pipecolic acid (a presynaptic modulator of γ-aminobutyric acid levels), and serine (an obligatory co-agonist at the glycine site of the N-methyl-D-aspartate receptor). Propionate, a short-chain fatty acid product of gut microbial-community metabolism of dietary fiber, affects expression of genes involved in intestinal gluconeogenesis via a gut–brain neural circuit involving free fatty-acid receptor 3; this effect provides a mechanistic explanation for the documented beneficial impact of dietary fiber in enhancing insulin sensitivity and reducing body mass and adiposity.

Studies of a mouse model (maternal immune activation) with stereotyped/repetitive and anxiety-like behaviors indicate that treatment with a member of the human gut microbiota, *Bacteroides fragilis*, corrects gut barrier (permeability) defects; reduces elevated levels of 4-ethylphenylsulfate, a metabolite seen in the maternal immune activation model that has been causally associated with the animals' behavioral phenotypes; and ameliorates some behavioral effects. These observations highlight the importance of further exploration of potentially co-evolved relationships between the microbiota and host behavior.

Immune Function Many foundational studies have shown that the gut microbiota plays a key role in the maturation of the innate as well as the adaptive components of the immune system. The intestinal epithelium, which is composed of four principal cell lineages (enterocytes plus goblet, Paneth, and enteroendocrine cells), acts as a physical and functional barrier to microbial penetration. Goblet cells produce mucus that overlies the epithelium, where it forms two layers: an outer (luminal-facing) looser layer that harbors microbes and a denser lower layer that normally excludes microbes. Members of the Paneth cell lineage reside at the base of crypts of Lieberkühn and secrete antimicrobial peptides. Studies in mice have demonstrated that Paneth cells directly sense the presence of a microbiota through expression of the signaling adaptor protein MyD88, which helps transduce signals to host cells upon recognition of microbial products through Toll-like receptors (TLRs). This recognition drives expression of antibacterial products (e.g., the lectin RegIIIγ) that act to prevent microbial translocation across the gut mucosal barrier.

The intestine is enriched for B cells that produce IgA, which is secreted into the lumen; there it functions to exclude microbes from crossing the mucosal barrier and to restrict dissemination of food antigens. The microbiota plays a key role in development of an IgA response: germ-free mice display a marked reduction in IgA+ B cells. The absence of a normal IgA response can lead to a massive increase in bacterial load. B cell–derived IgA that targets specific members of the gut microbiota plays an important role in preventing activation of microbiota-specific T cells.

Gut bacterial species elicit development of protective T_H17 and T_H1 responses that help ward off pathogen attack. Members of the microbiota also promote the development of a specialized population of CD4+ T cells that prevent unwarranted inflammatory responses. These regulatory T cells (T_{regs}) are characterized by expression of the transcription factor forkhead box P3 (FOXP3) and by expression of other cell-surface markers. There is a paucity of T_{regs} in the colonic lamina propria of germ-free mice. Specific members of the microbiota—including a consortium of *Clostridium* strains isolated from the mouse and human gut as well as several human-gut *Bacteroides* species —expand the T_{reg} compartment and enhance immunosuppressive functions.

The microbiota is a key trigger in the development of inflammatory bowel disease (IBD) in mice that harbor mutations in genes associated with IBD risk in humans. Moreover, components of the gut microbiota can modify the activity of the immune system to ameliorate or prevent IBD. Mice containing a mutant ATG16L1 allele linked to Crohn's disease are particularly susceptible to IBD. Upon infection with mouse norovirus and treatment with dextran sodium sulfate, expression of a hypomorphic ATG16L1 allele leads to defects in small-intestinal Paneth cells and renders mice significantly more susceptible to ileitis than are wild-type control animals. This process is dependent on the gut microbiota and highlights how the intersection of host genetics, infectious agents, and the microbiota can lead to severe immune pathology; i.e., the pathogenic potential of a microbiota may be context-dependent, requiring a confluence of factors. An important observation is that members of the gut microbiota, including *B. fragilis* or members of *Clostridium*, prevent the severe inflammation that develops in mouse models mimicking various aspects of human IBD.

The gut microbiota has been implicated in promoting immunopathology outside of the intestine. Multiple sclerosis develops in conventionally raised mice whose CD4+ T cell compartment is reactive to myelin oligodendrocyte protein; their germ-free counterparts are completely protected from development of multiple sclerosis–like symptoms. This protection is reversed by colonization with a gut microbiota from conventionally raised animals.

Inflammasomes are cytoplasmic multiprotein complexes that sense stress and damage-associated patterns. Mice deficient in NLRP6, a component of the inflammasome, are more susceptible to colitis induced by administration of dextran sodium sulfate. This enhanced susceptibility is associated with alterations in the gut microbiota of these animals relative to that of wild-type controls. Mice are coprophagic, and co-housing of NLRP6-deficient mice with wild-type mice is sufficient to transfer the enhanced susceptibility to colitis induced by dextran sodium sulfate. Similar findings have been reported for mice deficient in the inflammasome adaptor ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain). ASC-deficient mice are more susceptible to the development of a model of nonalcoholic steatohepatitis. This susceptibility is associated with alterations in gut microbiota structure and can be transferred to wild-type animals by co-housing.

Obesity and Diabetes Germ-free mice are resistant to diet-induced obesity. Genetically obese *ob/ob* mice have gut microbial-community structures that are profoundly altered from those in their lean wild-type (+/+) and heterozygous +/*ob* littermates. Transplantation of the *ob/ob* mouse microbiota into wild-type germ-free animals transmits an increased-adiposity phenotype not seen in mice receiving microbiota transplants from +/+ and +/*ob* littermates. These differences are not attributable to differences in food consumption but rather are associated with differences in microbial community metabolism. Roux-en-Y gastric bypass produces pronounced decreases in weight and adiposity as well as improved glucose metabolism—changes that are not ascribable simply to decreased caloric intake or reduced nutrient absorption. 16S rRNA analyses have documented that changes in the gut microbiota after this surgery are conserved among mice, rats, and humans; animal studies have demonstrated these changes along the length of the gut but most prominently downstream of the site of surgical manipulation of the bowel. Notably, transplantation of the gut microbiota from mice that have undergone Roux-en-Y gastric bypass to germ-free mice that have not had this surgery produces reductions in weight and adiposity not seen in recipients of microbiotas from mice that underwent sham surgery.

The gut microbiota confers protection against the development of type 1 diabetes mellitus in the non-obese diabetic (NOD) mouse model. Disease incidence is significantly lower in conventionally raised male NOD mice than in their female counterparts, while germ-free males are as susceptible as their female counterparts. Castration of males increases disease incidence, while androgen treatment of females provides protection. Transfer of the gut microbiota from adult male NOD mice to female NOD weanlings is sufficient to reduce the severity of disease relative to that among females receiving a microbiota from an adult female or an unmanipulated female. The blocking of protection by treatment with flutamide highlights a functional role for testosterone signaling in this microbiota-mediated protection against type 1 diabetes.

NOD mice deficient in MyD88, a key component of the TLR signaling pathway, do not develop diabetes and exhibit increased relative abundance of members of the family-level taxon Lactobacillaceae. Consistent with these findings, investigators have documented lower levels of representation of members of the genus *Lactobacillus* in children with type 1 diabetes than in healthy controls. Components of lactobacilli have been shown to promote gut barrier integrity. Studies