



IgE & non-IgE Mediated Food Hypersensitivity

By, Lauren Zendarski





Hypersensitivity

- Food Allergy
- GALT inhibits responses to non dangerous antigens.
- Characteristics
- Repeated exposure to an antigen.
- Dynamic Immune system
- IgE mediated (type 1) or Non-igE mediated (Type II III or IV)

Prevalence	Infant/child	Adult
Milk	2.5%	0.3%
Egg	1.5%	0.2%
Peanut	1%	0.6%
Tree nuts	0.5%	0.6%
Fish	0.1%	0.4%
Shellfish	0.1%	2%
Wheat, soy	0.4%	0.3%
Sesame	0.1%	0.1%
Overall	5%	3–4%



Immune responses

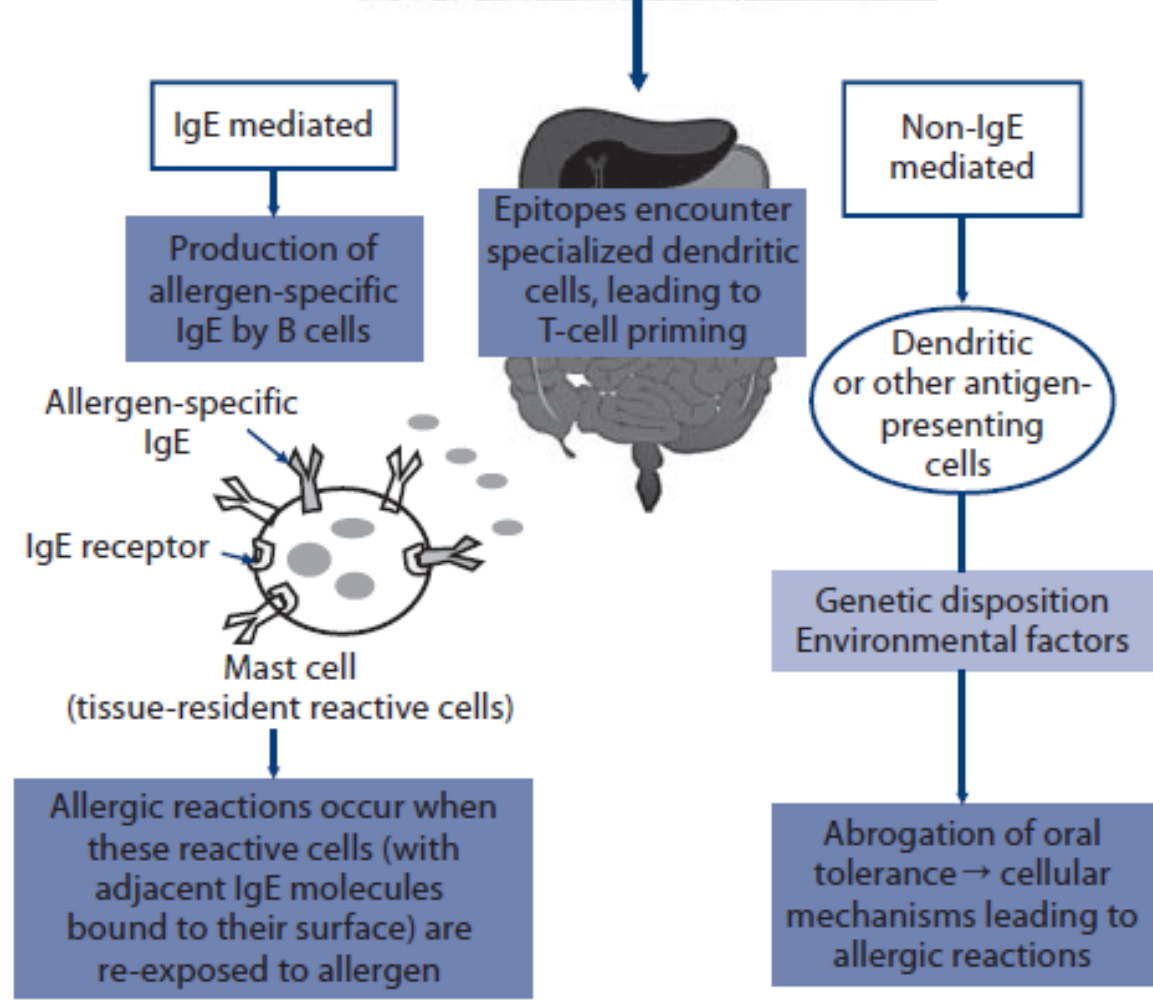
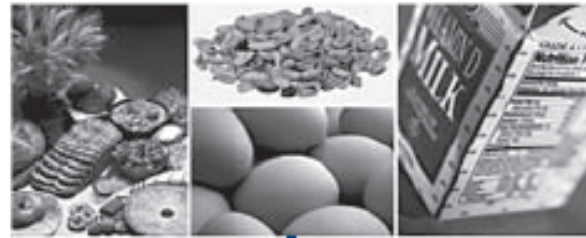
- Responses to food antigens depend on:
 - Dose of antigen
 - Distribution
 - Timing
 - State of the host
- Antigens ripple through immune networks triggering array of responses



Major Allergens Share a Common Feature

- Water solubility of glycoproteins
- Size of protein (10-70 kDa)
- Relative stability to heat, acids and proteases
 - Role of conformation of epitope-denatured by heat.
- Cross reactivity between food

Allergy to	Related food	Approximate clinical reaction rate
Peanut	most beans	5%
A tree nut	other tree nuts	35% (higher for: walnut-pecan, almond-hazel, cashew-pistachio)
A fish	other fish	50%
Shellfish	other fish	50%
Grain	other grain	20%
Cow's milk	goat/sheep milk	>90%
	mare's milk	5%
	beef	10%





Allergic Food Hypersensitivity

IgE mediated	Non IgE mediated
Quick onset	Delayed Onset
Obvious link between exposure and symptoms	Unclear link
Well defined mechanism	Mechanism unclear
Easy to diagnose	Hard to diagnose
Validated tests	No Validated tests



Where Adverse Food Reactions Have Been Shown To Play A Role

- Irritable Bowel Syndrome
- Inflammatory Bowel Disease
- Celiac Disease
- Migraine
- Fibromyalgia
- Rheumatoid Arthritis
- Dyspepsia
- Chronic Fatigue Syndrome
- Autism Spectrum Disorders
- ADD/ADHD
- Chronic Otitis Media
- Eczema
- Chronic Urticaria
- Cyclic Vomiting Syndrome



Types of Hypersensitivity

- Type I: Immediate hypersensitivity
- Type II: Antibody dependent cytotoxicity
- Type III: Antigen-antibody complex mediated
- Type IV: Cell-mediated hypersensitivity



Type I Hypersensitivity

- Immediate or anaphylactic-type
- IgE-mediated
- Occurs within minutes-true food allergy.
- Common problems
 - Hay fever, asthma, rhinitis, atopic dermatitis, urticaria (hives), and anaphylaxis



Type I- IgE

- 1) The food is eaten.
- 2) Reaches the stomach and small intestine where the proteins are not digested correctly
- 3) Intact proteins cross the small intestine and reach the blood and lymph system.
- 4) The immune system makes antibodies against the proteins
- 5) Allergic people make Immunoglobulin E (IgE) which non allergic people don't .
- 6) IgE binds to the surface of mast cells or basophils which sensitizes them.



The Second Time Exposure

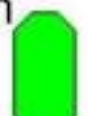
- 1) The person eats the food a second time.
- 2) The protein enters the body
- 3) Binds to and cross-links two to IgE antibodies.
- 4) Causes the mast cell or basophil to degranulate.
- 5) Granules contain 40 different substances that cause allergic reactions.

