Journal of Oral Microbiology

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Commentary

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Responsible Editor: Philip D. Marsh, Oral Microbiology at Leeds Dental Institute, United Kingdom.

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Received: 11 May 2016; Revised: 13 June 2016; Accepted: 13 June 2016; Published: 28 June 2016

S Liu et al. recently launched interesting concepts on how microRNAs (miRNAs) can control the gut microbiome. One paper by Liu and Weiner, *Control of the gut microbiome by fecal microRNA*, was published in Microbial Cell 2016; 3: 176–7; another by Liu S, da Cunha AP, Rezende RM, Wei Z, Bry L, Comstock LE, et al., *The host shapes the gut microbiota via fecal micoRNA* appeared in Cell Host Microbe 2016; 19: 32–43. A commentary to these papers is given here.

MicroRNAs (miRNAs), detected in the early 1990s, are small non-coding RNAs, 18–23 nucleotides in length. They are synthesized in the nucleus and are processed and function in the cytoplasm. miRNAs can also exist extracellularly and circulate in body fluids. They have mainly been associated with the posttranscriptional regulation of gene expression on a cell-autonomous level. Recently, Liu and Weiner (1) and Liu et al. (2) described miRNAs in the gut lumen and feces of both humans and mice. The two main sources of fecal miRNA were intestinal epithelial cells (IEC) and Hopx-expressing cells (mice). The most abundant miRNAs in feces were present in an extracellular vesicle form. Interestingly, a deficiency of IEC-miRNA caused gut dysbiosis, but wild-type fecal miRNA transplantation restored the gut microbiota. Most noteworthy, the researchers found that miRNAs were able to regulate the gut microbiome. By culturing bacteria together with miRNAs, they observed that the miRNAs of the host were able to enter bacteria, such as *Fusobacterium nucleatum* and *Escherichia coli*, and co-localize with bacterial nucleic acids. miRNAs specifically regulated gene transcripts and influenced bacterial growth. However, there was a different capability of miRNAs to enter bacteria, and this might explain different miRNA effects on bacterial gene transcription and growth. Furthermore, the oral administration of synthetic miRNA mimicked specific bacteria affected in the gut. These findings describe hitherto unknown pathways by which the gut microbiome is regulated by the host. Oral administration also raises the possibility of miRNAs being used therapeutically to manipulate the gut microbiome in the treatment of disease. Last but not least, the research raises additional questions: Could the oral microbiota be regulated by miRNAs? and, in turn, Could miRNAs be used for treatment of oral diseases?

It is well known that the gut contains a myriad of commensal microbes. Dysbiosis in this microbiome may have consequences for the development of the immune system; metabolism; and diseases, such as autoimmune disorders, autism, and cancer. It is therefore important to understand what regulates the gut microbiome and identify strategies to prevent gut diseases. miRNAs can exist extracellularly in the body and indicate specific diseases. The authors of "The host shapes the gut microbiota via fecal micoRNA" found that miRNAs were part of the feces in both humans and mice. miRNAs within feces were mainly produced by gut epithelial cells and Hopx+ cells (Fig. 1). The abundance of miRNAs was inversely correlated with the abundance of microbes, thus indicating that microbes might take up miRNAs from the host and that these miRNAs might in turn affect the microbes. When miRNAs from the host entered bacteria, they co-localized with bacterial nucleic acids, which provide the temporal and spatial basis for regulation of gene expression. All bacterial gene sequences examined were found to pair with different miRNAs. Transcripts of the bacterial genes were altered by miRNA treatment, which also affected bacterial growth. 16S rDNA sequencing indicated that IEC-specific miRNA knockout caused dysbiosis in the microbiota of the gut, which was accompanied by the aggravation of colitis in a dextran sulfate sodium model in mice. A deficiency in epithelial-originated miRNAs led to a more diverse gut microbiota and changed epithelial barrier integrity. Fecal miRNA transplantation restored the gut microbiota.

