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FIGHTING EAR INFECTIONS

TWO NEW APPROACHES

Research scientists in the House Ear Institute's Department of Cell and Molecular Biology recently published their findings from two separate research studies of middle ear infections, or otitis media (OM). Both studies aim to identify targets for new treatments for ear infections, which after the common cold, are the second most common ailment affecting children age eight and younger. Otitis media accounts for more than 31 million visits to the doctor each year in the U.S., and is cited as the most

frequent reason for taking children to the emergency room. Current treatment for middle ear infections is antibiotic therapy, sometimes in repeated courses, to discourage recurring infections. This treatment method has been used over the past three decades, resulting in a dramatic worldwide emergence of antibiotic-resistant bacteria. This has led to a reduction of the number of effective antibiotics for OM and has begun to pose a major public health threat. HEI researchers are studying the pathological processes underlying OM to identify potential therapies that can combat the specific bacteria causing infection, and boost the body's innate immunity to the disease.

One research study, led by Jian-Dong Li, M.D., Ph.D., in the Section on Signal Transduction, focuses on understanding the process of inflammation in the

pathogenesis of middle ear infections, which has recently been identified as a hallmark of other diseases like lung infection, heart disease and cancer. The study examines multiple, simultaneous causes of bacteria-induced inflammation. This study for the first time shows that NTHi, a common bacterial pathogen in otitis media in children and chronic obstructive pulmonary disease (COPD) in adults, cooperates with TNF- α , a common cytokine, to synergistically induce inflammation through activation of NF- κ B (a transcription regulator) via signaling pathways. This work should help us understand the molecular mechanisms underlying the regulation of inflammation in the middle ear and lead to new therapeutic strategies for NTHi-induced infections. Co-investigators on this study are Takahiro Watanabe, M.D., Hirofumi Jono, Ph.D., and David J.

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Lim, M.D. at HEI, and Jiahui Han, Ph.D., at the Department of Immunology, The Scripps Research Institute.

A second study, led by David J. Lim, M.D., in HEI's Section on Pathogenesis of Ear Diseases, takes a different approach to solving middle ear infections with a focus on the function of innate immune molecules as defenders against pathogens to protect the host. These naturally occurring molecules constantly survey the body in order to clear it of microorganisms that can cause ear infections. However, in young children, the immune system is protected against infection by their mother's immunity for only the first three months. After that, they are especially vulnerable to ear infections until their bodies begin producing immunoglobulins (antibodies) around age five. Their only defense comes from their innate immune system during this period. The aim of the HEI study is to understand the role of innate immune molecules in the normal defense and maintenance of the middle ear, in order to potentially boost the body's natural defense – its own antibiotics – against bacterial infection. Co-investigators on this study are Haa-Yung Lee, Ph.D., Ali Andalibi, Ph.D., Paul Webster, Ph.D., Karen Teufert, M.D., Jian-Dong Li, M.D., Ph.D., Sung-Kyun Moon, M.D., Ph.D., Sung-Ho

Kang, M.D., Ph.D., at HEI and Tomas Ganz, M.D., at Department of Medicine, University of California, Los Angeles (UCLA).

THE MECHANICS OF HEARING TROUBLE-SHOOTING BEFORE HEARING LOSS HAPPENS

In the Section on Cell Structure and Function, the team led by Federico Kalinec, Ph.D., is exploring the function of the inner ear from two perspectives: First, understanding the structure and function of the outer hair cells (OHC), which play a critical role in hearing as well as a protective role for inner hair cells; and second, investigating how to prevent life-saving drugs and noise from having a noxious effect on the inner ear and killing the OHCs.

The first of these objectives seeks a comprehensive understanding of the processes involved in the OHC's operation. Outer hair cells are the auditory sensory cells responsible for signal amplification in the

cochlea and the inner ear's ability to discern between different sounds. They are primary targets for sensorineural hearing loss resulting from viruses, aging, excessive noise and drugs that are toxic to the ear. A knowledge of the structure and function of normal outer hair cells will help us understand and characterize their pathologies, creating the foundation for future pursuits in repairing and regenerating these auditory sensory cells.

