

Biological Basis of the Allergic Response

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Allergic reactions

- Also known as type I hypersensitivity reactions
- Requires prior exposure and sensitization (IgE)
- Atopy: familial disposition towards allergy
 - “He comes from an atopic family”
- Allergic sensitization
 - Production of IgE and arming of Fc ϵ RI-bearing cells but does not necessarily mean clinical disease

Sequence of Events (Priming)

- 1) Ag Presented
- 2) TH2 Response
 - (IL4, IL5 and IL-13)
- 3) IL-4 -> IgE Production
- 4) IgE loads mast cells

A.B. Kay, NEJM 2001, 344:1, 30-37

Antigen Uptake and Presentation

MHC/peptide-TCR
Signal 1

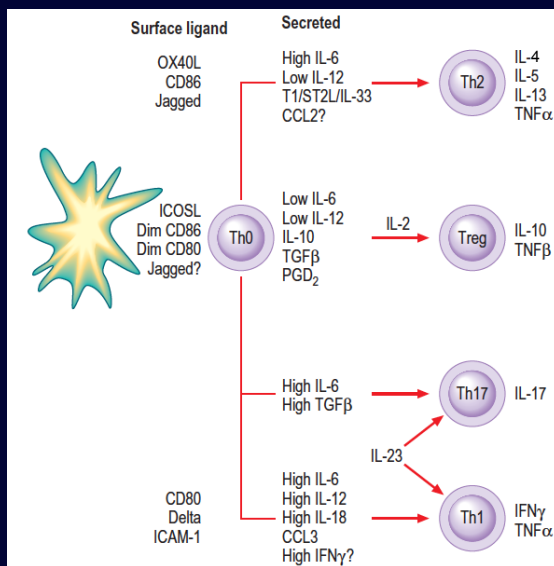
DC T cell

Ag uptake → Ag processing → Signal 2 → T cell response

DCSIGN-ICAM-3	Activation
CD80/86-CD28	Differentiation
B7RP-ICOS	
PDL1/PDL2-PD1	
CD40-CD40L	
OX40L-OX40	

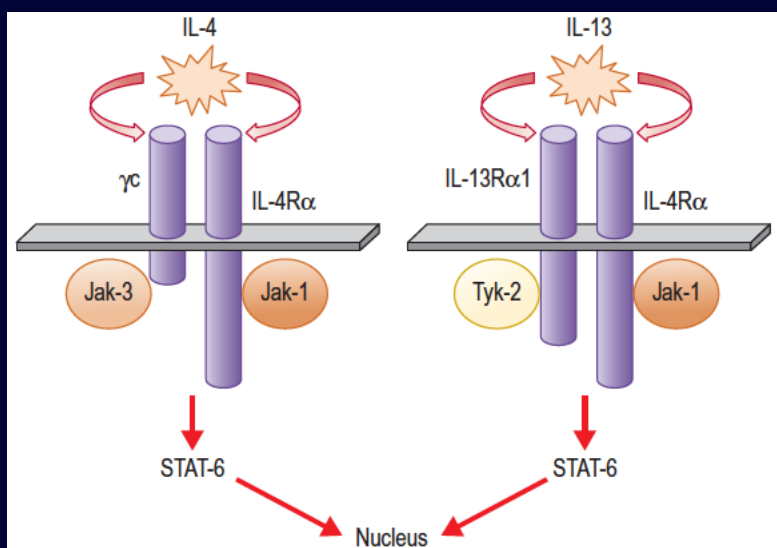
Lambrecht and Hammad, Middleton's Allergy: Principles and Practice, 8th Edition, 2013

