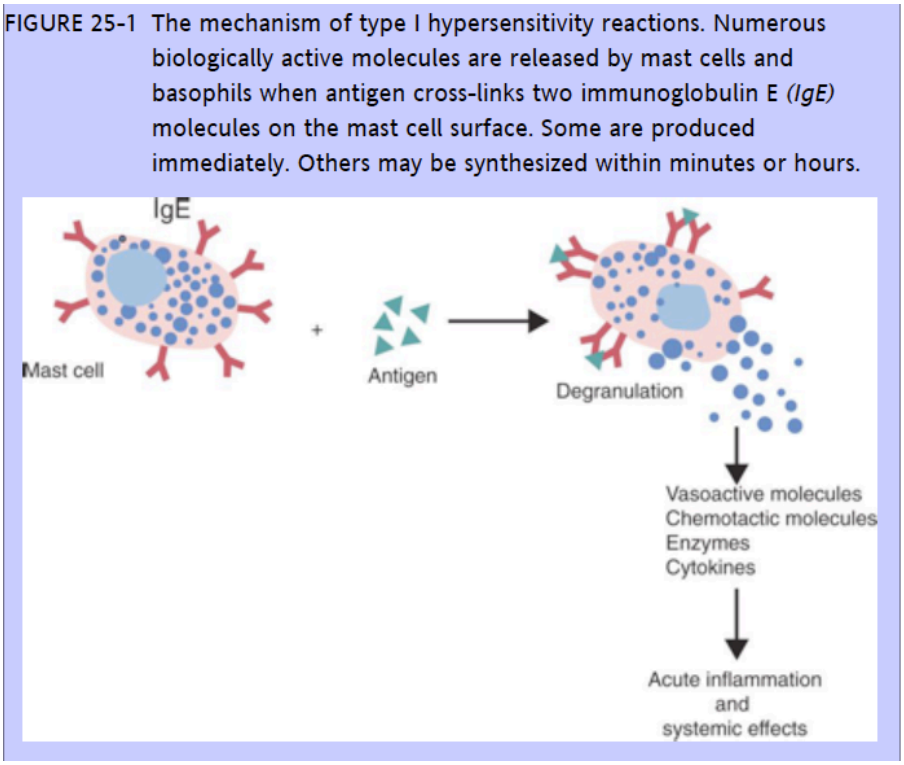
TYPE 1 HYPERSENSITIVITY

Key Points

1. IgE attached to mast cells mediates type 1 hypersensitivity reactions
    - Reactions develop within seconds or minutes after exposure to antigen (Ag)

2. Clinical signs (acute inflammation and systemic effects caused by rapid degranulation of mast cells that occurs once Ag binds and cross-links two IgE molecules, causing release of vasoactive molecules, chemotactic molecules, enzymes and cytokines



3. Severity and location of clinical signs depends on number and location of mast cells, basophils, eosinophils, which depends on degree of sensitization of animal, amount of antigen involved and route of administration

Specific allergic conditions

- Food allergy
- Allergic inhalant dermatitis
- Atopic dermatitis
- Allergies to vaccines and drugs
- Allergies to parasites: sarcoptes scabiei dogs, octodectes cyanotis in cats
    i. Flea allergy dermatitis may also be type IV HS mediated
- Eosinophilic granuloma complex (cats)

Allergic anaphylaxis

- Severe, life threatening generalized or systemic hypersensitivity reaction
- Clinical signs determined by organ involvement and differs among species
- Symptoms are result of vasoactive molecules contracting smooth muscle of bronchi, GIT, uterus and bladder

