

Mast Cell Activation Disorders

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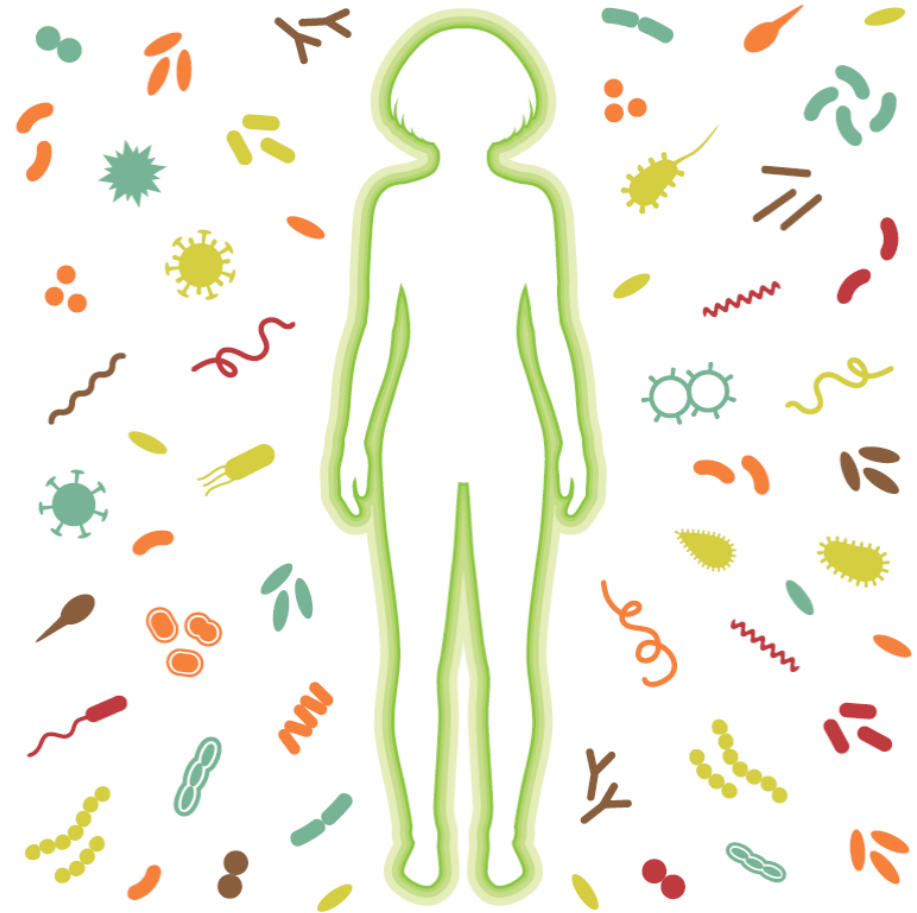
Medical Director, Comprehensive Allergy & Asthma Care, PLLC



Our Journey on mother Earth: “Life on the edge”

(Our) immune systems ...
(are) embodied
expectations of injury and
the corresponding
programs of protection
and repair.”

- Peter Sloterdijk



The Great Wall of China...

Protection along the Northern Border of China



A fortification!

Built for defensive purposes in the 3rd century

It is

- 1500 miles along**
- 6 meters wide**

In imperial times, the Great Wall of China was easily breached and was not in itself a very effective defense against resolute adversaries.

Rather, it was a communication route and housed, far from the imperial centre, a string of lonely guards who quickly engaged invaders and slowed their progress, while alerting and beckoning more substantial back-up forces.

