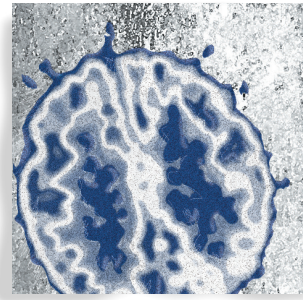# Translational research

The mind-body-microbial continuum

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Our understanding of the vast collection of microbes that live on and inside us (microbiota) and their collective genes (microbiome) has been revolutionized by culture-independent "metagenomic" techniques and DNA sequencing technologies. Most of our microbes live in our gut, where they function as a metabolic organ and provide attributes not encoded in our human genome. Metagenomic studies are revealing shared and distinctive features of microbial communities inhabiting different humans. A central question in psychiatry is the relative role of genes and environment in shaping behavior. The human microbiome serves as the interface between our genes and our history of environmental exposures; explorations of our microbiomes thus offer the possibility of providing new insights into our neurodevelopment and our behavioral phenotypes by affecting complex processes such as inter- and intra personal variations in cognition, personality, mood, sleep, and eating behavior, and perhaps even a variety of neuropsychiatric diseases ranging from affective disorders to autism. Better understanding of microbiome-encoded pathways for xenobiotic metabolism also has important implications for improving the efficacy of pharmacologic interventions with neuromodulatory agents.

Advances in DNA sequencing technology have provided researchers with the exciting opportunity to examine microbial diversity at different sites on the human body without having to rely on cumbersome and oftentimes inadequate culture-based methods.[1] Our guts contain tens of trillions of microbes, by far the largest collection among our various body habitats. The gut ecosystem is dominated by members of one of three domains of life on earth, Bacteria, although members of the other two known domains, Archaea and Eukarya, are also represented, as are their viruses. Culture-independent ("metagenomic") studies have shown that (i) early colonization of the body is affected by the mode of delivery[2]; (ii) assembly of the gut microbial community occurs over the course of the first 3 years of life[3]; (iii) there is pronounced interpersonal variation in the bacterial species composition of a given body habitat[1,4]; (iv) within an individual microbial community structure varies considerably between body habitats[1]; and (v) feces provide an excellent, safely obtained representative sample for defining interpersonal differences in gut community ecology.[5]

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Twin studies have also provided important insights about the relative effects of genotype and environment in shaping the structures of our microbial communities. Remarkably, the overall degree of similarity of gut bacterial community composition is the same in adult mono- and dizygotic twin pairs.[6] Moreover, members of the same family share a greater degree of similarity in their gut bacterial community configurations than do those belonging to different families.[6] Each individual contains a distinct collection of gut bacterial species, even if they are a member of a monozygotic twin pair.[6,7] While there does not appear to be a core set of abundant bacterial species in a given body habitat that is shared among all humans,[7,8] there is a shared set of microbial genes, at least in the gut.[6] Families not only share this core microbiome but also have a greater degree of overall similarity in the variable component when compared with unrelated individuals.[6]

Together, these findings reveal a flow of microbes and microbial genes that occur between members of a family and across generations within a kinship. This flow appears to be influenced by early environmental exposures, as evidenced by the lack of a significant difference in the overall degree of phylogenetic similarity of gut communities among mono- compared with dizygotic twin pairs. Early environmental exposures include physical contact among family members, but also exposure to various diets, including mother's milk. As such, it is reasonable to conclude that features of our human postnatal development, including central nervous system (CNS) functions, are influenced by factors that also impact the assembly and operations of our microbial communities. The fact that intrapersonal variation in microbial community composition within a body habitat is substantially less than interpersonal variation means that each individual represents his or her own best control for assessing the effects of various disturbances/perturbations (eg, dietary, pharmacologic) on microbiota/microbiome structure and function, while family provides the "next best" reference controls. One of the striking features of a variety of neuropsychiatric diseases (eg, affective disorders) is their variance, with differences observed across individuals in terms of their susceptibility, in the combination of systems that are disturbed, and in the therapeutic and adverse responses to various medications. This article underscores the possibility that the microbiome represents a source of this observed variance.

