Regulating Wnt signaling: a strategy to prevent neurodegeneration and induce regeneration

During the past three decades, Wingless/Int (Wnt) signaling has emerged as an essential regulator crucial for neuronal development and maintenance (Inestrosa and Arenas, 2010). In addition, Wnt signaling was recently shown to be involved in the regulation of synaptic function and plasticity, which is critical for learning and memory (Oliva et al., 2013). Deregulation of Wnt signaling has been proposed as a key contributor to the pathogenesis of neurodegenerative disorders including Alzheimer’s disease (AD) and Parkinson’s disease (PD). This increasing knowledge of the specific roles of Wnt signaling cascades during different stages of life has suggested innovative therapeutic strategies for the treatment of neurodegenerative diseases. The reviews under the theme ‘Wnt Signaling Cascades in Neurodevelopment, Neurodegeneration and Regeneration’ published in this issue of JMCB provide an up-to-date overview of the importance of Wnt signaling in midbrain dopaminergic (mDA) development, synaptic maintenance in the hippocampus, neuroinflammatory responses, development of neurodegenerative diseases, and highlight new therapeutic approaches.

The majority of dopamine-synthesizing neurones are located in the ventral midbrain. This cell population is crucial for the control and modulation of motor function, cognition, affect, motivation, and reward behaviours. Degeneration of these neurones leads to the typical extrapyramidal motor dysfunctions seen in individuals with PD. The aetiology of PD is poorly understood but work performed over the last two decades has identified a growing number of genetic defects that underlie this condition. Dr Berwick and Harvey reviewed an increasing body of evidence connecting genes implicated in PD, such as LRRK2 and PARK2, with Wnt signaling. These observations provide clues to the normal function of these proteins in healthy neurones and suggest that deregulated Wnt signaling might be a frequent pathomechanism underlying PD. The involvement of LRRK2 in Wnt signaling is of particular interest, since patients harbouring LRRK2 mutations develop PD symptoms that are indistinguishable from idiopathic PD.

Dr Marchetti’s group summarized recent evidence suggesting that PD risk factors associated with increased inflammation (including aging and neurotoxin exposure) antagonize Wnt/β-catenin signaling in dopaminergic neurones and neuronal stem cells in the subventricular zone, which is important for adult neurogenesis. Wnt signaling was further suggested to participate in neuroimmune responses via crosstalk between astrocytes, microglia, neurones, and stem/neuroprogenitor cells. Supporting evidence showed an inter-dependence of inflammation and Wnt/β-catenin signaling in MPTP-induced loss and subsequent repair of dopaminergic neurones. Pharmacological intervention targeting inflammatory responses prevented β-catenin downregulation and restored neurogenesis (L’Episcopo et al., 2012). This suggests an interaction of Wnt signaling with inflammatory pathways activated following neuronal insults with implications for the pathogenesis and treatment of PD.

The review by Dr Joksimovic and Awatramani highlights the importance of β-catenin, a central component of the canonical Wnt/β-catenin signaling cascade, for the specification and differentiation of mesodiencephalic dopaminergic neurones. Wnt/β-catenin signaling was shown to be critical for the neurogenic potential of these neurones that originate from the subventricular zone, which is important for adult neurogenesis. Wnt signaling was further suggested to participate in neuroimmune responses via crosstalk between astrocytes, microglia, neurones, and stem/neuroprogenitor cells. Supporting evidence showed an interdependence of inflammation and Wnt/β-catenin signaling in MPTP-induced loss and subsequent repair of dopaminergic neurones. Pharmacological intervention targeting inflammatory responses prevented β-catenin downregulation and restored neurogenesis (L’Episcopo et al., 2012). This suggests an interaction of Wnt signaling with inflammatory pathways activated following neuronal insults with implications for the pathogenesis and treatment of PD.

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Wnt1 is one of 19 Wnt ligands found in mammals. This canonical Wnt ligand was found to be an important signal for the Wnt/β-catenin cascade during the development of mDA neurones and crucial for the maintenance and protection of neurones in the adult brain. Wnt1-expressing progenitors in the ventral midbrain give rise to three dopaminergic neuronal cell populations in the substantia nigra, ventral tegmental area, and retrorubral field. Wnt1 regulates several steps in mDA development including patterning, specification, proliferation, neurogenesis, differentiation, and survival and was shown to be necessary and sufficient for the generation of mDA neurones. Evidence suggests that Wnt1 signaling is at least in part mediated by the Frizzled-3 receptor, the LRP6 co-receptor, and several transcription factors. Overall, studies reviewed by Dr Wurst and Prakash indicate the crucial importance of the balance between the Wnt/β-catenin–Lmx1a–Lmx1b–Otx2 network and the Shh–Foxa2 network for the development of mDA neurones.

