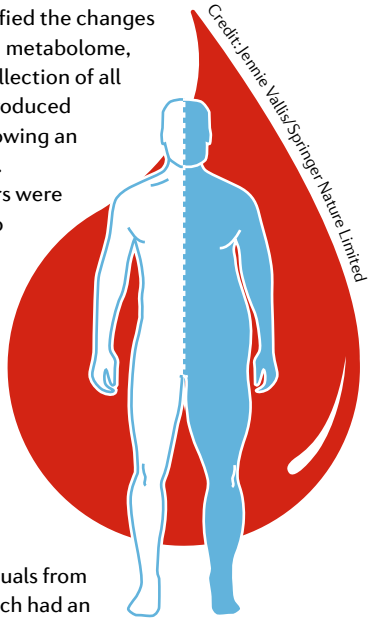
OBESITY

The predictive power of an unhealthy metabolome



New research has identified the changes that occur to the human metabolome, which represents the collection of all the small metabolites produced during metabolism, following an increase in body weight. Furthermore, the authors were able to use these data to predict whether an individual would go on to develop the metabolic syndrome.

In their study, the authors used whole-genome sequencing and untargeted metabolomics to assess the diversity of the metabolome in human obesity in >2,000 individuals from the TwinsUK cohort, which had an average follow-up time of 13 years. "We were taken by surprise by the large-scale perturbation of the metabolome following weight gain — many pathways and systems were altered with increasing body weight," explains co-corresponding author Amalio Telenti.

Furthermore, individuals who had the same BMI, but different metabolome signatures, had slightly different genetic signatures. "Specifically, people with an unhealthy metabolome but healthy BMI had a lower genetic risk of obesity than people who had a healthy metabolome but unhealthy BMI," adds Elizabeth Cirulli, the other corresponding author on the study.

Therefore, the data suggest that how an individual's metabolome reacts to excess weight or a positive calorie intake, and not the physical measurement of obesity by BMI, is what is important for overall health. In other words, some people are genetically predisposed to have a BMI in the overweight or obese categories, but if these individuals lead healthy lifestyles they can have healthy metabolomes and benefit from good overall health. By contrast, people who are genetically predisposed to have a BMI in the normal-weight category that lead unhealthy lifestyles can suffer from negative health outcomes.

"It is really exciting that we are able to use a blood test to characterize the overall health of a person in a more robust way than we can do by measuring BMI alone," concludes Cirulli. "I think future studies using metabolites to characterize different aspects of a person's health will lead to breakthroughs in how we can assess a person's risk of developing different diseases."

Alan Morris

ORIGINAL ARTICLE Cirulli, E. T. et al. Profound perturbation of the metabolome in obesity is associated with health risk. *Cell Metab.* https://doi.org/10.1016/j.cmet.2018.09.022 (2018)

GENETICS

In utero gene editing as a treatment for heritable metabolic syndromes

Some heritable diseases manifest during the fetal stage, causing considerable morbidity or mortality after birth. Editing the genome and correcting these mutations in utero before the onset of disease could be a new treatment to cure these diseases, particularly in conditions that currently have no treatments. Now, new research by Kiran Musunuru, William Peranteau and colleagues provides proof-of-concept work showing that gene editing disease-causing genes during fetal development in mice could be a viable therapy option.

To perform the gene editing, the researchers used a CRISPR-based base editor (BE3) instead of standard CRISPR–Cas9 genome editing, as BE3 does not cause double-strand breaks and is more efficient at single base pair changes than CRISPR–Cas9. "We initially focused on *PCSK9*, which encodes a protein that is crucial in the regulation of plasma cholesterol homeostasis, as a proof-of-concept, and then turned our attention to a grievous liver disorder that affects neonates, hereditary tyrosinaemia type 1 (HT1)," explains Musunuru.

One of the consequences of the loss of function of *PCSK9* in humans is reduced levels of cholesterol. To test whether knockout of murine *Pcsk9* would result in reduced levels of PCSK9 and cholesterol in postnatal mice, the researchers injected a BE3 construct that would introduce a nonsense mutation into *Pcsk9* via the vitelline vein, which directly delivers the construct to the entire fetal liver, at embryonic day 16. At postnatal day 1, the mice that were injected with the viral construct showed base editing of *Pcsk9* that was restricted to the liver. The in utero edited mice showed decreased levels of PCSK9 and total cholesterol.

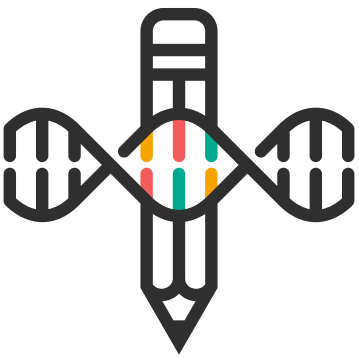
Following the success of the proof-of-concept experiments, the researchers used BE3 as a therapeutic treatment in a mouse model of HT1. HT1 is caused by mutations in *FAH*, which disrupts the metabolism of tyrosine, leading to liver and kidney failure. Treatment with nitisinone inhibits an upstream enzyme (HPD) in the tyrosine metabolism pathway, preventing the accumulation of toxic metabolites.

To treat HT1 using base editing, the researchers introduced a nonsense mutation into *Hpd* in *Fah*$^{-/-}$ mice (a mouse model of HT1) using the in utero editing technique. The *Fah*$^{-/-}$ mice die shortly after birth if they are not treated with nitisinone. "What we were surprised to see is that the fetal gene editing not only cured the disease in the *Fah*$^{-/-}$ mice, but the edited mice also did much better than nitisinone-treated *Fah*$^{-/-}$ mice, gaining more weight and thriving well into adulthood," notes Musunuru.

The team will investigate other heritable liver disorders that can also be treated using this technique. "In utero gene editing has the potential to offer a new treatment approach for select diseases that cause significant morbidity and mortality and for which treatments do not currently exist," concludes Peranteau.

Ivone Leong

ORIGINAL ARTICLE Rossidis, A. C. et al. In utero CRISPR-mediated therapeutic editing of metabolic genes. *Nat. Med.* **24**, 1513–1518 (2018)



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