Available online at www.sciencedirect.com
SCIENCE DIRECT®
Molecular Immunology 42 (2005) 19–30
Molecular Immunology
www.elsevier.com/locate/molimm

Evidence that negative feedback between antibody concentration and affinity regulates humoral response consolidation to a non-infectious antigen in infants

Duaine R. Jackola[a,*], Carol L. Liebeler[a], Ching-Yuang Lin[b], Yi-Kai Chiu[c], Malcolm N. Blumenthal[a], Andreas Rosenberg[a]

[a] *The Asthma and Allergy Center, University of Minnesota Medical School, Minneapolis, Mayo Mail Code 434, 420 Delaware St. S.E., Minneapolis, MN 55455, USA*
[b] *Children's Hospital, Changua Christian Hospital and Institute of Medical Research, Chang Jung Christian University, Taiwan*
[c] *Institute of Microbiology and Immunology, National Yang-Ming University, Taiwan*

Received 24 June 2004; accepted 13 July 2004
Available online 25 August 2004

Abstract

The dynamics of human antigen-specific immunoglobulin (Ig) responses in early life are not well characterized. We have previously observed an inverse relationship between allergen-specific Ig concentration and allergen-Ig-binding affinity in allergen-sensitive atopic adults, suggesting a possible feedback relationship between these variables. We prospectively studied children (6 months to 6 years) with and without atopic sensitization to the Der p 1major allergen. Experimental results showed the following trends. (1) In both study groups, there was little change with age in average Der p 1-specific Ig (IgG1 or IgE) concentrations or allergen-Ig-binding affinities, and concentrations and affinities were independent. (2) Among individuals, however, there was a negative correlation between Ig concentration changes and affinity changes with age. (3) The rate of increase with age of the non-atopic Der p 1–IgG1 total binding capacity (Ig concentration × Ig affinity) paralleled that for the atopic Der p 1–IgE total binding capacity, and there was a comparable 'consolidation' of responses with age reflected by a narrowing of the variance of total binding capacity values. Except for the Ig classes involved, development of a humoral response to a non-infectious allergen is similarly regulated in atopic and non-atopic children, with Ig total binding capacity as the key regulatory variable. These results also suggest that there is a time-dependent feedback relationship between Ig concentrations and affinities that establishes an optimal Ig total binding capacity for a given environmental 'antigen load'. A theoretical model is proposed to account for this relationship.
© 2004 Elsevier Ltd. All rights reserved.

Keywords: Affinity; Allergen; Antibodies; Atopy; Human; IgE; IgG1

1. Introduction

Prolonged exposure to antigens engenders fundamental changes in T-cell-dependent humoral responses. Based upon evidence derived from animal models and in vitro cell culture (Steward and Steensgaard, 1983; Cerutti et al., 1998), a great deal has been learned about the key mechanistic features. These involve structural and functional changes of immunoglobulins via the complementary activities of somatic hypermutation (SH), leading to antibody 'affinity maturation', and isotype class switch recombination (CSR) that promotes specific functional changes upon secondary antigen exposure(s) (Wabl and Steinberg, 1996; Kouskoff et al., 1998; Stavnezer, 2000; McHeyzer-Williams et al., 2001). Ultimately, the interplay of SH and CSR progressively leads to the most energetically favorable repertoire for a particular challenge (Berek and Ziegner, 1993; Hodgkin, 1997),

* Corresponding author. Tel.: +1 612 626 4624; fax: +1 612 624 9188.
E-mail address: jacko001@umn.edu (D.R. Jackola).

0161-5890/$ – see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.molimm.2004.07.006

represented by a pool of terminally differentiated, antigen-specific memory B and plasma cells (McHeyzer-Williams and Ahmed, 1999).

However, little is known regarding the dynamic outcomes of these processes in humans during the course of natural exposure to environmental allergens, a major source of persistent antigen exposure, particularly during the earliest postnatal years when antigen encounters first occur. Maturation of the immune system during the earliest years of life is critical for establishing normal cellular and humoral responses; else pathologies may ensue upon exposure to otherwise innocuous environmental challenges.

Given a certain 'antigen load', the most suitable physiological effectiveness (ability to remove antigen from the system) may be engendered either by increasing the production of specific antibodies (concentration) or enhancing the antigen–antibody-binding properties (affinity). Further, if the 'antigen load' is relatively constant, then there should be some optimal combination of concentration and affinity resulting in the most energetically efficient use of resources for the given challenge (a total antigen binding capacity).

