

Current Topics

RESEARCH ADVANCES

Probiotic Heals Leaky Guts in Mice, Improving Autism-Like Symptoms

Carol Potera

Feeding *Bacteroides fragilis* bacteria to mice with autism spectrum disorder (ASD) changes the gut microbiome and improves autism-related behaviors, according to Sarkis Mazmanian at the California Institute of Technology (Caltech) in Pasadena and his collaborators. “Some forms of autism may have an etiology that lies in the gut, not the brain,” he says. “It’s an extraordinary new concept that needs a lot more validation.” Details appeared December 5, 2013 in *Cell* [doi:10.1016/j.cell.2013.11.024].

Autism and ASD are general terms for a group of human disorders involving central nervous system development that typically include difficulties in social interaction and communication, and that also may entail repetitive behaviors. To approximate this human condition in mice, the Caltech researchers injected pregnant mice with an immunostimulant that mimics a viral infection. The offspring of such mice develop ASD-like behavioral symptoms along with increased intestinal permeability and changes to the gut microbiota and metabolites. These latter disturbances are consistent with the gastrointestinal distress and increased intestinal permeability that are prevalent in children with ASD, who also show changes to the gut microbiome.

Mazmanian and his collaborators already knew that *B. fragilis* can repair leaky guts in mice without behavioral abnormalities. Those findings led them

to wonder what might happen if they repaired the leaky gut disorders in ASD mice. More grandly, could treating such mice with probiotics affect their abnormal ASD-related behaviors?

ASD mice fed *B. fragilis* not only showed improvements at the gut level but were better than before being fed the probiotic at communicating with one another, and also showed less repetitive behavior and signs of anxiety, such as being easily startled, according to Mazmanian. ASD mice that ate a comparable diet but without *B. fragilis* showed no such changes in their behavior, he says.

Repairing leaky guts helps to stop bacterially produced metabolites from entering the blood, and that might account for those changes, Mazmanian continues. In particular, blood levels

of 4-ethylphenylsulfate are 46 times higher in mice with ASD than in mice without this disorder, he says. Further, injecting normal mice with this chemical induces them to show anxious behavior. Treating them with *B. fragilis* returns blood levels of 4-ethylphenylsulfate to normal and improves behavior. Strikingly, some autistic children have high levels of a similar chemical, 4-methylphenol sulfate, in their urine.

Rob Knight at the University of Colorado in Boulder calls this Caltech study “groundbreaking,” and points, in particular, to identifying a specific probiotic that can repair leaky guts, albeit in mice, as critical. Provided a comparable probiotic could be identified for people, he adds, “the implications for the mental health of humans are extraordinary.”



Researchers find that altering gut microbiome with probiotics in mice can alleviate symptoms of autism spectrum disorder, pointing to a promising avenue of research on the syndrome in humans. (Photo © faslooff/iStockphoto.)

Probiotic studies of ASD children are in the early planning stages, according to Mazmanian. *B. fragilis* is not commercially available and is not approved for humans. Whether it proves safe or effective for children with ASD remains to be determined, he says. Although “parents of children with ASD are desperate for solutions,” he adds, “we don’t want to oversell our research and give people false hope.”

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RESEARCH ADVANCES

Drug Target Discovery Is Focus for ID Structural Genomics Centers

John Otrompke

The Seattle Structural Genomics Center for Infectious Disease (SSGCID) and the Chicago-based Center for Structural Genomics of Infectious Diseases (CSGID) recently received renewal grants, worth \$25 million over five years and dedicated to solving three-dimensional (3-D) structures of proteins or other macromolecules from microorganisms of biodefense and emerging infectious disease (ID) importance. Solving such structures is part of a broader effort toward discovery and early-stage drug development. Support for the centers comes from the National Institute of Allergy and Infectious Disease (NIAID), part of the National Institutes of Health.

X-ray crystallography is an important component of the work being done by the two consortia. The primary mission for SSGCID, for example, is to determine the structure of about 70 protein targets from the NIAID Category A-C agents, as well as emerging and re-emerging microorganisms responsible for infectious disease, each year for the next five years. Similarly, CSGID applies state-of-the-art, high-throughput structural biology technologies to characterize the

3-D atomic structure of similar proteins.

SSGCID has 5 to 10 structures that are in the early-to-mid stage of lead optimization for drug discovery, while others are very early-stage vaccine candidates, according to SSGCID director Peter Myler from the Department of Global Health at the University of Washington, Seattle. Tuberculosis and malaria are a major focus for the center, he adds. Additional microbial agents under study include the Middle East respiratory syndrome coronavirus (MERS-CoV), a SARS-like respiratory tract-infecting organism that was found in Saudi Arabia in 2012 and continues to circulate throughout the Middle East, and the Bas-Congo virus, which is a relative of the Ebola and rabies viruses.

Researchers affiliated with SSGCID solved about 650 structures in seven years, of which about 40 or 50 were collaborative projects with outside researchers, Myler continues. From 20 to 30 of those structures have been investigated for drug discovery, he says. “During the first five years of our existence, we selected most of our targets by ourselves, but since then, more than half of our targets have been requests by outside investigators.” The center has solved about 250 structures requested by about 160 different researchers from outside the consortium.

“It’s possible that some of the compounds we’re working on could get into phase 1 trials within the next year or two,” says CSGID director Wayne Anderson of Northwestern Feinberg School of Medicine in Chicago. One of the structures that researchers from CSGID and their collaborators are working on—protein PA4794 from the bacterial pathogen *Pseudomonas aeruginosa*—was selected as the NIAID “structure of the month” last January. PA4794 has N-acetyltransferase activity, and selectively acetylates peptides with C-terminal lysines, and this type of protein modifying activity has important “regulatory potential” and

MINITOPIC

U.S. Joins Global Effort To Curb Infectious Diseases

The United States joined 26 other countries as well as several international organizations, including the World Health Organization, the Food and Agriculture Organization, and the World Organization for Animal Health, in efforts to make the world “safe and secure from the threat of infectious disease, and committing to the goals of the Global Health Security Agenda.” Top officials in the Obama administration will confer with representatives from other nations to review progress and chart the way forward on “building a global system for preventing, detecting, and responding to such threats.” At the national level, these efforts are being led by the Departments of Health and Human Services, State, Defense, and Agriculture. In a narrower but similarly spirited development, more than 30 European universities, institutes, and companies, led by GlaxoSmithKline in London and Uppsala University in Sweden, launched a six-year program, called European Gram-Negative Antibacterial Engine (ENABLE), to develop novel antibiotics against gram-negative bacterial pathogens. The portfolio will be expanded through “open calls” to groups outside this consortium, with a goal of completing phase 1 clinical trials for at least one novel antibacterial agent by 2019.

“could prove to be a drug discovery target,” NIAID officials point out.

Meanwhile, investigators at SSGCID recently characterized several proteins from *Mycobacteria tuberculosis* (Mtb) and nontuberculosis (NTM) mycobacteria. They succeeded in solving structures for 16 of the 179 Mtb targets, and