exome sequencing studies of sporadic tumors,\textsuperscript{7} this discovery is noteworthy in that it provides a new and rational target for investigation. IPMK is an inositol phosphate kinase, and the authors describe a link between IPMK and p53-mediated apoptosis. It will be important to understand the importance of this interaction in the context of homeostasis and transformation of enteroendocrine cells. Previous reports that hemizygous deletion of Ipmk in mice did not seem to result in carcinoid tumors suggest that the role of IPMK is likely to be complex. Further studies are warranted, because additional insights may be gained into other molecular partners of IPMK or critical pathways that intersect with IPMK in carcinoids.

A sobering but increasingly pervasive message is that genetics may not hold the key to deciphering carcinoid tumors. A role for genetics is certainly not excluded, but alternative mechanisms must be considered. For example, the identification of multiple genes that regulate histones and chromatin in pancreatic neuroendocrine tumors and pulmonary carcinoids raises the intriguing possibility that epigenetic mechanisms may be more relevant.\textsuperscript{3,4} In addition, there may be mutations in noncoding regulatory regions of the genome that are not sequenced routinely. New hypotheses that explore whether carcinoid tumors may instead be driven by alterations in the metabolome or the microenvironment also deserve consideration. The need for discovery is great, because therapeutic options in carcinoid remain limited and inadequate.\textsuperscript{11} A focus on innovative “postgenetic” strategies may provide new clues to unravel the mysteries of these unconventional tumors.

DANIEL C. CHUNG
Gastroenterology Division
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

References

Reprint requests
Address requests for reprints to: Daniel C. Chung, MD, Massachusetts General Hospital, 55 Fruit Street, GRJ 704, Boston, Massachusetts 02114, e-mail: dchung@partners.org; fax: (617) 643-0195.

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The authors disclose no conflicts.

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Fecal Microbiota Transplantation for Ulcerative Colitis: Not Just Yet

The role of the gut microbiome in human disease and inflammation has gained international attention over the past decade. The success of fecal microbiota transplantation (FMT) in treating Clostridium difficile infections (CDI) has raised the possibility that FMT may be beneficial in other diseases associated with alterations in gut microbiota, or dysbiosis.\textsuperscript{1} Excitement around the possibility of FMT for inflammatory bowel disease (IBD) among patients and clinicians has grown rapidly, as anecdotal reports and small case series have suggested that FMT may have a beneficial effect.\textsuperscript{2,3} A recent meta-analysis showed that FMT in IBD is variable in efficacy with beneficial effects seemingly limited to patients with...
Crohn’s disease and the pediatric population. In this issue of *Gastroenterology*, the first 2 randomized, controlled studies evaluating the efficacy of FMT in ulcerative colitis (UC) are presented.

Moayyedi et al report the results of a randomized, placebo-controlled trial using FMT to induce remission in patients with mild-to-moderate UC. Seventy-five subjects received weekly FMT or placebo (water) via retention enema for 6 weeks. Investigators and recipients were blinded to the treatment allocation. The primary endpoint was remission, defined as Mayo Score of <3 with an endoscopic subscore of 0 at week 7. Six donors were used in this study, with the majority of subjects receiving FMT from 2 donors (A and B). The data safety and monitoring board (DSMB) recommended discontinuing the study at interim analysis because of futility in reaching the primary efficacy endpoint. The authors presented interim data at an international conference in May 2014, reporting a negative study. With the addition of 22 subjects already enrolled, this study attained significance for the primary end point of remission. Each of these additional subjects had received active FMT from a single donor: “donor B.” Overall, the authors found that subjects who received FMT achieved remission significantly more than those receiving placebo (9/38 [24%] vs 2/37 [5%]; *P* = .03). Although only cursory microbiome analyses were performed, it seems that patients who received active FMT developed an increase in microbial diversity compared with those who received placebo.

In the study reported by Rossen et al, 50 patients, also with mild to moderately active UC, were treated with either donor stool or autologous FMT (infusion of their own stool as placebo) delivered via nasoduodenal tube at baseline and again 3 weeks later. Only 37 completed assessment for the primary endpoint—clinical remission combined with a ≥1-point decrease in the Mayo endoscopic score at week 12. There was no difference in clinical and endoscopic remission between the 2 groups in either the intention-to-treat or per-protocol analyses. This study was also terminated at interim analysis by the DSMB because of futility. The assumed treatment effect (70%) was too high, resulting in a study that was, unfortunately, underpowered to test the hypothesis that FMT is beneficial in UC. The authors did show that subjects who responded favorably to FMT shifted to develop a microbiota profile similar to their respective donors, whereas nonresponders did not shift.

These 2 studies make valuable contributions to the existing literature. Both represent an improvement compared with previous case series and cohort studies that were limited by small numbers of patients, open-label design, vague FMT protocols, incomplete reporting of IBD-specific data, and poorly defined outcomes. A major limitation on the studies from Moayyedi et al and Rossen et al is that they both dramatically overestimated the treatment effect of FMT for UC. Because of this error, the studies were terminated by their respective DSMB owing to futility.

