prevalence may be about 10% that of Lyme disease.

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2014 ICAAC
Host Gene Changes Affect How Bacteria Colonize Those Hosts

Shannon Weiman

Single-nucleotide polymorphisms (SNPs) in genes encoding immune receptors, signaling molecules, and other molecules not classically associated with immune responses can affect how well some bacterial pathogens or commensal species colonize individual hosts, according to several researchers who spoke during the 2014 Interscience Conference on Antimicrobials and Chemotherapy (ICAAC), held in Washington, D.C., last September. Exploring these associations, researchers hope to reveal mechanisms underlying disease pathology and other host-microbe interactions.

Some individuals are particularly susceptible to invasive pneumococcal disease (IPD), according to Anna Sangil Betriu of the Hospital Universitari Mutua Terrassa in Catalonia, Spain. Some 43 SNPs in 10 immune genes are linked to rare cases occurring in otherwise healthy individuals, “which may explain their susceptibility,” she says. Most prominent are minor alleles in the interleukin-1 receptor 1, which mediates innate inflammatory responses, and in two inhibitors of nuclear factor kB that regulate signaling of innate and adaptive responses. “If confirmed, these findings may help us to better understand the genesis of the illness, and to identify people at risk,” she says.

A single SNP in the gene for the leptin receptor (LEPR) appears to confer a threefold-greater susceptibility to infections by Clostridium difficile, according to Rajat Madan of the University of Virginia in Charlottesville. This same Q233R mutation in LEPR is also linked to susceptibility to Entamoeba histolytica infections, he notes.

Leptin, better known for its role in appetite and obesity, also influences gut integrity, microbiome composition, and inflammatory responses, Madan says. “Leptin is pro-inflammatory and augments the host defense during infections, presumably by enhancing immune responses.” The mutation impairs LEPR activation of signal transducer and activator of transcription 3 signaling, reducing mucosal chemokine production and neutrophil recruitment in mice, thus rendering them less able to clear C. difficile from the gut, he says. These findings “demonstrate a connection between metabolism and immunity.”

In other cases SNPs in host genes may influence the gut microbiota, thereby indirectly affecting susceptibility to pathogens or the likelihood of developing still other types of diseases, according to Jose A. Oteo of the Centro de Investigación Biomédica de La Rioja in Rioja, Spain. “Changes in gut microbiota composition may be responsible for a plethora of pathologies, including inflammatory bowel diseases, colon cancer, and obesity,” he says. For example, a SNP in the adrenomedullin gene (rs4910118), which decreases circulating levels of adrenomedullin, a peptide with antimicrobial properties, may dictate gut colonization by specific bacterial species. In female mice, knocking out this gene reduces the abundance of Bacteroidales and Clostridiales, while increasing Enterobacteriales, a bacterial order suggested to be implicated in high-fat-, diet-induced obesity, he says. He and his collaborators plan to examine whether humans with this SNP exhibit similar changes in microbiota and how this may influence their likelihood of developing various diseases. “This SNP is linked to cancer and high blood pressure,” he notes.

MINITOPIC
White House Imposes Another Voluntary Halt to Gain-of-Function Research

The White House Office of Science and Technology Policy and Department of Health and Human Services announced in October that it was suspending funding for “gain-of-function” research, pending a “deliberative process” to assess its risks and benefits. Such gain-of-function studies typically try deliberately to enhance the pathogenicity or transmissibility of infectious agents such as the influenza and MERS viruses. The White House asked the National Science Advisory Board for Biosecurity (NSABB), which is a federal advisory board operating under the auspices of the National Institutes of Health, and the National Research Council of the National Academies to conduct this policy review. NSABB members were scheduled to confer late in November before issuing a statement on these issues. While this two-part review is under way, the government is asking researchers “to voluntarily pause their research, whether federally funded or not, while risks and benefits are being reassessed.” An earlier voluntary moratorium on such research involving the H5N1 influenza virus ended in 2013 when several sets of researchers announced they would resume their investigations.

