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The Effects of Mutant Zn,Cu Superoxide Dismutase on Amyotrophic Lateral Sclerosis Patients

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Amyotrophic lateral sclerosis (ALS) is a degenerative motor neuron disease, which leads to muscle atrophy and death, with no known cure. ALS is the most common of the motor neuron diseases, affecting around 5 of every 100,000 people in the world today (A.DA.M. Medical Encyclopedia, 2012). It has been observed that a mutation in the enzyme Zn,Cu superoxide dismutase (SOD1) is a major contributor to this disease while having multiple effects. By categorizing what symptoms certain mutations in SOD1 cause, early diagnostic techniques and possible treatments can be created. Studies have shown that mutant SOD1 causes abnormal mitochondrial dynamics, altered metabolic profiles, and changed phenotypes for microglia in neurons. The overall cause of ALS is still unknown, with only 10% of the cases diagnosed being genetic in origin (A.DA.M. Medical Encyclopedia, 2012). Before a cure can be created, more of the pathways of the disease need to be studied.

Introduction

One of the most important systems in animals' bodies is the nervous system. The main working unit of the nervous system is the neuron. By sending electrical signals through these cells, a person can think, move, feel, and much more. With this said, if there is a problem with this working cell, it would be very important to develop a way to fix it. One disease that affects motor neurons is ALS. This degenerative motor neuron disease causes voluntary nerve cells to die, which causes muscle atrophy and, eventually, death. ALS is the most common of the motor neuron diseases, affecting around 5 of every 100,000 people in the world today. One cause of this disease is a mutation in the enzyme SOD1, which destroys superoxide radicals found inside the body. A mutation to this enzyme can have varying effects for a motor neuron. Due to this, many experiments have recently been conducted to learn as much about this disease and the effects of this enzyme as possible.

Recent Progress

One way that a mutation in SOD1 can damage the cell is by causing abnormal mitochondrial dynamics (Magrané 2012). When a neuron is working, it needs a high amount of energy at its active sites, mainly axons. Problems with getting mitochondria to these sites can cause the neuron to decrease in functionality. The mutation affects mitochondria in several different ways. For one, it causes problems with transport of mitochondria in the neuron by decreasing motility. This causes high energy sites of the neuron to be deficient of mitochondria when these sites need them. This affects mitochondrial fusion, which is important to keep mitochondria healthy. It was also shown to decrease the overall energy output of

mitochondria. All of these factors combined lead to an energy deficit in a neuron, especially at high energy sites.

Another way that mutant SOD1 affects ALS patients is by changing the metabolic constituents in the cerebrospinal fluid (CSF) of said patients (Wuolikainen 2012). One particular mutation of SOD1, classified as D90A, affected metabolites the most. D90A SOD1 reduced the amount of several amino acids, including arginine, lysine, and serotonin, in the CSF of those tested. Those diagnosed with ALS without a mutation of SOD1 displayed no distinct differences in metabolic constituents.

The last effect of mutant SOD1 to be discussed is its changing of expressed phenotypes for microglia (Liao 2012), which function in the immune response for neurons. Depending on the stage of ALS, microglia display either a M1 or M2 phenotype. M2 phenotype is displayed during the beginning stages, slower progressing, of ALS with mutant SOD1. This phenotype has about the same microglial function of regular microglia, protecting neurons. M1 phenotype is displayed during later stages, fast progressing, of ALS with mutant SOD1; which causes the microglia to have a toxic effect on the neurons they surround, destroying them. It was also observed that astrocytes play a role in this phenotypic change, increasing M2 phenotype and therefore microglia protective qualities. These results show that mutant SOD1 causes a change, in time, of microglia from M2 phenotype to M1, causing their function to change from protective to toxic.

Discussion

The results from these experiments allow for a deeper understanding of ALS. With this understanding, new diagnostic tools, therapies, and even treatments can be created. For example, by mapping the metabolic constituents in a person's CSF, one can determine what mutation, if any, of SOD1 is present. This can allow medical professionals to determine what is causing a certain case of ALS. Medical scientists can also take advantage of the protective effects of M2 phenotypic microglia to slow the progression of the disease. Incorporating a method of introducing astrocytes to these microglia to express the M2 instead of M1 phenotype is one possible technique that can be used for therapies slowing this disease. Correcting mitochondrial dynamics can also help in fighting the disease progression. By correcting the problem with mitochondrial motility and function, one can ensure that the neuron gets energy to sites that need it and works in the way it is supposed to. All of these studies help shed light on what pathways ALS takes to cause degeneration of motor neurons and what exactly causes these effects. This information is vital in creating a treatment that can cure the disease for good, instead of therapies that only slow the disease. There is still much left to be answered. Mutations in the enzyme SOD1 has been shown to cause a plethora changes to the neuron and other supportive cells. Specific mutations of the enzyme also cause different changes. All pathogenic pathways of these mutations need to be determined before a cure of ALS caused by mutant SOD1 can be created. The base cause of ALS overall is also still a mystery. All avenues of onset of ALS, including those not caused by mutant SOD1, need to be discovered in order to help all patients with this disease. Even once all is known about the disease ALS, a safe medication for the disease can be difficult to create due to the many factors that causes it. All of this seems daunting, but new discoveries are being made constantly that allow another step closer to the final goal, a cure for ALS.

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