-Christophe Benoist & Diane Mathis
Mast cells in autoimmune disease Nature, 2002



Innate Immune System Components

Anatomic Barriers

- Skin - 22 square feet
- Mucosa of the
 - Gastrointestinal tract, 25 feet,
 - Respiratory tract, 25 sq. feet,
 - Urogenital tract, 20 sq. feet

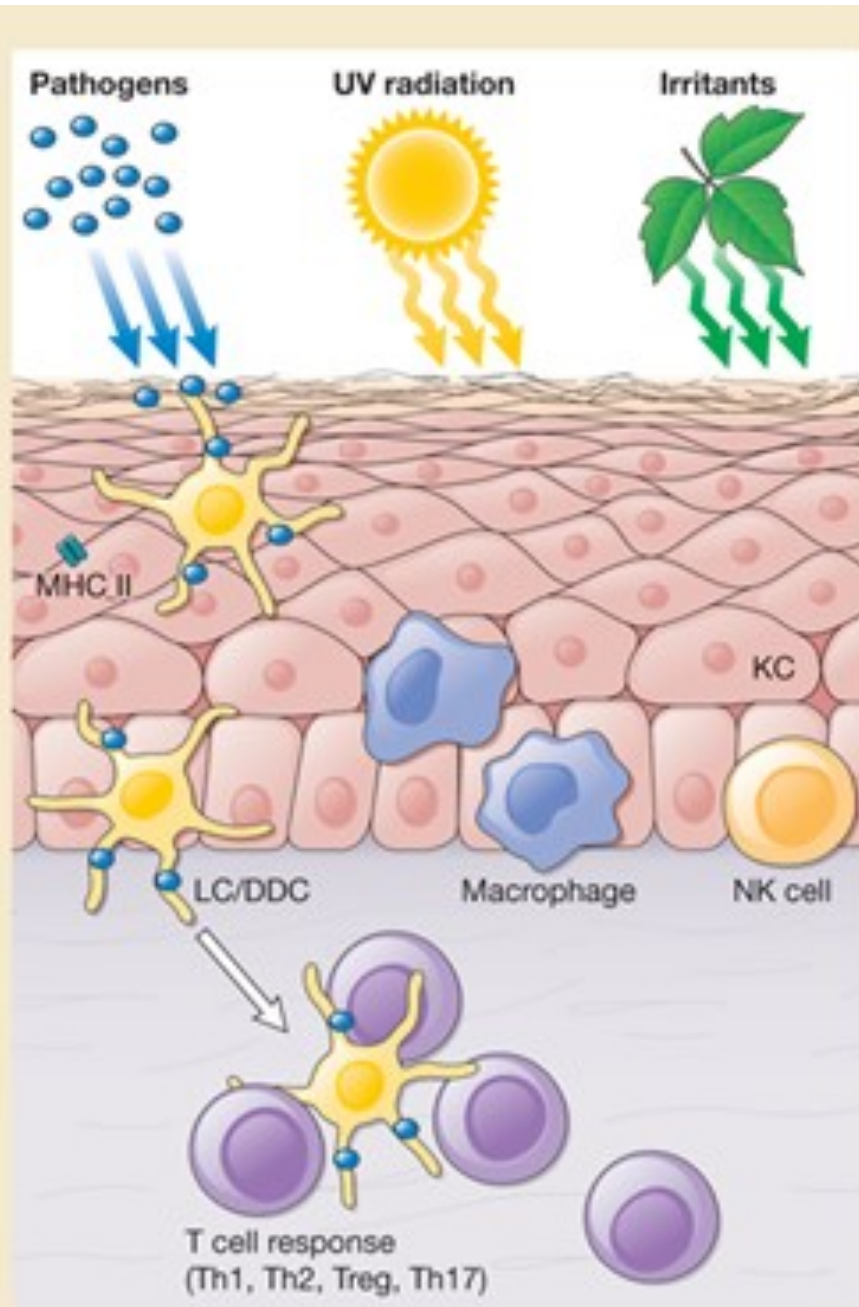
Physiologic Barriers

- Temperature, pH, Flow

- **Inflammatory Mediators** -> redness, swelling, heat, pain