Histamine, prostaglandins, leukotrienes

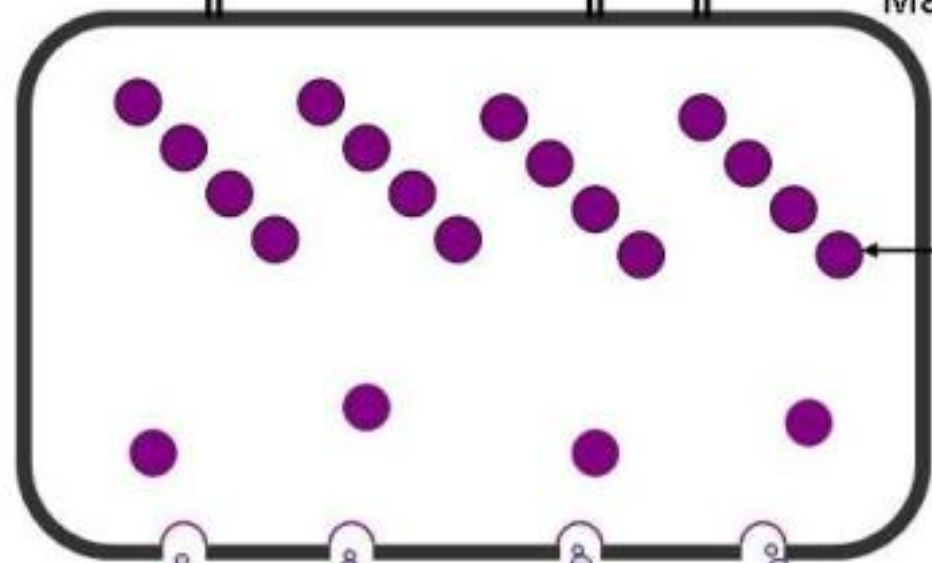


IgE antibody

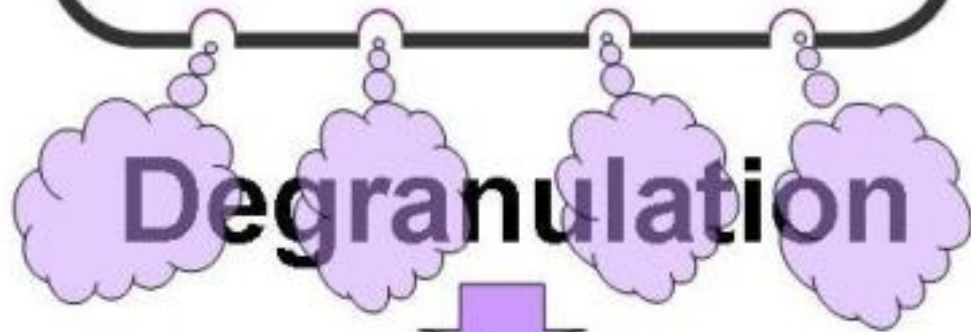
Allergen



Mast cell



Histamine containing granules



Degranulation

Inflammatory mediators

Symptoms: rashes, wheezing, vomiting



Symptoms

- **Respiratory**
 - asthma, wheezing, bronchiospasms
- **Dyspnea**
- **Cutaneous**
 - urticaria (hives), eczema, rash, pruritis, welts, flushing
- **Gastrointestinal**
 - vomiting, diarrhea, abdominal pain
- **Inflammation,**
 - vasoconstriction, hypotension, chest pain, nausea
- **Anaphylaxis Shock**
 - Amount, Deadly

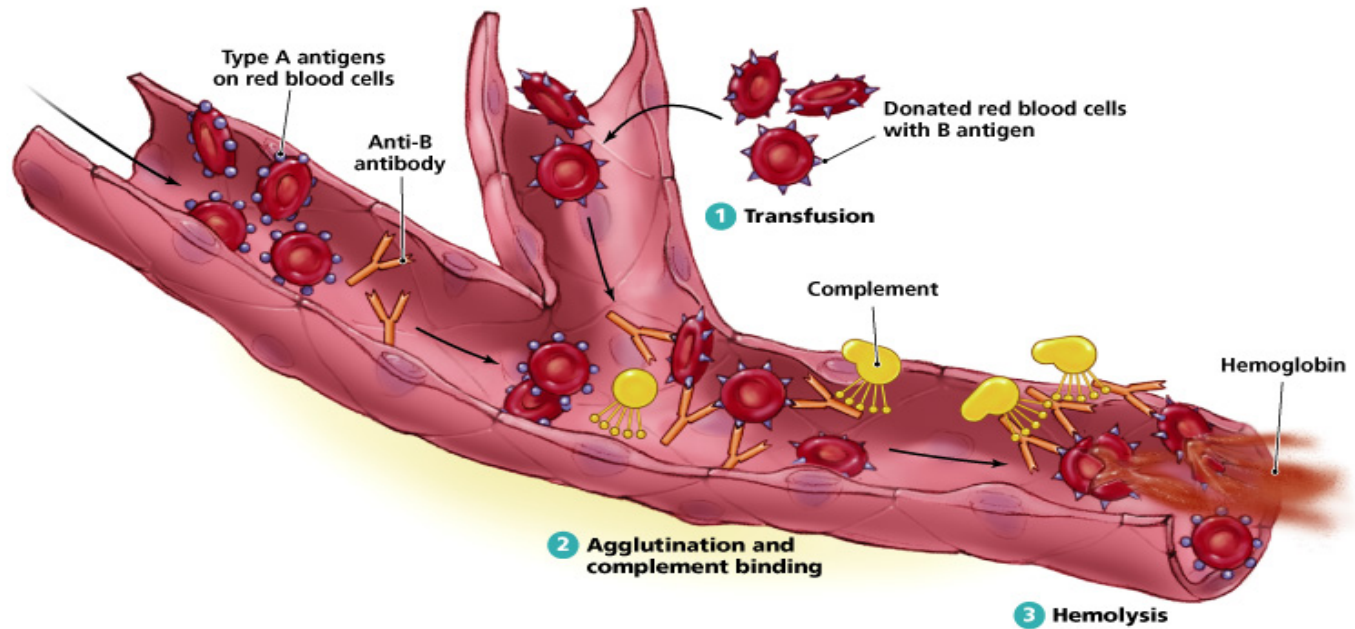


Type II Antibody mediated Type III Immune Complex

- Resemble the type of immune response triggered by an invading pathogen—a virus or bacterium
- IgG, IgM Complement
- Minutes-hours
- Unlike IgE, IgG does not directly initiate degranulation of mast cells.
- Coupling of IgG and its homologous (specific) antigen leads to:
 - specific sequence of reactive proteins is activated, designed to lead to the final destruction of the invader by a process of **cell lysis**



Type II

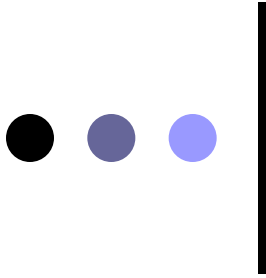




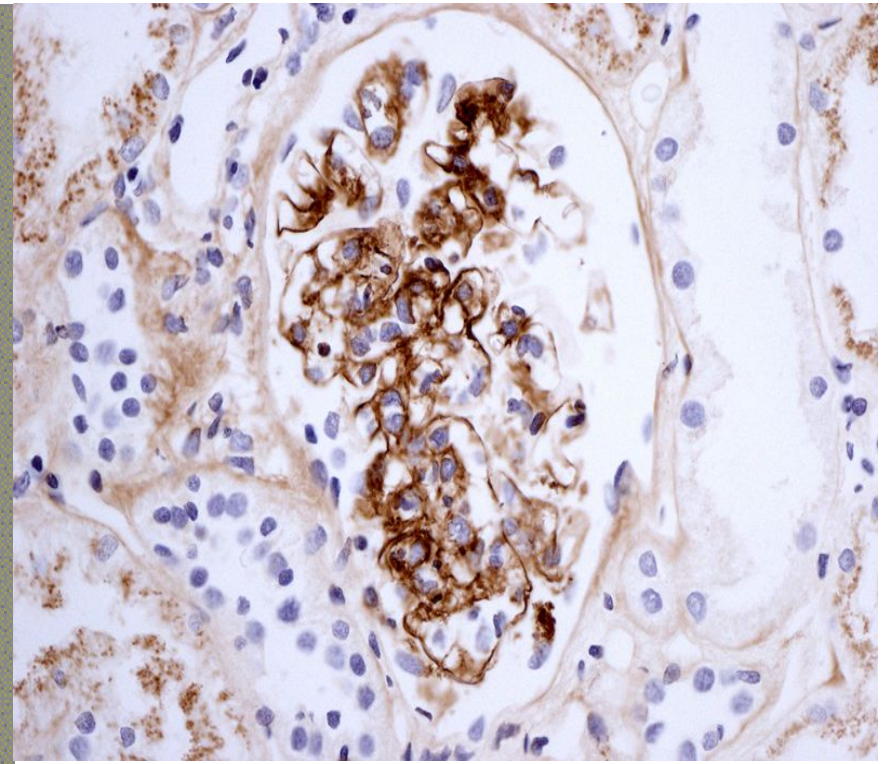
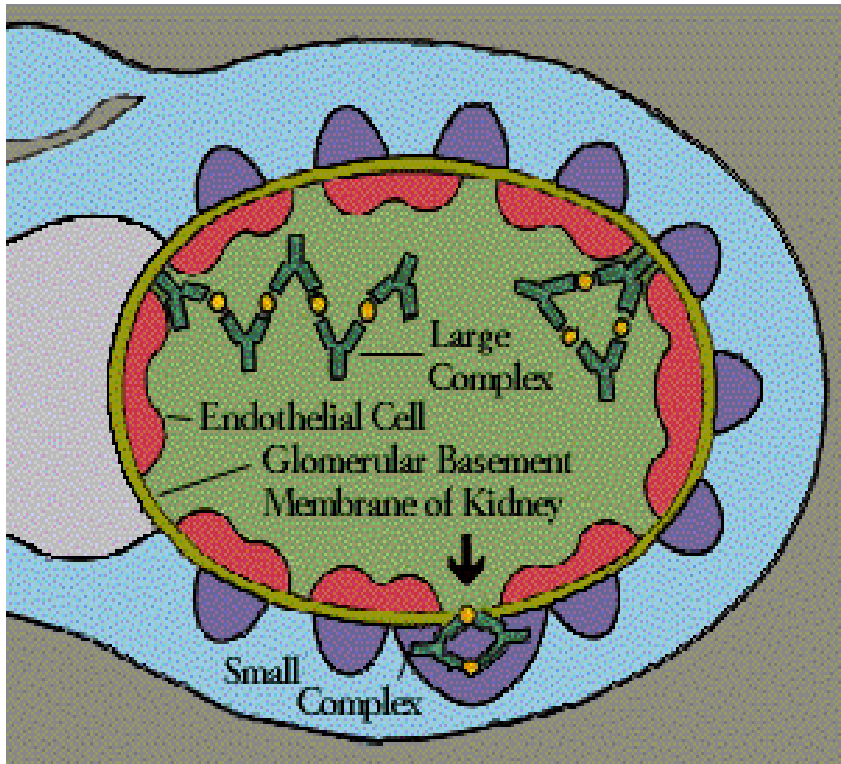
Difference between II & III

