**Myostatin-Related Muscle** **Hypertrophy** (MRMH) is a single gene disorder characterized by an increase in muscle mass and strength. Patients with MRMH are able to live a normal life with no other functional or cognitive effects. Mutations in the Myostatin (MSTN) gene leads to failure to control muscle growth by inhibiting myoblast differentiation. Myostatin has two inactive subunits and is only activated when cleaved by the Carboxypeptidase protease [1]. Activated Myostatin then binds to the Activin type ll receptor, which recruits the Alk-3 or Alk-4 proteins [2]. Alk-3 and Alk-4 are co-receptors that activate a cell signaling cascade that activates transcription factors that regulate muscle development. When these transcription factors interact with myoblasts, myostatin genes inhibit their differentiation into mature muscle fibroblasts [1]. *While muscle differentiation is well characterized, the role of myostatin in other tissues such as lung, heart and the vascular system is not well defined*. Alk-4, also plays roles in cell growth, differentiation and death [2]. Because Alk-4 is not recruited when the myostatin gene is mutated, control over the previously mentioned tissues is compromised. Alk-4 malfunction is also a known contributor to the development of lung cancer [3]. Therefore, *the relation between MRMH and lung cancer is unknown.*

**Goal:** Determine if myostatin regulates lung cell differentiation. **Hypothesis:** Loss of the myostatin gene alters the function of Alk-4 leading to altered cell growth and apoptosis in lung cells and eventually lung tumors. **Long term goal**: Determine if myostatin loss puts patients at risk of lung cancer.The model organism I will be using is mus musculus because the MSTN gene and it’s domains are identical. Mice also display similar phenotypes as humans.

**Specific AIMS 1:** Identify conserved amino acids in MSTN that are responsible for the recruitment of Alk-4 in the lung **Approach:** I will align the protein sequences for all MSTN homologs using Clustal Omega to identify conserved regions in species. I will then use CRISPR to mutate particular regions of amino acids in mice and determine if these mutations give rise to tumors in the lungs. **Hypothesis:** Specific Amino Acids are responsible for recruiting Alk-4 in the lungs **Rationale:** If Amino Acids in MSTN that are responsible for recruiting Alk-4 are mutated or dysfunctional, Alk-4 will not be able to regulate lung cell growth and apoptosis, giving rise to tumors in the lungs.

**Specific AIMS 2**. Identify how regulation is changed when mutations in MSTN cause tumors in the lungs **Approach:** Run lung samples from the mice produced in the previous AIMS through RNA-seq and subsequently GO to determine what genes are upregulated and downregulated in mutated mice **Hypothesis:** All genes controlling recruitment of Alk-4 in the lungs as well as other genes regulating cell proliferation and differentiation will be downregulated in the lungs due to the mutated MSTN gene. **Rationale:** If genes involved in recruitment of Alk-4 and regulation of lung cells are downregulated, we can conclude that they are responsible for tumors in the lungs

**Specific AIMS 3:** Determine how Alk-4 interacts with proteins involved in cell regulation in lungs. **Approach**: Use Mass Spectroscopy to determine the biological interactions of Alk-4 protein in wild type and mutant type mice lungs. **Hypothesis:** With the loss of Alk-4, cells will not have a regulating protein to interact with, thus losing regulation interactions. **Rationale:** Understanding how protein interactions change can help us understand how Alk-4 influences cell regulation.

**Conclusion:** The effects of MRMH, beyond increased muscle mass, are virtually unstudied. A better understanding of other body systems that this disease effects can aid in diagnosing and preventative treatment.

**References**

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