Immune Cells

- NK cells, DCs, Macrophages



Antimicrobial response

Defensins
Cathelicidins/
Psoriasin
Reactive Oxygen Species

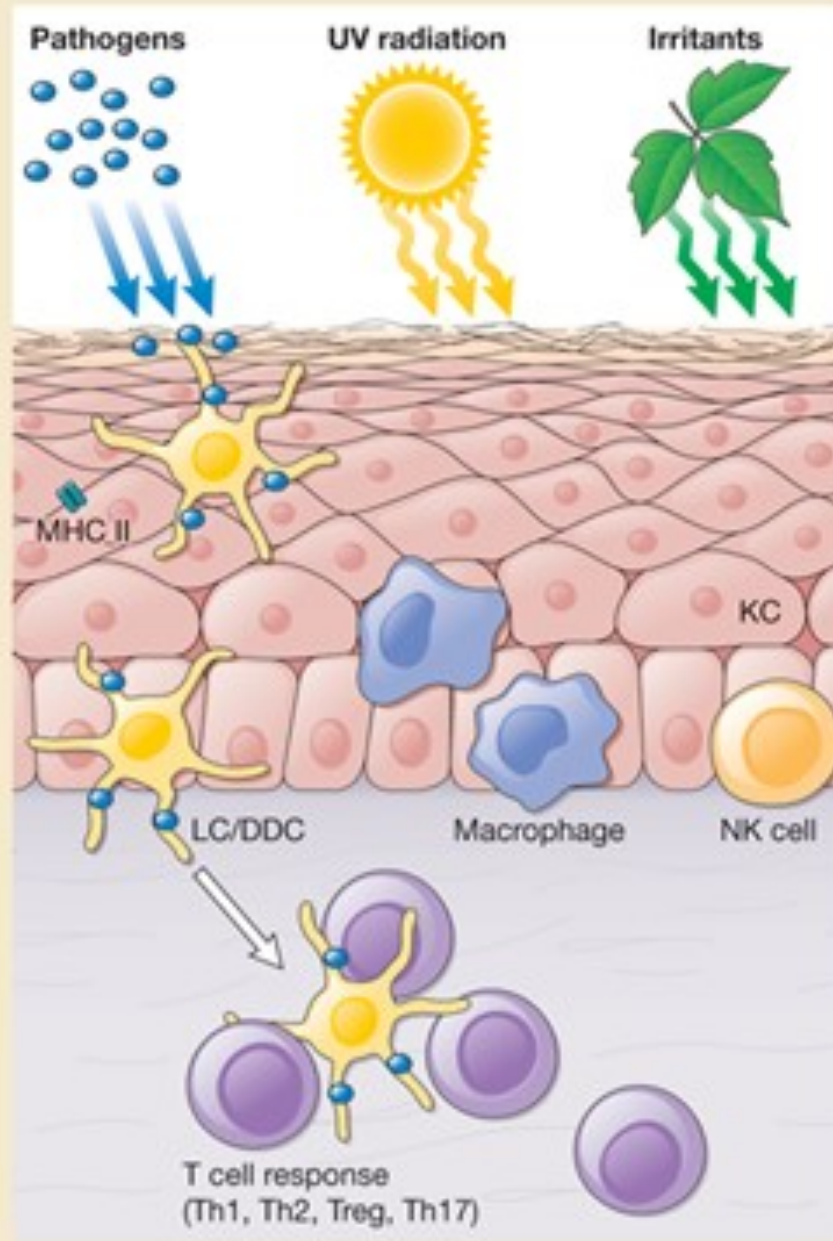
Inflammatory response

Cytokines,
Chemokines
Neuropeptides
Reactive Oxygen Species

Recruiting the adaptive Immune response

T cells, B cells

Two important observations are not captured in this common depiction of our innate immune system...