Antigen Presentation Leads to T cell Differentiation



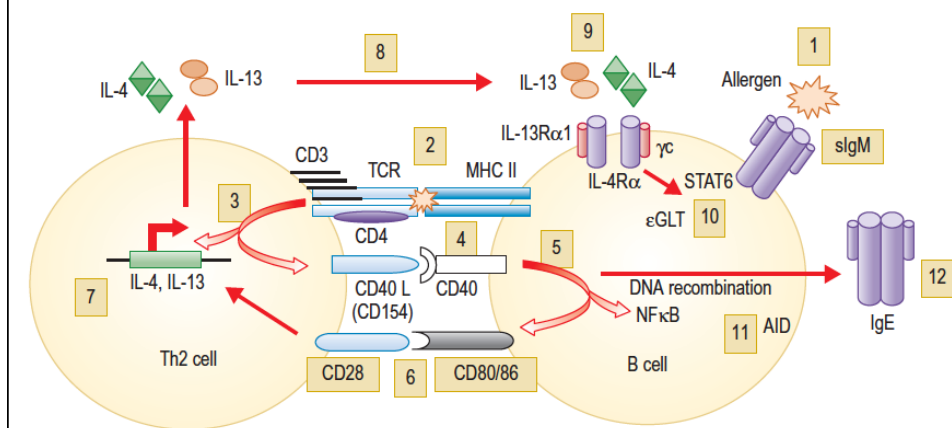
Lambrecht and Hammad, Middleton's Allergy: Principles and Practice, 8th Edition, 2013

IL-4 and IL-13 cytokine receptors



Oettgen, Middleton's Allergy: Principles and Practice, 8th Edition, 2013

Th2 cells influence B cells to make IgE through isotype switching

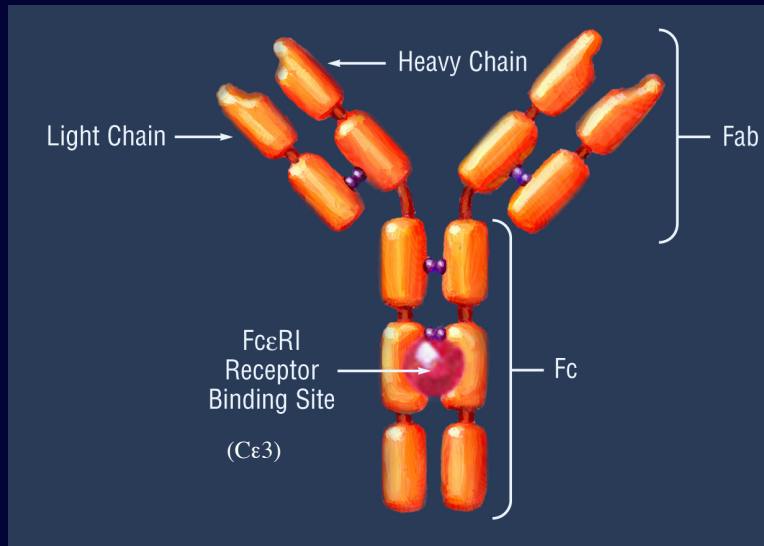


Oettgen, Middleton's Allergy: Principles and Practice, 8th Edition, 2013

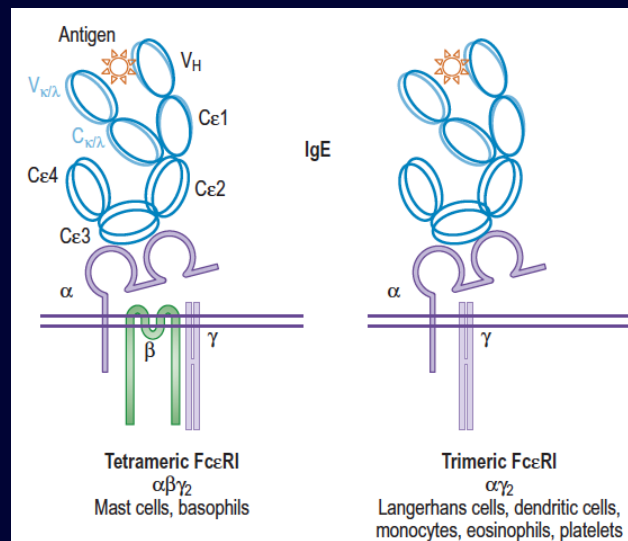
What Makes an Antigen IgE-Promoting ?