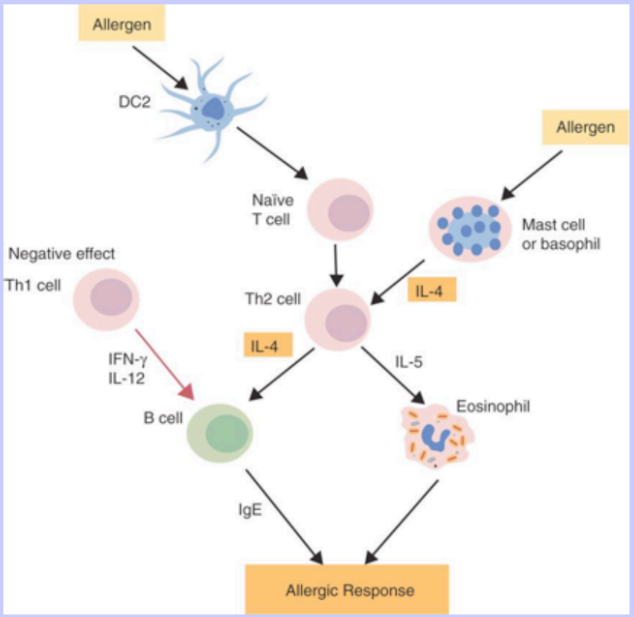
Induction of type I hypersensitivity

- **Normal animals** respond to Ag in the environment, inhaled air or food by producing IgG or IgA antibodies
- **Atopic animals** respond by mounting exaggerated Th2 response and producing IgE antibodies
    - Referred to as *type I hypersensitivity reactions or allergies*
- Normal animals infested by parasitic worms and insects also produce large amounts of IgE
    - Only well characterized beneficial feature of type I hypersensitivity

IgE

- Immunoglobulin with 4-chain structure
- MW 200 kDa
- **Location**
    - Most found in bloodstream
        - Firmly bound to Fce receptors on tissue mast cells (½ life 11-12 days)
    - *Very* small amount also in serum (serum ½ life 2 days)
- **Production**
    - Th2 cells produce IL-4 or IL-3, these IL together with CD40 trigger B cell IgE synthesis
    - IL-4 also produced by stimulated mast cells

FIGURE 25-2 The role of interleukin-4 *(IL-4)* in induction of immunoglobulin E *(IgE)* responses. IL-4 is produced by Th2 cells. Once released, it promotes the development of more Th2 cells, which are major sources of this cytokine and promote IgE responses. The degranulation of mast cells also releases IL-4, which further promotes this reaction. Natural killer cells may also serve as an initial source of IL-4. The response to IL-4 is inhibited by interferon-γ *(IFN-γ)* and IL-12.



- **IgE receptors**
    - Two types: high-affinity FceRI; low-affinity FceRII (CD23)
    - Two forms of FceRI
        - abg2: found on mast cells, basophils, neutrophils, eosinophils
        - ag2: found on antigen presenting dendritic cells, monocytes
    - Presence of FceRI ensures mast cells are constantly coated with IgE
        - Bind almost irreversibly (high affinity)
    - FceRII (CD23) is a selectin
        - Found on B cells, NK cells, macrophages, dendritic cells, eosinophils, platelets
        - Binds IgE AND complement receptor CR2 (CR21)

FIGURE 25-3 The structure of FceRI. The tetrameric form containing two γ chains is found on mast cells and basophils.

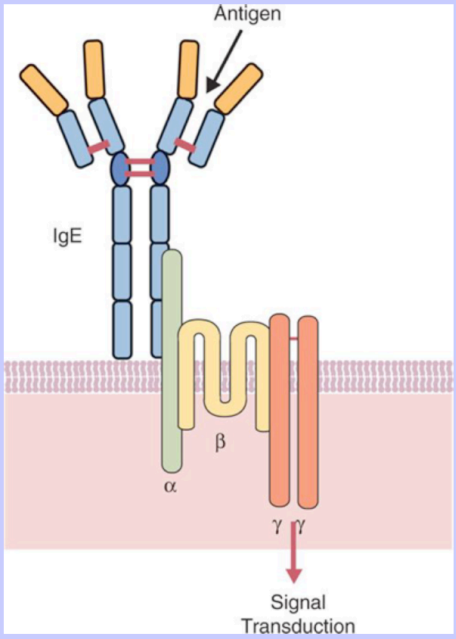
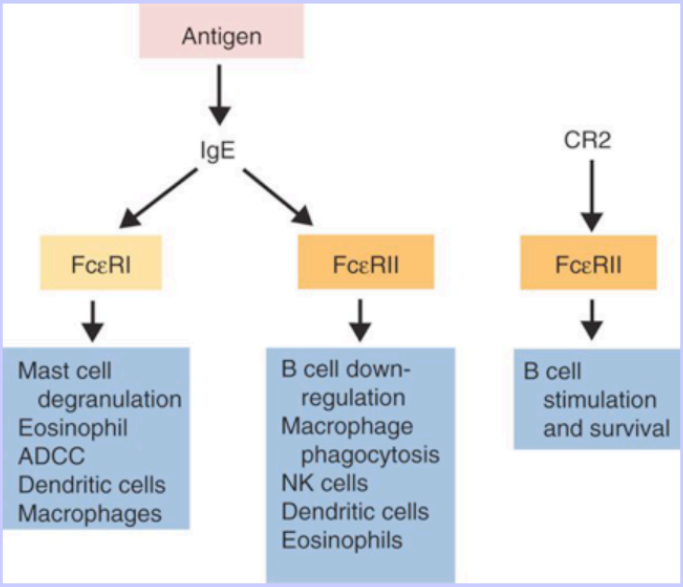