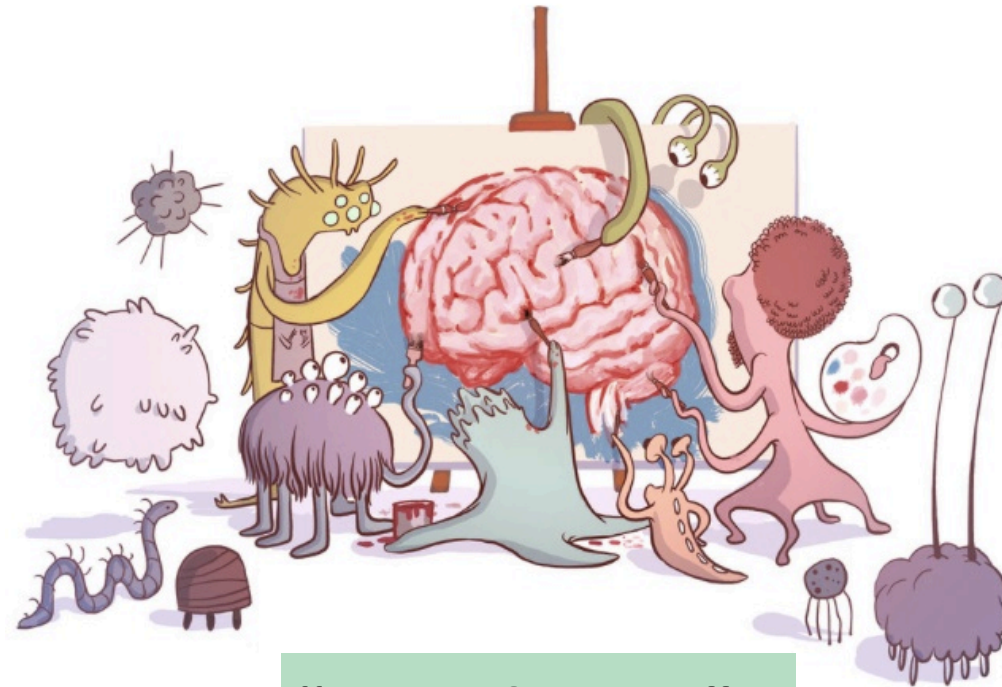


- 1. Antimicrobial response:**
- defensins
 - cathelicidins/psoriasin
 - reactive oxygen intermediates

- 2. Inflammatory response:**
- cytokines
 - chemokines
 - neuropeptides
