staphylococcal protein A, which modulates adaptive host immunity, she points out.

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RESEARCH ADVANCES

Exploring Antibiotic Resistance Uncovers Host-Pathogen Quirks

Jeffrey L. Fox

Antibiotic resistance is not so simple a bug-drug phenomenon. In some cases, the host immune system or other factors impinge on drug treatments in ways that change their effectiveness in treating patients, the development of resistance, and strategies for combating resistance or for developing new drugs. Here are some highlights from the 2013 ASM General Meeting (GM), held in Denver, Colo., last May.

Some tuberculosis (TB) patients struggle with Mycobacterium tuberculosis infections while being treated with antibiotics and then sometimes are “blamed for failing therapy when taking drugs for which their bug is susceptible,” says Sarah Fortune of the Harvard School of Public Health in Boston, who spoke during the GM plenary session, “Bedside to Bench: Microbiology in the Clinics.” Despite M. tuberculosis supposedly having a low capacity for genetic diversity and, presumably, for developing resistance, “genomic sequencing suggests the picture is more complicated,” she says.

Some of that complexity resides in the numbers of drug-resistant mutations that can occur in M. tuberculosis, a pathogen that replicates slowly and which may become latent during infections, Fortune continues. “Contrary to expectations, this microbe acquires mutations at the same rate regardless of the status of an infection, latent versus active, and at the same rate as when growing in culture,” she says. “This is really surprising and goes against dogma.”

Another surprise is that the bacterial burden in patients (or in experimentally infected macaques) remains “stunningly” constant, even during antibiotic treatment because the bacterial “corpses ‘hang around for a long time,’” Fortune says. Cumulative mutations that are responsible for drug resistance reflect time-dependent damage to DNA, not changes in replication rates between active and latent bacteria. An important upshot is that very early diagnosis, when the bacterial burden is low, followed by earlier and more intense treatment of TB patients could help to slow the rate of multidrug resistance (MDR) development and thus might ease the challenges in treating MDR TB on a global scale.

“Treatment failure is not due only to drug resistance,” says Bruce Levin of Emory University in Atlanta, Ga., referring more generally to infectious diseases, when he spoke during the GM plenary, “Translating Knowledge of Bacterial Pathogenesis into Next Generation Antimicrobials.” One problem stems from relying too heavily on minimal inhibitory concentration (MIC)-based measurements when assigning antibiotics for treating patients, Levin asserts. Although “easily measured” and thus well liked, MICs usher in “tremendous bias,” he says. “How many antimicrobial drugs are we not using because they fail this test? But what will replace it?”

One contender is the Hill function, an independent but admittedly messier measure that entails following how long it takes for antibiotics to kill particular bacterial pathogens, according to Levin, a proponent of this alternative to MICs for the past decade. Although “MICs are here to stay,” he says, Hill functions offer an additional set of insights, particularly when evaluating antimicrobial drug candidates that MIC testing might rule out or for situations such as biofilms or persist cells where MIC-based choices also may fall short.

With Pierre Ankomah, Levin is extending this modeling approach, attempting to account also for host-immune responses as they contribute to antibiotic failure or success. Such modeling suggests that treating patients with high doses of such drugs decreases the immunopathologic effects of some infections, Levin says, sharing newfound quietude. “We’re now defenders of orthodoxy—promoting high-dose chemotherapy.”

Jeffrey L. Fox is the Microbe Current Topics and Features Editor.

MINITOPIC

Salmonella Toxin May Account for Its unusual Lethality

Typhoid fever is so lethal in large part because Salmonella enterica serovar Typhi produces a toxin composed of two toxic subunits that can cause in mice many of the symptoms associated with infection by this bacterial pathogen, according to Jorge Galan of Yale University in New Haven, Conn., and his collaborators. One of those protein toxin subunits is a DNase that inflicts DNA damage and induces cell-cycle arrest, while the other subunit, which resembles the pertussis toxin, has ADP-ribosyl transferase activity. When mice are injected with the intact toxin, they become lethargic and die, while other tests indicate that their circulating immune cells become severely depleted. “What makes this so exciting for us is that vaccines and therapeutics that target toxins have an excellent track record of success;” Galan says. Details appeared July 10, 2013 in Nature (doi:10.1038/nature12291).