- Type III reaction

- External sources but also antigens to “self.”
- Immune complexes are formed when antigens bind to antibodies and form a complex, which can cause an immune reaction, damaging organs or tissues.



Type III





Delayed II & III

- Not so obvious and generally go unrecognized
- Symptom is delayed after exposure to trigger food.
- Examples
 - celiac disease –wheat
 - other cluster around gastrointestinal tract dysfunction
 - migraine, fibromyalgia, fatigue, depression, chronic rhinitis, sinusitis, asthma, and arthralgias are typical associations.

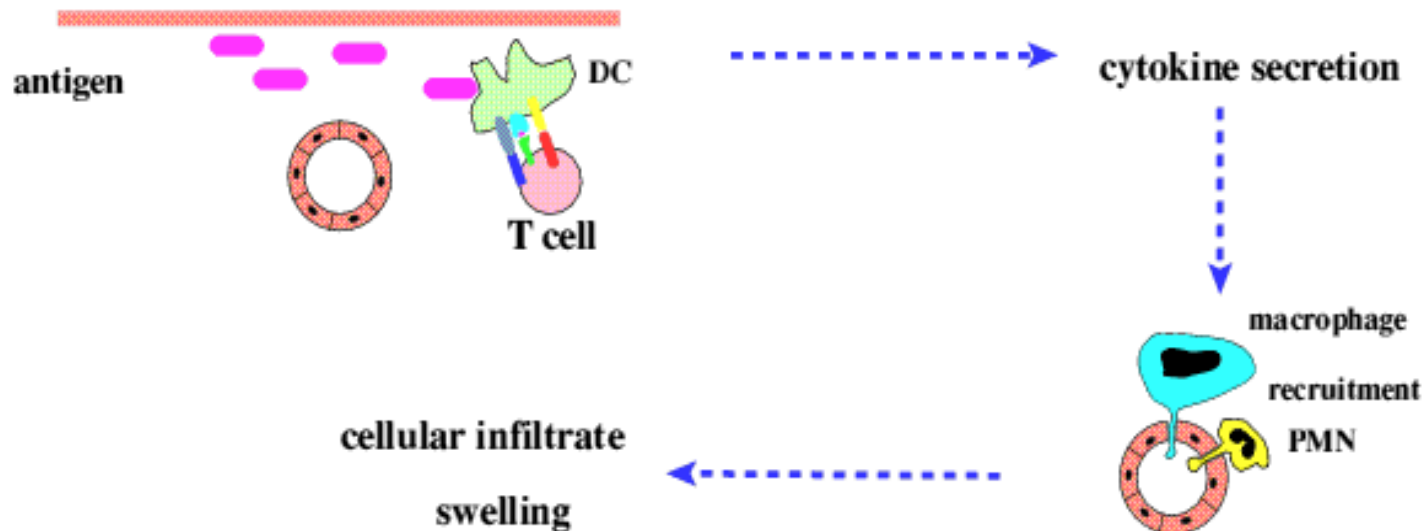


Type IV Hypersensitivity

- Cell-mediated response
 - Cell to cell contact antigen and T-cell lymphocytes- skin
 - Soluble inflammatory mediators, cytotoxicity- damage to surrounding area
 - The lymphokines promote a reaction mediated through macrophages beginning in hrs, but reaching a peak in 2 to 3 days.

- ● ●
- 1. Antigen Enters into the subcut tissue.
- 2. A Th1 effector cell recognizes antigen and releases cytokines which act on vascular epithelium
- 3. Recruitment of T cells, phagocytes fluid and protein to site of antigen injection causes visible lesion

Type IV Hypersensitivity





Example of Type IV

- However, a type of dermatitis on the hands of sensitized individuals in contact with raw foods such as a
 - Potato
 - Tomato
 - Apple
 - Watermelon rind
 - Carrot



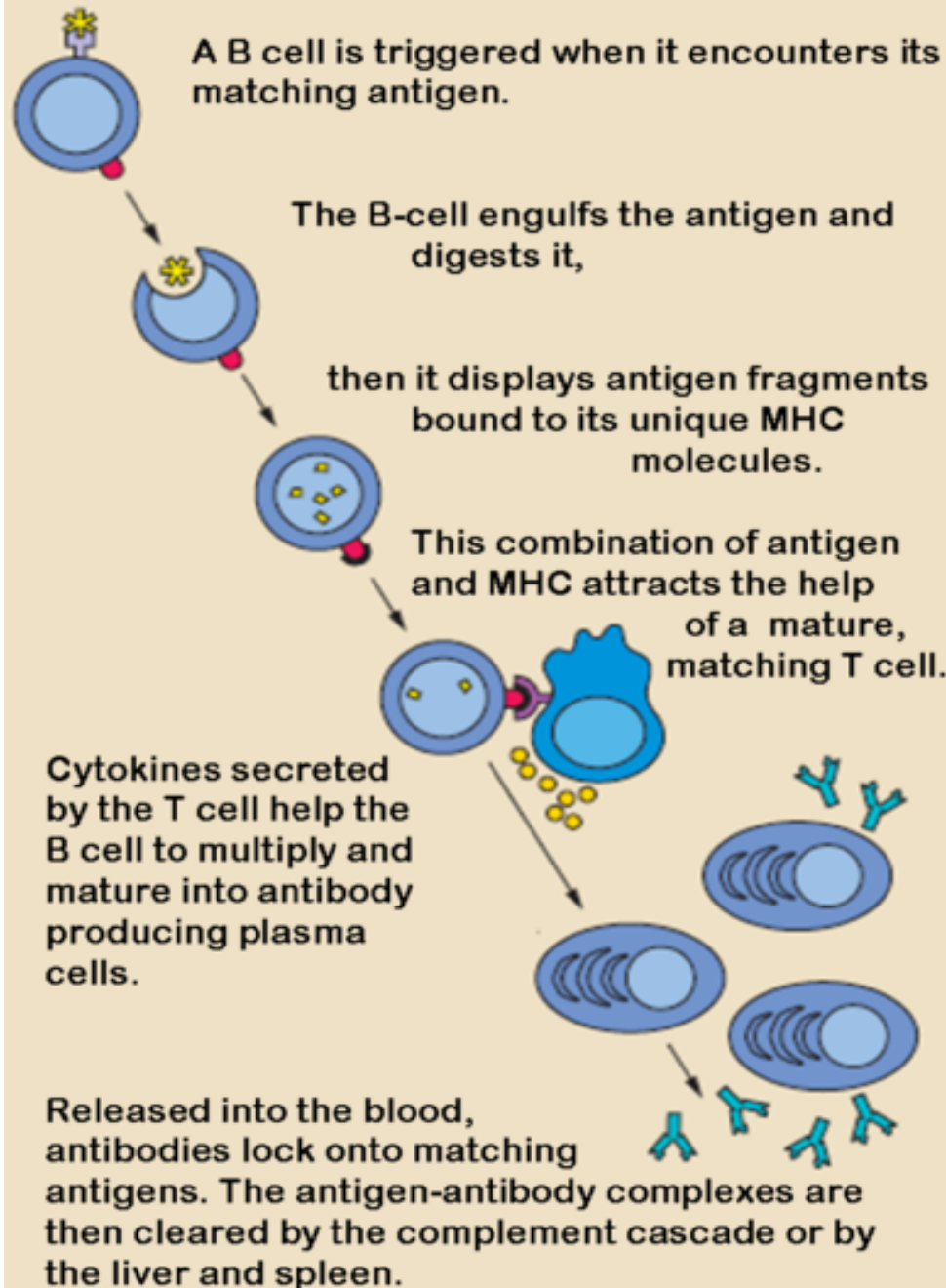
Diagnosing Issues

- Allergy only confirmed in 3-5% of reactions- IgE mediated
 - Prick Test, RAST
- Non-IgE difficult to diagnose
 - Multiple causes (II, III, IV)
 - Delayed
 - Most tests- IgE
 - Food Diary?



