Sticky protein helps reinforce fragile muscle membranes

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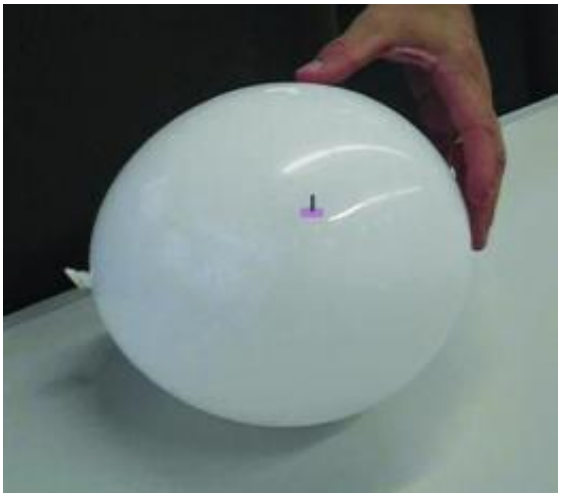

Just as the piece of pink tape prevents a pin from bursting this balloon, the sturdy basal lamina reinforces muscle cell membranes and keeps small tears from bursting open -- but only if the protein "glue" affixing the basal lamina to the membrane is working. Credit: Renzhi Han, University of Iowa

A new study by scientists at the University of Iowa shows why muscle membranes don't rupture when healthy people exercise.

The findings shed light on a mechanism that appears to protect cells from mechanical stress. The study, which appears online July 20-24 in Proceedings of the National Academy of Sciences (*PNAS*) Early Edition, also helps explain why muscle damage is so severe when this mechanism is disrupted, which occurs in certain congenital and limb-girdle muscular

dystrophies.

Specifically, the team identified a protein called alpha dystroglycan as the "glue" that binds muscle membranes to a tough layer of extracellular proteins called the basal lamina.

Just as a piece of sticky tape can prevent a pin from bursting a balloon, the sturdy basal lamina reinforces muscle cell membranes and keeps small tears from bursting open -- but only if the dystroglycan "glue" affixing the basal lamina to the membrane is working.

"This study helps us understand how membrane structure is designed to protect cells, which is a universally important process," said senior study author Kevin Campbell, Ph.D., professor and head of molecular physiology and biophysics at the UI Roy J. and Lucille A. Carver College of Medicine and a Howard Hughes Medical Institute investigator. "The findings may also have clinical implications for muscular dystrophies that are caused by abnormal dystroglycan."

These congenital muscular dystrophies include Fukuyama Congenital Muscular Dystrophy, Walker-Warburg Syndrome and Muscle-Eye-Brain disease and limb-girdle muscular dystrophy 2I. In these so-called dystroglycanopathies, too few sugar groups are added to alpha dystroglycan, leading to a version of the protein that does not attach properly to the basal lamina. Detachment of the basal lamina from the muscle membrane appears to be a common feature of these conditions, and patients develop a very severe muscular dystrophy.

Working with a mouse model of these diseases, the researchers, including Renzhi Han, Ph.D., a UI research scientist and the first author of the study, found that injecting functional dystroglycan into muscle that lacks this component restored muscle membrane integrity and protected the muscles from damage.

"Injecting the protein helped us prove that glycosylated dystroglycan is required to attach the membrane to the extracellular proteins and thus reinforce the membrane integrity," said Campbell, who also holds the Roy J. Carver Chair of Physiology and Biophysics. "However, this tool also suggests that delivering functional dystroglycan to muscles may be a possible therapeutic approach for treating these muscular dystrophies."

Another experiment, which also confirmed the role of glycosylated dystroglycan in binding the membrane and the basal lamina, also may have clinical implications.

The team showed that a virus called LCMV (Lymphocytic Choriomeningitis virus), which binds tightly to alpha dystroglycan, also disrupts the basal lamina muscle membrane interaction and compromises the integrity of the muscle membranes. LCMV is a member of a group of viruses that can cause hemorrhagic diseases. The study suggests that these viruses disrupt the dystroglycan basal lamina interaction, rendering the cell membrane susceptible to rupture.

"Considering how essential cell membranes are for life, these barriers are remarkably fragile. In addition, many tissues, including muscle, GI tract and skin, are constantly under mechanical stress, which can rupture cell membranes," Campbell said. "Our findings support the idea that reinforcement of the membrane basal lamina attachment is a basic cellular mechanism that allows cell survival in tissues subjected to mechanical stress."

Source: University of Iowa (news : web)