Microbial communities that affect behavior

The literature is replete with descriptions of the effects of infection with a variety of eukaryotic, bacterial, and viral species on host behavior. An effect with a well-understood evolutionary basis is the interaction between *Toxoplasma gondii*—the eukaryotic pathogen that causes toxoplasmosis—and its rodent host. *T. gondii*, like many parasites, has a complex lifestyle that is partly completed in one host (rodent) and then in another host (feline); the rodent host loses its innate fear of the smell of bobcat urine, and thus seeks out locations with that smell,[9,10] increasing its chances of being consumed and transmitted to the other host. *T. gondii* has also been linked to behavioral effects in nontarget hosts, including humans, where gender-specific effects on personality traits including self-control, warmth, and novelty seeking (eg, tendency towards high-risk activities) have been observed.[11-13] Many viruses affect behavior; for example, bornavirus (has been related to mania and schizoaffective disorders[14-16]); human immunodeficiency virus (linked to cognitive impairment, affective disorders, and psychosis[17-19]), rabies (a zoonotic infection caused by an enveloped single-stranded RNA virus that in its fulminant form is associated with hydrophobia[20]). The same is true of bacteria; cognitive and emotional disturbances have been associated with *Brucella suis* infection[21]; manic and psychotic symptoms resistant to antipsychotics but treatable with antibiotics during infection with *Leptospira*[22]; baseline depression and anxiety caused by *Mycobacterium tuberculosis*[23]; and obsessive-compulsive disorder (OCD) and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).[24,25]

Poorly understood from a mechanistic perspective, but perhaps more intriguing, are cases where an entire microbial community impacts host behavior. These effects have been noted when comparing the phenotypes of mice reared from birth and from generation to generation under sterile conditions in specialized gnotobiotic isolators that prevent any exposure to environmental microbes ("germ-free" animals) with mice that have been reared in the presence of microbes but under specified pathogen-free conditions ("conventionally raised" animals), or mice that were reared germ-free and then colonized at a given point in postnatal or adult life with a microbiota transplanted from a conventionally raised donor (so called "conventionalized" animals). For example, germ-free mice exhibit basal behaviors in the ele-

vated plus maze (EPM) that are indicative of reduced anxiety levels.[26] Using an implantable detector of locomotion for quantitative phenotyping, Backhed et al[27] found that germ-free wild-type (C57Bl/6J) mice have significantly increased movement compared with their microbe-laden counterparts, whether on a standard plant polysaccharide-rich, low-fat chow diet or a diet high in simple sugars and fat (Western diet). Conventionally-raised genetically engineered mice lacking Toll-like Receptor 5 (TLR5), a component of the innate immune system that recognizes bacterial flagellin, have an altered gut microbiota, eat substantially more than their conventionally-raised wild-type counterparts, and become obese. The same phenotype can be transmitted to germ-free wild-type mice by transplanting a gut microbiota from a conventionally-raised TLR5 knockout donor,[28] suggesting that it is the induced change in the microbiota that is changing the eating behavior. Fascinatingly, these mice also develop metabolic syndrome, which is a frequent complication of the use of certain psychotropic drugs. It is outside the scope of this review to cover the extensive literature relating certain psychotropic drugs to the development of obesity and metabolic syndrome. However, data from models such as the TLR5 knockout mice indicate that there can be links between the microbiota and metabolic syndrome,[28] and we know that the microbiota can have large effects on the metabolism of certain drugs.[29] Therefore it is tempting to speculate that the microbiota should be considered as a possible factor influencing metabolic syndrome in response to psychotropic drugs in a subset of patients. In mice, microbial communities also appear to be instrumental in generating scents (skin odor) and affect mate preferences.[30,31] This link between odor and mate preference has also been suggested, but not established in humans,[32] although the connection between bacteria and mate choice has been established in fruit flies[33] and may therefore be widespread.

Diet, behavior, and the gut microbiota

There are numerous reports of diet affecting various manifestations of psychiatric disorders, including schizophrenia, mono- and bipolar depression,[34] attention deficit –hyperactivity disorder (ADHD),[35,36] and autism,[37,38] although the underlying mechanisms are obscure and not all studies are adequately controlled. Diet has also been shown to play a key role in shaping the structure and functional properties

of the gut microbiota in both humans[5,34] and in mice.[29,39-43] In considering the underlying mechanisms for how diet affects behavior, the microbiota cannot be overlooked, because associations between diet and psychiatric disorders are often thought to be related to metabolites of dietary components.[35,44,45] The enzymes that produced these metabolites may be encoded in our human genome, or in the genomes of the microbes that inhabit our gut. The surprisingly high compositional variation in gut bacteria across individuals[6] stands in stark contrast to the surprisingly small amount of genetic diversity uncovered in the sequencing of our human genomes. Differences in our microbial communities may thus be one of the most important factors in differences in the metabolites that individuals extract from determining the differences in the metabolites that different individuals may extract from similar diets.