 - eicosanoids

- 3. influence adaptive immune response:**
- activation of T cells

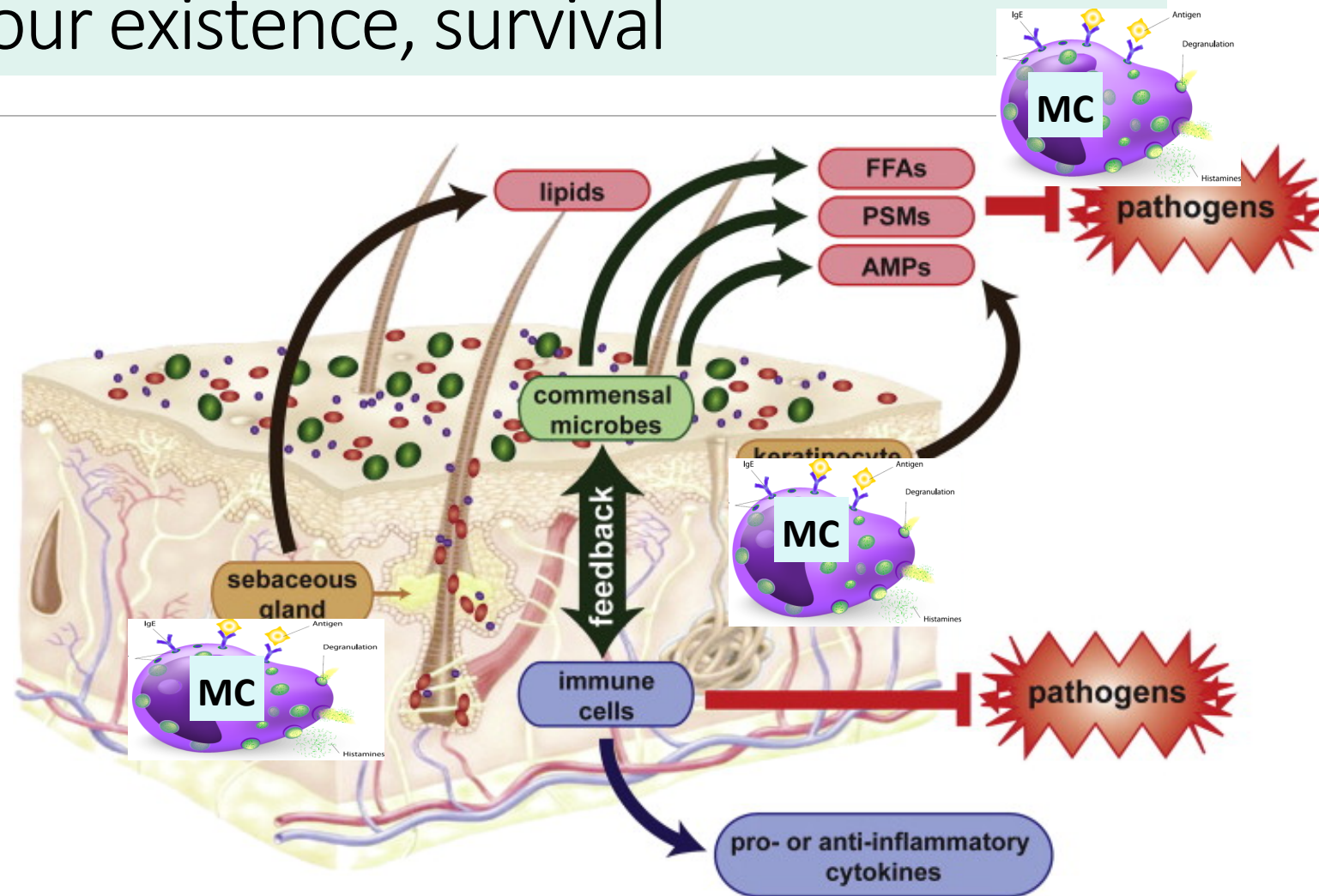
Our Immune system = defense against dangers, such as infectious agents, toxins and trauma...



