LRRK2 – a target for development of novel therapeutic strategies for the treatment of Parkinson's disease

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Parkinson's disease is the second most common neurodegenerative disorder affecting 40,000 Australians. Patients of Parkinson's disease develop symptoms that impair their control of bodily movement including bradykinesia, rigidity and resting tremor. Post-mortem examination of the brains of Parkinson's disease patients shows that pathology of the disease is typified by premature death of nerve cells (referred to as neurons) in a region of the brain called substantia nigra pars compacta. Nerve cells in this region of the brain secrete a biochemical called dopamine which functions as a chemical mediator for communication with nerve cells. Premature death of nerve cells in substantia nigra pars compacta results in dopamine deficiency which in turn causes impairment of communication among nerve cells that control bodily movement. The symptoms of Parkinson disease can be alleviated by treatment with a drug called levodopa, which can travel from blood vessels to brain cells. In brain cells, levodopa is modified by specific enzymes to dopamine.

Intuitively, drugs capable of preventing or slowing down premature death of nerve cells in substantia nigra pars compacta (referred to as nigrostriatal neurons) are potentially effective for the treatment of patients of Parkinson's disease. Understanding how nigrostriatal neurons undergo premature cell death is the best avenue to cure or slow down the progression of Parkinson's disease by developing effective drugs and other therapeutic strategies.

There are two types of Parkinson's disease patients: sporadic (a term to indicate the lack of external identifiable cause) and familial (or hereditary). The exact causes of sporadic Parkinson's disease are not known. Environmental factors such as exposure to pesticides are implicated to be contributing factors. Familial Parkinson's disease patients, however, carry mutations to specific genes that encode proteins that control survival of neurons. Some of these proteins are classified as neuroprotective as they are essential for maintaining survival of neurons. Their mutations often abolish their neuroprotective ability, leading to premature death of the nigrostriatal neurons. Some of these proteins, however, are potentially toxic to neurons. Their mutations abnormally stimulate the cytotoxic activity of these proteins, allowing them to induce premature death of the nigrostriatal neurons. The LRRK2 protein is a potentially cytotoxic cellular proteins expressed in nerve cells. Mutations of the genes encoding LRRK2 contribute to premature death of nigrostriatal neurons, accounting for 1-2 % of all Parkinson' disease cases (Cookson, 2010; Paisan-Ruiz, et al., 2004; Zimprich, et al., 2004). Furthermore, genetic analysis reveals that increased protein level of LRRK2 is risk factor of development of sporadic Parkinson's disease (Cho, et al., 2013; Simon-Sanchez, et al., 2009).

LRRK2 is an unusual enzyme – it exhibits two different types of enzymatic activities(Lee, et al., 2012; Mata, et al., 2006). The first type of activity (referred to as GTPase activity) relates to its ability to convert a biochemical called GTP to form another biochemical called GDP. The second type of activity (referred to as kinase activity) relates to its ability to transfer a chemical group called phosphate from the cell's energy source ATP to other proteins in cells.

Biochemical analysis reveals that among the prevalent Parkinson's disease-associated *LRRK2* mutations, some cause an abnormal increase in the kinase activity of LRRK2 and some abolish or significantly reduce the GTPase activity of LRRK2 (Sloan, et al., 2012; Taymans, 2012). These results suggest that modulating the kinase activity or GTPase activity of LRRK2 is therapeutically beneficial for the treatment of Parkinson's disease (Lee, et al.,

2010; Rudenko, et al., 2012). Indeed, results from experiments with animal models and nerve cells confirm that abnormal activation of LRRK2 kinase activity can cause nerve cell death and brain damage similar to those found in Parkinson's disease patients. Thus, chemical compounds inhibiting the LRRK2 kinase activity are potential drugs for the treatment of Parkinson's disease patients.

Studies by many researchers demonstrate that mutations that modulate LRRK2 GTPase activity can cause LRRK2 to acquire the ability to cause nerve cell death and brain damage in mouse models(Tong, et al., 2009). In light of this, compounds that interfere with the neurotoxic function of LRRK2 GTPase activity are expected to protect premature nerve cell death (Rudenko, et al., 2012; Taymans, 2012). However, little is known about the regulation and function of LRRK2 GTPase activity. Thus, further investigation is needed to provide us with the conceptual framework for the development of therapeutically effective compounds that target the LRRK2 GTPase activity.

In summary, the Parkinson's disease-causative enzyme LRRK2 is a potential target for effective therapeutic strategies for Parkinson's disease. Further investigation to elucidate the structure, regulation and function of LRRK2 will facilitate development of these strategies.

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