Major depression leaves a metabolic mark

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Credit: George Hodan/Public Domain

Major depression comes with an unexpected metabolic signature, according to new evidence reported in the Cell Press journal *Current Biology* on April 23. The findings in humans and mice offer new insight into the nature of depression. They may also yield new ways to measure and monitor mental health at the molecular level.

"Our most notable finding is that the amount of mitochondrial DNA changes in response to stress," says Professor Jonathan Flint of the

University of Oxford.

Mitochondria are compartments in cells responsible for generating energy. An increase in mitochondrial DNA suggests a change in mitochondria and cellular energetics, Flint explains.

"We see an unexpected link between cellular energetics and major depression, which has always been seen as a mood disorder."

Flint and his colleagues stumbled across this serendipitously, while in search of genes that increase depression risk among thousands of women with recurrent major depression and healthy controls (see http://www.well.ox.ac.uk/converge). Many of the women with depression also had experienced adversity in childhood, including sexual abuse.

Flint said the researchers noticed something rather unusual in the DNA. The samples taken from women with a history of stress-related depression contained more mitochondrial DNA than other samples.

"We were surprised at the observation that there was a difference in mitochondrial DNA—so surprised it took us a long time to convince ourselves it was real, and not an artifact," Flint says.

The new discovery prompted Flint and his team to evaluate another molecular level phenomenon associated with depression in earlier studies. Telomeres, repeated DNA sequences that physically cap the ends of chromosomes, shorten with each cell division (and therefore with one's age). Changes in metabolism have been shown to alter the rate of aging, so the researchers wondered whether they might see a change in telomeres' erosion too. And indeed they did.

To test these hypotheses further, Flint's team looked to laboratory mice

that were put through four weeks of stress. The studies in mice showed not only that stress caused both molecular changes, but also that the changes were partly reversible and elicited by administration of the stress hormone corticosterone.

Flint says the molecular changes they observed might reflect the body's way of coping with major environmental stressors. As our brains perceive a threat—lack of food or a history of abuse, for example—it may initiate a series of protective metabolic changes.

"Depression might in some sense be considered a metabolic reaction to perceived stress," Flint says.

The researchers also hope that the molecular changes can serve as biomarkers of stress and its consequences. It is possible, for example, that a decline in mitochondrial DNA levels post-treatment could be used as an indicator of success.

More work is still needed. "We have only a snapshot of the relationship between the molecular markers and depression," Flint says. "We want to know how they change over time—before, during, and after a depressive illness. That information will tell us much about their clinical utility."

More information: *Current Biology*, Flint et al.: "Molecular signatures of major depression" dx.doi.org/10.1016/j.cub.2015.03.008

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