Antibody Binds to Movement

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Memory B-cell antibody targets misfolded SOD1. Treatment with α-miSOD1 ameliorates ALS motor symptoms.

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease that affects motor neurons by biological mechanisms such as misfolded protein aggregation, which causes neuronal death. Lower and upper motor neurons allow the signaling of voluntary movement from the nervous system to the muscles (Taylor et al. 2016). There is not a clear cause for ALS as 90% of all patients are considered sporadic (SALS), which means there is no inherited gene mutation. Nevertheless, research on familial ALS (FALS) has allowed the identification of over 50 genes related to ALS: C9ORF72, FUS (fused in sarcoma), TDP-42 (TAR-DNA binding protein) and SOD1 (superoxide dismutase 1), among others (Mejzini et al. 2019). SOD1 is an enzyme that has a key role in the detoxification of superoxide anion radicals in the cell and when this gene is mutated, misfolding creates toxic inclusions and aggregation (Mejzini et al. 2019). Writing in *Science Translational Medicine*, Maier et al. (2018), explore the possibility of an immunological response triggered by misfolded SOD1 that generates neo-epitopes and B cell memory alongside with the possible use of it for immunotherapy. Memory B cells and antibodies are produced by plasma as an immunological response from the body (they are the soldiers of the body). These memory B cells identify the pathogen bound to and through interacting with T-helper cells (Akkaya et al. 2019). The production of antibodies is started by cell differentiation and proliferation of antibody-specific B cells (Akkaya et al. 2019). This mechanism is seen in human bodies to create immunity and faster immunological responses and has been used in vaccination as a preventive measure. Nevertheless, memory B cells have not been previously investigated in their efficacy to target and treat neurodegenerative diseases caused by misfolded protein aggregation. Maier et al. (2018) explores an advancement in understanding further mechanisms of ALS and possible treatments. The lack of a cure or an effective treatment of ALS drives the necessity of innovation in this field. One of the main obstacles for drug efficacy in neurodegenerative diseases is the crossing of the blood brain barrier (BBB). The BBB is a protective lining of endothelial cells that maintains the internal environment under regulated conditions. This barrier poses an obstacle for any foreign substances to enter the central nervous system (CNS) as it is a very selective membrane. In Maier et al. (2018), they will propose a treatment that will potentially improve motor function in ALS patients by crossing the BBB (Maier et al. 2018; Villabona-Rueda et al., 2019).

