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Department of Pediatric Pneumology & Immunology

Charité–Universitätsmedizin Berlin

DISSERTATION

Evolution of serum IgE and IgG antibodies to 35 molecules in childhood

Zur Erlangung des akademischen Grades

Doctor medicine (Dr. med.)

vorgelegt der Medizinischen Fakultät

Charité – Universitätsmedizin Berlin

von

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Abstrakt

HINTERGRUND: Die häufig beschriebene Schutzfunktion allergenspezifischer IgG-Antikörper wurde vor kurzem durch Daten ergänzt, die ein Differentialbild für atopische und nicht-atopische Patienten sowie eine "(vor-) atopische" IgG-Antwort beschreiben. Abgesehen von der Route und der Expositionsdosis können die physikalisch-chemischen Eigenschaften von Proteinen für die Unterscheidung zwischen Antigenen und Allergenen entscheidend sein.

ZIEL: Wir haben versucht, die Längsentwicklung von Allergen-spezifischen IgG- und IgE-Profilen von einer breiten Gruppe von allergenen Molekülen in der Kindheit zu untersuchen.

METHODEN: Die deutsche Multicenter-Allergie-Studie untersuchte eine Geburtskohorte, die 1990 geboren wurde. Blutproben wurden im Alter von 1, 2, 3, 5, 6, 7, 10, 13 und 20 Jahren gesammelt. Die Teilnehmer wurden in die vorliegende Analyse aufgenommen, wenn sie (1) ≥1 Serumprobe im Alter von 1-3 Jahren hatten; (2) ≥2 Serumproben im Alter von 5-7 Jahren und (3) eine Serumprobe im Alter von 10 Jahren. Kinder wurden als "atopisch" betrachtet, wenn sie eine positive IgE-Antwort (Cut-off ≥ 0,30 ISU) auf mindestens ein Molekül zeigten, während diejenigen, die IgE niemals zu irgendeinem untersuchten Molekül produzierten, als "Nicht-Atopics" gruppiert wurden. IgE- und IgG-Antikörper gegen native und rekombinante allergene Moleküle wurden mit einem Multiplex-Mikroarray-Ansatz (ImmunoCAP ISAC TM -103 und ISAC TM -112, TFS, Schweden) getestet. Fünfunddreißig Moleküle wurden für die Analyse nach Ausschlusskriterien ausgewählt, die zuvor validiert wurden.

ERGEBNISSE: Wir fanden eine differentielle Evolution der IgG- und IgE-Reaktionen auf einen breiten Satz von Allergenmolekülen: 1) IgE-Reaktionen waren meist gegen eine eingeschränkte Gruppe von luftgetragenen Molekülen gerichtet, mit einer Sequenz- und Prävalenzhierarchie, die - auf Populationsniveau - weitgehend während des ganzen ersten Lebensjahres beibehalten: Phl p 1> Bet v 1> Feld d 1> Phl p 5> Der p 2> Der p 1; 2) Im Gegensatz dazu war das IgG-Repertoire viel breiter und verbreitete sich bei den meisten Kindern zuerst zu tierischen lebensmittelbasierten Molekülen, dann zu pflanzlichen Lebensmitteln und schließlich zu luftgetragenen Molekülen; 3) Eine ungewöhnlich starke und anhaltende IgG-Antwort geht einer IgE-Antwort auf das gleiche luftgetragene Molekül vor oder begleitet sie.

SCHLUSSFOLGERUNGEN: Obwohl die Evolution von allergenspezifischen IgG- und IgE-Reaktionen im Laufe der Kindheit stark abweicht, geht eine starke IgG-Antwort voran oder begleitet das Auftreten von IgE bei atopischen Probanden. Die Ergebnisse deuten darauf hin, dass die Erzeugung von hochaffinitätsallergenspezifischem IgE in den meisten Fällen eine intermediäre IgG_1-Phase und sequentielle Klassenumschaltung ($\mu \rightarrow \gamma_1 \rightarrow \varepsilon$) erfordert.

Abstract

BACKGROUND: The often described protective role of allergen-specific IgG antibodies has been recently complemented by data describing a differential picture for atopic vs. non-atopic patients, as well as a „(pre-)atopic“ IgG response. Apart from the route and dose of exposure, the physico-chemical properties of proteins may be decisive for the distinction between antigens and allergens.

OBJECTIVE: We sought to investigate the longitudinal evolution of allergen-specific IgG and IgE profiles to a broad panel of allergenic molecules in childhood.