We mean you no harm!

“Microbiome”

Port of Entry, “vetting” process— to allow entry to entities that support and may enhance our existence, survival



Mast Cells: Beyond Allergy?



Immunology 101

Innate



- 1st line of defense
- Non-specific
- Rapid response
- No memory

Components:

- Complement
- White blood cells:
 - Macrophages
 - Neutrophils
 - Natural Killer cells

Adaptive

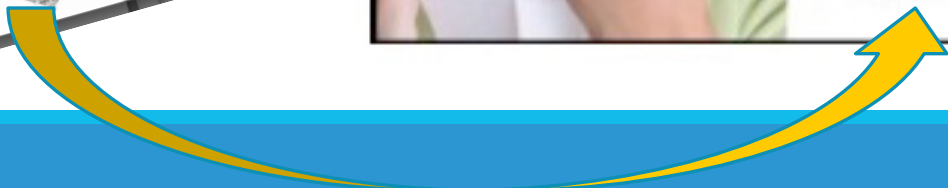


- Slower response
- Specific
- Memory

Components:

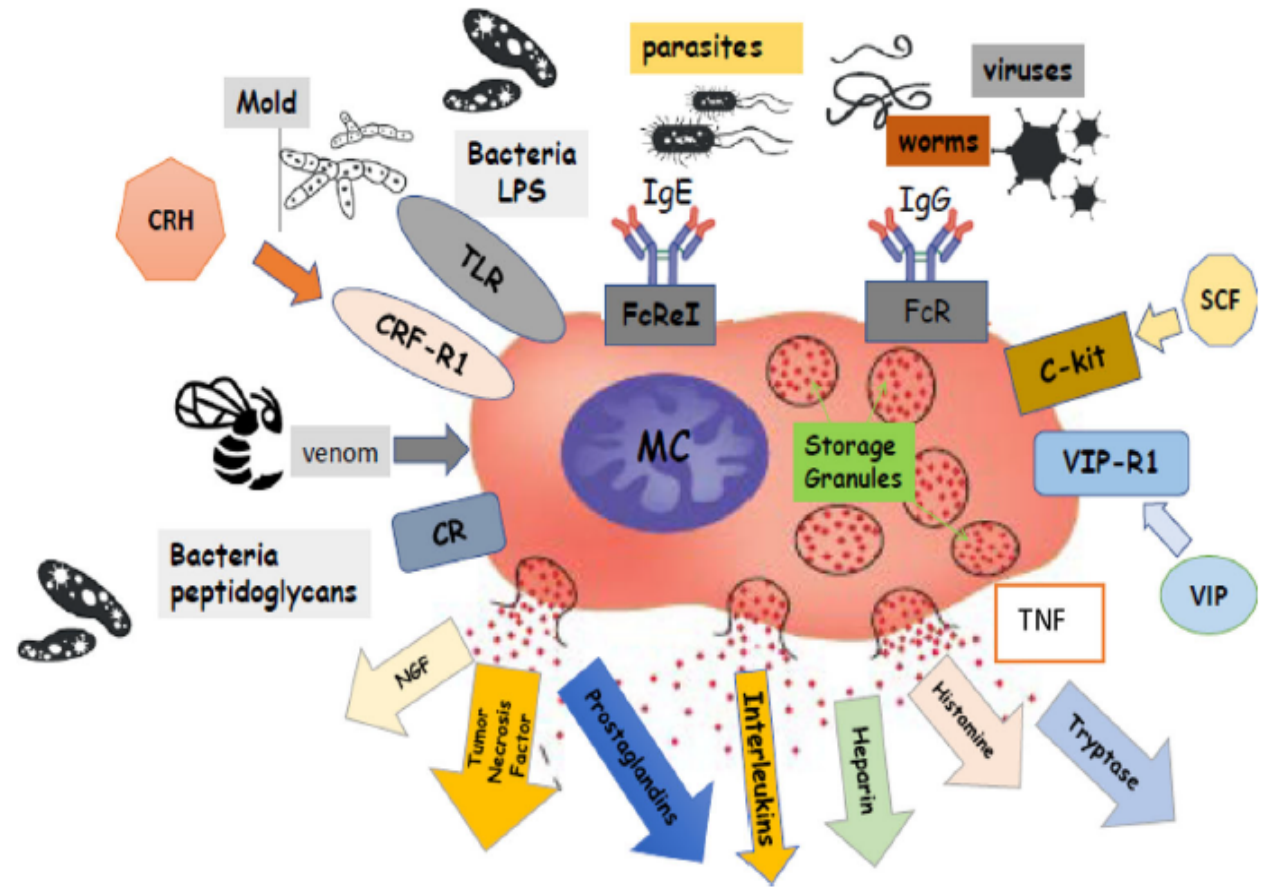
- Antibodies
- B cells
- Helper T cells
- Killer T cells
- Dendritic cells

spilling com-
osis factor
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neu-
dis-
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y can
effec-
rol over the

