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2010 : February 2010 - Fast Breaking Papers : Chris Karp Discusses the Molecular Underpinnings of Allergenicity

fast breaking papers - 2010

February 2010

(Late commentary entry added in Feb. 2010 for Dec. 2009)



Chris Karp talks with *ScienceWatch.com* and answers a few questions about this month's Fast Breaking Paper Paper in the field of Immunology.



Article Title: Allergenicity resulting from functional mimicry of a Toll-like receptor complex protein

Authors: Trompette, A;Divanovic, S;Visintin, A;Blanchard, C;Hegde, RS; Madan, R;Thorne, PS;Wills-Karp, M;Gioannini, TL;Weiss, JP;Karp, CL
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(addresses have been truncated.)

SW: Why do you think your paper is highly cited?

I think that there are several possible interlinked reasons. Firstly, the general underlying biological problem is one that has been fairly intractable to investigation—what the molecular underpinnings of allergenicity are; that is, why specific, otherwise apparently innocuous proteins are recognized in a maladaptive way by the adaptive immune systems of many people.

Secondly, the mechanism defined for the allergen studied in this paper, the major dust mite allergen, is particularly satisfying—functional mimicry by Der p 2 of a lipid-binding member of an innate immune signaling complex protein.

Thirdly, there may well be a generality to the findings. Other members of this family of proteins are major allergens; more generally, as most defined major allergens are thought to be lipid-binding proteins, there is a strong suggestion that intrinsic adjuvant activity by such proteins and their accompanying lipid cargo may have some generality as a mechanism underlying the phenomenon of allergenicity.

SW: Would you summarize the significance of your paper in layman's terms?

There is an ongoing epidemic of allergic asthma, particularly in countries throughout

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- [Institutional Interviews](#)
- [Journal Interviews](#)
- [Podcasts](#)

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- [Featured Analyses](#)
- [What's Hot In...](#)
- [Special Topics](#)

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- [Sci-Bytes](#)
- [Fast Breaking Papers](#)
- [New Hot Papers](#)
- [Emerging Research Fronts](#)
- [Fast Moving Fronts](#)
- [Corporate Research Fronts](#)
- [Research Front Maps](#)
- [Current Classics](#)
- [Top Topics](#)
- [Rising Stars](#)
- [New Entrants](#)
- [Country Profiles](#)

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the Western world. Allergy, and allergic asthma, occurs when a particular kind of immune response, harmful to the responding host, is made against specific proteins (allergens). Allergic people tend to mount these harmful immune responses against the identical, otherwise innocuous, proteins.

Why these particular proteins tend to be targets of such immune responses has largely been unclear. The studies reported in this paper suggest that the major allergen from dust mites, Der p 2, drives activation of immune responses because it is a functional mimic of a host protein whose role is to facilitate activation of the immune system.

"We and others are very interested in further defining the molecular mechanisms underlying activation of the innate immune system by allergens."

SW: How did you become involved in this research, and were there any problems along the way?

It was something of an "aha" moment. I was at a toll-like receptors (TLR) meeting in Taormina, Sicily to present data on an endogenous inhibitor of TLR signaling—RP105. During the conference, Nick Gay, a superb structural biologist from Cambridge, gave a presentation in which, after lamenting the current lack of any crystal structure for a TLR, or the TLR4 helper molecule MD-2, he modeled MD-2 based on a solved crystal structure—Der p.

Well primed—both by the work of my wife (Marsha Wills-Karp) on asthma pathogenesis as well as by my work on lipopolysaccharides (LPS) signaling and my interest in the hygiene hypothesis—I put a very talented person in the lab (Aurelien Trompette) to work on determining whether the structural similarities between MD-2 and Der p 2 were matched by functional similarities.

SW: Where do you see your research leading in the future?

We and others are quite interested in further defining the molecular mechanisms underlying activation of the innate immune system by allergens. The clear hope is that a better molecular understanding will lead to novel preventive and therapeutic approaches to allergic asthma and other allergic diseases.

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KEYWORDS: TLR4-MD-2 COMPLEX; CRYSTAL-STRUCTURE; ALLERGIC DISEASE; CELL ACTIVATION; ENDOTOXIN; MD-2; ASTHMA; LIPOPOLYSACCHARIDE; RESPONSES; EXPOSURE.

 PDF

[back to top](#) 

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