Novel antibody for ALS, selective to the toxic form of SOD-1

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Technology

Prof. Engel design and developed anti-Superoxide Dismutase 1 (SOD1) peptide and antibody that prevent SOD1 aggregation, as potential therapeutic agents for Amyotrophic Lateral Sclerosis (ALS). Prof. Engel's lab characterized the backbone dynamics landscape of misfolded SOD1 to pinpoint surface areas predisposed to aberrant protein-protein interactions (PPIs). SOD1 is an ALS pathogenic protein, whose misfolding results in the formation of amyloid aggregates. The mechanism underlying SOD1 pathogenesis in ALS remis obscure, but one possible mechanism involves gain of interaction in which the misfolded soluble SOD1 forms abnormal PPIs with various cellular proteins, including with other SOD1 molecules. Prof. Engel's analysis enabled them to formulate a working hypothesis for the mechanism of the gain-of-function of misfolded SOD1, according to which an abnormal PPI potential results from the increased mobility of the SOD1 surface backbone. Guided by the backbone dynamics landscape, in the lab identified a SOD1-derived peptide that can bind SOD1 proteins and divert the typical amyloid aggregation of ALS-related SOD1mutants toward a potentially less toxic amorphous aggregation pathway. In addition, they developed monoclonal antibody, SE21, targeting the β6/β7-loop region of SOD1. First, it was shown that the expression of scFv-SE21 efficiently suppressed formation of aggregates SOD *in vitro*. Later, vector encoding intra- scFv-SE21 was injected to intrathecally to newborn (P0) hSOD1G37R TG mice (similar to human disease, in late disease onset). Imaging and biochemical methodologies revealed the widespread infection of brain and spinal cord (SC) tissues, including motor neurons. Using body weightand the first appearance of motor abnormalities as a parameter to define disease onset, they succeed to demonstrated that animals treated with intra-scFv-SE21 had a dramatically attenuated disease onset (~90 days). The onset delay was directly translated into a prolonged survival without a significant effect on disease progression. These results strongly support the idea that the β6/β7 loop is an important pathogenic epitope and its blocking prevents SOD1 neurotoxicity *in vivo*, thus potentially constituting a powerful strategy for ALS treatment/prevention.

Application

Potential therapeutic agents for treatment and prevention of ALS.

Advantages

- Novel peptide and antibody
- Dramatically attenuated disease onset
- Specific to the toxic form of SOD-1 and not to the normal one that have essential role in healthy tissue

Patent

WO2017/115367A1; WO2020/110122