Possible help in fight against muscle-wasting disease (w/ Video)

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(PhysOrg.com) -- A compound already used to treat pneumonia could become a new therapy for an inherited muscular wasting disease, according to researchers at the University of Oregon and the University of Rochester School of Medicine and Dentistry in New York.

The five-member team reports that pentamidine, when tested in genetically altered mice, counters genetic splicing defects in RNA that lead to type 1 myotonic dystrophy -- one of nine types of muscular dystrophy -- also known as DM1 and Steinart's disease.

The compound was among 26 tested in the UO lab of chemist J. Andrew Berglund. Pentamidine carries approval of the U.S. Food and Drug Administration for treating a severe type of pneumonia in people with weakened immune systems, as well as leishmaniasis, sleeping sickness

and some yeast infections. However, levels used successfully in the experiments would be toxic in humans, Berglund said.

With modifications, he added, pentamidine could be adapted to reverse RNA splicing defects that drive type 1 myotonic dystrophy. "The fact that a very small library of compounds yielded a molecule capable of reversing the splicing defects associated with DM1 in both cell and mouse DM1 models suggests that a small molecule strategy could lead to a drug for this disease," he said.

The experiments -- done by former UO doctoral student M. Bryan Warf and Catherine M. Matthys, who has since graduated from the UO, and Rochester's postdoctoral researcher Masayuki Nakamori -- identified pentamidine and neomycin B as compounds that worked against abnormal genetic instructions. Pentamidine, however, was found to be the most effective in the mice. Berglund, a member of the UO Institute of Molecular Biology, and Dr. Charles A. Thornton, a neurologist at Rochester, were co-authors of the study.

The research -- supported primarily by grants from the National Institutes of Health and the Muscular Dystrophy Association -- was published in the Nov. 3 issue of the journal *Proceedings of the National Academy of Sciences*. In a separate commentary in PNAS, Thomas A. Cooper of the Baylor College of Medicine in Houston hailed the findings, noting that the compound is the first to show such promise of reversing splicing defects. Cooper also noted that such a therapeutic approach is attractive because of the potential benefits to multiple organs affected by the disease.

DM1 is caused by an expanded section of DNA in a gene on chromosome 19. The expanded DNA results in synthesis of longer-than-normal strands of RNA sequences, or repeats, of the chemicals cytosine,

uracil and guanine. These abnormal pieces get trapped in the nuclei of muscle fibers, and protein molecules called MBNL in each nucleus become stuck to the CUG repeats. This leads to errors in the splicing process in which important proteins are made incorrectly or not at all. In turn, disruptions in muscle fibers cascades into changes in ion channels that impacts the ability of muscles to relax after use.

Researchers found that pentamidine disrupted the complexes formed by the expanded repeats and the MBNL protein that becomes stuck to them, allowing the protein to return to its proper location in the cell. The compound also inhibited interactions of MBNL with the cytosine-uracil-guanine repeats and partially rescued two splicing errors in the mice.

Pentamidine has not been yet tested in people with DM1, Berglund cautioned, but its FDA approval for other uses is important.

"Although pentamidine is not ready for use as a therapy for DM1, this work does demonstrate that a small molecule strategy is a viable approach to this disease," Berglund said. "Almost all human diseases are currently treated with small molecules. Pentamidine is an exciting lead compound because it is relatively easy to chemically modify, and hopefully one of these modified compounds could lead to a safe, long-term treatment for DM1 in the future."

Provided by University of Oregon (news : web)