The second pursuit has a more immediate application – development of intervention strategies to prevent damage. Some drugs that are critical to maintaining a patient's health are also toxic to the ear (ototoxic) and can cause hearing loss by killing the outer hair cells. Their benefits in combating life-threatening diseases, however, may often outweigh the risks. For instance, the use of the ototoxic antibiotic gentamicin has increased in recent years because of its efficacy, low price, and the increased incidence of penicillin- and cephalosporin-resistant organisms. At this time, there is no better drug than gentamicin for combating *Pseudomonas aeruginosa* infections, a severe threat to cystic fibrosis patients. Moreover, gentamicin is in the first line of defense against bioterrorist threats involving *Yersinia* (plague) and tularemia.

Did you know that if a songbird loses its hearing, it will stop singing? Just like humans, birds need to hear the sound of their own voice in order to carry a tune or modulate their vocal tone.

The evidence that infection during pregnancy, in particular urogenital tract infection, is causally linked to premature birth has led to an increasing number of pregnant women being treated with gentamicin. Aminoglycoside antibiotics like gentamicin may cross the placental barrier and affect the ear of the developing baby. Although exposure to ototoxic medication has been listed as one of the 10 major risk factors for hearing loss in children, there are no published reports of clinical strategies aimed at preventing or ameliorating drug-induced hearing loss during the perinatal period. Recent research by Dr. Kalinec's team provides strong evidence that supplementation of the mother's diet with L-carnitine, a natural micronutrient and antioxidant required for normal cell function, might prevent gentamicin-induced hearing loss and cochlear damage in newborns. Moreover, this protective effect could be extended to other aminoglycoside antibiotics and antineoplastic agents such as cisplatin. These results provide the basic conceptual framework for the design of clinical trials using L-carnitine as a simple strategy for the prevention of drug-induced ototoxicity during pregnancy and in normal and premature newborns.

Co-investigators in these studies are Nozomu Matsumoto,

M.D., Ph.D., Gilda M. Kalinec, Ph.D., Shaping Chen, Ph.D., and Paul Webster, Ph.D., at HEI, Raul Urrutia, M.D. and Martin Fernandez-Zapico Ph.D., at Mayo Clinic, Rochester, Minnesota, and Nora Esteban-Cruciani, M.D., Montefiore Children's Hospital and Albert Einstein College of Medicine, New York.

WHAT BIRDS TEACH US UNRAVELLING THE MYSTERY OF NERVE CELL REGENERATION IN THE EAR

Scientists discovered several years ago that, unlike humans and other mammals, birds and many other animals are able to regenerate nerve cells in their inner ears after they become damaged. For example, if a bird is exposed to intense sound that damages the hair cells in the inner ear (cochlea), it can hear again in three weeks. When a hair cell is destroyed in a bird, one of the supporting cells receives a signal to divide and it makes two cells. One of these becomes a support cell and one of them becomes a hair cell. Thus it does two things: it replaces the hair cell and it replaces itself. By doing this, the bird regains its hearing.

Scientists Neil Segil, Ph.D., and Andy Groves, Ph.D., are collaborating to investigate where the hair cells and supporting cells



come from at the embryonic stage of development. Their aim is to identify the stem cells or progenitors that give rise to hair cells. They don't yet know if there are cells in the mature inner ear of mammals that have the same regenerative ability that is found in birds, but their hope is to identify the cells that are capable of dividing and giving rise to hair cells. Then, they may be able to determine if these same cells are still present in the adult, and can ask why such cells do not normally participate in regeneration. Current knowledge is insufficient to design clinical trials aimed at hair cell regeneration in humans. By first identifying the cells that give rise to hair cells in the embryonic inner ear and then studying their properties, they hope to provide the information needed to design treatments that will eventually lead to cell regeneration and the restoration of hearing. Co-investigators in these studies are Angelika Doetzlhofer, Ph.D., and Patricia White, Ph.D. ❖