Is the gut microbiome involved in autistic spectrum disorders?

DSM-IV (and *ICD-10*) classifies a number of disorders under the broad category pervasive developmental disorder (PDD) or Autistic Spectrum Disorders (ASD) and include: autism or autistic disorder (OMIM 209850), Asperger syndrome (AS), Rett syndrome (RTT; OMIM 312750), childhood disintegrative disorder (CDD), and pervasive developmental disorder-not otherwise specified (PDD-NOS).[46] The prevalence of the broader ASD phenotype can approach ~0.5% in some populations.[36] Depending upon the phenotyping method used and disease severity, symptoms can be detected in very early childhood.[47] Host genetic factors appear to play a key role, with a large British study reporting a significantly higher concordance rate of certain phenotypic characteristics among monozygotic compared with dizygotic twins (60% to 92% versus 0% to 10%).[48] Genome-wide association studies have revealed a number of loci strongly associated with ASDs, including those involved in synaptogenesis and synaptic function (eg, neurexins and the neuroligins that bind them[49,50]).

Although heritability in the British twin study was calculated to be >90%, environmental influences may be still considerable. A "gut-brain" linkage for ASDs has been proposed, based in part on reports that children with ASDs often experience a range of gastrointestinal disorders. [51,52] A few reports indicate that children with ASDs have a greater representation of members of the

bacterial family Clostridiales[51-53] in their fecal microbiota, although as noted below, comprehensive analyses of gut microbial ecology in affected and reference control populations have not yet appeared in the literature.

Microbial metabolism may have an impact on disease pathogenesis in ASD. Initial evidence for this came from a small study of autistic children treated with the minimally absorbed glycopeptide antibiotic vancomycin; short-term improvement was reported,[54] leading to the suggestion that autistic symptoms may be related to the production of neurotoxic metabolites by the gut microbiota. Two subsequent studies of metabolites in urine have supported that microbial metabolism results in altered metabolite profiles in children with ASD. The application of pattern recognition analysis to compare ^{1}H-NMR spectra from the urine of children with ASD to their relatives and age-matched controls indicated that among the metabolites that changed in concentration with autism were mammalian-microbial cometabolites, including dimethylamine, hippurate, and phenyacetyl-glutamine.[45] Another study showed that urinary levels of 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA) are higher in children with autism compared with neurotypical controls.[44] One potential source of this compound is the conversion of phenylalanine from the diet to m-tyrosine and then to 3-hydroxyphenyl-propionic acid by microbial enzymes, followed by conversion to HPHPA by human enzymes.[44] *m*-Tyrosine induces a characteristic behavioral symptom in rats that includes stereotypical behavior, hyperactivity, and hyper-reactivity,[55] indicating that this compound may be specifically contributing towards autistic behaviors. A microbial origin for HPHPA is supported by its decrease in urine after patients were treated for Clostridial infections with metronidazole, an antibacterial agent with specificity toward anaerobic bacteria.[44] Some species within the Clostridiales are known to produce phenylpropionic acid and/or monohydroxyphenylpropionic acid, which are very closely related biochemically to m-tyrosine and HPHPA.[44]

A link between autism, gastrointestinal problems, and gut microbiota suggests that diet has the potential to impact symptoms, and parents of autistic children have long been exploring the impact of dietary and microbiota manipulations on behavior, for instance commonly using gluten-free and/or casein-free (GF/CF) diets, probiotics, and nutritional supplements. Two randomized controlled trials of the GF/CF diet indicated that it may improve symptoms in some children,[37,38] although these trials were small, both in terms of size and duration. Although the GF/CF diet may improve symptoms by inducing changes in the microbiota and/or their metabolites, another mechanism is by increasing gut integrity. Abnormally high intestinal permeability (IPT), or a "leaky gut," has also been associated with autism, suggesting that autistic individuals may have increased sensitivity to components of our diet and their metabolites, because they can more easily access the bloodstream.[56] Autistic individuals on a GF/CF diet had significantly lower intestinal permeability compared with individuals on an unrestricted diet.[56] Genetic factors have also been implicated in impaired gut integrity in autistic individuals; a mutation affecting the expression of the gene encoding the MET receptor tyrosine kinase has been associated with both ASD and gastrointestinal conditions, and functions in both brain development and gastrointestinal repair.[57] To our knowledge no study has evaluated how the GF/CF diet affects the structure, gene expression, and function of the gut (fecal) microbiota or microbiome.