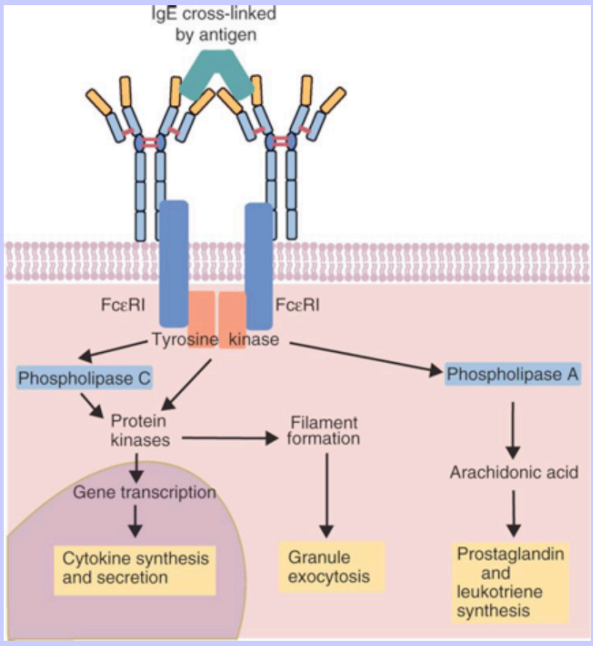
FIGURE 25-5 The combination of the Fcε receptors with their ligands stimulates a variety of different responses in mast cells depending on the nature of these stimuli.



<u>Response of Mast cells to Ag</u>

- IgE binds to mast cell and primes cell to bind Ag and resides in tissues
- Ag enters tissues → encounters mast cell → cross-links 2 bound IgE → mast cell releases contents of lysosomes and inflammatory mediators
- Ag crosslinks two FceRI → activates tyrosine kinases → activates Phospholipase C and A
- Activation of phospholipase C and A leads to:
    - Cytokine synthesis and secretion
    - Granule exocytosis
    - Prostaglandin and leukotriene synthesis

FIGURE 25-6 A simplified view of mast cell signal transduction. The process is triggered by cross-linking two bound immunoglobulin E *(IgE)* molecules with antigen. The combined signal eventually leads to degranulation (granule exocytosis), leukotriene and prostaglandin synthesis, and cytokine production.



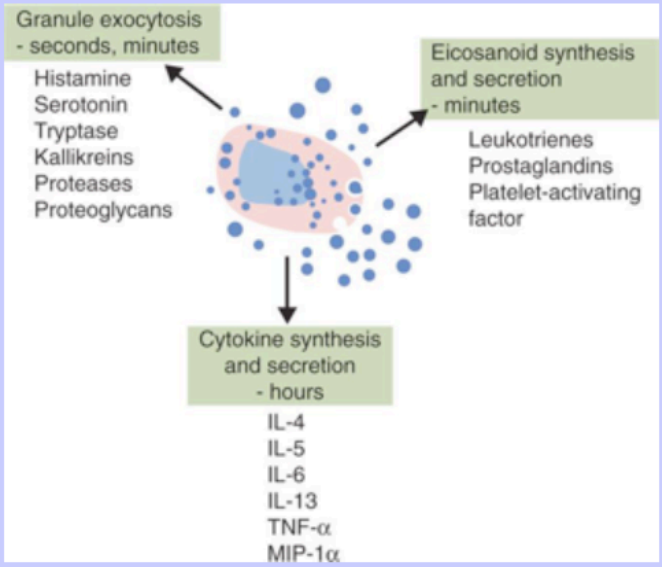
- Mast cell responses extremely rapid

Mast cell derived mediators (3 categories)

1. Molecules released from exocyosed granules (seconds, minutes)
2. Eicosanoids (lipids) synthesis and secretion (minutes)
3. Cytokine (protein) synthesis and secretion (hours)

- Most important mediators: histamine, serotonin, prostaglandins, leukotrienes
- Cytokines are proinflammatory and/or promote Th2 responses

FIGURE 25-8 The soluble mediators released from degranulating mast cells. These fall into three categories: molecules released from exocytosed granules, lipids (eicosanoids) synthesized within minutes, and proteins synthesized over several hours.



