WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Fecal microbiota transplantation (FMT) is highly effective at preventing recurrent *Clostridioides difficile* infection (rCDI). However, the mechanisms of action remain largely unknown. MicroRNAs (miRNAs), short non-coding RNA sequences which bind to complementary sequences of mRNA and can regulate gene expression, may be a potential mechanism by which commensal microbiota communicate with the human host.

NEW FINDINGS

We identified several significant alterations in circulating miRNAs following successful FMT treatment in 2 independent rCDI patient cohorts. miRNA signatures were validated in animal models and human colonoids. We further demonstrate that FMT-regulated miRNAs regulate cell properties and target IL-12B, IL-18, FGF21 and TNFRSF9, integral in pathways linking to inflammation, autoimmunity and cancer.

LIMITATIONS

Deeper characterization of the epitranscriptome in FMT is required.

IMPACT

These results describe a new mechanism of action of FMT against rCDI and provide potential new therapeutic targets for conditions associated with intestinal dysbiosis.

LAY SUMMARY

Successful fecal microbiota transplantation for recurrent *Clostridioides difficile* infection associates with increased expression of specific microRNAs in blood and colonic tissues. These microRNAs target inflammatory proteins and can protect gut barrier from damage from *C. difficile* toxins.