This complex developmental process is further regulated by the β-catenin-independent non-canonical Wnt/PCP pathway. The Wnt/PCP pathway is activated by the non-canonical ligand Wnt5a and functions very differently, often in an antagonistic manner to Wnt1-induced pathways. Nonetheless, double Wnt1/Wnt5a knockout mice revealed that Wnt1 and Wnt5a also cooperate in order to regulate mDA neurone development. This cooperation can be explained by some of the shared signaling components between the Wnt/β-catenin and Wnt/PCP pathways (such as Frizzled receptors and DVL proteins) but also by interaction with common targets involved in the regulation of the cytoskeleton, cell cycle, or neurogenesis. The importance of Wnt inhibitors such as Dkk1 in promoting mDA neurone development should also be noted. Somewhat surprisingly, deletion of Dkk1 was shown to result in a phenotype that resembles loss of Wnt signaling function, causing a severe loss of mDA neurones and loss of all brain structures anterior to the midbrain (Ribeiro et al., 2011). Therefore it can be concluded that a very precise level of Wnt signaling and balance between Wnt/β-catenin and Wnt/PCP signaling at different time points is required for optimal mDA differentiation. These signaling pathways have thus become very attractive targets for regenerative medicine, to control stem cell behaviour and create stem cell-derived mDA neurones. All these aspects were thoroughly discussed in Dr Arenas’ review.

Foetal tissue transplantation in the striatum of PD patients showed that mDA neurones were able to integrate and function albeit with variable clinical outcomes (Lindvall and Björklund, 2011). Currently neural stem cells derived from human ventral midbrain or pluripotent stem cells are considered better sources for cell replacement therapy, since they are expandable and allow for standardization. Dr Parish and Thompson summarized the advances driven by the potential of Wnt signals to expand foetally-derived tissue in vitro, to promote the differentiation of pluripotent stem cells, and subsequently to increase graft integration, function, and survival. In addition, fibroblasts were recently reprogrammed into induced DA neurones and transplanted into rodents, resulting in behavioural recovery in an animal model of PD. For the direct neuronal reprogramming protocols, small molecules capable of modulating Wnt signaling are of benefit. However, currently available stem cell-derived mDA neurone preparations still contain various neurone subtypes. The generation of substantia nigra pars compacta subtype neurones that are diminished in PD might be improved further by the development of small molecules capable of modulating individual branches of Wnt signaling selectively to control subtype specification. As concluded by Dr Arenas, generation of selective small molecule Wnt modulators could also represent a novel therapeutic strategy for the systemic treatment of PD and other neurodegenerative diseases such as AD.

AD is a condition that affects 20% of the population over the age of 80, leading to progressive cognitive decline and functional impairment. This has clear implications for an aging population, with current estimates suggesting that worldwide >115 million people will suffer from dementia by 2050. The pathological hallmarks of AD are neuritic plaques and neurofibrillary tangles, composed of amyloid-β peptide (Aβ) and hyperphosphorylated tau, respectively, leading to synaptic dysfunction and ultimately neurodegeneration. Dr Inestrosa and Varela–Nallar reviewed the central role of Wnt signaling in the function of neuronal circuits in higher brain areas affected in AD. Studies suggested that β-catenin was protective in AD, whereas DKK1 was found to be elevated in AD patients and animal models of AD. Blockade of canonical Wnt signaling with DKK1 was shown to cause synapse disassembly in mature hippocampal neurones. Consistently, Aβ oligomers induce the expression of Dkk1, whereas Dkk1-neutralizing antibodies protect synapses against Aβ toxicity, suggesting that Dkk1 is required for Aβ-mediated synapse loss (Purro et al., 2012). Inhibition of DKK1 with small molecules is therefore a promising strategy for the treatment of AD, as discussed in the review by Dr Salinas’ group.

In conclusion, recent studies have demonstrated that the fine regulation of Wnt signaling during development and in adult life is of key importance in the prevention of developmental defects and neurodegeneration. The crosstalk between Wnt signaling and additional pathways such as inflammatory signaling cascades has also important implications for healthy brain function and neurological diseases. We are now in a position where the modulation of Wnt signaling has become a promising strategy for developing future disease-modifying therapies in our search for new treatments for neurodegenerative diseases.

References