- **Intestinal B Cell-activating factor:
An indicator of non-IgE mediated
hypersensitivity reactions to food?**

- G Arslan Lied, K. Lillestol, et al.
 - Class: A
 - Grade: +
- Aim: Examine B cell activating factor (BAFF) in serum and gut lavage fluid





Materials and Methods

- Exclusion:

- IBS
- Pregnant or Lactating
- Severe anaphylactic reactions

- Inclusion:

- Abdominal complaints attributed to food hypersensitivity (non-IgE)



Patients

○ N=77

- GI examinations, full medical history, family history, suspected food triggers, Serum IgE, skin pricks using panel of inhalant allergens.
- Stools collected to rule out disease.

N=20 Control

Questionnaire, examinations



Intestinal lavage procedure

- Overnight fast
- Thin nasoduodenal tube positioned distal part of duodenum
- 3L of isotonic polyethylene glycol solution -40 min
- First clear passage collected
- Frozen at -80 C, no repeat freezing



Analysis of BAFF

- Thawed centrifuged- 10 min at 3,000 rpm at 4C.
- Measured by immunosorbent assay
- After washing unbound substances – enzyme linked antibody specific for BAFF was added.



Results

- N=60 patients gut lavage
- N=17 serum BAFF
- N=20 control gut lavage
- N=11 Control Serum BAFF
- **P <0.0002**

Gut Lavage	Patients	Controls
Median	34 pg/mL	13.4 pg/mL
IQR	24.3- 44.8 pg/mL	0-26.8 pg/mL

Intestinal B Cell-activating factor: An indicator of non-IgE mediated hypersensitivity reactions to food?

G Arslan Lied, K. Lillestol, et al. Aliment Pharmacol Ther 2010; 32: 66-73

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BAFF in serum

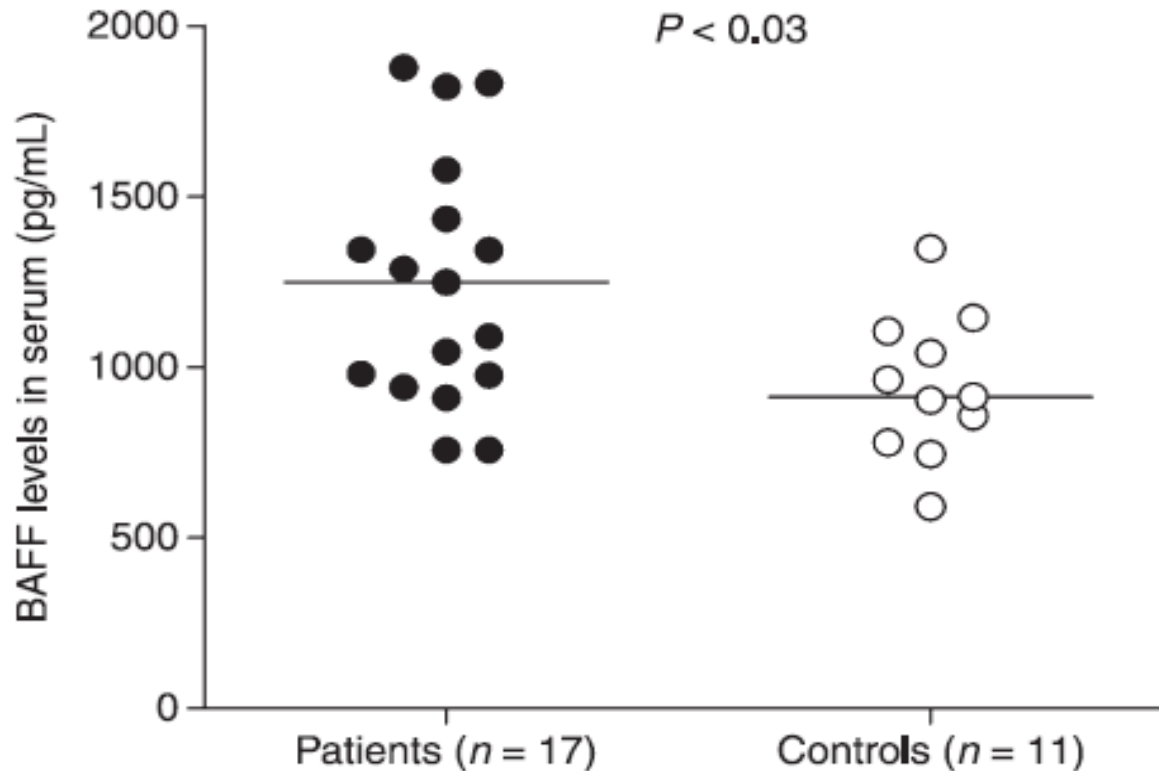
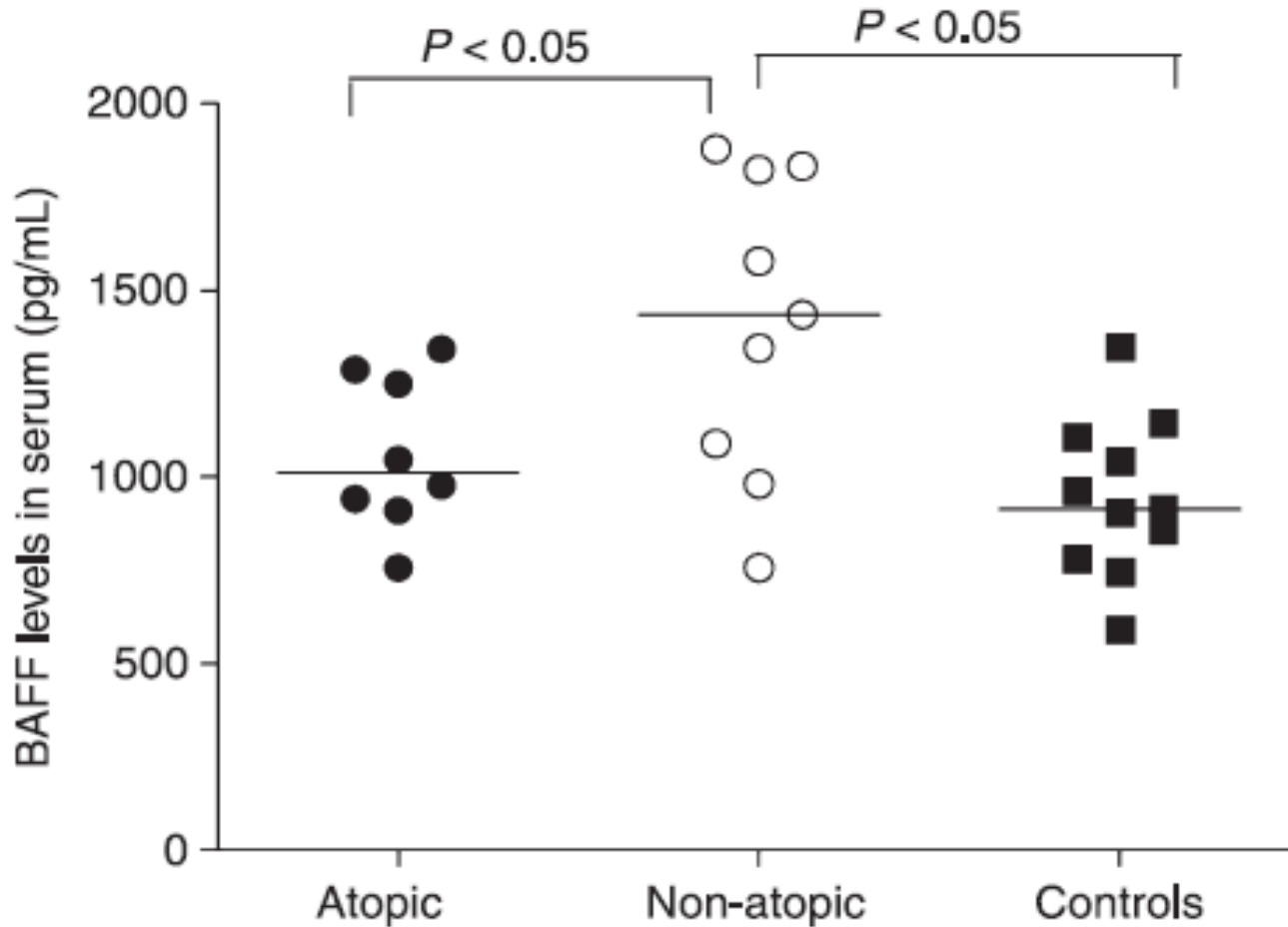


Figure 2 | B cell-activating factor concentrations in serum in patients with self-reported food hypersensitivity ($n = 17$) and in healthy controls ($n = 11$). Individual results are reported with median values ($P < 0.03$).

