosis pseudo-glioma syndrome (OPPG), a recessive disorder characterized by low bone mass and abnormal eye vasculature [107], while LRP5 missense ('gain-of-function') mutations has been observed in patients with autosomal dominant high bone mass (HBM) diseases [108,109].

TCF7L2 has strong relationship with diabetes mellitus type II [110]. Although the diabetes-associated TCF7L2 gene polymorphism does not alter protein coding, but its association with the disease has been confirmed in numerous populations [111]. Some studies have suggested that the predisposing TCF7L2 variant causes a decreased insulin secretion from pancreatic β-cells, but other pathogenic mechanisms involving additional tissues/organs or endocrine functions remain to be elusive.

Demyelinating diseases also caused by dysregulation of Wnt signaling pathway. Wnt controls multiple aspects of OL development including the specification of OPCs, OPCs differentiation, myelination, and remyelination. Here Wnt shows paradoxal role. It's promoting and inhibitory effects are under great debate along with the timing and intensity of Wnt activation. Wnt signaling dysregulation with cancer has been well documented, particularly with colorectal cancer [112]. Constitutively activated β-catenin signaling, prevent its degradation, leads to excessive stem cell renewal/ proliferation that predisposes cells to tumorigenesis [113].

Nkx2-2 and Oligodendrogenesis

Nkx2.2 regulates the expression of myelin structure genes and oligodendrocyte differentiation. It is plausible that the Nkx2.2 homeodomain transcription factor may directly bind to the promoters of MBP and PLP genes and subsequently regulate their expression [114]. Common binding sites for Nkx2.2 are found in PLP and MBP promoters, thus overexpression of Nkx2.2 transcription factor can induce gene expression from the PLP promoter in transient transfection assays [114]. In Nkx2.2 knockout mice, the number of myelin basic protein (MBP)-positive and proteolipid protein (PLP)-positive oligodendrocytes is drastically reduced and delayed in both the spinal cord and the brain. PLP and MBP expression is not inhibited completely, which indicates that Nkx2.2 may have a partially redundant function with other transcription factors such as Olig1/Olig2 or Sox10 which are co-expressed in oligodendrocyte progenitors. It is possible that Nkx2.2 may enhance or modulate the activities of these transcription factors. Wnt signaling pathway also plays its role in expression of Nkx2-2. Wnt pathway inhibitors regulate the threshold response of a ventral Shh target gene, Nkx2.2, to establish its restricted expression in the ventral spinal cord. Identification and characterization of an Nkx2.2 enhancer reveals that expression is directly regulated positively by Shh signaling and negatively by TCF7l2

Table 1. Wnt components mutations related diseases

Wnt3(158)	Ligands for Wnt/βcatenin signaling	LOF Tetra-amelia
Wnt4(105)	Ligands for Wnt/βcatenin signaling	LOF Mullerian-duct regression and virilization
Wnt5b(159)	Ligands for Wnt/βcatenin signaling	Type II diabetes (?)
Wnt7a(160)	Ligands for Wnt/βcatenin signaling	LOF Fuhrmann syndrome
Wnt10a(161)	Ligands for Wnt/βcatenin signaling	LOF Odonto-onchyo-dermal hypoplasia
Wnt10b(162)	Ligands for Wnt/βcatenin signaling	LOF Obesity
RSPO1(104)	Wnt agonist	LOF XX sex reversal with palmoplantar hyperkaratosi
RSPO4(163)	Wnt agonist	LOF Autosomal recessive anonychia and hyponychia congenita
SOST(164)	LRP5/6 antagonist predominantly expressed in osteocytes	LOF High bone mass, Sclerosteosis, Van Buchem disease
Norrin (83, 164)	Specific ligand for FZD4 and LRP5 during eye developmen	LOF Familial Exudative vitreoretinopathy
LRP5(108, 165)	Wnt co-receptors	GOF Hyperparathyroid tumors GOF High bone mass LOF Osteoporosis-pseudoglioma LOF FEVR eye vascular defect
LRP6(166)	Wnt co-receptors	LOF Early coronary disease and osteoporosis
FZD4(167)	Wnt receptor	LOF Familial Exudative vitreoretinopathy
Axin1(168, 169)	Facilitates β-catenin degradation, Tumor suppressor	LOF Caudal duplication, Cancer
Axin2(170, 171)	Facilitates β-catenin degradation, Tumor suppressor	LOF Tooth agenesis, Cancer
APC(172, 173)	Facilitates β-catenin degradation, Tumor suppressor	LOF Familial adenomatous polyposis, Cancer
WTX(174, 175)	Facilitates β-catenin degradation, Tumor suppressor	LOF Wilms tumor
β-catenin(CTNNB1)(176, 177)	Primary Wnt effector, Oncogene	GOF cancer
TCF4 (TCF7L2)(110, 178)	+ β-catenin transcriptional partner	Type II diabetes (?)