- Protein, not lipid; can rarely be carbohydrate
- Mucosal exposure
- Low concentration but must be multivalent
- Stable, water soluble
- Many have protease activity
 - e.g., grass pollens, dust mite
- Some resemble helminthic parasite antigens
 - Filarial tropomyosin is similar to house dust mite, shellfish and cockroach proteins

Unique Characteristics of IgE

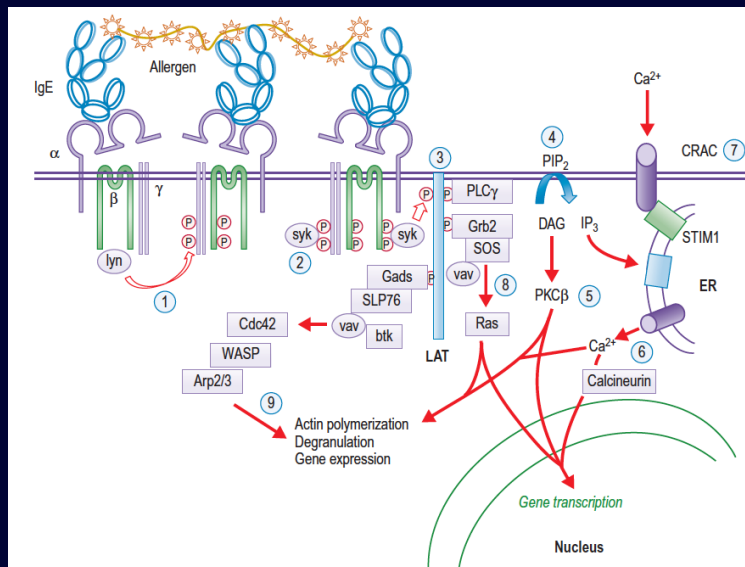


IgE-FcεRI interactions



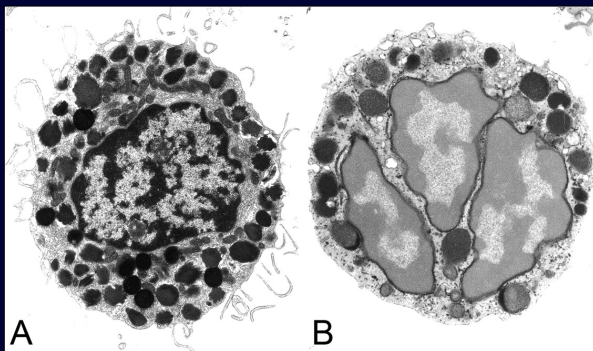
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Consequences of FcεRI triggering



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Mast cells and Basophils

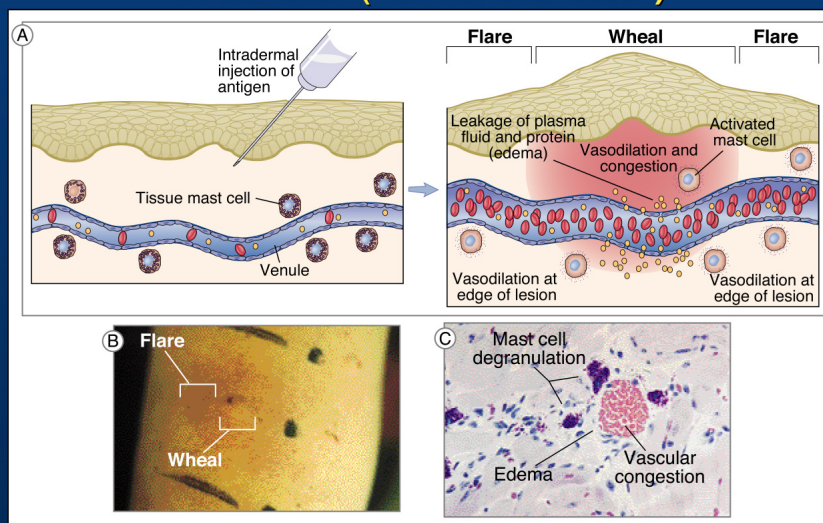


Dvorak AM, J. Histochem Cytochem 53:1043, 2005

Mediator	MC	Baso
Histamine	+++	+
Tryptase	+++	+/-
LTs	+++	+
PG's	+++	-
IL-4	+/-	+++
IL-13	+	+++
Other cytokines	+++	+

Courtesy of John Schroeder

Immediate hypersensitivity reaction in the skin ("wheal and flare")

