**Breaking the persistence of persister cells**

by Debbie Neumayer

Our bodies harbor many types of bacterial micro-organisms. These tiny creatures usually multiply, divide, and die without much ado, and most times we don't suspect they are there. If any of them get out of line, specialized immune system warrior cells will grab them and make them into a meal. Unfortunately, modern medicine is trained to treat bacterial infections with drugs instead of supporting the immune system's natural abilities to eliminate these pathogens. So the family doctor usually prescribes an antibiotic that is designed to kill the unwanted microscopic invaders. However, some strains of modern-day bacteria are gaining an upper hand by eluding the effects of drug therapy.

Among these stubborn survivors are unique microbes that scientists have dubbed "persister cells" because they flourish, in spite of diligent efforts to eliminate them. Persister cells are described as "rare, nongrowing cells" that pre-exist in certain bacterial populations. Colonies of persister cells can create a protective shield by secreting special carbohydrates with which they encapsulate themselves and then attach to a selected surface. This combination of bacteria and carbohydrates is known as a biofilm and it forms quite a fortress. Within this cover, persister cells are very hardy. According to the *Journal of Bacteriology*, "biofilms are responsible for nearly 65 percent of all human infections in the West. These include infections of catheters, orthopedic devices, heart valves, urinary tract infections, and lungs of cystic fibrosis patients."

Research conducted on a variety of bacterial species reveal that levels of persisters increased with the density of the culture. Normally, antibiotics work against bacteria by "shorting out" a targeted phase of their reproduction and growth. However, persister cells don't behave or grow like regular bacterial cells and thus traditional efforts to kill them don't work, either. This feature has puzzled the scientific community ever since 1944 when Joseph Bigger noticed that penicillin did not sterilize a culture of staphylococcus bacteria. He identified persister cells as the culprits.

Understanding persister cells has mystified researchers until the discovery of the HipA protein. This gene acts as a toxin, allowing persister cells to bypass regular bacterial life cycles, as well as tolerate the bacteriocidal actions of antibiotics. Scientists have found that persister cell formation depends upon genetically encoded HipA toxins. Thus, through this mutation, antibiotic resistance is passed from one generation of cells to another.

Scientists postulate that persister cell tolerance to antibiotics may be linked to a shutdown of some part of the cellular life cycle by the HipA toxin. When HipA is active, persister cells exhibit multi-drug tolerance (MDT). Laboratory experiments conducted with *E. coli* demonstrate that when the HipA toxin is deleted from this bacterial population, there is a sharp 10-to-100-fold decrease in the level of persisters. Researchers admit they have not yet solved the mystery of persister cells, but they are making progress and continue to study this "enigmatic phenomenon." They report that "identification of MDT genes is an important first step in understanding [resistance] of biofilms to antibiotic therapy."

Perhaps the scientific community should expand their research to include probiotic therapy. Where the word antibiotic means "against life," probiotic means "for life." Probiotics is the umbrella term for a variety of "friendly bacteria" strains that improve immune function and produce their own distinctive, powerful weapons against infections in the body. They also help protect against candida yeast overgrowth, bowel disorders, lactose intolerance, and a wide range of other illnesses. Shown effective against many harmful bacteria, viruses, and fungi, probiotics could very well be the answer to stubborn persister cell biofilm populations.

Probiotics are easily incorporated into any daily dietary program—directly through supplementation or by eating high-quality yogurt on a regular basis. Learn much more about these fascinating microorganisms in Natasha Trenev's well-researched book "Probiotics: Nature's Internal Healers"—a title available nationwide.

## REFERENCES

Keren I, Shah D, Spoering A, Kaldalu N, Lewis K. Specialized persister cells and the mechanism of multidrug tolerance in Escherichia coli. *J Bacteriol.* 2004 Dec;186(24):8172-80.

Lewis K. Persister cells and the riddle of biofilm survival. *Biochemistry* (Mosc). 2005 Feb;70(2):267-74.

Kint CI, Verstraeten N, Fauvart M, Michiels J. New-found fundamentals of bacterial persistence. *Trends Microbiol*. 2012 Dec; 20(12):577-85.