Regulation of mast cell degranulation

- Two G protein linked surface receptors for catecholamines: alpha and beta adrenoceptors
- Epinephrine has both alpha and beta adrenergic activity
    - Alpha effects: causes vasoconstriction in skin and viscera
    - Beta effects: cause smooth muscle to relax
    - *Suited to combat vasodilation and smooth muscle contraction produced in type 1 HS*

System	α Receptor Stimulation or β Blockade	β Receptor Stimulation or α Blockade
Mast cells	Enhances degranulation	Suppresses degranulation
Smooth muscle	Contracts	Relaxes
Blood vessels	Constricts	Dilates

Inflammatory responses to Ag

- Immediate phase
    - 10-20 minutes, acute inflammatory response
    - result of mast cell degranulation
- Late phase reaction
    - 6-12 hours, characterized by redness, edema, pruritus
    - result of release of inflammatory mediators from eosinophils, neutrophils attracted to site by mast cell derived chemotactic factors

Basophils

- Least numerous granulocyte
- Granules contain complex mixture of vasoactive molecules similar to those in mast cells

Eosinophils

- Considered terminal effector cells of allergic response
- Originate in bone marrow and spend 30 minutes circulating in bloodstream before migrating into tissues (½ life 12 days)
- Contain 2 types of granule
    - Small primary granules: arylsulfatase, peroxidase, acid phosphatase
    - Large crystalloid granules: eosinophil cationic protein, eosinophil peroxidase, eosinophil derived neurotoxin
- **Eosinophil activation (3 mechanisms)**
    1. Th2 + mast cells: produce IL-5 and eotaxins that stimulate release of eosinophils from bone marrow
    2. Chemotaxis: Eosinophils attracted to sites of mast cell degranulation by eotaxins, histamines, leukotrienes, 5-HT, platelet activating factor, IL-8 complexes to IgA
    3. Direct activation of eosinophils: by some common allergens. Stimulate chemotaxis

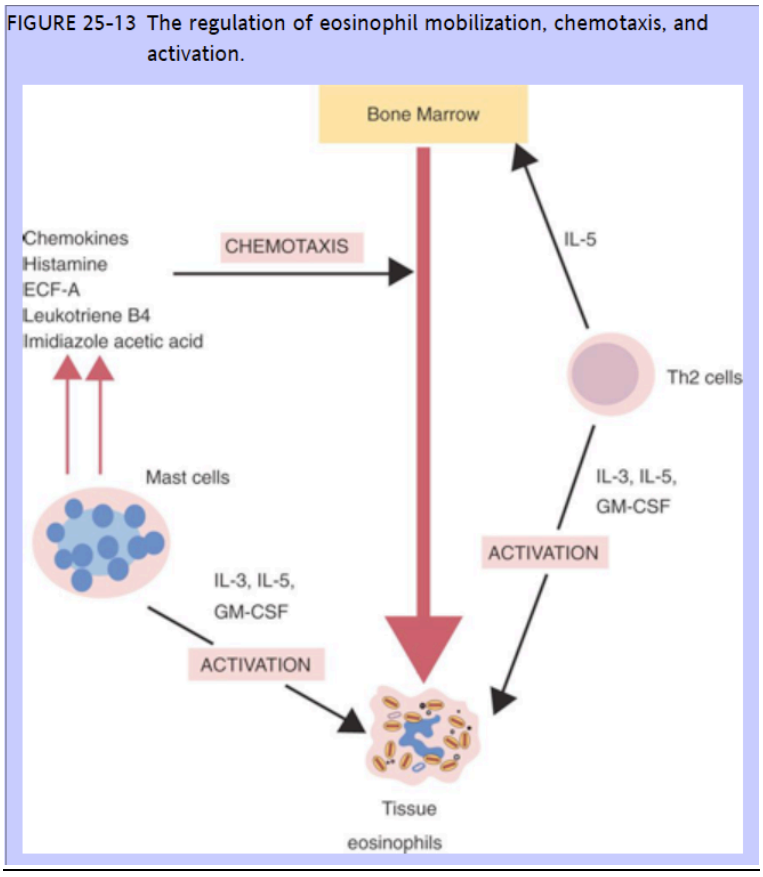
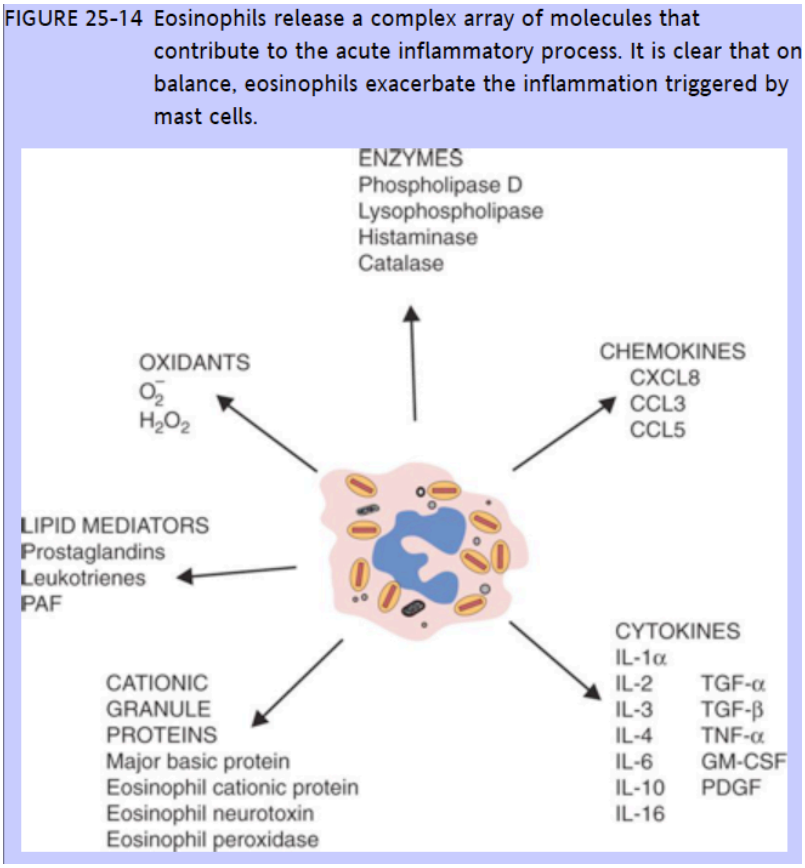