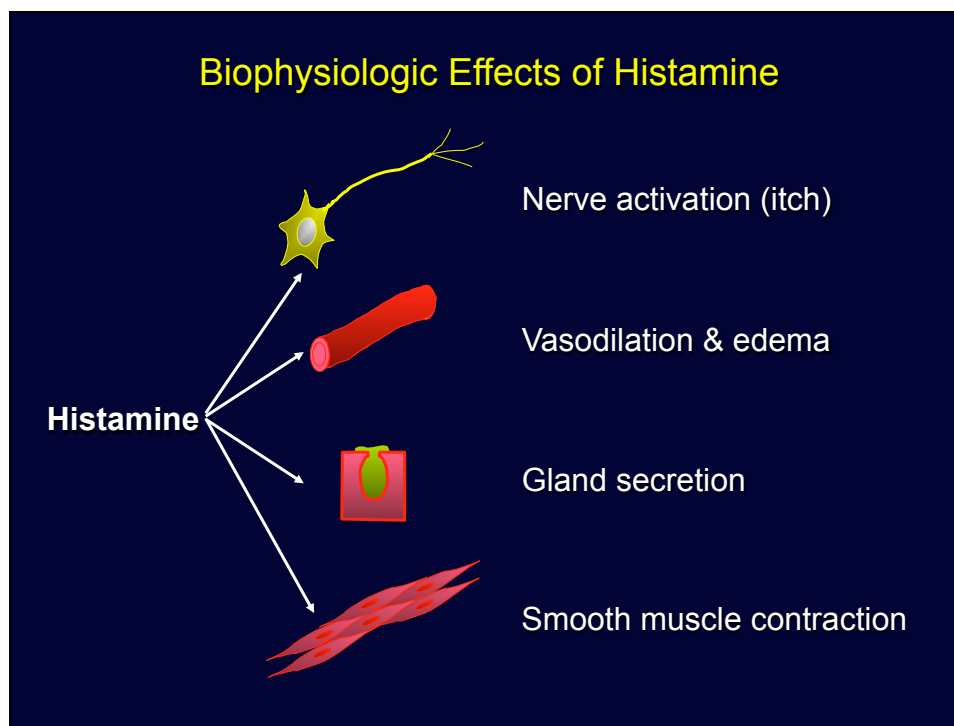


From Abbas, Lichtman, & Pober: Cellular and Molecular Immunology. W.B. Saunders, 1999, Fig. 19-3

Detection of Specific IgE-Mediated Sensitivity



- Skin Testing: wheal and flare responses
- Laboratory measurement of serum specific IgE levels, more recently including component testing



Various Mediators of Allergic Diseases and their Receptors




Mediator	Receptors
Histamine	H1 – H4
PGD ₂	DP1, DP2
PGE ₂	EP1 – EP4
PGF _{2a}	FP, IP, TP
Sulfidopeptide LT	CysLT1, CysLT2
Sphingosine-1-P	S ₁ P ₁ – S ₁ P ₅

Definition and Diagnosis of Anaphylaxis


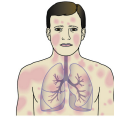


Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:

1 Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)



AND AT LEAST ONE OF THE FOLLOWING:

		
Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)	Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)	Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)

OR **2** Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger* for that patient (minutes to several hours):

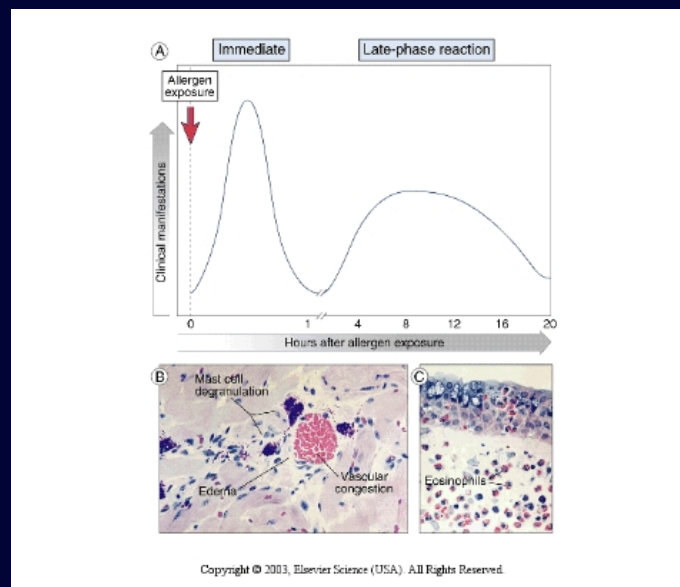
			
Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)	Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)	Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)	Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)

OR **3** Reduced blood pressure (BP) after exposure to a known allergen** for that patient (minutes to several hours):

