

EXPLORE THE ISSUE BEING INVESTIGATED

In Search of New Antibiotics: How Salamander Skin Secretions Combat Microbial Infections

The antibiotic penicillin was discovered by Alexander Fleming in 1929. Called a “miracle drug,” it saved millions of lives. Penicillin kills growing bacteria by inhibiting an enzyme that carries out a key step in the formation of the bacterial cell wall. The enzyme normally catalyzes the formation of cross-links between the cell wall strands, and without these links the cell wall has no strength; the bacterium swells and ruptures, unable to withstand its own osmotic pressure.

However, not long after the discovery of penicillin, strains of bacteria resistant to it began to emerge. In response to penicillin resistance, researchers have developed new antibiotics. Over the past sixty years, we have seen a foot race between the emergence of antibiotic-resistant strains by disease bacteria on the one hand, and the development of new antibiotics by researchers on the other hand. Unfortunately, in recent years, it appears the bacteria may be pulling ahead. Diseases such as tuberculosis, gonorrhea, and malaria, once easily eradicated with drugs, now have developed antibiotic-resistant strains. The process of tweaking antibiotics to attack these resistant strains is becoming less and less effective. So researchers are seeking new classes of antibiotics that work in different ways.

Two key factors in the development of antibiotic resistance in bacteria are: 1. mutations of bacterial genes that confer resistance on an organism, and 2. the acquiring of antibiotic resistance from other bacteria, which spread genes from one cell to another on infectious bits of DNA called plasmids. While the initial doses of an antibiotic may kill most of the bacteria, the few bacteria that have undergone mutation to antibiotic-resistance, or that have acquired such resistance genes from other bacteria, survive and quickly multiply. The result is the creation of a drug-resistant strain that can spread to other individuals, infections that cannot be successfully treated with the antibiotic.

A key to developing antibiotics less susceptible to antibiotic resistance is to identify drugs that target bacterial structures less likely to undergo mutations. Penicillin and similar antibiotics typically act on bacterial enzymes. Because enzymes typically have very narrowly-defined specific functions, cells can often tolerate the loss or change of a particular enzyme, making the cell able to survive the “experimentation” that eventually leads to antibiotic resistance. The bacterial cell is less tolerant of mutational alter-

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ation to other more broadly functioning components. A new class of antibiotics have been discovered that act on the bacterial cell membrane. These antibiotics are small, membrane-active peptides that interact with and disrupt the bacterial cell membrane. The phospholipids and membrane proteins that make up the cell membrane are fundamental cell building blocks that function to provide a barrier to noxious substances as well as maintaining the internal contents of the cell. Disruption of this barrier would be lethal to the bacterium.

Where did researchers find these membrane-disrupting peptides? On the skin of amphibians. Skin is an important defensive organ for an amphibian. The dermal glands of amphibians secrete a variety of substances that aid in the protection of the animal. Mucus secreted on the skin helps retain moisture. Other substances are antipredatory, toxic or sticky secretions that keep predators away. Several species of frogs are known to release antimicrobial peptides onto their skin, offering the frogs protection from invading microorganisms. But many other amphibians also have dermal secretions -- might there be other sources of antimicrobial peptides?

John Dankert of the University of Louisiana at Lafayette has studied the dermal secretions of the red-backed salamander, *Plethodon cinereus*. This species of salamander is lungless, relying on cutaneous respiration. Its skin is thin and well vascularized, providing an easy route for microbial entry. Although *P. cinereus* is territorial and so fights often, its wounds rarely become infected, indicating an active defense against bacteria. *P. cinereus* seemed to Dankert to be an ideal candidate for the presence of antimicrobial peptides in dermal secretions.