Why was 1 study positive and the other negative? There were several major differences between these 2 trials (Table 1). Moayyedi et al administered 6 FMT infusions via the lower gastrointestinal (GI) route, whereas Rossen et al administered only 2 and via the upper GI route. The upper GI route might render the active constituent of FMT ineffective by the time it reaches the diseased colon. It is also possible that there is a dose response or a threshold required for engraftment to be attained to alter effectively the gut microbiome and the downstream inflammatory cascade. Furthermore, treatment with anti-tumor necrosis factor (TNF) seemed that patients who received active FMT developed an increase in microbial diversity compared with those who received placebo.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Moayyedi et al&lt;sup&gt;5,6&lt;/sup&gt;</th>
<th>Rossen et al&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Double-blind, randomized (1:1), controlled</td>
<td>Double-blind, randomized (1:1), controlled</td>
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<tr>
<td>Study population</td>
<td>Adult patients with mild to moderate UC</td>
<td>Adult patients with mild to moderate UC</td>
</tr>
<tr>
<td>Sample size calculation</td>
<td>130</td>
<td>80</td>
</tr>
<tr>
<td>Subjects randomized (n)</td>
<td>75</td>
<td>50</td>
</tr>
<tr>
<td>Completing therapy (n)</td>
<td>70</td>
<td>37</td>
</tr>
<tr>
<td>Anti-TNF permitted?</td>
<td>Yes, at stable doses for ≥12 weeks</td>
<td>No</td>
</tr>
<tr>
<td>Route of FMT delivery</td>
<td>Retention enema</td>
<td>Nasoduodenal tube</td>
</tr>
<tr>
<td>Placebo</td>
<td>Water</td>
<td>Autologous FMT</td>
</tr>
<tr>
<td>Donor stool</td>
<td>6 volunteers, fresh or frozen</td>
<td>15 donors, fresh</td>
</tr>
<tr>
<td>Dose schedule</td>
<td>Weekly for 6 weeks</td>
<td>2 doses (0 and 3 weeks)</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>Remission (Mayo score ≤2 with an endoscopic score of 0) at week 7.</td>
<td>Remission (simple clinical colitis activity score ≤2 combined with ≥1-point decrease in Mayo endoscopic score at week 12</td>
</tr>
<tr>
<td>Subjects who achieved the primary endpoint</td>
<td>9/38 (24%) treated with FMT vs 2/37 (5%) controls <em>(P = .03)</em></td>
<td>7/23 (30.4%) treated with FMT vs 5/25 (20%) controls <em>(P = .51)</em></td>
</tr>
<tr>
<td>Microbiome analyses</td>
<td>Yes; increased diversity in FMT treated subjects compared with the control group.</td>
<td>Yes; increased diversity of responders in both groups. FMT treated group developed similar microbiota profile to respective donor.</td>
</tr>
</tbody>
</table>

FMT, fecal microbiota transplantation; TNF, tumor necrosis factor; UC, ulcerative colitis.
factor was permitted in 1 study (Moayyedi et al) and not the other, and those subjects on immunosuppression did better, raising the question as to whether immune factors may have a role in successful FMT induction. These uncertainties make our ignorance clear; we still do not understand the active component of FMT. Is it a bacteria or bacterial metabolite, or is it the interaction between microbial and host factors?

The results from Moayyedi et al suggest that FMT is a heterogeneous treatment, and the effect may be donor dependent. Although donor B’s impact seemed to sway the results of this study, it is important to note that use of stool from this donor did not attain significance versus placebo in achieving remission \((P = .06)\). It is intriguing to suggest that 1 person’s stool may be more effective than another, but this study was not designed or powered to make that conclusion. The microbiota of this donor was enriched in members of the \textit{Lachnospiraceae} family and the \textit{Ruminococcus} genus, a similar profile to another donor in this study associated with FMT success. Previous studies have revealed that certain bacterial taxa, including \textit{Lachnospiraceae}, are depleted in IBD.\textsuperscript{7} However, the small size of this study does not permit meaningful analyses of subgroups by donor or elucidate mechanisms of effect. Further investigation is required before we can say whether donor B has “the right stuff.”

It is clear that FMT is not nearly as effective in IBD as it is in CDI. CDI occurs as a result of marked disruption of the indigenous gut microbiota by antibiotics.\textsuperscript{9} Treatment with FMT results in high cure rates for recurrent CDI, regardless of recipient, donor, or delivery method.\textsuperscript{10,11} Unlike CDI, IBD is a complicated disease with a complex pathologic interplay between genetic, immunologic, environmental, and microbial factors. IBD may be characterized by dysbiosis, but it is unclear if this is a cause or an effect of the underlying inflammatory process. Although FMT can lead to lasting changes in the gut microbiota that correlate with treatment as seen in CDI,\textsuperscript{12} manipulating the microbiome may not be an effective strategy for treating IBD. Interestingly, although numbers are small, the data from Moayyedi et al suggest that newly diagnosed UC patients may have the best outcomes with FMT. Is there a window of opportunity to treat patients with FMT after diagnosis?

