MedicalXpress

Confused cells lead to genetic disorders like heart problems, premature aging

April 21 2016

It has been disorienting to the scientific and medical community as to why different subtle changes in a protein-coding gene causes many different genetic disorders in different patients—including premature aging, nerve problems, heart problems and muscle problems. no other gene works like this. According to a new study, co-authored by Binghamton University faculty Eric Hoffman, it has to do with cell "commitment."

From initial conception of an egg and sperm, the cells that start dividing need to start making decisions as to what type of tissue or organ they are supposed to become (often called 'cell lineages'). This is part and parcel of 'stem cells' - e.g. how to get cells to make certain decisions to become nerve, heart, muscle, or something else.

The study, "Laminopathies disrupt epigenomic developmental programs and cell fate," published on April 20 in *Science Translational Medicine*, provides a unifying model for this process, and how it is disrupted by subtle mutations of the LMNA gene.

"A one-letter change, a one amino acid change, in this big protein, we see in patients that have severe muscle problems. Just a couple letters away, the same amino acid change instead causes loss of fat in other patients," said Eric Hoffman, associate dean for research at Binghamton University's School of Pharmacy and Pharmaceutical Sciences and co-author of the study. "What we show is that's because of subtle changes in the context of a cell trying to make a decision whether it's going to be

muscle or fat. It really needs to make sure the right areas are taken out of circulation. If you start taking the wrong areas or not enough areas or too many areas out of circulation, the cell starts getting confused; it's not being given the right instructions."

Different parts of the genome need to become attached to the outside of the nucleus (nuclear envelope—the key structure that separates animals with organs, from bacteria), where these attached regions are taken out of genetic circulation (called heterochromatin - never to be used again). In a way, this attachment process defines what part of the genome is no longer useful to that particular cell/organ type—and this type of discarding of the DNA keeps a cell focused on what it is supposed to be (e.g. a heart cell not suddenly confused if it should be nerve instead).

"We provide a model for how these very subtle changes in a single protein cause such dramatically different clinical problems because of this process of taking parts of the genome out of circulation during cell commitment, when a cell's trying to make these decisions," Hoffman added.

More information: J. Perovanovic et al, Laminopathies disrupt epigenomic developmental programs and cell fate, *Science Translational Medicine* (2016). DOI: 10.1126/scitranslmed.aad4991

Provided by Binghamton University