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The microbial one-hit wonder

Brigida A. Rusconi1 and Rodney D. Newberry2

Intestinal inflammation, in the absence of infection, occurs from contributions by genetics and environment. Chen et al. (2021. J. Exp. Med. https://doi.org/10.1084/jem.20210324) challenge this concept by demonstrating that a dominant transmissible dysbiotic microbial community predisposes to intestinal inflammation in absence of genetic alterations.

Decades of studies have led to the understanding that alterations, or dysbiosis, of the gut microbiota can be a significant contributor to intestinal inflammation. Yet our understanding of how we arrive at these dysbiotic states, how they are maintained, and why it is so difficult to reverse them have remained cryptic. In this issue, Chen et al. (2021) identify that a genetic alteration in goblet cells results in a mucus secretory defect that induces a dysbiotic state potentiating intestinal inflammation, and once established, this dysbiosis becomes dominant, transmissible over the healthy microbiota and genetics, and drives an inflammatory phenotype, suggesting that in some situations “one hit” from the dysbiotic gut microbiota could be sufficient to potentiate intestinal inflammatory disease (see figure).

Forkhead box protein O1 (Foxo1) belongs to the family of proteins that are mainly studied for their role as transcription factors. Prior work demonstrated that loss of Foxo1 in immune cells results in the development of intestinal inflammation (Wu et al., 2018). Furthermore, Foxo1 has been implicated in controlling cell proliferation and apoptosis in multiple organisms and cell types (Eijkelenboom and Burgering, 2013). In this manuscript, Chen et al. use an intestinal epithelial cell (IEC)-specific Cre recombinase system (Vil1Cre; see panel A of figure), as well as epithelial cell subset-specific Cre recombinases to investigate the role of Foxo1 in the control of intestinal barrier integrity and subsequent susceptibility to intestinal inflammation (Chen et al., 2021). The authors narrow down the phenotype to reduced secretion of mucus by goblet cells resulting in a thinning of the mucus layer. In epithelial cells Foxo1 is located cytosolically and interacts with Atg5 to regulate autophagy and subsequent mucin granule release (see panel A of figure). The importance of the cytosolic location was confirmed with Foxo1AAA animals that express a Foxo1 variant that is restricted to the nucleus, which fails to correct the loss of Foxo1 in IECs. The lack of transcriptional activity of Foxo1 in goblet cells is further highlighted by the nearly identical mRNA profiles of Vil1Cre Foxo1fl/fl and Foxo1fl/fl mice. Not even genes involved in mucus production were altered in absence of Foxo1. However, loss of Foxo1 by IECs resulted in a reduction in the mucus layer, increase in mucinase-producing bacteria, decrease in short-chain fatty acid (SCFA)-producing bacteria, and increased susceptibility to colitis (see panel A of figure). This phenotype was transmissible and dominant in co-housed WT mice and could be rescued by SCFA or continuous supplementation with SCFA-producing bacteria. SCFA have been shown to promote mucus production and secretion, suggesting that loss of SCFA-producing bacteria in this self-sustaining dominant microbial community underlies the transmissibility of this colitogenic phenotype to WT mice (see panel A of figure). This is an excellent example of how a single genetic alteration can result in additive effects and a potentially transmissible phenotype in the absence of genetic alterations in the recipient.

The effects of a dysbiotic community are often framed as a loss of protective commensals or the gain of detrimental bacteria. Chen et al. show in this issue that changes in the host’s mucus layer promote the presence of bacterial taxa with strong mucin-degrading activities that displace beneficial commensals, such as Akkermansia muciniphila. Oral supplementation with A. muciniphila reduced dextran sulfate sodium (DSS) colitis severity and improved intestinal barrier function in Vil1Cre Foxo1fl/fl mice (see panel A of figure). These results point to the requirement of continuous supplementation of beneficial commensals in hosts that are not able to maintain the niche due to genetic alterations. Similar shifts in the intestinal microbial community have been observed in other animal models with impaired mucus. The mucus provides a unique niche for

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As a result of improved TJs, dietary sup-
et al., 2008). Indeed, dietary supplementa-
lar localization of TJs in
by affecting tight junctions (TJs; Waldecker
in the mucosal layer. SCFAs have been
bacteria that produce SCFAs, which reside
surprising that
anti-microbial peptides. It is therefore not
prevents invasion of pathogenic bacteria
compartment (Olszak et al., 2014), the re-
duced inflammation observed in animals
SCFAs could be partially mediated
immune cells and not only the
epithelial compartment. Vil1Cre Foxo1fl/fl mice
do not have any defects in the
immune compartment at steady-state but could still
have an abnormal inflammatory response
upon injury due to intrinsic changes to the
immune compartment.