If FMT can make some IBD patients better, could it make others worse? Although the rate of serious adverse events in both of these studies was low, IBD flares and infections after FMT have been described,\textsuperscript{13–15} and larger clinical trials to establish both efficacy and safety are critical before FMT can be considered ready for prime time. Although these 2 trials provide interesting data, we need more studies to establish the active ingredient or ingredients in FMT, the ideal donor, the ideal recipient, the best mode of delivery, and the best “dose.” An adequately powered trial will likely require several hundred patients and may not be feasible in the near future. The availability of stable, encapsulated formulations and frozen banked donor material will facilitate these studies.

We have been treating our IBD patients with immunomodulation for several decades. Perhaps microbial modulation via FMT is another treatment strategy, but we are not there just yet. Based on the current data, FMT should remain in clinical trials and not clinical practice. There are 5 randomized, controlled trials of FMT in UC that are registered on clinicaltrials.gov that hopefully will shed additional light on the subject (NCT02291523, NCT02330653, NCT02390726, NCT01896635, and NCT02335281).

**ARI M. GRINSPAN**
Department of Medicine
The Dr. Henry D. Janowitz Division of Gastroenterology
Icahn School of Medicine at Mount Sinai
New York, New York

**COLLEEN R. KELLY**
Department of Medicine
Lifespan Women’s Medicine Collaborative
The Miriam Hospital
Alpert Medical School of Brown University
Providence, Rhode Island

References


Obesity and Hepatocellular Carcinoma: A Complex Relationship

Hepatocellular carcinoma (HCC) has seen a dramatic increase in incidence over the last 4 decades. This increase in incidence has mirrored an increase in end-stage hepatitis C infection, and has also mirrored worsening of the obesity epidemic that has plagued the United States and the rest of the world. Prior studies have shown an association with obesity and HCC, but have not controlled consistently for well-known risk factors. A pathophysiological relationship between obesity, the presence of non-alcoholic steatohepatitis (NASH), and HCC has also been hypothesized previously. In the current issue of Gastroenterology, Hassan et al report a case-control study from a large, referral-based cancer center to assess the impact of early age obesity on the risk of developing HCC. The authors used questionnaires to identify common risk factors for the development of HCC and to identify past obesity. Statistical analysis revealed a significant relationship between early age obesity and the onset of HCC. This is an interesting report which addresses obesity as a life-long risk factor for eventual development of HCC—a challenging area with confounding variables but one that seems to be increasingly important.

This study has the advantage of a large population and the ability to control for many known risk factors for HCC, such as viral hepatitis, and the findings are consistent with a growing clinical impression that obesity imparts a substantial risk of HCC. Nonetheless, one can reasonably raise some questions regarding these conclusions. For example, there is the possibility of recall bias owing to the questionnaire-based data collection. However, this method for measuring past obesity using memory recall has been evaluated previously and it was found to be generally reliable. On the other hand and somewhat interestingly, one of these studies also pointed out that obese individuals tended to underestimate their weight and lean individuals tended to overestimate their weight, an observation that if present in this study would only magnify the observed effect.

There are also limited data on the effect of occult cirrhosis on the outcome. This is a challenging and somewhat thorny issue; cirrhosis, an established risk factor for HCC, may be present without overt manifestations, presumably through silent progression of NASH for which obese patients are at substantial risk. The question becomes to what extent the risk of HCC in obesity is independent of NASH and related liver injury. Thus, it would be interesting, albeit challenging and maybe impossible, to see a comparison of obese patients with HCC without underlying NASH-related liver injury compared with controls to assess directly the impact of obesity outside the setting of unrecognized liver disease. Relevant to the probability that most such cases are related to NASH, another factor to consider is the use of statin medications. Previous studies have suggested that statins may actually reduce the risk of HCC, although the possible mechanisms of this effect have yet to be confirmed or elucidated.

Despite these limitations, this is the first study of this size to control specifically for other known risk factors of HCC when evaluating the impact of obesity on HCC. It also allows for analysis of the potential synergistic effect that obesity may have on other risk factors for HCC. A challenging aspect of evaluating current obesity in patients with cirrhosis is the presence of ascites at the time of presentation that, along with body mass wasting, can obscure the assessment of obesity. By instead evaluating “past obesity,” this study avoids this bias and demonstrated an association between prior obesity and HCC risk. This is the first study of its kind to suggest a temporal relationship between past obesity and the occurrence of future HCC. This information should help to inform future studies to not only model the impact of obesity on development and prognosis...