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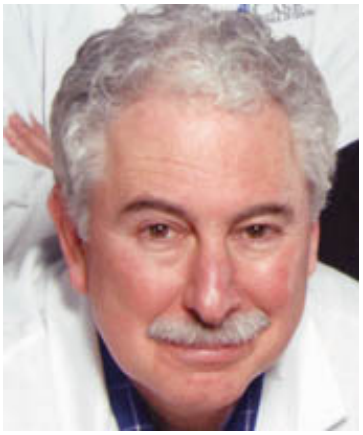
Human defensins may be a new "antibiotic" to thwart disease

Dental and medical researchers collaborate on new research projects



Imagine getting a cold, the flu or strep throat. Instead of swallowing an antibiotic or an over-the-counter medication, you rev up your body's natural immune engine to fight off viral, fungal or bacterial infections. A team of researchers, under the direction of Aaron Weinberg from the Case Western Reserve University's School of Dental Medicine, are unraveling the biological mechanisms that allow our body to ward off disease to create new therapeutic treatments.

Case researchers will advance the understanding of innate defenses with two new research projects funded by the National Institutes of Health.

Recent advances in dental medical research, such as Weinberg's research into the innate oral defenses against HIV, have shown that the mucous lining of the mouth continually wards off bacteria that are good and naturally occurring in the oral cavity, but become a menace once they cruise through the blood stream.

Weinberg is among a number of Case researchers at the dental and medical schools in a race to find new strategies to fight diseases as "super bugs" outsmart antibiotics by mutating to become increasingly resistant to the family of drugs' disease-preventing benefits.

His work in this new research frontier drew attention from the National Academy of Sciences, which invited him last spring to participate in a national meeting to discuss new research opportunities across many disciplines to study antimicrobial therapeutics.

This new direction focuses on "immuno-modulation" of adaptive immune cells by beta defensins, a family of small peptides naturally and normally produced in the human body.

"The big goal is to find a way to circumvent the use of conventional antibiotics," said Weinberg.

Why study the body's innate immune system to fight disease? According to Weinberg, unlike antibiotics, that are products of bugs, to fight bugs, it would be almost impossible for a pathogen, like the bacteria for strep throat, to undergo the extreme mutation processes it would need to evolve to resist the body's own defenses.

Weinberg is interested in the peptides called the human beta defensins (hBDs) that are found in the epithelial cells of the mucous membranes of the mouth and provide the first line of defense against microbial pathogens invading the body through the mouth. These hBDs have the ability to "send up a red flag" alerting the presence of a pathogen to jump start the body's immune responses.

"Down the road, we hope that with a little tweaking of the immune system, we can get a more robust immune response," said Weinberg.

New Research Projects

The first research project that advances the understanding of hBDs is the four-year *in vitro* study, *"Beta defensin protection of human oral epithelial cells,"* in collaboration with Thomas McCormick (Department of Dermatology), Michael Kinter (Lerner Research Center, CCF) and Hisashi Fujioka (Depratment of Pharmacology). This study will further investigate how the beta-defensins work in the oral cavity. Unlike other areas of the body that only produce the hBDs when inflamed or infected by a pathogen, hBD2 and hBD3 are continually expressed in the mouth's lining. They are particularly effective in warding off *Porphyromonas gingivalis*, which causes periodontal disease.

The second, four-year study is *"Defense of oral epithelial cells from candida by hBDs."* Weinberg will conduct research with Amy Hise (Department of Global Health and Disease) and Thomas McCormick from the medical school. Researchers will look at how the fungal pathogen, *Candida albicans*, affects the expression of beta-defensins in mice, and the role these peptides play in protecting against the pathogen in vivo. This study builds on a prior in vitro research that studied the role hBD2 and hBD3 have in preventing HIV infections through the mucosal lining of the mouth.

In this new mouse study, areas of the tongue will be exposed to the fungal infection and compared with other areas to track the expression of the beta-defensins.

Researchers will also look at biological responses hBDs trigger and their potential to increase a number of functions, including T-cell production to fight diseases.

Because *C. albicans* is building a resistance to antiretroviral therapies to treat AIDS, this research offers potential help for HIV/AIDs patients.

"These antimicrobial peptides have been around for eons. Organisms have not been able to establish a wide resistance to them, and that is telling us something about the inherent advantages of using these beta-defensins," said Weinberg.

For more information: Susan Griffith 216-368-1004.

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