LETTER

Diet-responsive MicroRNAs Are Likely Exogenous

In a recent report Title *et al.* (1) fostered miRNA-375 and miR-200c knock-out pups to wild-type dams and arrived at the conclusion that milk microRNAs are bioavailable in trace amounts at best and that postprandial concentrations of microRNAs are too low to elicit biological effects. Their take home message is flawed. First, the majority of microRNAs in bovine milk are encapsulated in exosomes, thereby conferring protection against degradation and a mechanism for intestinal transport (2). Second, numerous dietary microRNAs have been cataloged among human samples (3). Third, the mere absence of a postprandial increase does not equate with zero absorption. Abundant microRNA targets in the intestinal mucosa or liver could be promoting rapid microRNA degradation, the classical concept of first-pass elimination. Artificial microRNA targets ("sponges") have been used successfully to decrease the abundance of microRNAs in experimental settings. Fourth, the authors spaced sample collections days apart, which risks missing increases in microRNAs following milk consumption.

Title *et al.* (1) proposed that low concentrations of microRNAs lack biological activity. This notion is unsound as recent work suggests microRNAs may work at concentrations in the femtomolar to picomolar range (4, 5). We do agree with their proposal that other exosome cargos may contribute to the biological effects of milk intake and that studies of dietary microRNAs need to take advantage of protocols that allow distinction between microRNAs derived from dietary sources *versus* those derived from endogenous synthesis.

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