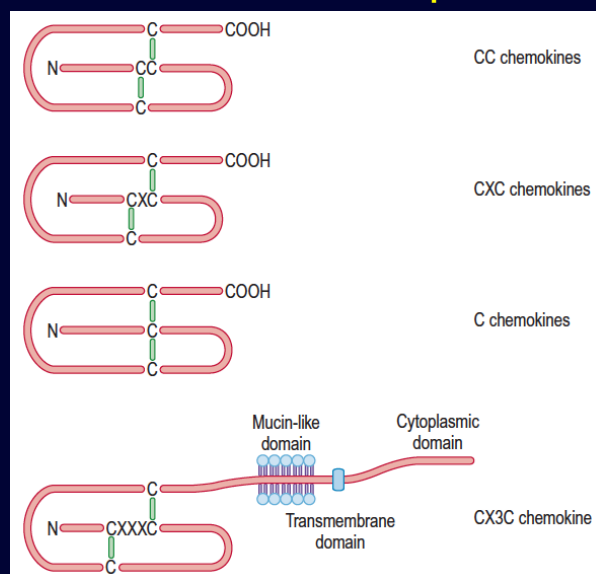
 Infants and children: low systolic BP (age-specific) or greater than 30% decrease in systolic BP***	 Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline
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Simons et al., J Allergy Clin Immunol 127:587, 2011

Allergic responses are not just immediate



Chemokine receptors



Mikhak and Luster, Middleton's Allergy: Principles and Practice, 8th Edition, 2013

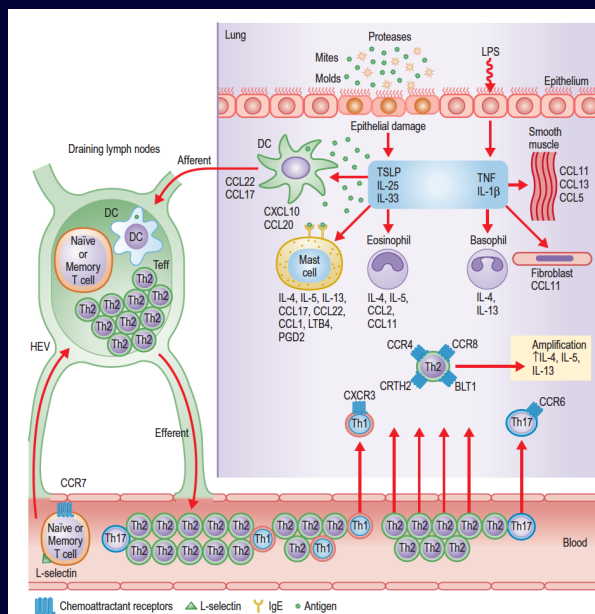
TABLE 7-3

Cellular Expression of Chemokine Receptors*

Cell Type	Chemokine Receptor
Naïve T cells	CXCR4, CCR7
Th1 cells	CCR5, CXCR3
Th2 cells	CCR4, CCR8
Th17 cells	CCR6
Eosinophils	CCR3
Basophils	CCR3

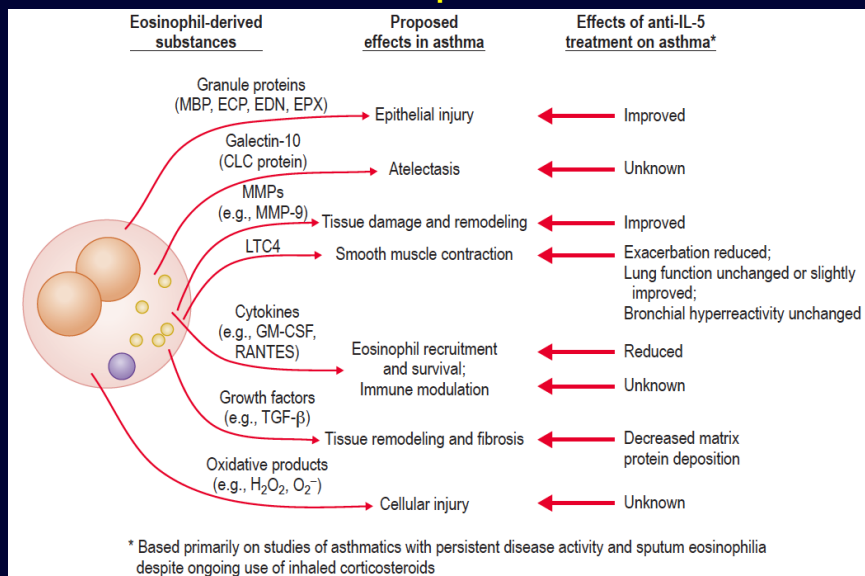
Mikhak and Luster, Middleton's Allergy: Principles and Practice, 8th Edition, 2013

