

Mucopolidosis Type IV (“MLIV”) was first described in scientific literature in 1974. MLIV is a severe neurological genetic disorder. Currently, there are about 120 diagnosed cases up worldwide. MLIV is a highly rare disease, but when it strikes, its effect is devastating. Most of the patients are unable to walk unassisted, fail to develop speech and most of the expressive language, and usually lose their eyesight completely by the late teens.

MLIV is caused by mutations in the MCOLN1 gene that was mapped to the human chromosome 19. MCOLN1 gene encodes mucolipin-1 (MLI) protein. ML-I protein is a 580 amino acid molecule of about 65kDa in mass (where “kDa” is a unit of microscopic mass). ML-I is a transient receptor potential (TRP) trans-membrane protein, which means this protein is embedded in a cell membrane. ML-I contains six transmembrane domains with a channel pore located between domains five and six. ML-I was found to be a cation channel that is highly permeable to Na^+ , K^+ , and Ca^{2+} , indicating that ML-I serves as a passage-way for these chemicals in and out of the cell, making it essential for the cell’s existence and normal functions.

A total of fourteen ML-I mutations have been described in medical literature to date. Two of these mutations are common among the “Ashkenazi” Jewish (AJ) population – who are Jews that from Eastern Europe. These mutations result in the absence of the ML-I protein in children with such mutation and manifest the most severe representations of the disease among the MLIV patients.

Several high-powered laboratories worldwide (such as Susan Slaugenhaupt’s Laboratory, Craig Montell’s Laboratory, Paul Luzio’s Laboratory and a few other research teams) are interested in the molecular pathophysiology of MLIV disease and in the ML-I protein. ML-I protein’s exact cellular location and the mode of function(s) remain largely unknown. Major AJ MLIV-causing mutations produce no protein, no ML-I channel activity, and the most severe disease phenotypes.

All body cells have a family of mucolipin proteins: ML-I, ML-2, and ML-3. What is their functional similarity is yet to be determined.

When ML-I protein is mutated, most of the patient’s cells store certain granules in the cellular lysosomes filled with lipids, sphingolipids, cholesterol, and other molecules normally destined for degradation or recycling by the cell machinery. The fact that some tissues show apparent storage of such molecules while others do not may imply that there could be some other protein or multiple proteins that perform similar function to that of an ML-I protein, or that there may be some partial compensatory mechanism in the human genome. The fact that the severity of the disease varies even among siblings and the very slow progression of the disease itself possibly

mean that there exists a compensatory mechanism in the body that may counteract or at least alleviate the harmful effects of the mutation.

Furthermore, ML-I may play a crucial role in the vesicular trafficking of the cell. When the protein is mutated, late endosome/lysosome vesicle transport is impaired. ML-I channel activity was found to be regulated by a pH-dependent and Ca^{2+} dependent mechanism. Regulation of the channel activity by the change in the pH is absent in most of the MLIV causing mutations. Calcium (Ca^{2+}) is critical in many intracellular processes. It is often involved into a cascade of the signal transduction events. In MLIV, the Ca^{2+} -dependent pathway is impaired which in turn leads to the impairment of the membrane trafficking. As a result, the late endosomal/lysosomal membrane fusion can’t occur and granule storage within lysosomal compartment is apparent. ML-I is thought to contribute to the Ca^{2+} efflux from the late endosomal/lysosomal compartments.

Fibroblasts from the MLIV patients with various ML-I mutations were studied by a noted scientist, Janice Laplante. The researcher compared their ML-I channel activity with that of the wild type (wt), or non-mutant fibroblast ML-I channel activity. Mutant fibroblasts were transfected with the wt ML-I. When compared to the untransfected mutant cells, the fusion process in the newly transfected cells was apparent. That may lead to the possibility of a rescue of the mutation in certain cells or tissues.

How exactly does the membrane fusion occur is yet to be determined. How does the ML-I channel get activated, and what is the mechanism that contributes to the local increase of Ca^{2+} ? How does the membrane fusion event get triggered? There are still many questions to be addressed by scientists.

Paul Luzio and Robert Piper studied the *Caenorhabditis elegans* CUP-5 protein that is an orthologue homolog to ML-I protein. The researchers found pH-dependent gating of the ML-I Ca^{2+} dependent channel. The gated channel was open at neutral pH and closed at an acidic pH. Low pH is required to maintain high free Ca^{2+} levels in lysosomes. Changes in pH may trigger channel opening as well as the channel assembly. These changes in turn may induce membrane fusion properties that are critical in the vesicular trafficking.

The mouse model of the disease is on its way. The mouse model may give many useful insights on the MLIV disease and the ML-I protein whose mutation causes it. We are all hoping for the major breakthrough in the area of MLIV research that would lead to the alleviation and/or potential cure of the disease.

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