Although in vitro evidence has shown that SH precedes CSR (Liu et al., 1996), suggesting that the two are mechanistically independent of one another, they are not mutually exclusive processes for dealing with an antigen challenge, which proposes that there is an interplay between the two, possibly via a feedback mechanism. The most readily measured product of the humoral response, antibody concentration, may not be a suitable independent variable, as we have observed among adults that there is an apparent inverse relationship between concentration and the antibody-binding affinity for allergens (Pierson-Mullany et al., 2002). However, this observation suggests that there may be a negative feedback relationship involved.

Among some people, common environmental allergens produce a pathologic response involving the production of allergen-specific IgE (Blumenthal and Björkstén, 1997). Aside from the pathologic consequences, however, allergens are ideal models for the humoral responses that develop due to prolonged exposure to non-infectious antigens. We have shown among adults, either atopic or non-atopic, that there is a dynamic interplay between a response 'potential', reflected by the type and amount of specific immunoglobulin produced, and the 'driving force' of the antibody, reflected by its binding affinity for the antigen/allergen that induced its production (Jackola et al., 2002). There was an inverse relationship between optimal specific immunoglobulin concentration and its binding affinity, suggesting, again, a feedback regulation leading to a most efficient total binding capacity. However, the age-dependent progress of immunoglobulin changes in the earliest years of life leading to these outcomes has not been established.

House dust mite allergens, like Der p (*Dermataphagoides pteronyssinus*), are common, non-infectious allergens that provide an essentially constant environmental 'antigen load'. We prospectively followed two groups of children from Taiwan, with and without Der p atopic sensitivities, for development of antibodies specific to the Der p 1 major allergen. We report here the changes that occurred with age in the Der p 1-specific immunoglobulins that these groups of children produced. We focused upon the dynamics of the changes in specific immunoglobulin concentrations and binding affinities and, in particular, the possibility of feedback interactions between these variables in the presence of the presumed constant antigen challenge.

2. Methods

2.1. Study population and screens for atopy

As part of an ongoing prospective study of the etiology of house dust mite (Der p; *D. pteronyssinus*)-associated atopic disorders in Taiwan, two groups of unrelated children were randomly selected, 15 children per group. Children's parents provided written informed consent according to the guidelines of the Institutional Review Board, Changua Christian Hospital, Changua, Taiwan. Atopic children had characteristic symptoms of atopic dermatitis and/or bronchial asthma and had positive serum screens for Der p-IgE production, using purified Der p extracts with a Pharmacia-CAP® analyzer (lowest detection limit = 0.35 IU/ml; 1 IU = 2.42 ng). Non-atopic children had no symptomatic evidence of Der p-associated or other allergen sensitivity and serum screens were negative for Der p-IgE. In addition to cord blood samples, each of the children was screened for Der p sensitivity at ages: (1) 6 months to 2 years, (2) 2–4 years and (3) 4–6 years.

2.2. Serum immunoglobulin assays

Whole blood was obtained by sterile venipuncture. Serum was separated and stored frozen (−80 °C) until assayed. Quantitative determinations for allergen-specific immunoglobulin concentrations were made, and allergen-immunoglobulin-binding affinity distributions were done using an assay of our device (Pierson et al., 1998).

2.2.1. Der p 1-specific immunoglobulin assays

Der p 1 is a major allergen that was purified by methods previously described (Pierson et al., 1998). The purified Der p 1 was used in a 'reverse sandwich' ELISA assay for tests of Der p 1-specific IgE and IgG1 as described (Jackola et al., 2002).

2.2.2. Binding affinity distribution functions

Our basic experimental method provides information regarding allergen–antibody (Ag–Ab)-binding reactions in vitro (Pierson et al., 1998). Briefly, flat-bottomed microtest plates (Costar #3912, Corning, Inc., Corning, NY) are coated with a mouse anti-human, anti-IgE (clone GE-1, Sigma, St. Louis, MO) or anti-IgG1 (clone 8C/6-39, Sigma) monoclonal antibody (mAb). To this is added a serum sample known to

Download English Version:

https://daneshyari.com/en/article/9142205

Download Persian Version:

https://daneshyari.com/article/9142205

Daneshyari.com