The potential of LINGO-1 as a therapeutic target for essential tremor

Essential tremor (ET) is probably the most common movement disorder. Because the etiology of ET is unknown, treatment of ET is symptomatic and is geared towards reducing the patient's embarrassment and disability. The first line treatment is oral pharmacotherapy but, in some cases, the disease has a bad therapeutic response. Besides pharmacological treatment, other therapies for ET patients with the most severe symptoms involve surgical approaches, mainly deep-brain stimulation or thalamotomy. In addition, considerable efforts are being made to search for new treatment options for ET, and therapies addressing genes related to ET, and/or their protein products are plausible candidates in ET therapy.

One promising candidate gene related to ET risk is LINGO1, which has been unambiguously related to ET risk in several independent studies and in diverse human populations. The protein encoded by the LINGO1 gene, designated as LINGO-1 (leucine-rich repeat and Ig domain containing 1) is a negative regulator of neuronal survival, oligodendrocyte differentiation and axonal outgrowth and regeneration. LINGO-1 is over-expressed in the cerebellar cortex of ET patients, and it seems to be involved in the degeneration of Purkinje cells.

The goal of anti-LINGO-1 therapy in neurodegenerative diseases is to ease the brakes of neuronal growth and recovery. Evidence obtained in vitro and in animal models of different neurodegenerative disorders suggests that LINGO-1 antagonism may be useful in multiple sclerosis, Parkinson's disease, essential tremor or spinal cord injury.

The strong linkage between LINGO1 gene variations and the risk of developing ET has positive and negative implications. Among all neurodegenerative diseases studied, only ET has a clear genetic association with ET, which reinforces the potential of anti-LINGO-1 therapy particularly in ET patients. By turn, because of the genetic linkage between LINGO1 and ET, putative functional variations in the LINGO1 gene may influence the outcome in ET patients participating in clinical trials with anti-LINGO-1 therapy.

Anti-LINGO-1 therapies are already under clinical trials for multiple sclerosis patients, but no clinical trials for Parkinson's disease or ET have commenced so far. In order to maximize the potential of trials of anti-LINGO-1 therapy, and in order to avoid false-negatives regarding the clinical utility anti-LINGO-1 therapy in ET patients, the patients involved in the clinical trials should be stratified according to LINGO1 genotypes, phenotypes and clinical presentation. Before going any further, it is important to start thinking about how to design such trials and, when the right moment arrives, how to assess potential confounders that may influence the outcome of such potentially promising therapy.

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