Stomach SIDT1 mediates dietary microRNA absorption

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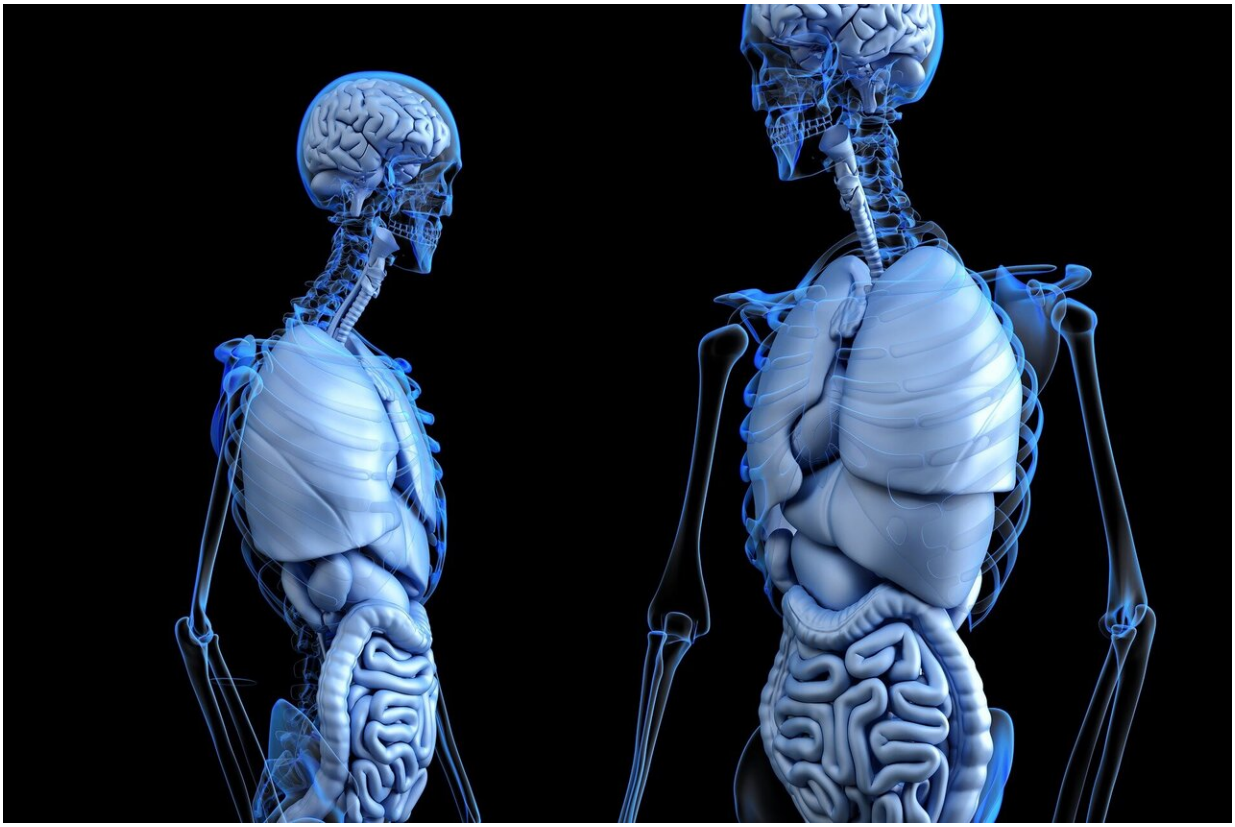

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In a new study published in *Cell Research*, Chen-Yu Zhang's group at Nanjing University School of Life Sciences, China, reports that SIDT1 in the mammalian stomach mediates host uptake of dietary and orally

administered microRNAs (miRNAs), thus exerting biological functions in the host.

In previous studies, Chen-Yu Zhang's group has demonstrated that intact plant miRNA in foods can be absorbed through the mammalian digestive system and mediate cross-kingdom gene regulation. The discoveries also provide new insight into the oral administration of RNA therapeutic drugs. Although accumulated evidence shows the existence of intact dietary miRNAs within mammalian hosts, the absorption of dietary miRNAs in animal gastrointestinal tract has been frequently questioned, mainly due to the unknown mechanism of absorption.

In the current study, they show that an SID-1 transmembrane family member 1 (SIDT1), a mammalian homolog of SID-1 expressed on gastric pit cells in the stomach is required for the absorption of dietary miRNAs. SIDT1-deficient mice show reduced basal levels and impaired dynamic absorption of dietary miRNAs. Notably, they identified the stomach as the primary site for dietary miRNA absorption, which is dramatically attenuated in the stomachs of SIDT1-deficient mice. Mechanistic analyses revealed that the uptake of exogenous miRNAs by gastric pit cells is SIDT1 and low-pH dependent. Furthermore, oral administration of plant-derived miR2911 retards liver fibrosis, and the protective effect was abolished in SIDT1-deficient mice. This study not only reveals the major mechanism of dietary miRNA absorption, but uncovers a novel physiological function of the mammalian stomach, but also shed light on orally delivered small-RNA therapeutics.

This work is important for the following reasons:

1. In this study, the researchers demonstrated the molecular mechanism of mammalian dietary miRNA absorption, which is one of the most groundbreaking as well as most controversial discoveries in the field of extracellular RNA research in the last

decade. Identification of the absorption mechanism provides strong evidence of the physiological existence and functionality of mammalian dietary miRNA absorption, thus ending the 10-year debate on this topic.

2. This work also newly found that the stomach not only absorbs water and alcohol, as is broadly known in classic physiology, but also senses and takes up functional dietary miRNAs. This provides a unique new understanding of digestion physiology.
3. A low-pH condition is required for efficient exogenous miRNA uptake via SIDT1. This finding reveals an evolutionary explanation for functional dietary miRNA absorption, in which the stability of dietary miRNAs is granted in stomach, where RNase activity is largely absent in this low-physiological-pH gastric environment.
4. By oral administration, plant-derived miR2911 can be absorbed via SIDT1 and can subsequently alleviate liver fibrosis in mice, providing a new therapeutic strategy for small-RNA-based treatment. This natural mammalian absorption pathway of dietary miRNA will be easily harnessed for the oral delivery of therapeutic miRNAs, which could be a potential direction in for the development of RNA-based medicine.

More information: Qun Chen et al, SIDT1-dependent absorption in the stomach mediates host uptake of dietary and orally administered microRNAs, *Cell Research* (2020). DOI: 10.1038/s41422-020-0389-3

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