Retraction

Dietary RNA is ripe for investigation

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This article has been retracted at the author's request on 23 July 2020. The sponsorship and full scope of the supplement were not made clear to him during the editing process. Nature Outlooks editorial guidelines and processes are being reviewed in light of this. We are grateful to the author for bringing this to our attention.

Perspective: Dietary RNA is ripe for investigation

RNA in food could have profound effects on the human digestive system and on health more generally, says Kenneth Witwer.

In the mid-nineteenth century, German philosopher Ludwig Feuerbach reviewed a monograph on the influence of food chemicals on the make-up and function of the body. In his essay, he asserted that food affects even cognition, coining the phrase: "you are what you eat". To change the world, give people better food, he said.

The study of nutrition has progressed substantially since then. How the body extracts molecular building blocks and energy from food is well understood. But could food be more than just fuel? In 2012, an article suggested just that: a dietary component that interacts with the genetic code.

The authors of the study[1] reported that short molecules of RNA called microRNAs (miRNA) from rice accumulate in tissues, and regulate an important liver enzyme. This regulation was so effective that, surprisingly, a plant-based diet seemed to significantly boost levels of circulating cholesterol in mice. This, and other reports from the same group on dietary-RNA-containing particles, including extracellular vesicles (EVs), generated considerable excitement.

But despite numerous replication and analysis studies, little or no systemic uptake of dietary RNA has been observed. A faithful replication of the initial experiments, but comparing mice given a nutritionally balanced rice-based diet with animals fed just rice, showed that the cholesterol finding was not the result of miRNA transfer, but rather a starvation response to a nutritionally insufficient rice diet[2]. In a study this year in cows, researchers found that during the 24-hour window after birth in which calves can absorb antibodies from their mother's milk, proteins and lipid membranes transferred readily into the circulation — but RNA did not[3].

However, systemic transfer, which involves molecules crossing multiple barriers in the body, is not the only way that dietary RNA could affect health beyond serving as fuel[4]. Dietary-RNA carriers have access to the epithelial and immune-surveillance cells of the alimentary tract. They probably also interact with the diverse species of the community of microorganisms that live in the gut.

Such interactions could be exploited to deliver therapeutic small RNA strands to combat specific health conditions. Early evidence of the transfer of RNA from one organism to another came from the finding that bacteria, given orally, could transfer therapeutic RNA to human colorectal cancer cells transplanted into mice[5]. The bacteria don't need to replicate to have these effects, so bacterial EVs could be a safer and highly scalable alternative to live organisms. And bacterial vesicles are not the only possible delivery vehicles. Indeed, food plants, blended and broken up into nanoparticles that resemble EVs, could deliver RNAs and small-molecule drugs to epithelial cells[6]. Food-based RNA-delivery strategies are likely to be very low risk, because there is no evidence that dietary RNA is harmful.

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Particles produced from these plant 'smoothies' might affect the gut microbiome — just as host epithelial EVs have been shown to do — and RNAs could play a part in this phenomenon. Because the health of the microbiome is now a recognized factor in conditions such as cancer and neurodegenerative disease, the effects of dietary RNA and EVs should be investigated more intensively. Theoretically, dietary RNA found in food or engineered RNA additives could attenuate or eliminate pathogens by targeting essential genetic elements. It could also be used to fine-tune the balance of microbes in the gut, because different RNA molecules exert different effects across the diverse gut-microbe populations.

In his essay, Feuerbach opined that the uprising of the German people had failed because they ate too many potatoes. A diet richer in beans, he thought, would have brought about political change. Such a notion now seems quaint, and bolstering a person's political activism through dietary microRNA is a far-fetched idea.

Nevertheless, opportunities abound to study whether dietary RNA is delivered to the cells of the alimentary tract and the microbes that live there. But these investigations must include appropriate controls to determine whether dietary extracellular RNA is mostly a source of nutrition in the form of molecular building blocks or whether specific RNA sequences are transferred into microbial or host gut cells where they regulate other nucleic acids.

If the latter is true, researchers will need to determine whether native dietary RNA is therapeutically effective, or if it is necessary to introduce vesicles loaded with naturally occurring or synthetic RNA. Similarly, can a 'smoothie', or even unprocessed food, deliver RNA, or must EV-like particles be separated and concentrated from these sources?

Finally, the mechanisms of delivery and the use of RNA in the recipient cell must be unravelled. Knowing exactly how RNA is taken up and incorporated into regulatory complexes will allow researchers to exploit and enhance these pathways. Although it is not possible to predict how these experiments will turn out, the findings could lead to the use of specific foods and methods of processing as therapy or to enhance gut health.

Depending on the outcome, Feuerbach's ideas might turn out to be correct on a molecular level he could not have anticipated.

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