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Common molecular defect offers treatment hope for group of rare disorders

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Duke Medicine researchers studying tiny, antennae-like structures called cilia have found a potential way to ease some of the physical damage of numerous genetic disorders that result when these essential cellular components are defective.

Different genetic defects cause dysfunction of the cilia, which often act as sensory organs that receive signals from other cells. Individually, disorders involving cilia are rare, but collectively the more than 100 diseases in the category known as ciliopathies affect as many as one in 1,000 people. Ciliopathies are characterized by cognitive impairment, blindness, deafness, kidney and heart disease, infertility, obesity and diabetes.

Recent research has added key insights into the overall role and function of cilia in cells and what occurs when the organelle is defective.

"Cilia are required for regulation of a whole host of signaling pathways for cellular development," said Nicholas Katsanis, PhD, professor of cell biology and director of the Center for Human Disease Modeling at Duke. "They are not the only signaling regulators, but they are critical. It's been important for us to understand how they do this."

In the current study, published April 1, 2014, in the *Journal of Clinical Investigation*, Katsanis and colleagues describe a common mechanism that appears to account for how dysfunctional cilia cause so many different problems in cellular signaling pathways.

Using both cells and animal models, they focused on the ubiquitin-proteasome system, the cell's machinery tasked with regulating the cellular environment by breaking down proteins that are either damaged or in need of removal.

"Imagine regular housekeeping" Katsanis said. "Taking out waste is part and parcel to the process, but not if you end up throwing away your valuables."

The researchers also set out to test whether they could somehow bolster the function of the proteasome to see if this would have a therapeutic effect. When non-defective genes were introduced in zebrafish, the animals showed physical improvements indicative of corrections in multiple signaling pathways, Katsanis said.

More significantly, similar improvements occurred in the animals by administering common compounds, including mevalonic acid and the nutritional supplement sulforaphane, an antioxidant found in broccoli and other cruciferous vegetables. Both are known to improve proteasomal activity.

"While the animals were not as good as normal controls, they were much better – we saw clear physical improvement with each of the compounds," Katsanis said. "This now gives us a hypothesis that explains at least in part why, for whatever reason ciliopathy is caused, it can result in different signaling pathways going awry, and a potential avenue for therapies."

Katsanis said additional research should focus on the proteasome system, and other potential therapeutic targets that could improve the proteasome.

"Understanding cilia dysfunction is important, because its association

with so many disorders pose a significant societal and medical burden. And we look forward to seeing wither the insights we have learned in these studies are applicable to other diseases," Katsanis said, adding that more work will be required to follow up this lead.

"As exciting as these findings are, we need to act cautiously and responsibly before we jump into clinical trials in humans," he said. "Nonetheless, there is now a clear path toward that goal."

Provided by Duke University Medical Center