Maier et al. (2018) hypothesizes that the use of a human B memory cell can present an antibody with a high binding affinity to misfolded SOD1 without affecting the natural unmutated dimers. This recombinant antibody will improve the motor performance of ALS patients. In order to test this, the researchers performed an ELISA (direct enzyme-linked immunosorbent assay) to test the affinity of the antibody with misfolded SOD1 and native dimers. This ELISA assay is known as a *primary detection antibody* which is an immunoassay that tests the binding of a specific antibody to a protein of interest (Alhajj and Farhana 2020). This assay showed an exclusive affinity to misfolded SOD1 in denatured and oxidized conditions which indicates possible use for treatment of these toxic inclusions. Further, to confirm the possible detection of SOD1 in human post-mortem spinal cord sections, samples of SALS and FALS patients were injected with α-miSOD1. Microscopic images revealed that α-miSOD1 detected misfolded SOD1 in a majority of SALS patients and FALS patients with and without SOD1 mutation but with a hexanucleotide expansion mutation on C9ORF72.Moreover, there was no detection of misfolded SOD1 in non-neurological controls (NCC). Further, these results were congruent with transgenic SOD1 transgenic mice–α-miSOD1 detected aggregations from a pre-symptomatic stage (30-days old) to an end stage. To evaluate the effect of the chimeric derivative of α-miSOD1 on mice, researchers administered intracerebroventricularly a stable dosage of ^{ch}α-miSOD1 over regulated intervals of time using osmotic pumps after 60-days of age until end stage (Keraliya et al. 2012). A chimeric derivative is an antibody or glycoprotein molecule with various domains from different species, in this case, of rodents. By combining different domains and replacing as much of the non-binding antigen as possible with the species affinity, the chronic anti-human response to the antibody will be reduced (Chimeric Antibody 2020). This reduction of chronic response improves the reliability of the effects shown in the mice models by exposure to α-miSOD1. Some mice were presenting mitochondrial dysfunction and denervation as soon as 7-days old. Upon treatment with chα-miSOD1, mice showed an improved upright gait and wider angles between the iliac crest and the hind limbs which means that their motor function was better overall. Additionally, the survival rate of ^{ch}α-miSOD1-treated mice was significantly higher compared to the vehicle-treated littermate controls. This could partially be explained by the 51% decrease of aggregate load in the ventral horn of the lumbar spinal cord sections collected by the ^{ch}α-miSOD1-treated mice compared to the vehicle controls and a decrease in microglial activation measured in a Iba1 assessment. Next, they treated the mice from a peripheral administration by weekly injecting intraperitoneally ^{ch}α-miSOD1 into transgenic mice that showed slow progressing ALS motor symptoms. A comparing group was injected with an epitope isotype-antibody-matched within the amino acids 110 to 120 of SOD1. Decrement in motor symptoms and coordination was decreased in those treated with ^{ch}α-miSOD1 as well as motor impairment and survival rate. Additionally, a two-fold increase in motor neuron quantification indicated an overall improvement in the ventral horn health in ^{ch}α-miSOD1-treated mice compared to vehicle controls and isotype groups. This showed the efficacy of ^{ch}α-miSOD1 to cross the blood brain barrier from being injected intraperitoneally. Finally, Maier et al (2018) experimented on a fast-progressive ALS mice combined B6SJL background, which is a recombinant ALS-type of transgenic mice, to investigate the effect of intraperitoneal administration on neuroinflammation. They found that after three weeks of treatment with ^{ch}α-miSOD1, there was a 37 and 43% reduction in microgliosis and astrogliosis, respectively. Furthermore, there was a reduction of 25% of SOD1 aggregates and 66% of misfolded SOD1. This established an association between neuroinflammation, aggregates, and disease progression. The final issue arising when this information is integrated is whether α-miSOD1 is an effective treatment for ALS patients. The model mice that were used were highly over-expressive of SOD1 which might deviate the results of the treatment if it was applied on humans. Additionally, the human spinal cord samples were post-mortem which affects the evaluation of α-miSOD1 in on-set disease progression in humans. Nevertheless, this research sets off groundbreaking observations about how antibodies react to misfolded proteins, especially SOD1. This can lead to further studies on how immunotherapy can impact neurodegenerative diseases caused by aggregated and misfolded protein.

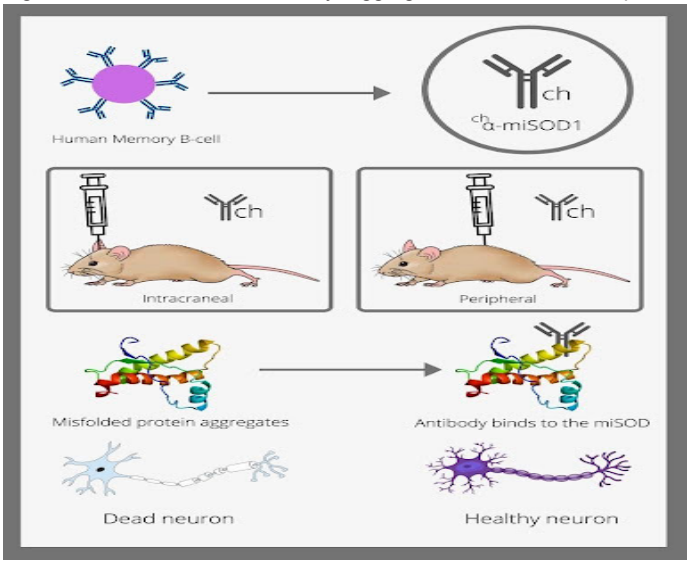

Figure 1. Memory B cells develop immune responses in humans. The use of the human memory B cells library indicated a potential antibody for the targeting of misfolded superoxide dismutase 1 (SOD1). SOD1 is

a common enzyme that helps with oxidative radicals regulation in the cells of the nervous system, but when misfolded, there is neuronal death due to mitochondrial dysfunction and superoxide accumulation. The development of a chimeric antibody (^{ch}α-miSOD1) was administered intracerebroventricularly and intraperitoneally to SOD1-Tg mice. This administration in low and high doses indicated correct targeting for misfolded SOD1 accumulation and improvement in motor function and survival rate.