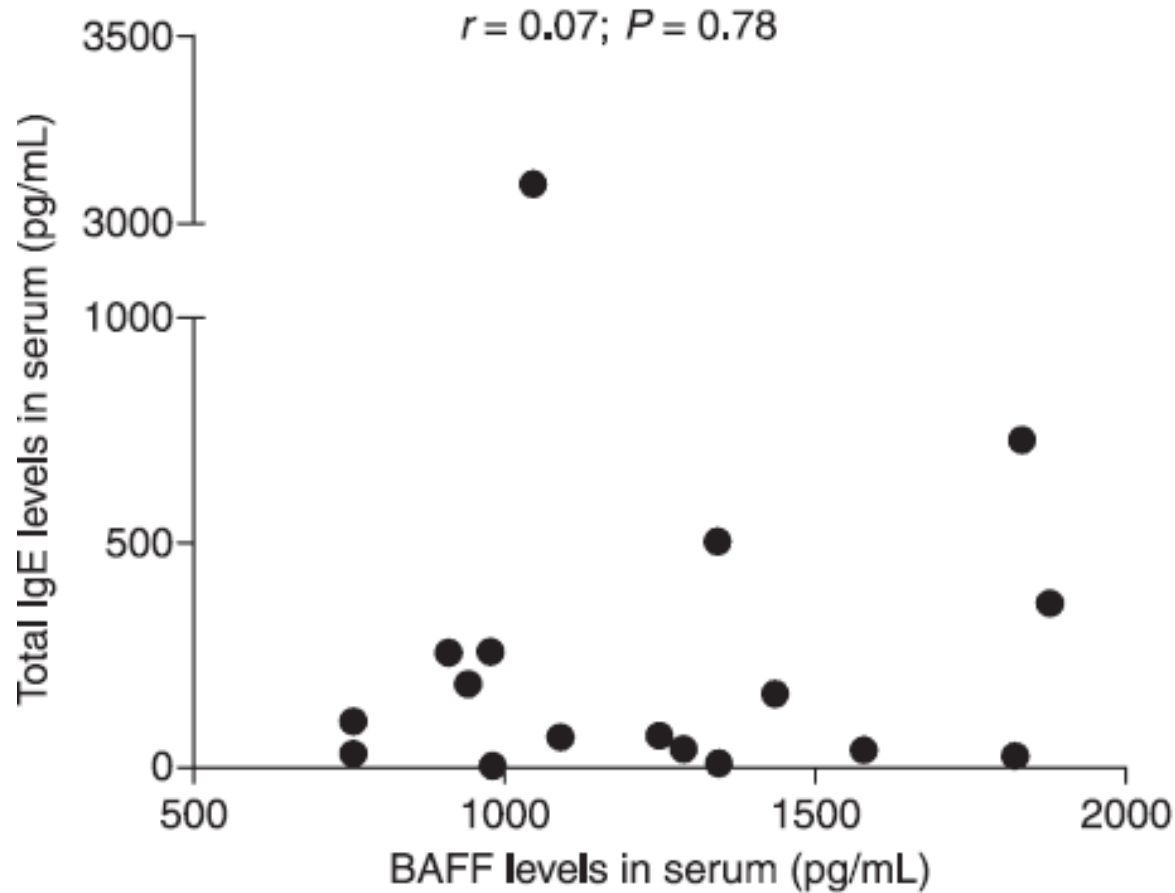
Atopic vs non-atopic



Intestinal B Cell-activating factor: An indicator of non-IgE mediated hypersensitivity reactions to food?

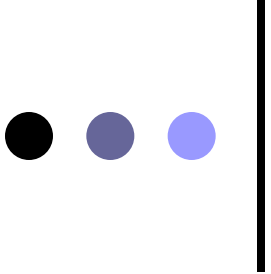
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Correlation between BAFF and IgE

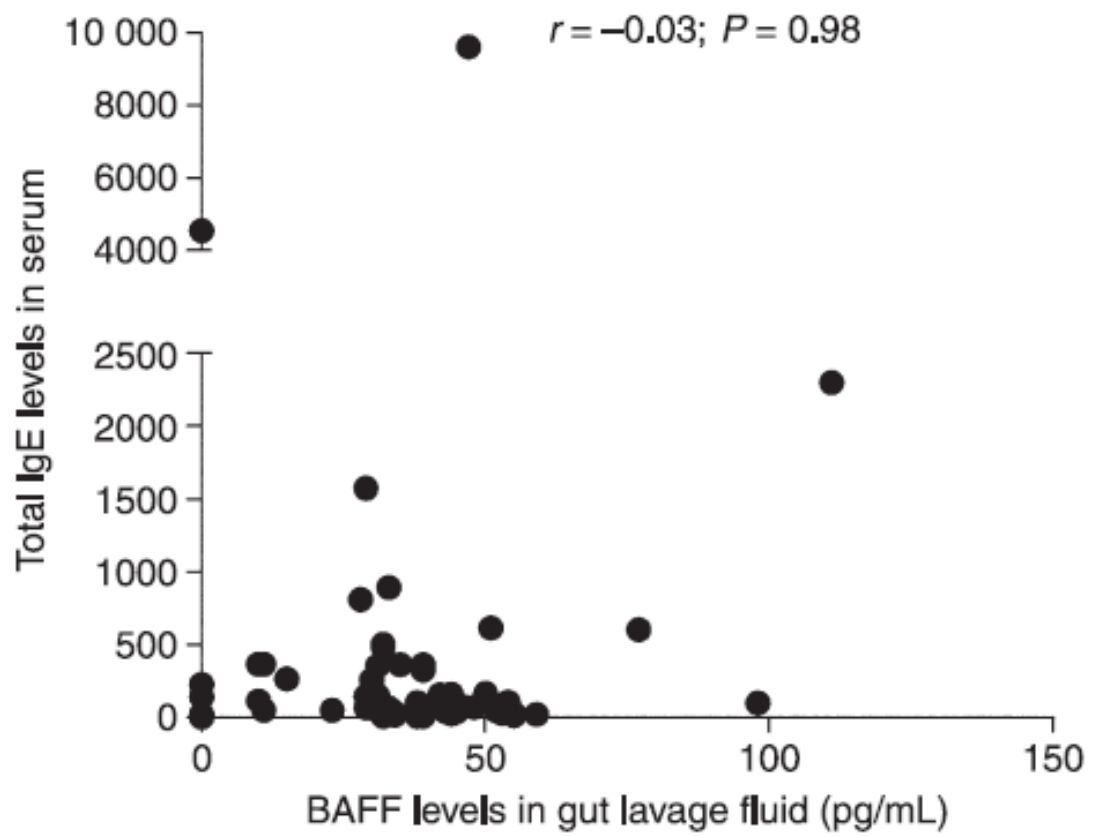


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IgE and gut lavage Correlation



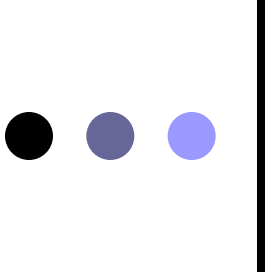
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Conclusion

- Increased levels of BAFF in blood and gut lavage fluid suggest that **BAFF might be a new mediating mechanism.**
- Higher levels in non-atopic compared with atopic and no correlation between BAFF and IgE levels suggest that **BAFF might be particularly involved in non-IgE mediated reactions.**



Local release of B cell–activating factor of the TNF family after segmental allergen challenge of allergic subjects.

