1. Abstract

The Institute of Medicine estimates $635 billion dollars are spent annually on people with chronic pain conditions. One debilitating symptom of these conditions is hypersensitivity to touch, where daily activities can be painful. Few therapeutics to ameliorate mechanical hypersensitivity exist because the mammalian ion channels that sense touch are poorly understood. The mechanosensitive channel of large conductance (MscL) is an ion channel in Mycobacterium tuberculosis which allows bacteria to respond to mechanical stimuli by electrochemical response, regulating membrane ion flow. Research shows structural changes in MscL cause the protein to open, allowing ions into the cell. Key amino acids can last for weeks, months, or even years.

Understanding the structure and function of MscL may help us understand how MscL causes the protein to open, allowing ions into the cell. Important amino acids include the hydrophobic residues Ile14 and Val21, which create a constriction at the cytoplasmic surface. Gly62, Gly63, Gly64, Lys33, Ile59, Ile61, Ile63 and Ile39 (TEAL), are thought to play a role in the diameter of the channel pore.

2. Chronic Pain

Billions of dollars are spent annually on people with chronic pain conditions. Some individuals may have hypersensitivity to gentle touch or normal limb movement, which is one of the most troublesome aspects of inflammatory pain. Pain is caused by the signals that are firing in the sensory neurons that can last for weeks, months, or even years. Transient Receptor Potential Ankyrin 1 (TRPA1) is an ion channel protein that is thought to regulate neuron sensory processes such as touch. Mechanosensitive channel of large conductance (MscL) is a homology model for TRPA1 since TRPA1 has not yet been isolated. Understanding the structure-function relationships of the MscL-channel protein may lead to better comprehension of how human mechanosensitive ion channels, like the Transient Receptor Potential Ankyrin 1, work and lead to a cure for hypersensitivity to touch.

3. Structure of MscL Protein

Research has shown that a structural change in MscL causes the protein to open, allowing ions into the cell. Important amino acids include the hydrophobic residues Ile14 and Val21, which create a constriction at the cytoplasmic surface. Gly62, Gly63, Gly64, Lys33, Ile59, Ile61, Ile63 and Ile39 (TEAL), are thought to play a role in the diameter of the channel pore. Residues at the N-terminus of the protein, Lys3, Phe5, Glu7 and Phe8, may play a role in sensing membrane stretch. Residues at the N-terminus of the protein, Lys3, Phe5, Glu7 and Phe8 (YELLOW) may play a role in sensing membrane stretch.

4. TRPA1

TRPA1 inflammatory response

5. Conclusions

MscL is a homology model for TRPA1 since TRPA1 has not yet been isolated. Understanding the structure and function of MscL may help us understand the structure and function of TRPA1.

1) The hydrophobic residues Ile14 and Val21 create a constriction at the cytoplasmic surface at the MscL and could indicate a constriction in TRPA1 also.

2) Residues at the N-terminus of the protein, Lys3, Phe5, Glu7 and Phe8, may play a role in sensing membrane stretch and if there are similar amino acids in TRPA1, stretching may also occur.

3) Amino acids Gly62, Gly63, Gly64, Lys33, Ile59, Ile61, Ile63 and Ile39 are thought to play a role in the diameter of the channel pore of the MscL and if similar amino acids are found in TRPA1, then may also play a role in the pore diameter.

4) Arg98, Lys99, Lys100, Glu102 and Glu104 help form a possible ligand binding site, and could potentially participate in the ion conduction pathway in MscL.

Understanding the structure and function of the homology protein MscL in the bacterial membrane may help us to someday regulate the function of the protein TRPA1 and may lead to therapeutic advancements in the treatment of chronic pain.