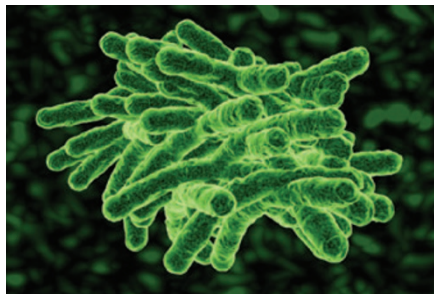
Disrupting bacterial binding to treat infections

Urinary tract infections (UTIs) present a substantial health problem for women, particularly when infections are chronic, recurrent or recalcitrant because of pathogenic mechanisms or antibiotic resistance. In the US, about 15 million women suffer from UTIs each year; 20–40% of women experience recurring infections. Healthcare costs associated with UTIs exceed $2.5 billion per year in the US, according to one estimate.

Most UTIs (85% or more) are caused by uropathogenic strains of *Escherichia coli*. The bacteria enter the urinary tract and use a special fiber called a pilus to attach to the epithelial cells and to each other, forming intracellular bacterial communities. These attachments protect bacteria from host defenses and from antibiotics, contributing to recurrent infections and antibiotic resistance. UTIs are commonly treated with the antibiotic trimethoprim-sulfamethoxazole (TMP-SMZ), but drug-resistant uropathogens are increasing in prevalence and distribution, making UTI a growing public health concern. There is a pressing need for new, effective treatments that neither suffer from nor contribute to antibiotic resistance.

Because pilus binding is essential for the colonization, invasion and resistance of uropathogenic *E. coli*, it represents a potential new target for antimicrobial drugs. Pilus binding is directed by mannose, a component of microbial cell walls. Recently, a group of researchers at Washington University School of Medicine (St. Louis, MO) led by Scott J. Hultgren and James W. Janetka investigated whether disrupting mannose-mediated activity could interfere with pilus binding and improve treatment of UTIs caused by uropathogenic *E. coli*. They developed a series of low-molecular-weight mannose derivatives called mannosides and evaluated their antimicrobial efficacy *in vitro* and their bioavailability in mice. The efficacy of the most promising of the mannosides, called compound 6, was then tested in a mouse model of chronic UTI. Within 6 hours of treatment, mice given compound 6 had significantly lower bacterial numbers in their bladders (*Sci. Transl. Med.* doi:10.1126/scitranslmed.3003021; published online 16 November 2011). Mice given TMP-SMZ also experienced a significant, but smaller, decrease in bacterial numbers.



Raycat at iStockPhoto.com

Compound 6 also prevented mice from developing UTIs when administered prophylactically. "This drug can block the spread of the bacteria that cause urinary tract infections far better than any other previously reported compound," said Hultgren in a press release. "If it has similar effects in humans, the potential applications would be very exciting."

The researchers have continued to modify compound 6 to improve its pharmacokinetic profile, especially its oral bioavailability. Hultgren and Janetka hope to begin human toxicity tests of the mannosides during 2012, with clinical trials to follow.

Monica Harrington

SYNAPSE DYSFUNCTION LINKED TO MENTAL ILLNESS

Although mental illnesses are primarily considered human disorders, investigators have attempted to model certain aspects of these disorders in animals to facilitate study of the underlying mechanisms. In such studies, researchers have noted that gene mutations can elicit certain abnormal behaviors in rodents that are very similar to isolated symptoms of mental illness in humans. These behaviors are called endophenotypes.

Mutation of proteins that make up the postsynaptic density (PSD), a protein complex located at the 'receiving' end of a synapse or electrochemical connection between neurons, have been associated with cognitive defects and mental illnesses in humans. Similarly, mutations in PSD proteins in rodents can produce endophenotypes of mental illnesses. In a recent example, scientists from California Institute of Technology (Pasadena) and University of California, Los Angeles, describe endophenotypes of schizophrenia and autism spectrum disorders associated with null mutations of the gene encoding PSD protein densin-180 in mice.

Compared with normal mice, mice lacking densin-180 had deficits in hippocampus-dependent and -independent short-term memory, in prepulse inhibition, used as a measure of the ability to filter sensory information, and in nesting behavior (*J. Neurosci.* **31**, 16194–16207; 2011). They also showed hyperactivity in response to stress and novelty, as well as abnormal aggression and anxiety behaviors. These defects are considered endophenotypes related to human mental illness. "Studies of mice with schizophrenia and autism-like features have reported similar behaviors," noted Mary B. Kennedy, who led the study, in a press release.

The densin-180 knockout mice also had lower amounts of other PSD proteins. Kennedy explained that "densin-180 helps to hold together a key piece of regulatory machinery in the postsynaptic part of excitatory brain synapses." Densin-180 functions as a scaffold in the PSD, influencing organization and signaling within the complex. This organizational role means that densin-180 influences multiple cellular functions; hence, the lack of densin-180 leads to complex behavioral phenotypes.

The study results are consistent with the hypothesis that genetic mutations that disrupt postsynaptic signaling at excitatory synapses can cause behavioral endophenotypes of mental illness. "We don't know precisely how the molecular defect leads to the behavioral endophenotypes. That will be our work going forward," Kennedy said. "The molecular mechanistic links between a gene defect and defective behavior are complicated and, as yet, mostly unknown. Understanding them goes to the very heart of understanding brain function."

Monica Harrington