In general, studies of the gut microbiota in children with ASDs have been very limited, typically examining just a few subjects, with shallow sequencing of bacterial 16S rRNA gene amplicons generated from just a few biospecimens/participant (ie, extensive time series studies have not been performed), and without concomitant analyses of (i) microbiome gene content (by shotgun sequencing of total fecal community DNA); (ii) microbiome gene expression (by RNA-Seq profiling of the community's meta-transcriptome); or (iii) microbial metabolism (or host-microbial cometabolism, eg, by MS or NMR). Several groups are currently conducting these types of analyses. The results may identify microbiota/microbiome biomarkers useful for improved classification schemes, for understanding pathophysiology, and for monitoring the efficacy of therapeutic interventions. With improved phenotyping (eg, using functional magnetic resonance imaging [fMRI] or monitoring eye-tracking) earlier diagnosis may be possible, allowing for prospective characterizations of microbial community metabolism and host-microbial cometabolism during postnatal development (and in the mother). This emphasis on the potential importance of microbial metabolism is based in part on the hypothesis that neuroactive compounds produced by the gut microbiota may play an important role in shaping synaptogenesis and synaptic

function in the developing brain, especially in individuals with genetic mutations affecting synaptic components or neurotransmitters that operate at various types of synapses.

The gut microbiome and therapeutics

The gut microbiota has the capacity to process xenobiotics (compounds foreign to a living organism), including over 30 known drugs administered to humans,[58-61] through a variety of biotransformations including reduction, dehydroxylation, acetylation/deacetylation, proteolysis, denitration, and hydrolysis.[60]

One avenue for exploring the inter-relationships between orally administered xenobiotics, the human gut microbiome, and host metabolism is to use gnotobiotic animals colonized with defined consortia of microbes from human or animal donors.[62] A notable example was the use of rats that were either germ-free or colonized with a human fecal microbiota to investigate the microbial production of equol, a metabolite with a proposed protective effect against cancer, from a soy-isoflavone containing diet.[63] Humans vary in their ability to produce equol from daidzein (a soy-isoflavone). This metabolic phenotype is transmissible via the microbiota, where germ-free rats colonized with a fecal sample from a high equol-producing human donor excreted significant amounts of equol, while gnotobiotic rats colonized with a fecal sample from a low equol-producing donor had no detectable equol in their urine.[63]

In addition to directly impacting the metabolism of xenobiotics, the gut microbiota can also modify inactive drugs that have been conjugated and secreted in the bile. These reactions rely on bacterial glucuronidases and sulfatases that have evolved to hydrolyze bile acids conjugated to glycine or taurine.[64] The resulting bacterial deconjugation allows the products to be reabsorbed. In some cases, this mechanism results in an extension of the half-life of certain drugs, including estrogens,[65] digitoxin,[60] indomethacin,[66] and even morphine.[60]

These observations raise the possibility of blocking microbial deconjugation through combination therapy, to avoid recirculation. As an illustration of this concept, Wallace et al[67] focused on CPT-11 (irinotecan), a chemotherapeutic drug currently in clinical use that has a dose-limiting side effect of severe diarrhea. The administered compound is a prodrug that is processed in vivo to yield the active metabolite SN-38.[68] SN-38 is then glucuronidated in the liver by uridine diphosphate (UDP)-glurunosyltransferase to form SN-38G,[69] which is secreted through the bile into the small intestine. As with other compounds, this inactive form is then reactivated by bacterial β-glucuronidases,[70] contributing to the development of delayed-onset diarrhea in 40% of treated patients.[71,72]

One approach to limit this bacterial metabolism would be to use broad-spectrum antibiotics.[71] However, recent metagenomic studies have highlighted the long-term effects that antibiotic treatment can have on the commensal microbiota,[73,74] potentially interfering with host-microbial interactions that contribute to maintaining health or preventing disease. Alternatively, if the bacterial enzymes of interest are known, as is the case for irinotecan deconjugation, these enzymes can be targeted. To achieve this goal, *E. coli* β-glucuronidase was purified, its X ray structure determined,[67] and used as the target or a chemical screen that yielded an inhibitor of the bacterial (but not mammalian) enzyme. The lead compound was not bactericidal for several members of the human gut microbiota in vitro, nor was it toxic to mammalian cells. Moreover, surveys of groups of mice treated with CPT-11 alone, or with the enzymatic inhibitor alone, or with both the inhibitor and CPT-11, revealed that combination therapy greatly reduced symptoms.[67]

These findings suggest that the gut microbiota is likely an important mediator of the bioavailability and toxicity of some drugs. How much of the interpersonal variation in pharmacokinetics is due to the microbial versus human component of our metagenomes? Does diet impact drug metabolism via the gut microbiota? As in the case of irinotecan, can combination therapies be developed that block or promote key microbial transformations? Can differences in the metabolism of orally administered drugs be used as biomarkers for differences in gut microbial metabolism that are relevant to the pathogenesis of neuropsychiatric disorders? Although current lists of orally administered drugs known to be subject to microbial modification is small, it seems prudent to explore this avenue when considering psycho/neuroactive drugs that have narrow therapeutic indices, or various idiosyncratic effects.