LOF: loss-of-function; GOF: gain-of-function

repressor activity.

BMP4 and Oligodendrocytes Development

OPCs Differentiation results from the integration of extracellular signals and the chromatin state of a cell. OPCs are characterized by euchromatin and amenable to "accept" environmental signals (i.e Wnt, Shh, Bmp4, Notch) to modulate gene expression and differentiation. Impaired OPCs generation after Shh loss-of function [115] and ectopic oligodendrogenesis after Shh gain-of function has been reported [38,116]. BMP4 increases the number of astrocytes at the expenses of oligodendrocytes [52], inhibits differentiation at later stage [53] and decreases myelin genes expression [54,117-119]. BMP4 signals activate Smad1/5/8 proteins (R-Smads), associate with the common mediator-Smad 4 (co-Smad) [120, 121] and activate gene expression by interacting with transcription co-activators [122, 123]. In OPCs competitive mechanism between Shh and BMP4 has been identified [118]. It involved the functional sequestration of Shh target molecules (i.e. Olig2) by the inhibitors of Id2 and Id4 (differentiation protein), which are induced by BMP4 [124-127]. In mouse cerebellar cultures, in contrast, BMPs interfere with the Shh-induced proliferation by decreasing the levels of Gli1 and Smo [128], while in the chick spinal cord, BMP has been shown to repress Shh target genes Olig2 and Nkx2.2 [129]. In the adult brain the inhibitory effect of BMP4 on oligodendrogliogenesis has been attributed to the effect of Smad4 on the expression of Olig2. In a series of elegant studies on mice lacking Smad4 in neural stem cells, higher numbers of Olig2+ cells and oligodendrocytes were detected, a finding that was replicated by infusion of noggin (BMP inhibitor) [130]. High levels of BMP4 have been reported in human brains from Multiple Sclerosis patients [131], in animal models of spinal cord injury, [132], in mice with induced experimental allergic encephalomyelitis [133] and in the cuprizone-induced demyelination model and they correlated with a dose-dependent increase of the astrocyte number at the expenses of oligodendrocytes [134]. The inhibition of BMP4 signaling by infusion of noggin reversed the effect and reduced the astrocyte numbers [134] while promoting oligodendrocyte regeneration and remyelination [135].

Wnt Signaling Pathway and OPCs Development

The Wnt pathway is a key signaling mechanism that controls multiple aspects of OL development including the specification of OPCs, OPCs differentiation, myelination, and remyelination. Wnt signaling via the canonical pathway is transiently activated in OPCs at the time of initial differentiation and then down-regulated when oligodendrocytes get mature [48,136]. Initial specification of the oligodendrocyte lineage requires coordination of various upstream and downstream transcription factors [23,137] including Tcf7l2, for the generation of mature, post-mitotic oligodendrocytes [58]. In contrast to other signaling pathways, Wnt shows paradoxal role in OPCs proliferation and differentiation. Effect of Wnt depends upon stage of maturation at the time of activation and intensity of activation.