Chemokines in Asthma



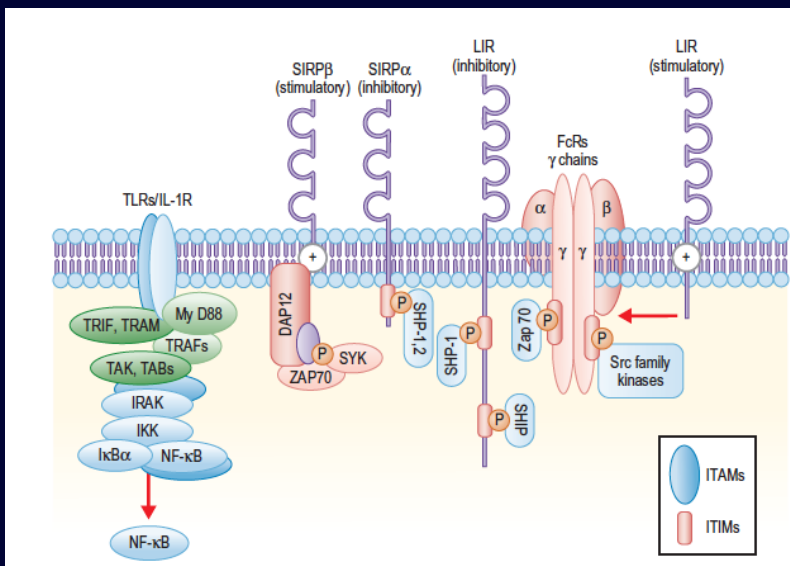
Mikhak and Luster, Middleton's Allergy: Principles and Practice, 8th Edition, 2013

Role of Eosinophils in Asthma



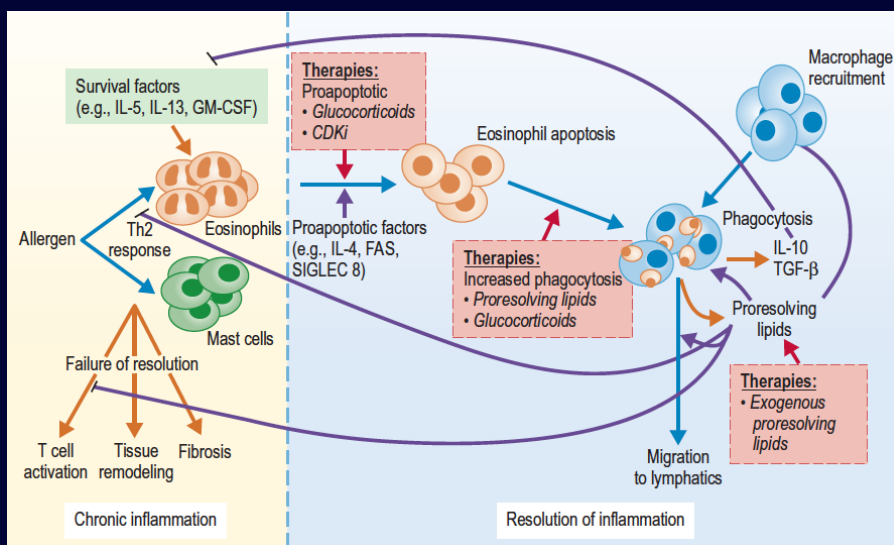
Kita and Bochner, Middleton's Allergy: Principles and Practice, 8th Edition, 2013

Modulation of Allergic Inflammation



Bertics et al., Middleton's Allergy: Principles and Practice, 8th Edition, 2013

Resolution of Chronic Allergic Inflammation



Dorward et al., Middleton's Allergy: Principles and Practice, 8th Edition, 2013

Key concepts

- Can't have allergies without IgE or Fc ϵ RI
- Mediators released during allergic reactions cause a characteristic pattern of signs and symptoms
- A myriad of preformed and newly synthesized biochemical and protein mediators, and their respective receptors, provide a range of therapeutic targets