Conclusions

Our microbial communities both reflect and help define the interactions between our human genotypes and our myriad environmental exposures. In the quest to under-

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stand the genetic and environmental factors that shape the many facets of normal human behavior, the variations in behavior that occur as we age, and the perturbations in our behavior associated with various forms of mental disorders classified according to currently used phenotypic/diagnostic parameters, it seems timely to incorporate studies of our microbiomes. The challenge ahead is in large part "cultural." Groups of clinician-scientists with deep understanding of higher brain function, including how to quantitatively phenotype these functions, must unite with those who study microbial ecology, familiarize each other with their respective conceptual, experimental and computational tools, and then coevolve plans for well-controlled clinical studies. This effort requires crossing traditional disciplinary boundaries and surmounting formidable language barriers. Moreover, since varying cultural traditions (lifestyles) play an enormous role in shaping features of human behavior and our microbial ecology, the "cultural" context in which these human studies are performed must be carefully defined. Nonetheless, the stage for these interdisciplinary initiatives is in many ways already set. For example, the National Institute of Health (NIH)'s Human Connectome Project is waiting to be "connected" to the NIH's Human Microbiome Project. ❏

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El continuo mente-cuerpo-microorganismos

Nuestro conocimiento acerca de la amplia variedad de microbios que viven dentro y fuera de nosotros (microbiota) y de sus genes colectivos (microbioma) ha sido revolucionado por técnicas "metagenómicas" independientes de cultivos y por las tecnologías para secuenciar el ADN. La mayoría de nuestros microbios viven en nuestro intestino, donde ellos funcionan como un órgano metabólico y confieren atributos que no están codificados en nuestro genoma humano. Los estudios metagenómicos están revelando características compartidas y distintivas de las comunidades microbianas que habitan en los diferentes hombres. Una pregunta central en psiquiatría es el papel relativo de los genes y del ambiente en la formación de la conducta. El microbioma humano sirve como la interfaz entre nuestros genes y nuestra historia de exposiciones al ambiente; por lo que las exploraciones de los microbiomas ofrecen una nueva aproximación al neurodesarrollo y a los fenotipos conductuales al influir en complejos procesos como las variaciones inter e intra personales en la cognición, la personalidad, el ánimo, el sueño y la conducta alimentaria, e incluso en una variedad de enfermedades neuropsiquiátricas que van desde los trastornos afectivos al autismo. Una mejor comprensión de las vías codificadas por el microbioma para el metabolismo xenobiótico también tiene importantes implicaciones para mejorar la eficacia de las intervenciones farmacológicas con agentes neuromoduladores.

Le continuum pensée-corps-microbe

Notre compréhension de la grande variété de microbes vivant sur et à l'intérieur de notre corps (microbiotie) ainsi que de leurs gènes (microbiome) a été révolutionnée par des techniques indépendantes des cultures dites « métagénomiques » et les technologies de séquençage de l'ADN . La plupart de nos microbes vivent dans notre intestin où ils fonctionnent comme un organe métabolique présentant des caractéristiques non codées dans notre génome humain. Des études métagénomiques ont montré des caractéristiques partagées et distinctives des colonies microbiennes habitant chez différents êtres humains. Le rôle relatif des gènes et de l'environnement dans l'élaboration du comportement est une question centrale en psychiatrie. Le microbiome humain est une interface entre nos gènes et nos antécédents d'exposition à un environnement ; l'analyse de nos microbiomes nous offre donc la possibilité de regarder autrement notre neurodéveloppement, nos phénotypes comportementaux en influant sur des processus complexes comme la connaissance, la personnalité, l'humeur, le sommeil et l'alimentation et peut-être même sur des maladies psychiatriques allant des troubles affectifs à l'autisme. Une meilleure compréhension des voies codées par le microbiome pour le métabolisme xénobiotique est importante pour améliorer l'efficacité des traitements pharmacologiques par neuromodulateurs.

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