Background

The liver is an essential organ involved in the digestive system that is responsible for filtering toxins out of the body and converting them into other chemicals safe for the body to remove. When the liver is severely damaged or diseased, the blood flow is diverted away from the liver to other organs for detoxification, a process that is referred to as portosystemic shunting. This causes increased stress on the other organs and tissues and results in a buildup of toxins inside the body that can have numerous negative effects. In patients suffering from cirrhosis, ammonia is diverted away from the liver to be converted into urea in the skeletal muscle. Eventually, because the skeletal muscle is unable to withstand the constant stress, a notable increase in muscle mass, or sarcopenia, is measured throughout the body. It is thought that the hyperammonemia is linked to the severe loss of muscle mass, or sarcopenia, also noticeable in cirrhotics.

Methodology

Myostatin knockdown and control C2C12 myoblast cells were grown in 10% FBS solution with DMEM until they were 80% confluent and then differentiated into myotubes in 2% horse serum for 24 hours. Protein was extracted from these cells treated with 10mM ammonium acetate for four, six, and 24 hours. The protein concentration of each sample was measured and then divided away from the liver to other organs for detoxification, a process that is referred to as portosystemic shunting. This causes increased stress on the other organs and tissues and results in a buildup of toxins inside the body that can have numerous negative effects. In patients suffering from cirrhosis, ammonia is diverted away from the liver to be converted into urea in the skeletal muscle. Eventually, because the skeletal muscle is unable to withstand the constant stress, a notable increase in muscle mass, or sarcopenia, is measured throughout the body. It is thought that the hyperammonemia is linked to the severe loss of muscle mass, or sarcopenia, also noticeable in cirrhotics.

Myostatin mediates skeletal muscle loss during hyperammonemia of Cirrhosis

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Purpose

Sarcopenia, or loss of skeletal muscle, is one of the most common complications resulting from cirrhosis of the liver and often negatively affects the health, survival, and quality of life of the patients, as well as the chances of liver transplant success. As of yet, there is no feasible treatment plan for patients suffering from sarcopenia and in order to effectively treat sarcopenia, it is necessary to first understand the specific molecular mechanisms responsible for the condition.

Hypothesis

The molecular mechanisms responsible for sarcopenia of cirrhosis are as of yet unknown. We hypothesize that impaired skeletal muscle protein synthesis and increased muscle autophagy as a consequence of hyperammonemia are responsible for sarcopenia in cirrhosis. We also hypothesize hyperammonemia induces myostatin expression, a known inhibitor of muscle growth, and that myostatin activates AMPK, a critical regulator of metabolic processes in cells. AMPK is an upstream inhibitor of mTOR which stimulates global protein synthesis via downstream signaling molecules.

Data

- During hyperammonemia, myostatin knockdown prevented an increase in myostatin expression.
- In myostatin knockdown during hyperammonemia, p-AMPK does not increase in contrast to controls.
- With myostatin knockdown, mTOR phosphorylation does not decrease.
- These data suggest that myostatin inhibits muscle growth through an AMPK-mTOR axis.