FIGURE 25-13 The regulation of eosinophil mobilization, chemotaxis, and activation.

- **Eosinophil degranulation and mediators**
  - Suited to extracellular destruction



Clinical Type I Hypersensitivity

- Severity and location of responses depends on number and location of mast cells, basophils, eosinophils, which depends on degree of sensitization of animal, amount of antigen involved and route of administration

- **Specific allergic conditions (small animals)**
  - Food allergy
  - Allergic inhalant dermatitis
  - Atopic dermatitis
  - Allergies to vaccines and drugs
  - Allergies to parasites: sarcoptes scabiei dogs, octodectes cyanotis in cats
    - Flea allergy dermatitis may also be type IV HS mediated
  - Eosinophilic granuloma complex (cats)

- **Allergic anaphylaxis**
  - Severe, life threatening generalized or systemic hypersensitivity reaction
  - Clinical signs determined by organ involvement and differs among species
  - Symptoms are result of vasoactive molecules contracting smooth muscle of bronchi, GIT, uterus and bladder

Species	Shock Organs	Symptoms	Pathology	Major Mediators
Horse	Respiratory tract	Cough	Emphysema	Histamine
	Intestine	Dyspnea	Intestinal hemorrhage	Serotonin
		Diarrhea		
Ruminants	Respiratory tract	Cough	Lung edema	Serotonin
		Dyspnea	Emphysema	Leukotrienes
		Collapse	Hemorrhage	Kinins
				Dopamine
Swine	Respiratory tract	Cyanosis	Systemic hypotension	Histamine
	Intestine	Pruritus		
Dog	Hepatic veins	Collapse	Hepatic engorgement	Histamine
		Dyspnea	Visceral hemorrhage	Leukotrienes
		Diarrhea		Prostaglandins
		Vomiting		
Cat	Respiratory tract	Dyspnea	Lung edema	Histamine
	Intestine	Vomiting	Intestinal edema	Leukotrienes
		Diarrhea		
		Pruritus		
Human	Respiratory tract	Dyspnea	Lung edema	Histamine
		Urticaria	Emphysema	Leukotrienes
Chicken	Respiratory tract	Dyspnea	Lung edema	Histamine
		Convulsions		Serotonin
				Leukotrienes

