The cerebellar pathophysiology of essential tremor

Ming-Kai Pan

Essential tremor (ET) is one of the most common movement disorders in human, and manifests as rhythmic oscillatory movements during action. In order to explore the pathophysiology, we started with the postmortem cerebellar pathology in ET patients. It showed that the synaptic pruning deficits of cerebellar climbing fibers (CF) are correlated with tremor severity. More importantly, the degree of such CF overgrowth is correlated with the loss of GluRδ2 protein, a synaptic stabilizing protein solely expressed in the cerebellar Purkinje cell (PC). The molecular target led us to identify a new mouse model with GluRδ2 loss. These mice recapitulated the CF pathology and developed the cardinal features of ET-like tremor. Using viral manipulation, in-vivo electrophysiology, optogenetic and pharmacological approaches for the tremor circuitry, we confirmed that GluRδ2 loss can lead to the overgrowth of CF-to-PC synapses, whose activities cause excessive cerebellar oscillations and hence tremor. Generating excessive cerebellar oscillations optogenetically is sufficiently recapitulates tremor symptoms in normal mice. To further validate the pathophysiology back to ET patients, we developed a new technique named cerebellar electroencephalography (cEEG), which confirmed that excessive cerebellar oscillations also exist in ET patients and can be a new physiological signature of ET. In summary, these results identify a pathophysiology of ET with matched mouse and human evidence spanning molecular (GluRδ2 loss), structural (CF synaptic pruning deficits), physiological (excessive cerebellar oscillations) and behavioral (action tremor) levels.