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Researchers investigate link between fungal proteins, innate immunity and asthma

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Researchers at Mayo Clinic and the Virginia Bioinformatics Institute (VBI) have received a second grant from the National Institute of Allergy and Infectious Diseases (NIAID) to advance understanding of the role of environmental fungi in chronic airway disorders. Recently NIAID awarded the researchers a further $1.8 million for these studies over a five-year period to investigate how the environmental fungus Alternaria triggers airway inflammation and bronchial asthma.

Exposure to the fungus Alternaria has long been implicated in the development and exacerbation of asthma, especially life-threatening asthma, although little is known about the molecular events in the immune system that underlie the etiology and progress of this chronic disease. By understanding how the innate immune system responds to environmental stimuli and helps shape the adaptive immune system, scientists hope in the long term to develop more specific therapies as well as prevention strategies for bronchial diseases.

Principal Investigator Hirohito Kita, M.D., from Mayo Clinic, remarked: “In this investigation, we will be looking closely at how fungal enzymes from Alternaria cause innate immune responses in a variety of cells and how they influence naïve T cells in the immune system to differentiate into T helper 2 cells or Th2 cells, a process which takes place in partnership with antigen-presenting cells called dendritic cells. Th2 cells are part of the adaptive immune system and are linked to the events that lead to inflammation of the airway.”

He added: “Th2 cells typically produce cytokine signaling molecules or interleukins and the production of these interleukins leads to the recruitment of a specific class of white blood cells (eosinophils) that usually destroy parasitic organisms larger than bacteria or viruses. Mounting evidence suggests that allergic airway disorders such as asthma and chronic sinusitis are actually the result of our bodies believing we are being attacked by parasites. Environmental fungi such as Alternaria do not typically cause invasive infections like parasites but for some reason, in certain people, the body thinks it is being attacked. This results in Th2 cells constantly recruiting eosinophils and chronic inflammation occurs because humans are continually exposed to common environmental fungi like Alternaria.”

The hypothesis that will be tested is that certain immunoactive enzymes from Alternaria activate dendritic cells through yet unidentified receptors that allow for tailoring of the adaptive immune response and the formation of Th2 cells. This in turn leads to the strong immune responses in the airways. The research team will use different approaches to determine the potential role of these receptors in the cascade of immune interactions that comprise inflammation of the airways. This should allow them to better understand how certain environmental stimuli are linked via the innate immune system to the adaptive immune system and development of inflammation and disease.

Dr. Chris Lawrence, Associate Professor at VBI and the Department of Biological Sciences at Virginia Tech, one of the leading experts in Alternaria biology and principal investigator of the Alternaria genome sequencing project funded by the National Science Foundation-United States Department of Agriculture (NSF-USDA) Microbial Genome Sequencing Program, stated: “Our part of the collaboration is critical and will involve the use of proteomics and functional genomics approaches to identify the novel enzymes produced by Alternaria that are triggers of innate immune responses that shape the adaptive immune system.

Recombinant fungal proteins will be used to dissect the different molecular steps involved in the development and progression of inflammation and asthma." He added: "We will create a series of fungal knockout mutants for specific genes that will be used to examine the specific role of fungal proteins in the activation of the innate immune system response. It is our belief that understanding how and why asthma patients develop Th2 immune responses to environmental proteins is one of the prerequisites for the future development of treatments, diagnostic tools and preventative measures for patients suffering from the disease. We are truly excited about being able to participate in this transdisciplinary, team-based scientific effort."

Asthma is a chronic disease characterized by recurrent attacks of breathlessness and wheezing. The most common chronic disease among children, it currently affects 300 million people worldwide.* In 2000, the Asthma and Allergy Foundation of America estimated that direct health care costs for asthma in the United States total more than $10 billion annually; indirect costs (lost productivity) add another $8 billion for a total of $18 billion. In 2005 alone, 255 000 people died of asthma worldwide.*

Source: Virginia Tech