Researchers discover new strategies for antibiotic resistance

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With infections increasingly resistant to even the most modern antibiotics, researchers at the Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center (LA BioMed) report in the September issue of *Nature Reviews Microbiology* on new clues they have uncovered in immune system molecules that defend against infection.

Drs. Michael R. Yeaman and Nannette Y. Yount present evidence that small proteins in the immune systems of humans and all kingdoms of life share fundamental structural and functional characteristics that enable these molecules to inhibit or kill microbial pathogens – even as these pathogens evolve to resist conventional antibiotics.

"These findings reveal that nature uses a recurring molecular strategy to defend against infection," said Dr. Yeaman. "A clearer understanding of this strategy provides new opportunities to develop innovative anti-infective therapies to better prevent or treat life-threatening infections that resist current antibiotics."

Most modern antibiotics work by targeting specific structures or functions in microbial pathogens. If the targets change due to mutation, pathogens can quickly become resistant to the antibiotics. In contrast, immune system molecules have retained the ability to fight infection – even as microbes evolve.

"While human ingenuity has thus far created antibiotics that pathogens seem to resist after just a few years, nature has created molecules in our

immune systems that retain the ability to defend against infection even after millions of years of evolution," said Dr. Yeaman. "We have a lot to learn from nature."

The September article sheds new light on the molecular basis for the antimicrobial capabilities of these molecules. Drs. Yeaman and Yount report that a structure they discovered in these molecules in 2004 – known as the y core – allows for "hypermutability," or unusually high rates of mutation or modification at specific sites within these molecules.

To do so, the y core structure often contains a "b bulge" motif – a region that affords structural variations otherwise prohibited in protein biochemistry.

"The ability of host defense molecules to change so quickly and with such diversity may be nature's way of keeping pace with rapidly evolving infectious microbes and other threats," said Dr. Yount.

These insights may drive new strategies for anti-infective discovery and development. Drs. Yeaman and Yount also said their discoveries significantly advance understanding of immune system evolution. Microbial pathogens are constantly moving targets; in turn – immune systems must adapt or lose effectiveness. Understanding how these molecules have continued to ward off infection could also accelerate development of immunotherapeutics to boost the body's own defenses against infection or other diseases, and reduce the resistance issues that plague today's antibiotics.

Source: Los Angeles Biomedical Research Institute