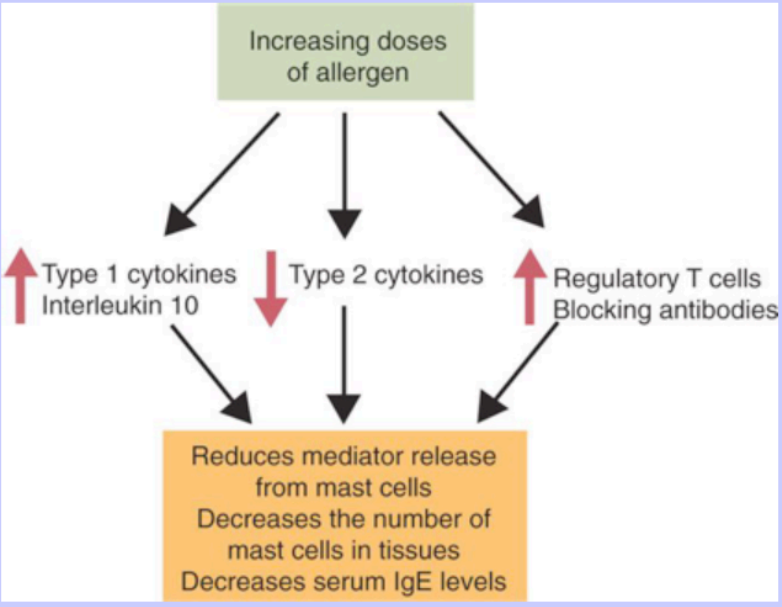
Diagnosis of Type I Hypersensitivity

- Direct skin testing
- Passive cutaneous anaphylaxis test
- Serological methods measuring IgE in body fluids
    - Western blotting
    - ELISA

Treatment of Type I Hypersensitivity

- Corticosteroids to reduce irritation and inflammation associated with allergic response
    - Inhibits nuclear factor kappa beta activity and blocks production of prostaglandins and leukotrienes
- Cyclosporine
- Desensitization therapy (allergy shots)
    - Promotes IgG rather than IgE production and reduces recruitment of inflammatory cells

FIGURE 25-17 The principles of desensitization therapy. Increasing doses of allergen promote a Th1 response, while at the same time reducing the Th2 response and regulating antibody production.



Questions:

1. Type I hypersensitivities are mediated by _____ attached to _____

2. Briefly describe the mechanism of type I hypersensitivity reactions

3. Name the two IgE receptors. Which has a stronger affinity for IgE and is found on mast cells

4. Name 4 of the most important mast cell derived mediators
   - Most important mediators: histamine, serotonin, prostaglandins, leukotrienes

5. Name the major shock organ, clinical sign observed with anaphylaxis and major mediator(s) involved in the dog and cat.

6. Describe the difference between an anaphylactoid reaction and anaphylaxis

Answers:

1. Type I hypersensitivities are mediated by IgE attached to mast cells

2. Describe the mechanism of type I hypersensitivity reactions
    a. Numerous biologically active molecules (vasoactive molecules, chemotactic molecules, enzymes, cytokines) are released by mast cells and basophils when antigen cross-links 2 IgE molecules on the mast cell surface.
    b. Some are produced immediately, others synthesized within minutes or hours

3. Name the two IgE receptors. Which has a stronger affinity for IgE and is found on mast cells
    a. Two types: high-affinity FceRI; low-affinity FceRII (CD23)
    b. Two forms of FceRI
        i. abg2: found on mast cells, basophils, neutrophils, eosinophils
        ii. ag2: found on antigen presenting dendritic cells, monocytes
    c. Presence of FceRI ensures mast cells are constantly coated with IgE
        i. Bind almost irreversibly (high affinity)
    d. FceRII (CD23) is a selectin
        i. Found on B cells, NK cells, macrophages, dendritic cells, eosinophils, platelets
        ii. Binds IgE AND complement receptor CR2 (CR21)

4. Name 4 of the most important mast cell derived mediators
    - Most important mediators: histamine, serotonin, prostaglandins, leukotrienes

5. Name the major shock organ, clinical sign observed with anaphylaxis and major mediator(s) involved in the dog and cat.

6. Describe the difference between an anaphylactoid reaction and anaphylaxis
    - IgE mediates immediate hypersensitivity reactions
    - These reactions develop within seconds or minutes after exposure to antigen (Ag)
    - If an immediate hypersensitivity reaction is systemic and life threatening it is called allergic anaphylaxis or anaphylactic shock
    - Anaphylactoid reaction: reaction that is similar to allergic anaphylaxis but nor as immunologically mediated