Inhibitory Effect of Wnt on OPC Development

The Wnt signaling pathway was initially described as an OL development inhibitor in embryonic spinal cord cultures [138]. Later on multiple in vivo studies confirmed that Wnt plays an inhibitory role in OPC differentiation during early postnatal development [48, 58, 139]. Azim et al in their study observed the negative impact of Wnt3a ligand on the OPCs differentiation. By the addition of Wnt3a agonist, $Sox10^+$ OPCs and OLs were increased while significant decrease was observed in PLP^+ OLs [140]. Lee et al reported that Wnt signaling, when antagonised by Apcdd1, which binds to LRP6 receptor and blocked its function, promotes OPCs differentiation [141]. Daam2 is required for canonical Wnt signaling during patterning in the dorsal spinal cord, functioning through the clustering and formation of Wnt receptor signalosomes [142]. Suppression of Wnt signalling pathway in Daam 2 knockout mice resulted in increased number of MBP^+ and PLP^+ OLs, further supporting that Wnt plays an inhibitory role in differentiation process [143]. OPC differentiation was also delayed following Wnt pathway activation by expressing a dominant-active β-catenin specifically in cells of the OL lineage [48,139]. Loss of APC or Axin2, stabilizes the β-catenin and exerts an inhibitory effect on myelination [144-147]. Similarly pharmacological agent (XAV939)[148] that stabilized by the Axin2 protein, resulting in increased MBP expression and number of PLP^+OLs in comparison of control group [9]. Together, these studies demonstrate that

both genetic and pharmacological activation of Wnt/β-catenin impair OPC differentiation, thereby preventing cells from maturing and producing myelin sheaths.

TCF7l2, important component of Wnt, also affects the differentiation of OPCs. Various studies suggest that β-catenin/TCF7l2 complex is inhibitory for OPC differentiation and subsequent myelination. Fancy et al described that Olig2-Cre/DA-Cat mice expressed TCF7L2, an important nuclear binding partner of β-catenin [48]. Two other independent studies demonstrated that deletion of Tcf7l2 inhibited OPC differentiation in the spinal cord, suggesting that TCF7L2 is actually necessary for OPC differentiation (58, 136). From these studies it can be assumed that β-catenin may mediate its negative effect on OPC differentiation at least in part by recruiting TCF7L2 to regulate the transcription of important Wnt pathway target genes. Fancy et al demonstrated that Tcf7l2 is normally expressed in OLs during postnatal development but not in adulthood, potentially rendering constitutively active β -catenin ineffectual as the mice aged, and providing a potential mechanism for the delay but not complete block in OPC differentiation in the DA-cat mice [48].

Promoting Effect of Wnt on OPC Development

Although the inhibitory effects of Wnt signaling pathway on OPC differentiation are well accepted, however some studies conflict this inhibitory effect. Those researchers have described Wnt as a positive regulator of OPCs development. Tawk et al showed that addition of Wnt1 or Wnt3a in OPCs culture increased the expression of PLP^{+}OLs by 3.5-fold and 2-fold, respectively [149]. Fancy et al described that microarray profiling has shown up regulation of Wnt ligand and receptors in lesions of MS and MS animal models [48]. Conditional knockout of β-catenin resulted in significantly decreased PLP^{+} and MPB^{+} OLs [150]. Knocking down of β-catenin and TCF molecules (all four types) decreased PLP promoter gene activity by 70%, reciprocally over expression of β-catenin increased PLP promoter gene activity in OLs lineage cells [89,149]. Knockout of TCF4 caused a myelin deficient phenotype [136]. Some other studies showed that in TCF4 knockdown mouses expression of PLP & MBP was undetectable in comparison to control, indicating that TCF4 is essential for oligodendrocytes lineage differentiation and maturation [58,151]. Microarray analysis of tissues from patients with multiple sclerosis revealed high expression of TCF4 in active lesion compared normal appearing white matter and silent chronic lesion [152].

From these controversial results described by various studies, it has been proposed that TCF7L2/β-catenin level must be tightly controlled for proper myelination [151]. Therefore the extent to which an experimental model increases the level of intranuclear β-catenin correlates with the effect on OL maturation [151].

