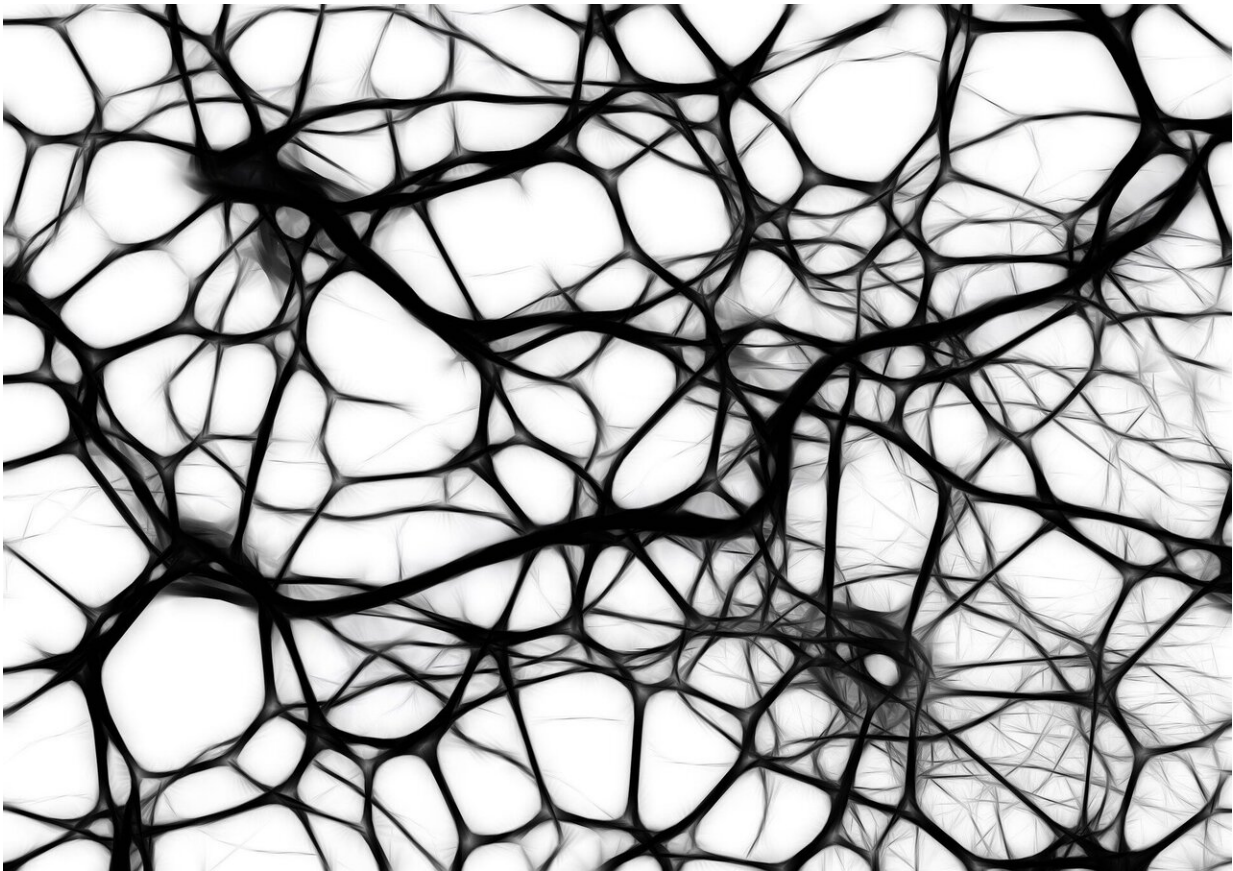


Rare inherited enzyme disorder yields insight into fibrosis

July 17 2019



Credit: CC0 Public Domain

What can a family of rare inherited disorders teach scientists about more common health problems like fibrosis? Plenty, based on research led by

St. Jude Children's Research Hospital scientists that appears today in the journal *Science Advances*.

The investigators have discovered an association between a deficiency in the enzyme neuraminidase 1 (NEU1) and the build-up of connective tissue ([fibrosis](#)) in organs such as the muscle, kidney, liver, heart and lungs. Fibrosis includes life-threatening conditions such as idiopathic pulmonary fibrosis.

Mutations in the NEU1 gene cause the lysosomal storage disease sialidosis, which belongs to a large group of related pediatric diseases. "This is the first time NEU1 has been associated with fibrotic conditions," said corresponding author Alessandra d'Azzo, Ph.D., a member and endowed chair of the St. Jude Department of Genetics. "NEU1 is an important enzyme that breaks down sugar-containing molecules in many cells of the body, but it has not really been on the radar for adult health problems.

"Based on these findings, it is tantalizing to hypothesize that NEU1 expression levels may help identify individuals at risk for fibrosis or inform their prognosis, particularly when information about the cause or possible treatment is lacking," she said. Fibrosis results when excess connective tissue is produced and accumulates and disrupts normal function of the muscle, lungs, liver, heart and other tissues. Connective tissue is produced in part by [fibroblast cells](#).

Early evidence

The findings build on earlier research from d'Azzo's laboratory. That work centered on mice that lacked the Neu1 gene. The mice developed muscle atrophy when connective tissue proliferated and invaded muscle.

In this study, researchers unraveled the underlying mechanism by

showing that mouse fibroblasts lacking Neu1 proliferated, migrated and released large numbers of molecules that promoted the relentless expansion of connective tissue. "The cells started acting more like [cancer cells](#)," d'Azzo said. She previously reported evidence about the potential role of NEU1 deficiency in cancer, particularly sarcomas, which are cancers of the [connective tissue](#).

The researchers found that mouse fibroblasts lacking Neu1 release excessive numbers of molecules that degrade the extracellular matrix, as well as tiny vesicles (exosomes). The exosomes are loaded with factors that promote fibrosis, including the growth factor TGF- β and the signaling molecule WNT. Normal mouse and human fibroblasts cells were activated to proliferate and migrate when exposed to exosomes containing TGF- β , WNT and related molecules released by Neu1-deficient fibroblasts.

Human disease

Researchers checked tissue from adults with idiopathic pulmonary fibrosis and found NEU1 production was significantly reduced (down-regulated) as compared to adults without the diagnosis. The investigators checked an RNA sequencing database of 89 [idiopathic pulmonary fibrosis](#) patients and found NEU1 was among the most down-regulated of 66 genes included in the database.

The research puts NEU1 deficiency, which is associated with a pediatric catastrophic disease, squarely on the radar as a possible risk factor for development and progression of fibrotic diseases in adults for which the primary cause is unknown.

The findings also confirm d'Azzo's belief that in-depth studies of rare pediatric diseases, such as the lysosomal storage disorders, often help to explain the disease mechanisms underlying disorders common in the

aging population.

More information: "Excessive exosome release is the pathogenic pathway linking a lysosomal deficiency to generalized fibrosis," *Science Advances* (2019).

advances.sciencemag.org/content/5/7/eaav3270

Provided by St. Jude Children's Research Hospital

Citation: Rare inherited enzyme disorder yields insight into fibrosis (2019, July 17) retrieved 27 April 2024 from

<https://medicalxpress.com/news/2019-07-rare-inherited-enzyme-disorder-yields.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.