- J Allergy Clin Immunol 2009;123:369-75
- Atsushi Kato, PhD,a HuiQing Xiao, MD
- AIM: To examine if BAFF is expressed/localized within allergen site or serum.
- Grade: +
- Class: A

Table 1

Subject characteristics

Subject	Disease	Age	Sex	Race	Allergen	Dose [*]
1	Allergic Asthma	20	Female	Cauc	RW	0.03 ^a × 0.5
2	Allergic Asthma	25	Female	AA	RW	0.03 ^a × 25
3	Allergic Asthma	35	Male	AA	RW	5 × 0.1
4	Allergic Asthma	43	Female	AA	RW	5 × 0.1
5	Allergic Asthma	28	Male	AA	RW	5 × 0.1
6	Allergic Asthma	37	Male	Cauc	DF	5 × 0.03
7	Allergic Rhinitis	28	Female	AA	RW	5 × 2.5
8	Allergic Asthma	27	Male	AA	DPT	5 × 0.3
9	Allergic Asthma	33	Male	Cauc	DPT	5 × 0.3
10	Allergic Asthma	35	Female	Cauc	DPT	5 × 0.06
11	Allergic Rhinitis	43	Female	Cauc	DPT	5 × 0.13
12	Allergic Asthma	33	Male	Cauc	DPT	5 × 0.001
13	Allergic Asthma	33	Male	AA	RW	5 × 10



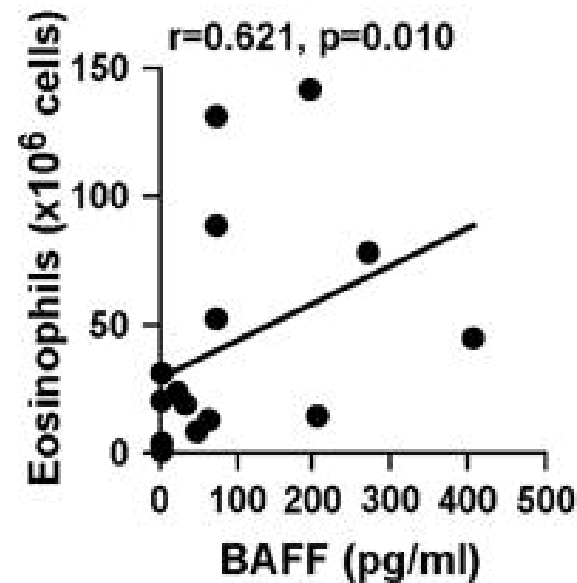
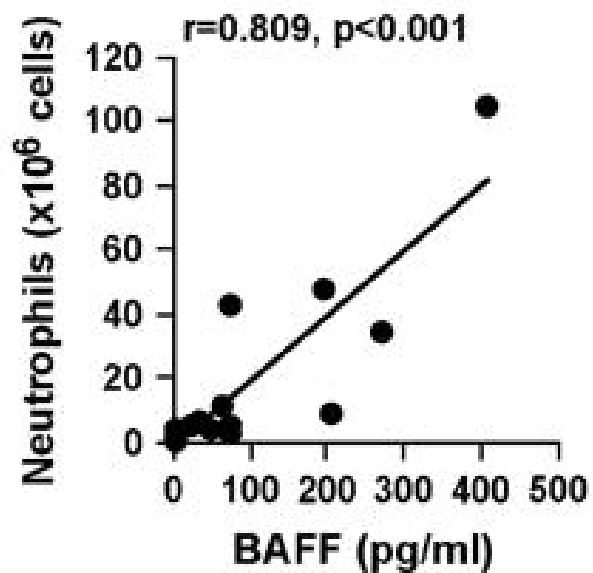
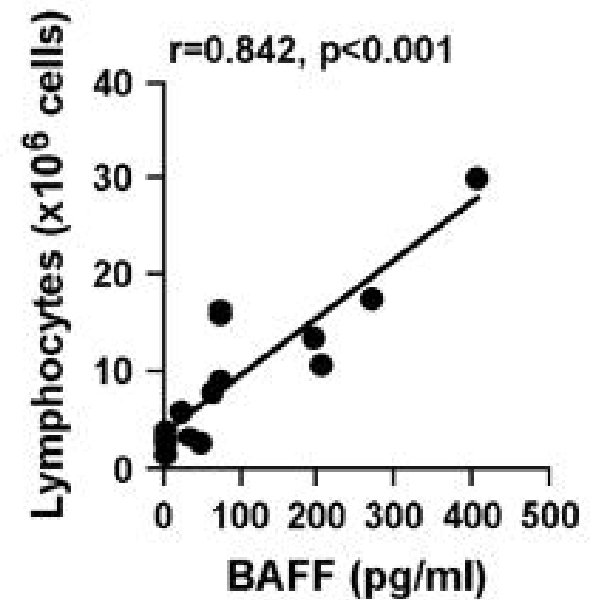
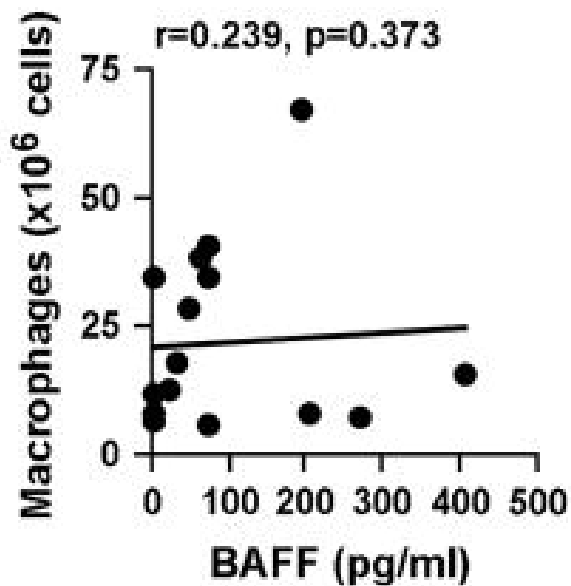
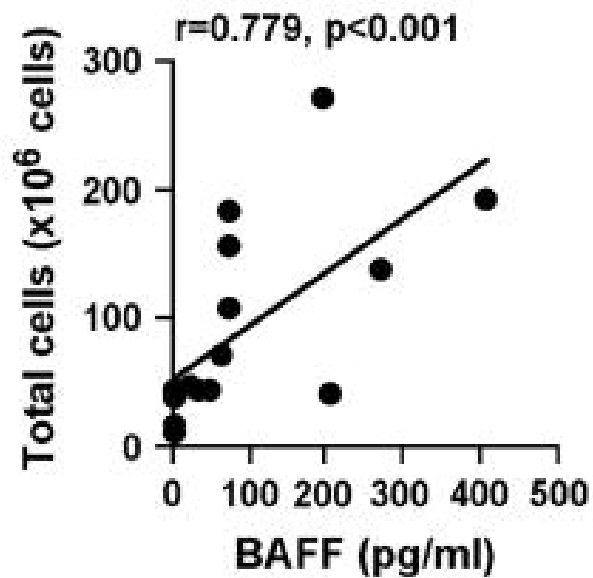
Methods