Wnt and OPCs Developmental Stage

Oligodendrocyte precursor cells (OPCs) are generated from progenitor zones in the forebrain beginning at various times during embryonic development [24]. The mechanisms regulating the spatial and temporal production of OPCs have not been clearly elucidated. Sonic Hedgehog regulates the production of OPCs from ventral progenitor zones [25] while In the telencephalon Wnt signaling plays a prominent dorsalizing role [153,154]. Wnt signaling has been observed significantly decreased in the cortical progenitor domain at embryonic period when OPCs are generated [48,58,138]. Langseth et al described that Wnt signaling negatively regulates the specification of OPCs from neural progenitors and that inhibition of Wnt signaling increased the production of OPCs in the cortex [155]. Kessaris et al described that Wnt is very high in cortical progenitors at E17.5 (before cortical OPC production) and decreased by P5 when OPCs production is prominent [24]. Wnt signalling via the canonical pathway is transiently activated in OPCs concurrently with the initiation of terminal differentiation. Both β-catenin activity and the expression of Tcf7l2 are subsequently down-regulated in mature oligodendrocytes [48,136]. Shimizu et al, described that addition of Wnt3a supernatant to CG4 cells (an OL progenitor strain) and to the dissociated primary cultured cells resulted in inhibition of differentiation step from OL progenitor to O4-positive stage [138]. Deletion of the Wnt effector Tcf7l2 blocks oligodendrocyte differentiation [58,136] . These results have potential relevance for remyelination in human disease given that Wnt signaling components are present in MS lesions, suggesting that dysregulated

Wnt/β-catenin signaling could contribute to the lack of remyelination, often seen in this disease [48].

These findings indicate that Wnt negatively regulate the OPCs production [150] at early developmental stage but at later stage promotes the differentiation of already established OPCs [155,156] and finally down regulated when oligodendrocytes becomes mature [157].

Wnt Intensity and OPCs Development

Along with activation of Wnt at various developmental stages, intensity of Wnt activation also plays an important role in oligodendrocytes development. During myelin formation, TCF7L2 must be associated with moderate level of β-catenin and either high or low levels of TCF7L2/β-catenin are detrimental for myelination. Either increased or decreased levels of TCF4/β-catenin expression have inhibitory effects on myelination process [151]. Dai et al observed the decreased number of $Olig1^+$ and $Olig2^+$ cells in β-catenin activated mice ($Cat^{G/+}$) in comparison to control, and expression of Sox10 and PDGFRα was also impaired. Along with the number, distribution of these cells also affected, at E13.5 cells were only detected in the ventral ventricular zone of spinal cord, in contrary to their wide distribution in control tissues. Fancy et al also demonstrated that DA β-catenin signalling is sufficient to impede the remyelination process in mice. Similar results were obtained in mice lacking a copy of the β-catenin antagonist, APC. Together, these findings suggest that constitutive expression of β-catenin in OPCs correlates with a significant impairment of the remyelination process [48]. On other hand β-catenin inactivation ($Cat^{L/L}$) resulted in increased production of precocious OPCs (E12.5) [150].

Conclusion

In summary, Wnt signaling cascade is a critical pathway involved in many developmental and disease processes. Wnt regulates the OPCs proliferation and differentiation. Inspite of widely accepted role of Wnt as inhibitory for OPCs proliferation and differentiation, recently evidences have emerged that Wnt enhances OPCs development. Wnt's inhibitory or enhancing effect depends on developmental stage & intensity of activation. In early stages, Wnt inhibits the OPCs formation from neural progenitors and differentiation into immature OLs but in late stages Wnt plays a promoting role in differentiation and maturation of OLs. Further research is needed for better understanding the mechanism of Wnt signaling cascade through which it promotes OPCs proliferation and differentiation. It will also helps in proper targeting by therapeutic agents in demyelinating diseases of central nervous system.

Conflict of Interest

There is no conflict of interest.

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