New cellular pathway triggering allergic asthma response identified

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Researchers at the University of California, San Diego School of Medicine, with collaborators in Korea and Scotland, have identified a novel signaling pathway critical to the immune response of cells associated with the initiation of allergic asthma. The discovery, they say, could point the way to new therapies that suppress the inflammatory allergic response, offering potential relief to millions of Americans with the chronic lung condition and potentially other allergic diseases.

The results are published in the January 19 online Early Edition of the *Proceedings of the National Academy of Sciences*.

Specifically, the scientists demonstrated that T helper 2 (Th2) type inflammation in allergic asthma involves dendritic cells (DC), a type of white blood cell, which trigger a reduction in the production of cyclic AMP or cAMP, a key messenger molecule for signaling inside cells. In mouse models, deletion of the gene that codes for a protein that promotes the production of cAMP resulted in spontaneous bronchial asthma, which shares many similarities with human asthma. Conversely, increasing cAMP levels inhibited the cells' inflammatory response that results in asthma's characteristic symptoms.

"These findings and the related mechanism are very different from the current residing view of activation of specific T helper cell responses," said principal investigator Eyal Raz, MD, professor of medicine.

"The role of cAMP formation and action in dendritic cells in the induction of allergic response was really surprising," added co-author Paul Insel, MD, professor of pharmacology and medicine. "It suggested to us that this signaling pathway is involved in other immune-related functions."

The immune response of humans, mice and other vertebrates consists of two fundamental components. The first is the innate immune system, which recognizes and responds to pathogens in an immediate, but generalized, way and does not confer long-lasting immunity. The second is the adaptive immune system in which highly specialized T and B cells eliminate or prevent pathogen growth - and create immunological memory in case of future encounters with the same pathogen.

Th2 immunity is one of two major aspects of adaptive immunity. Th1 responses target intracellular pathogens, such as viruses and bacteria that have invaded host cells. The Th2 response is more effective against extracellular pathogens (such as bacteria, parasites and toxins that operate outside of cells) and also plays a major role in allergic reactions and related diseases.

Allergic asthma is triggered by inhaled allergens, such as pet dander, pollen, mold and dust mites. It is characterized by inflammation and narrowing of the airways, resulting in wheezing, chest tightness, shortness of breath, coughing and other symptoms. The common form of allergic asthma is associated with an exaggerated Th2 immune response. Allergic asthma affects people of all ages, most often appearing in childhood. More than 25 million Americans suffer from the condition.

"This research will open a new field of exploration of DC-related molecules as mediators that influence Th2 induction and Th2 'bias,'" said Jihyung Lee, PhD, a post-doctoral fellow and first author of the study. "We have already identified some of these molecules. Others are under investigation and we hope to identify them in the near-future."

Co-author Nicholas Webster, PhD, professor of medicine and a member of the Veteran's Affairs San Diego Healthcare System, said: "Such molecules or ones that mimic or block them might be used as novel therapeutics of allergic and

asthmatic diseases." Raz noted that the genetic mouse model developed for the research shares multiple similarities with human allergic asthma, "We are quite optimistic the mice will reveal additional, novel insights into human allergy," he said.

More information: Cyclic AMP concentrations in dendritic cells induce and regulate Th2 immunity and allergic asthma, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1417972112

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