Citation: Journal of Oral Microbiology 2016, **8**: 32227 - http://dx.doi.org/10.3402/jom.v8.32227

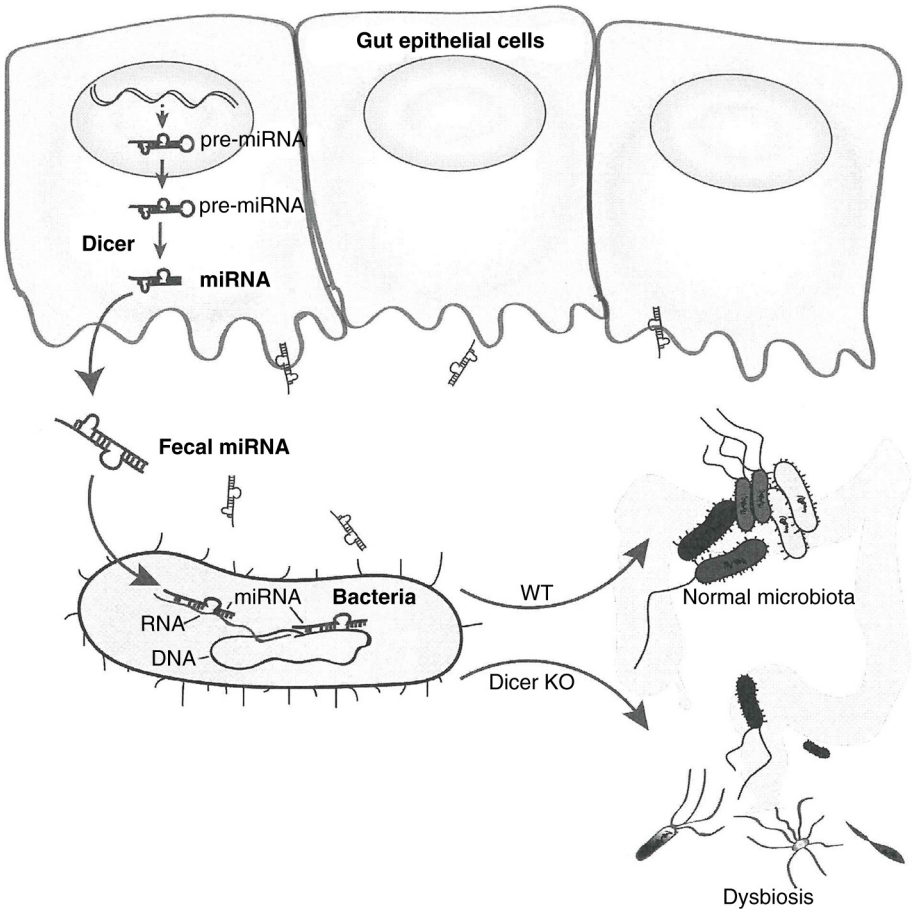

Fig. 1. Host gut epithelial cells and Hopx+ cells are the main sources of fecal miRNAs, which, again, are the main constituents of human and murine feces. The enzyme Dicer cleaves double-stranded pre-miRNA into short double-stranded RNA fragments called miRNA of 21–23 nucleotides. miRNAs enter bacteria and regulate expression of bacterial genes and bacteria growth. Fecal miRNAs are essential for maintenance of the normal gut microbiota. (Adapted from Liu et al. (2).)

The studies by Liu et al. (2) clearly showed that miRNAs were able to regulate bacterial gene expression and growth, and that their loss resulted in a dysbiotic microbiota and aggravated colitis. Whether these findings can be translated to the oral microbiota and used for the treatment of oral diseases is not known. However, miRNA has been found in both the oral mucosa and saliva.

Unfortunately, not much is known about the importance of miRNA for the microbiota and diseases in the oral cavity. Lipopolysaccharide-responsive miRNAs may have a role in fine-tuning the host response to periodontal pathogens (3), and miRNAs may act as key regulators of lipopolysaccharide-induced periodontitis (4). There are also indications that miRNA-146 functions as a negative regulator of periodontal inflammation (5), and it may directly or indirectly modulate or change the chronic periodontal pathology induced by periodontopathogens (6). Also, periodontal infections can alter miRNA profiles in secondary sites, such as the salivary glands and pancreas (7).

Different methods exist for measuring miRNAs in body fluids. The most commonly used are microarrays and quantitative polymerase chain reaction. Microarray analysis is a high-throughput technique used in a non-targeted approach when several miRNAs are to be analyzed, while polymerase chain reaction is more sensitive and usually used for the validation of results obtained from microarray analysis (8).

These findings suggest that studies on the role of miRNAs in regulating the oral microbiome are warranted.

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