METHODS: The German Multicentre Allergy Study examined a birth cohort born in 1990. Blood samples were collected at the ages of 1, 2, 3, 5, 6, 7, 10, 13 and 20 years. Participants were included in the present analysis if they had (1) ≥1 serum sample at age 1-3ys; (2) ≥2 serum samples at age 5-7ys and (3) a serum sample at age 10ys. Children were considered „atopic“ if they exhibited a positive IgE response (cut-off ≥ 0.30 ISU) to at least one molecule, while those never producing IgE to any oft he examined molecules were grouped as „non-atopics“. IgE and IgG antibodies to native and recombinant allergenic molecules were tested with a multiplex microarray approach (ImmunoCAP ISAC™-103 and ISAC™-112, TFS, Sweden). Thirty five molecules were selected for the analysis according to exclusion criteria previously validated.

RESULTS: We found a differential evolution of the IgG and IgE responses to a broad set of allergen molecules: 1) IgE responses were mostly directed against a restricted group of airborne molecules, with a sequence and prevalence hierarchy that - at population level - is largely maintained throughout the whole first decade of life: Phl p 1 > Bet v 1 > Feld d 1 > Phl p 5 > Der p 2 > Der p 1; 2) In contrast, the IgG repertoire was much broader, spreading in most children first to animal foodborne molecules, then to vegetable foodborne and finally to airborne molecules; 3) An abnormally strong and persistent IgG response precedes or accompanies an IgE response to the same airborne molecule.

CONCLUSIONS: Although the evolution of allergen-specific IgG and IgE responses throughout childhood differs widely, a strong IgG response precedes or accompanies the appearance of IgE in atopic subjects. The results suggest that the generation of high affinity allergen-specific IgE needs, in most cases, an intermediary IgG_1 phase and sequential class switching ($\mu \rightarrow \gamma_1 \rightarrow \varepsilon$).

Affidavit

"I, Xinyuan Huang, certify under penalty of perjury by my own signature that I have submitted the thesis on the topic '**Evolution of serum IgE and IgG antibodies to 35 molecules in childhood**' I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources."

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My interest in any publications to this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

Date Signature

Detailed Declaration of Contribution

Xinyuan Huang had the following share in the following publication:

He planned the study design, organized and supervised the conduction of this study and performed the analysis and interpretation of the results. He additionally collected and interpreted the eQTL data. He wrote the manuscript.

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Zepp[6], MD, Antje Schuster[7], MD, Raffaele D'Amelio[3], MD, Ulrich Wahn[1], MD, Thomas Keil[8,9], MD, Susanne Lau[1], MD, and Paolo Maria Matricardi[1*], MD; Evolution of the IgE and IgG repertoire to a comprehensive array of allergen molecules in the first decade of life; Allergy. 2018;73:421–430. https://doi.org/10.1111/all.13269

Signature, date and stamp of the supervising University teacher

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Signature of the doctoral candidate

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17	INTERNATIONAL ARCHIVES OF ALLERGY AND IMMUNOLOGY	5,175	2.720	0.006600
18	ALLERGY AND ASTHMA PROCEEDINGS	1,937	2.614	0.003140
19	JOURNAL OF ASTHMA	3,201	1.746	0.005060
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22	ASIAN PACIFIC JOURNAL OF ALLERGY AND IMMUNOLOGY	698	1.011	0.001040
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26	ALLERGOLOGIE	187	0.311	0.000080

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THE SELECTED PUBLICATION

Xinyuan Huang, Olympia Tsilochristou, MD, Serena Perna, M.Sc., Stephanie Hofmaier, Antonio Cappella, MD, Carl-Peter Bauer, MD, Ute Hoffman, MD, Johannes Forster, MD, Fred Zepp, MD, Antje Schuster, MD, Raffaele D'Amelio, MD, Ulrich Wahn, MD, Thomas Keil, MD, Susanne Lau, MD, and Paolo Maria Matricardi, MD;

Evolution of the IgE and IgG repertoire to a comprehensive array of allergen molecules in the first decade of life;

Allergy. 2018;73:421–430. https://doi.org/10.1111/all.13269

Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

Complete list of publications

Xinyuan Huang, Olympia Tsilochristou, MD, Serena Perna, M.Sc., Stephanie Hofmaier, Antonio Cappella, MD, Carl-Peter Bauer, MD, Ute Hoffman, MD, Johannes Forster, MD, Fred Zepp, MD, Antje Schuster, MD, Raffaele D'Amelio, MD, Ulrich Wahn, MD, Thomas Keil, MD, Susanne Lau, MD, and Paolo Maria Matricardi, MD;

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