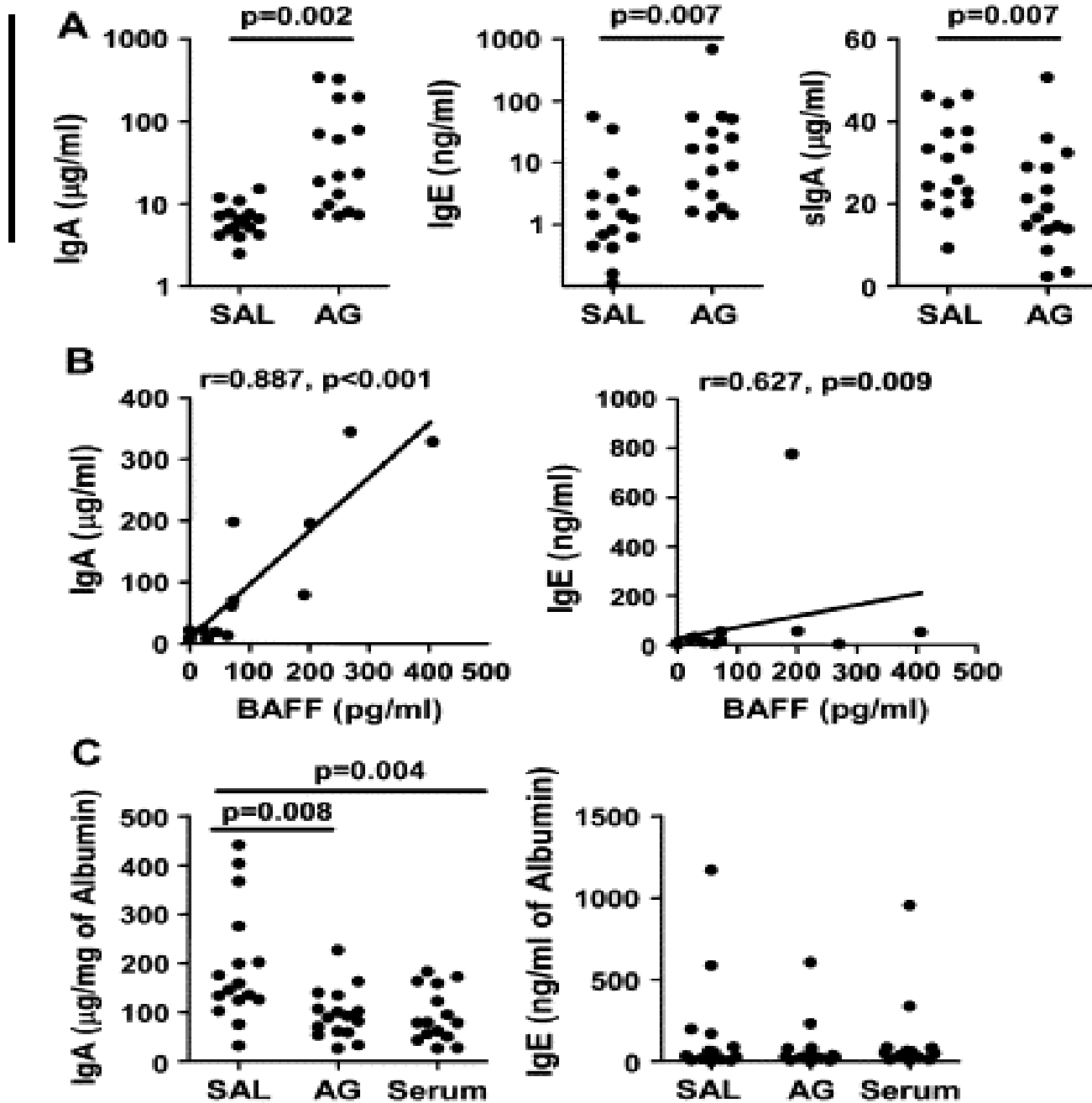
- Premedicated with 0.6 mg atropine and 0.1 mg fentanyl.
- Control: 5 mL of normal saline into right middle lobe
- SAC: 5 ml ragweed in opposite lobe.
- 2 subjects: 2 minute aerosols of SAL (saline) and AG (allergen).
- After 20 to 24 hours Bronchoalveolar Lavage (BAL) = BAFF expression



Statistical Analysis

- Reported as Medians (ranges, min to max).
- Differences analyzed using the Wilcoxon signed-rank test or the Mann-Whitney U test....lauren look up
- A P value $> .05$ significant.







Conclusion

- BAFF is upregulated in airways of allergic subjects after allergen exposure.
- BAFF significantly higher in BAL fluid than to serum.

What Are Currently Doing For Non-Ige Hypersensitivity?

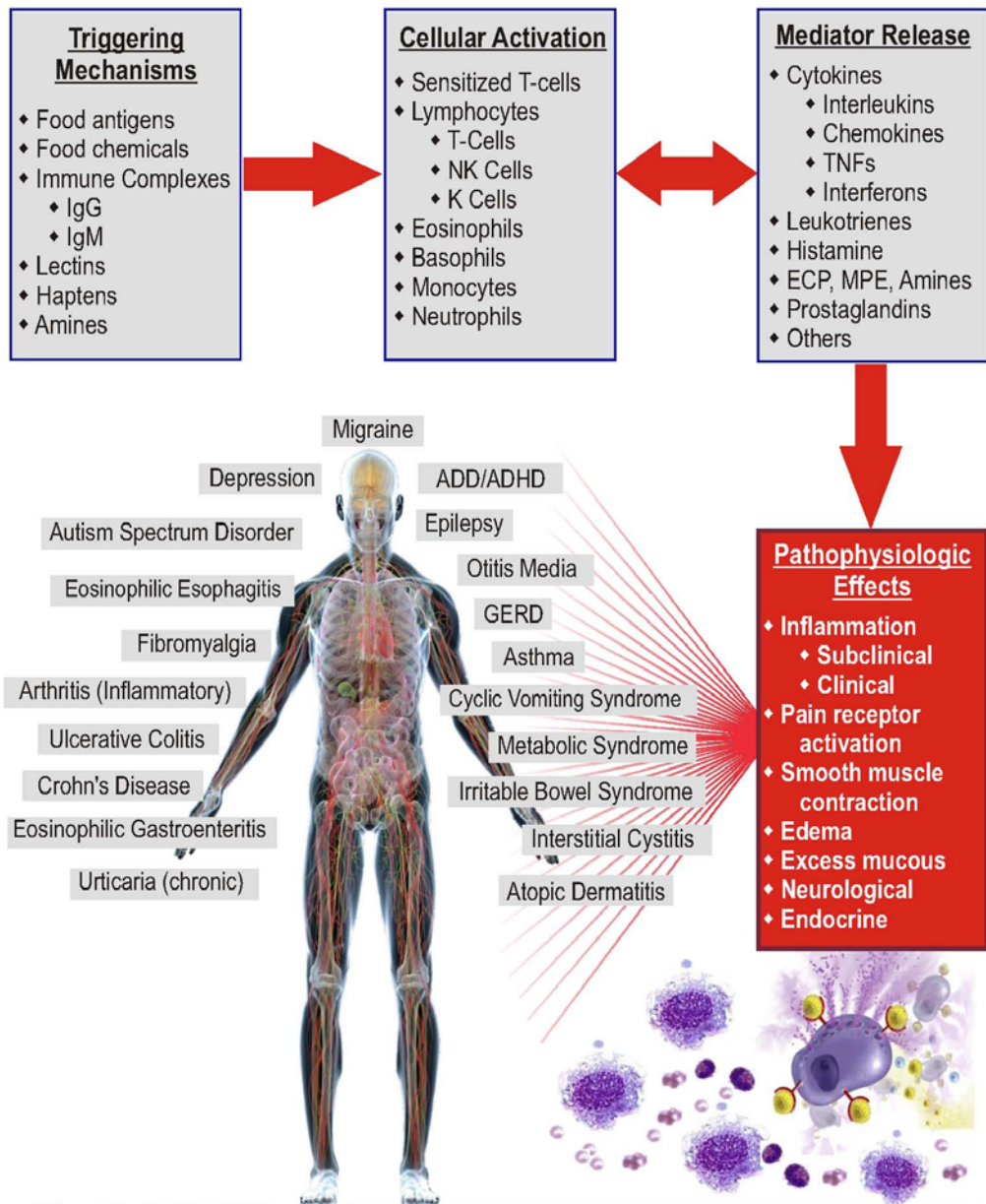


What about the diet?

- Typical recommendations
 - AVOID FOOD TRIGGERS
 - No universal bad food- patient specific
 - Multiple foods can cause symptoms
 - Single elimination trials are useless



Food and food-chemical sensitivities are complex immune, but non-IgE (non-allergic) mediated reactions involving multiple triggering mechanisms and multiple classes of leukocytes. Pathogenic reactions ultimately lead to release of proinflammatory and proalgesic mediators from associated white cells with resulting symptoms across a wide range of clinical conditions.





Why we feel sick..

