Novel Enzyme in CoQ10 Biosynthesis Pathway as a Novel Target to Treat Neurological Diseases

Category

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Technology

Metabolome studies of radioactively-labeled O2 in the Pacold lab have led to the discovery that 4-hydroxyphenlypyruvate dioxygenase (HPDL) catalyzes a critical step in the synthesis of the headgroup of Coenzyme Q10 (CoQ10). The product of HPDL is 4-hydroxymandelic acid (4-HMA) which is then converted into hydroxybenzoic acid (4-HB). 4-HMA is soluble and readily taken up by cells and incorporated into CoQ10. The Pacold lab study supports the idea that supplementation with 4-HMA, 4-HB or CoQ10 itself should be used to treat children with Cerebral palsy (CP) or neurodevelopmental disease induced by HPDL mutations.

Background

CP is a progressive and disabling neurodevelopmental disease of childhood, with an incidence as high as 4 in 1000 live births. Although CP was initially thought to be due to hypoxia at birth, it is now thought to be mostly due to pre-natal insults, and up to 50% of cases have no known cause. Recently, it has been found that inherited disorders can present with CP, which is consistent with consanguinity as a risk factor for CP. Three recent published papers identified mutations in HPDL that segregate with a spastic neurodevelopmental disorder with similarities to cerebral palsy. These mutations have not been functionally characterized, but are thought to inactivate HPDL. An HPDL knockout mouse also recapitulates the phenotype of the disease.

Application

Potential treatment for neurodevelopmental disorders

Advantages

- HPDL represents a novel target for treating CP or neurodevelopmental diseases
- HPDL supplementation represents a promising way of treating children with certain neurological disorders, mainly CP

IP Status

Provisional patent application filed

References

1. Michael Pacold, MD, PhD, et al. , https://www.nature.com/articles/s41586-021-03865-w