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RESEARCH HIGHLIGHT

Linking vitamin B12 and a trembling disorder

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Hyperactivity of LRRK2, a multifunctional serine/threonine protein kinase, is central to Parkinson's disease pathogenesis. Vitamin B12 turns out to be a potent inhibitor of its undesirable activity.

An estimated 7–10 million persons around the world suffer from Parkinson's disease (PD), a progressive debilitating disorder of the nervous system primarily affecting movement and often recognized by trembling of one or more limbs at rest. While for most patients with PD there is no family history of the disease and there is presently no known cause, ~15% have a family history of PD and are therefore considered to have a genetic basis. Common to both sporadic and genetic forms is the unexplained premature death of dopaminergic neurons in a region of the brain known as the *substantia nigra* as well as the accumulation of protein called α-synuclein. Several classes of drugs are in use that offer variable amelioration of the symptoms of PD. The best known drug is L-dopa, which partially restores the deficit of dopamine, improving overall mobility, but does not alter the inexorable course of the disease.

Important progress in the understanding of the pathogenesis and the biochemical underpinnings of PD has come from the identification of mutations in several genes in the inherited forms of the disease. Research in the function of the genetic causes has begun to elucidate new targets for drug treatment. One of the most intriguing genes is *LRRK2* that encodes a large multi-functional enzyme, a leucine-rich repeat kinase. *LRRK2* appears to play a pivotal role in the pathogenesis of both inherited and sporadic forms of the disease and has provided a targetable protein for the design of novel pharmacological agents to treat the disease.[1,2] The pathological LRRK2 mutations appear to increase its kinase activity, which in turn is associated with α-synuclein propagation. Several small-molecule LRRK2 inhibitors have been developed and have demonstrated efficacy in preclinical models. However, more widespread use of these drugs is precluded because LRRK2 can interact with several key signaling pathways within the cell so that use of these drugs suffers from a profile of serious pulmonary and other side effects.

Through a promising breakthrough reported in a recent paper in *Cell Research* by Schaffner et al.,[3] the roadblock resulting from the unacceptably high risk:benefit ratio of existing LRRK2 inhibitors may now be circumvented. This group has used a high-throughput screen of a small library of 2080 FDA-approved compounds to identify a naturally occurring and potent compound that directly binds LRRK2, altering the conformation of the protein and interfering with ATP binding, thus allosterically inhibiting its kinase activity. It turns out that the compound is vitamin B12 and more specifically, 5′ deoxyadenosyl-cobalamin (AdoCbl), the active form of the vitamin in one of the two only known enzymatic reactions in eukaryotic cells, catalyzed by mitochondrial methylmalonyl CoA mutase, the enzyme that converts methylmalonyl CoA to succinyl CoA. In vitamin B12 deficiency, blood levels of methylmalonate rise, as do homocysteine levels, homocysteine being a substrate for the other vitamin B12 reaction, methionine synthase.[4]

How and why AdoCbl has this regulatory effect on LRRK2 kinase is not known, nor whether its action is physiologic or pharmacologic. However, it is intriguing to note that B12 levels have been found to be lower in PD patients than controls[5] and that compared to patients with higher plasma B12, those with lower B12 develop impairments of gait and balance more rapidly.[6] It stands to reason that if AdoCbl can interdict LRRK2 activity, then normal intracellular levels of the compound might afford some natural protection against the activity of LRRK2 kinase, and higher levels of this vitamin cofactor would be associated with slower disease progression. In their report, Schaffner et al. demonstrated that there are contact sites in AdoCbl that interface with the kinase domain of the enzyme, disrupting the dimerization of LRRK2 required for its activity. They further showed that AdoCbl not only inhibited LRRK2 activity in cultured cells and brain tissue but also prevented neurotoxicity in primary rodent cultures as well as in *C. elegans* and *D. melanogaster* with transgenically expressed LRRK2 disease-causing variants. Additionally, AdoCbl alleviated defective dopamine release in an LRRK2 variant mouse model.

It remains to be seen whether forms of vitamin B12 or other biosimilar small molecules will slow or halt PD progression. There would be some potential practical hurdles to overcome using the photolabile forms of Vitamin B12 like AdoCbl and methyl cobalamin (MeCbl), which may not remain in their native state when administered orally. Vitamin B12 is usually administered in the forms of cyanocobalamin or hydroxocobalamin and these forms are converted to the AdoCbl and MeCbl forms intracellularly. It is also not known whether physiological intracellular concentrations of cobalamin would suffice or whether it would be necessary to achieve higher pharmacological concentrations for disease control in PD. Brain penetrability is another factor for the efficacy of neuroactive drugs and the blood–brain barrier is a significant impediment to drug treatment. In this regard, cobalamin and its various congeners do have a distinct advantage. The vitamin B12 binding protein, transcobalamin (TC), efficiently delivers its payload through specific receptors ubiquitously located on cell surfaces, ensuring a physiological delivery system that enables traversal of the blood-brain barrier. Although the naturally occurring ligand for this transporter is methylcobalamin, other forms of vitamin B12 also bind TC.

So far the finding that AdoCbl is a potent inhibitor of LRRK2 kinase activity with low risk for off-target effects has opened new doors for the development of novel therapies for amelioration of PD, one of several progressive debilitating neurodegenerative diseases. The question is whether this model may serve as a

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paradigm for others. There are literally hundreds of kinases that regulate cell signaling pathways and targeting several of these have proved useful in the treatment of various cancers.[7] Conceivably, the discovery of other naturally occurring specific kinase inhibitors or their analogs may provide opportunities to treat other devastating chronic neurodegenerative diseases including Alzheimer's and Huntington's diseases, amyotrophic lateral sclerosis, and multiple sclerosis.[8]

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ADDITIONAL INFORMATION

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