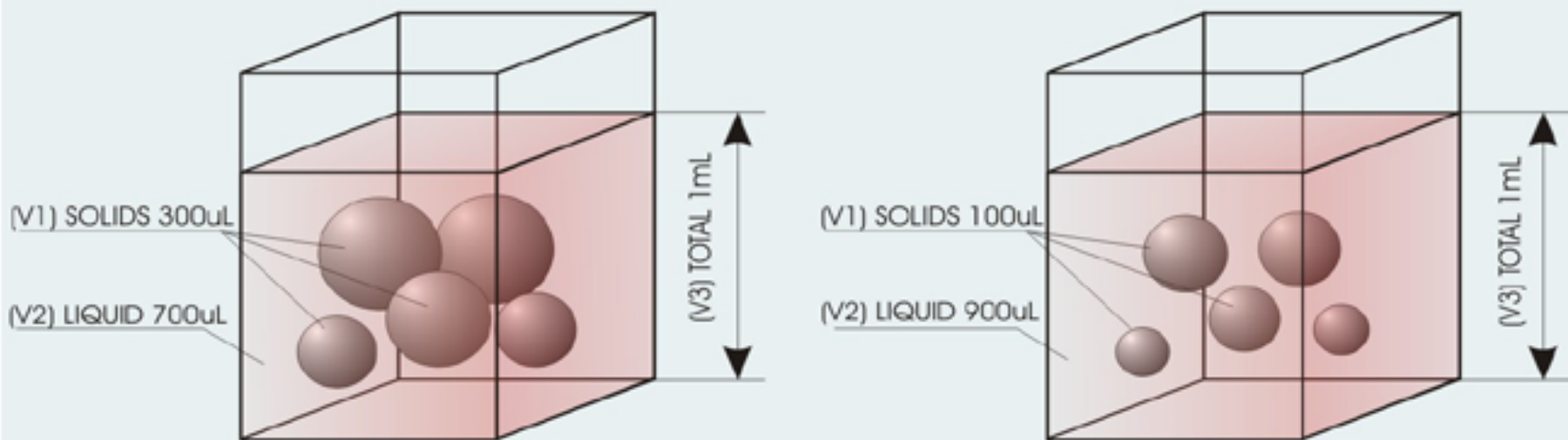
- 15-20% of the population
- Our immune system begins perceiving foods in the same way it perceives things which are truly harmful – bacteria, viruses, parasites, etc.
- Release of toxic chemicals called “mediators”(such as histamine, cytokines, and prostaglandins) from our immune cells.
- It's the inflammatory and pain-inducing effects of the mediators that give rise to symptoms, which ends up making us feel sick.

Mediator Release Testing (MRT)



- Eliminating the guesswork
- LEAP- olioantigenic diet.
- Analyze your blood's response to
 - 27 different chemicals
 - 123 different foods. |

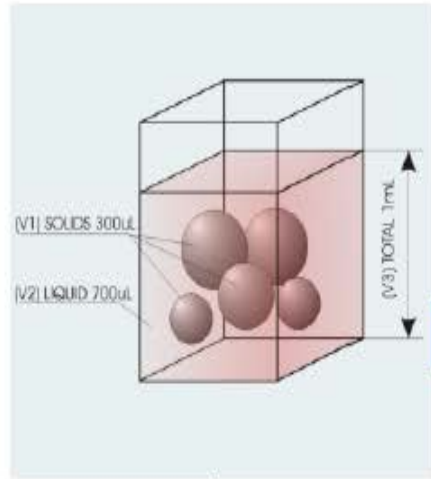
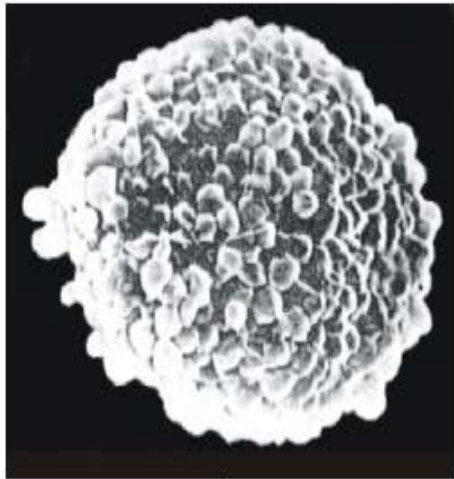
A sensitivity of 94.5%, a specificity of 91.7%, and split sample reproducibility consistently greater than 90%.



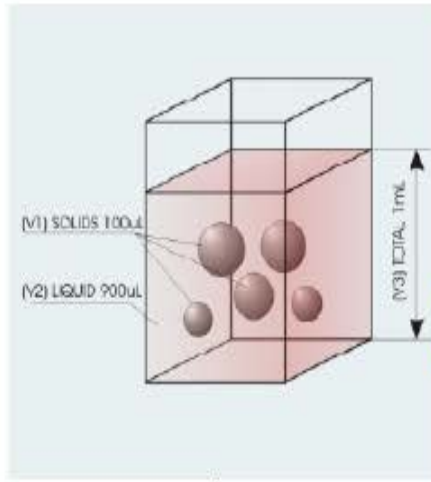
PRINCIPLE OF MEDIATOR RELEASE TESTING

V1+V2 = V3 as applied to in vitro antigen challenge of immunocytes where V3 is constant. The instrumentation measures V1 (cellular volume) and V2 (extracellular volume) precisely using patented method of measurement to detect any release of intracellular mediators when antigen is presented. Perceived harmful substances trigger mediator release in associated cells causing a decrease in the V1 solids (cellular) portion and an increase in the V2 liquid (plasma) portion of the tested sample.

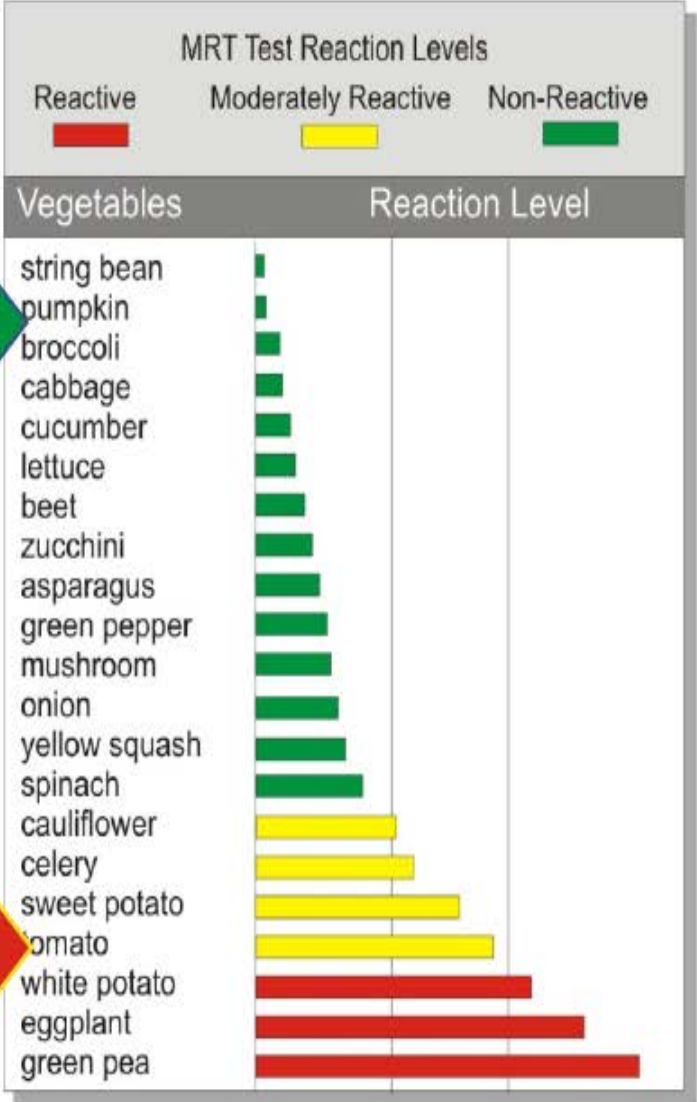
Significant reactions are categorized as either Reactive or Moderately Reactive. Non-significant reactions are categorized as Non-Reactive and form the basis for the LEAP ImmunoCalm® Dietary Management Program.



Non-Reactive Sample



Reactive Sample





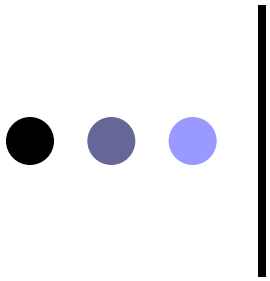
The LEAP ImmunoCalm Diet

- **Start an elimination diet.**
- **Limit chemically reactive foods.**
- **Refer for vitamin D testing.** lack of vitamin D increases gut permeability, thereby increasing food sensitivities
- **Consider the environment** – molds, yeast, mushrooms, pollen
- **Test for celiac disease**
- **Nix the herbal supplements.** may never know whether the foods or the herbs are triggering her symptoms.
- **Consider prescheduled plans.**



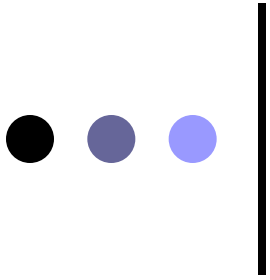
Benefits

- Based on individualized results of the MRT test.
- Isolates specific foods and/or additives provoke any form of non-IgE mediated hypersensitivity
- Unlike ELISA IgG (type 3), can identify reactions to food chemicals.
- Eliminates the Guess work



Key Points

- Type-1 – True food allergy
- Type II, II, IV-delayed
 - BAFF?
 - MRT
 - LEAP DIET



References



Questions

- Would you refer one of your patients to a LEAP Dietitian for food allergies?
- Do you feel BAFF could be used in the future for diagnosing non-IgE food allergies?
- What do you think is the future for non-IgE mediated food allergies is within the Academy?