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Several Strategies in Search for Agents To Treat MERS-CoV

Shannon Weiman

Researchers are seeking to identify and develop agents that target the Middle East respiratory syndrome coronavirus
**MINITOPIC**

**Progress in Developing Disparate Vaccines**

Regulatory officials and researchers announced progress with the development of several different kinds of vaccines, including:

- Officials of the Food and Drug Administration (FDA) in October approved Trumenba, a vaccine to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age. The vaccine is made by Wyeth Pharmaceuticals Inc., a subsidiary of Pfizer Inc., in Philadelphia, Pa.
- A tetravalent vaccine directed against the Dengue virus proved effective in protecting children against the virus, and use of the vaccine led to fewer hospitalizations during a phase 3 clinical trial in five Latin American countries where dengue is endemic, according to Gustavo Horacio Dayan of Sanofi Pasteur in Swiftwater, Pa., and his collaborators. Details appeared 3 November 2014 in the *New England Journal of Medicine* (DOI:10.1056/NEJMo1411037).
- An experimental nasal vaccine provides long-term protection for nonhuman primates against the deadly Ebola virus, according to Maria Croyle of the University of Texas at Austin and her collaborators. They reported recent findings during the annual meeting of the American Association of Pharmaceutical Scientists, held in San Diego, Calif., last November.
- A vaccine against the H1N1 influenza virus whose antigens were reformulated is “six times more active” than are conventional versions of the flu vaccine “in terms of hemagglutinin immunogenicity and in vivo protection,” according to Manuel Rosa-Calatrava of VirPath and Emmanuel Dejean of Calixar, both in Lyon, France.

(MERS-CoV), which kills about 30% of individuals that it infects. Promising leads are arising from target-based drug development approaches and also from efforts to repurpose drugs that already are approved for treating other conditions, according to several researchers who summarized recent progress during the 2014 Interscience Conference on Antimicrobial Agents and Chemotherapy, held in Washington, D.C., last September.

Several inhibitors of viral helicase, spike protein, and RNA synthesis enzymes look promising when tested in vitro against MERS-CoV, according to Jasper Chan of the University of Hong Kong in China. Several of them are also active against the closely related severe acute respiratory syndrome coronavirus (SARS-CoV). Additionally, monoclonal antibodies and plasma from patients recovering from MERS-CoV infections neutralize that virus, he says, noting that convalescent plasma is being evaluated in clinical trials in the Middle East.

The papain-like protease (PLpro) of MERS-CoV, which is essential for its replication, is another target for candidate drugs, according to Hyuan Lee and Michael Johnson of the University of Illinois, Chicago. Although many inhibitors of the SARS-CoV PLpro proved to be ineffective against the MERS-CoV PLpro, she and her colleague Hao Lei recently identified an inhibitor of both viral enzymes. “High-throughput screening of 25,000 compounds produced a dual inhibitor that acts as an allosteric inhibitor against SARS-CoV PLpro and also acts as a competitive inhibitor against MERS-CoV PLpro,” says Lee. The compound also works in synergy with other lead inhibitors against SARS-CoV PLpro.

However, this target-based approach is painstaking, and it could take years before any of these promising viral inhibitors are approved as drugs, Chan cautions. An alternate and perhaps faster strategy involves testing currently approved antiviral agents, in hopes of repurposing some of them to treat MERS-CoV infections. Broad-spectrum agents, such as type-I interferons, or those used to treat SARS such as ribavirin and lopinavir appear promising, he says. Moreover, interferons synergize with ribavirin in vitro and in rhesus macaques, he says.

Yet another strategy casts a wider net and seeks to repurpose other types of drugs. For example, several cancer drugs, antidepressants, and hormone receptor modulators show anti-MERS activity, according to Lisa Hensley of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Md. She says that Chris Coleman of the University of Maryland in Baltimore, Lisa Johansen of Zalicus in Cambridge, Mass., and their collaborators identified 6 SARS-CoV-specific inhibitors, 33 MERS-CoV-specific inhibitors, and 27 inhibitors of both viruses while screening a set of 290 drugs that were approved by the Food and Drug Administration (FDA) for other purposes. For example, chlorpromazine HCl, a neurotransmitter antagonist used to treat patients with schizophrenia, synergizes with various other drugs, Hensley says. Chan finds that mycophenolic acid, an immunosuppressant used to prevent rejection of transplanted organs, has anti-MERS-CoV activity, particularly in combination with Interferon β1b.

Between 2012 when MERS-CoV emerged and July 2014, this virus infected at least 837 people across 20 countries with a fatality rate of about 30%, according to the World Health Organization. SARS-CoV, which emerged in 2003, had a higher infectivity rate and caused about 8,000 cases worldwide that year and several dozen the next, but has not reappeared during the past decade. Its fatality rate was about 10%.