While widely accepted, the contribution of the gut microbiome and dysbiosis to
inflammatory bowel disease (IBD) may be
variable and complex, from potentially
being a less prominent component in very-
early-onset IBD, which can be a monoge-
netic disorder, to potentially a more dominant
component, which may be corrected with
fecal microbiota transplant (FMT). Mouse
models reflect the variability of dysbiosis
on susceptibility to intestinal inflamma-
tion, with the dysbiotic microbiotas often
viewed as recessive or dominant (Kiesler
et al., 2015). Cohousing WT mice with
Il10−/− mice prevents spontaneous colitis
in the latter, indicating that this recessive
dysbiotic microbial community can be
corrected by exposure to a dominant WT
intestinal community (see panel B of figure;
Shanmugam et al., 2014). In addition, other
 genetic models can be rescued by cohousing
or fecal transfer from WT mice (Kiesler
et al., 2015). Conversely, in some situations
the protective microbial community is not
entirely dominant or recessive. Deletion of
tata element modulatory factor (Tmf−/−) re-
results in decreased susceptibility to colitis
due to a more diverse microbial community
(Bel et al., 2014). When these mice are co-
housed with WT mice, WT become more
protected from colitis, while the Tmf−/− be-
come more susceptible (see panel C of fig-
ure). In this case, the microbiotas cause a
reversal of outcomes, likely due to exchange
of key taxa. However, when Tmf−/− mice are
separated following cohousing, the micro-
bial community drifts back to a protective
state (see panel C of figure). The concept of a
dominant colitogenic dysbiotic community
is illustrated by the Tbx21−/− Rag2−/− (TRUC)
mice (Garrett et al., 2007). Cohousing WT
mice with TRUC mice or cross-fostering WT
mice with TRUC dams induced colitis in
WT mice (see panel E of figure). This dem-
strates that not only can the colitogenic
dysbiotic microbiota dominate, it can be
maternally transmitted and potentiate col-
tis independent of the genetics of the off-
spring (Garrett et al., 2010). In this issue,
Chen et al. describe a microbial dysbiosis
occurring as a result of a genetic defect in
goblet cells, which is not only necessary, but
sufficient to induce increased susceptibility
to intestinal inflammatory insults in genet-
ically normal mice (Chen et al., 2021). Germ-
free Foxo1fl/fl mice reconstituted with fecal
content from Vil1Cre Foxo1fl/fl mice have reduced
mucus thickness and worsened DSS colitis.
Since germ-free mice have an abnormal

Defects in mucus secretion due to the loss of Foxo1 in goblet cells cause thinning of the mucus layer
impacting the microbial community and increasing susceptibility to DSS colitis (Chen et al., 2021). (A) Schematic of the findings described by Chen et al. Vil1Cre Foxo1fl/fl mice have a thinning of the mucus layer due to autophagy defect, causing a loss of A. muciniphila and SCFA with an increase in mucinase-rich members of the Bacteroides and Ruminococcus. This dysbiotic state is dominant and self-sustaining compared with other IBD mouse models. (B) Il10 KO model microbiota is recessive when cohoused with WT (Shanmugam et al., 2014). (C) Tmf−/− and WT microbiotas are both dominant when cohoused (Bel et al., 2014). (D) IEC-specific Foxo1 Cre model microbiota is dominant in cohousing over Cre negative (Chen et al., 2021). (E) TRUC microbiota is dominant in cohousing or cross-fostering over WT (Garrett et al., 2007).
intestinal immune compartment, the authors used cohousing of Vil1Cre Foxo1^fl/fl with Foxo1^fl/fl littermates to confirm the transmission of a dysbiotic state to Foxo1^fl/fl and increased sensitivity to DSS colitis (see panel D of figure; Chen et al., 2021). The use of littermates is a critical factor for studies that have a microbial component, since preweaning events can define the adult microbial community. For example, an initial publication described constitutive inflammasome KO mice to have a dysbiotic state that could be transmitted to WT mice (Elinav et al., 2011). However, subsequent studies using littermates showed that the dysbiotic community does not develop if the animals are raised together even in the F2 generation (Lemire et al., 2017). The data from Chen et al. allow for an expansion of the concept of microbially driven diseases as it demonstrates that there can be a transmissible disease state in absence of underlying genetic alterations. A recent publication by Petersen et al. describes a similar dominant microbial community in a genetic model of obesity (Petersen et al., 2019). Co-housing of T-Mydd88^−/− with WT littermates led to an increase of weight gain in the latter despite being on a regular diet.

The implications of the roles of the microbiota in these models has profound impact on our interpretations of the drivers and origins of IBD and how it might be treated. It has been appreciated that despite extensive genome-wide associations studies, the observed genetic polymorphisms do not account for all of the predicted heritability of IBD (Gordon et al., 2015), and that this “missing heritability” may in part be explained by the gut microbiota, which is largely maternally acquired. Overlaying these observations might suggest that an individual lacking genetic risk to develop dysbiosis might obtain a dominant and persistent dysbiotic microbiota from a mother with this genetic risk, thus contributing to the missing heritability phenomenon. Further, it might suggest that these individuals, or individuals acquiring this dysbiotic microbiota in other ways, could be refractory to FMT in the absence of apparent genetic risk for dysbiosis. Thus, the observations presented here further raise the question of whether dysbiotic gut microbial communities could provide one hit to potentiate intestinal inflammation.

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**References**


