APS Colloquium

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APS Colloquium home

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The Road to Find an Antidote Against Anthrax Infection

Bacillus anthracis is a bacterial pathogen that can infect most mammals including humans. Due to the hardiness of its spore and near 100% fatality of the inhalational form of the diseases, anthrax spores have been engineered to be a potent biological weapon. Exotoxins secreted by the anthrax bacteria, rather than the bacteria themselves, make anthrax deadly.

Anthrax exotoxins consist of three separate components: protective antigen, edema factor, and lethal factor. Protective antigen is a peptidyl transporter that delivers the other toxins into the host cells. Edema factor is a calmodulin dependent adenylyl cyclase, an enzyme that makes cyclic AMP. Cyclic AMP is an important messenger inside host cells which communicates the environmental changes. Edema factor makes an abnormally high level of cyclic AMP that causes cells to leak fluid and die (water accumulation in tissues is known as edema.) Lethal factor is a metalloprotease, and one of the known substrates is MAP kinase kinase. The proteolytic action of lethal factor toward MAP kinase kinase disarms the growth signal and also leads to cell death. The actions of lethal factor and edema factor together make anthrax deadly.

Using the BioCars and SBC synchrotron facilities at the Advance Photon Source, my lab, in collaboration with Dr. Andrew Bohm and Zenon Grabarek, has determined the molecular structures of edema factor with and without its activator, calmodulin. The structure of edema factor with its activator reveals the tube-shape catalytic pocket. This site is significantly different from that of the host cell adenylyl cyclase. In a search for the anti-toxin against edema factor, a structure-based inhibitor search and high-throughput chemical screen is in progress, and we believe that such chemicals can be found in the near future. The molecular structures of protective antigen and lethal factor were solved by Dr. Liddington and his colleagues. The structure of lethal factor reveals the shape of the protease active site, and Dr. Liddington believes that anti-toxins can be developed within two years.

As scientists around the globe search for the antidote to anthrax infection as well as improve technology for detection of anthrax spores, it is reasonable to believe that within the foreseeable future, we may develop the necessary tools to combat bioterrorists who use anthrax.

Dr. Wei-Jen Tang is an associate professor at the Ben-May Institute for Cancer Research at the University of Chicago. His research focuses on studying cell communication using a diffusible intracellular second messenger, cyclic AMP, as the model system. Dr. Tang has written numerous papers and review articles, and is on the editorial board for the Journal of Biological Chemistry. He has lectured around the country and in Taiwan, owns a few patents, and has won several awards, most recently the American Heart Association Established Investigator Award (1999).

Dr. Wei-Jen Tang obtained his B.S. degree from the Department of Zoology at the National Taiwan University. After obtaining his Ph.D. in microbiology and molecular biology at University of Texas, Austin, he continued his postdoctoral training with Dr. Alfred G. Gilman at the Department of Pharmacology, University of Texas Southwestern Medical Center at Dallas. In 1994, he joined the University of Chicago.