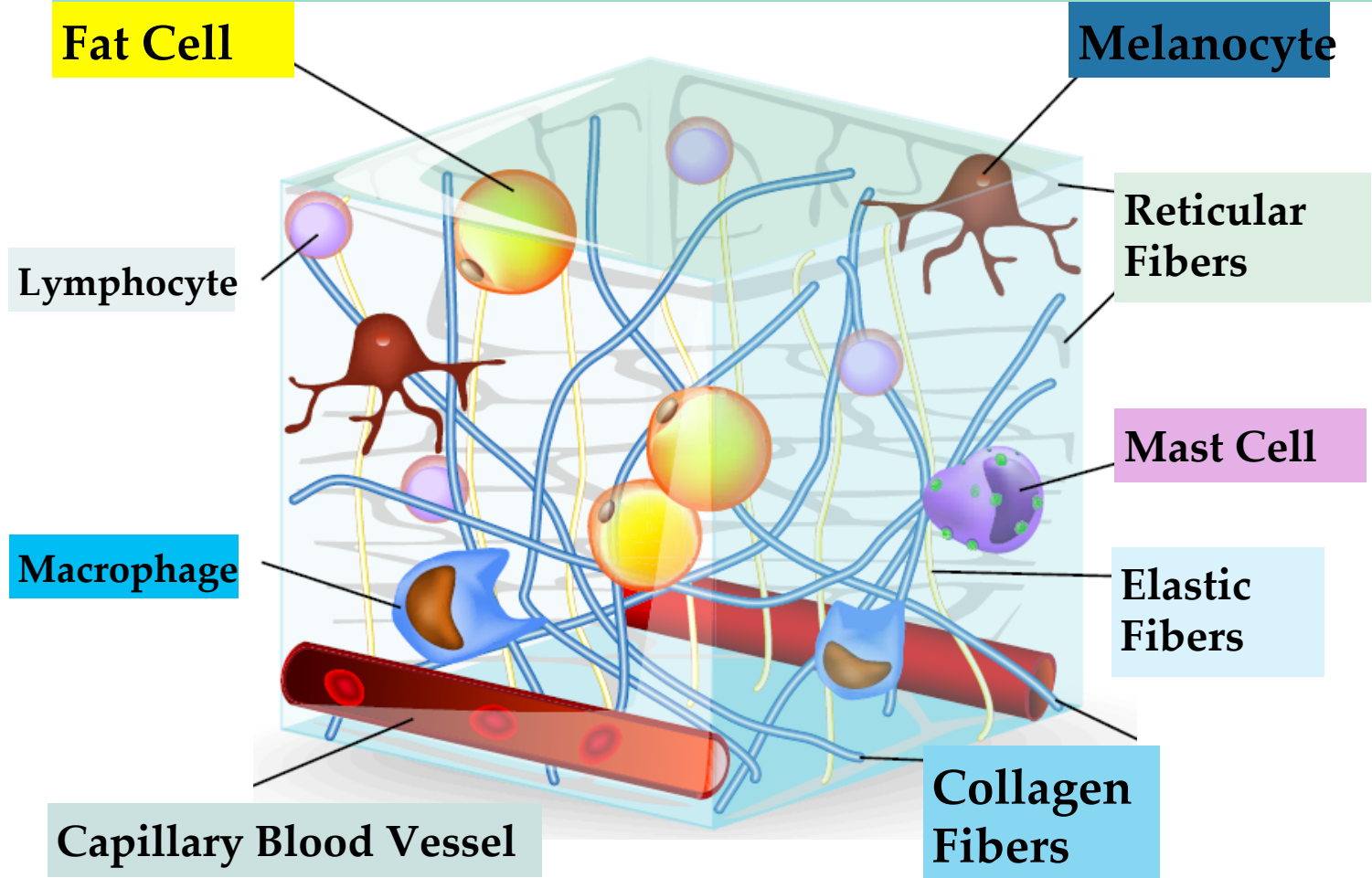


Mast Cell Orders

MAST CELL BIOLOGY 101



Mast Cell Orders: Surveillance. Protection. Coordinate Response and Repair.

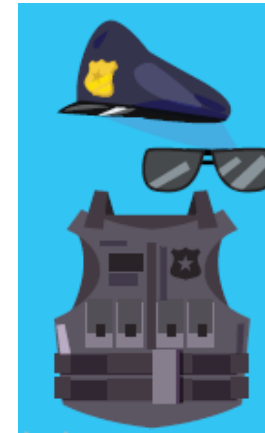


Homeostasis: Keeping the Peace

Like a police officer, who strives to serve and protect a neighborhood, “rookie” Mast Cells arrive and learn to meet the needs of local community of cells and tissue.

- Trained and prepared with different tools, each individual police officer must learn how to serve and protect his or her assigned, local neighborhood.

Depending on the nature and severity of the danger, the police officers will respond with a defined, regulated series of actions.



911...
what's your
emergency?

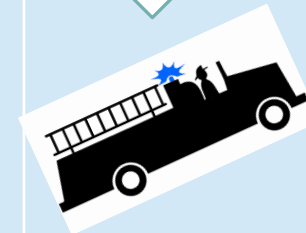
Depending on the nature and severity of the danger, the police officer will respond with a defined, regulated series of actions.



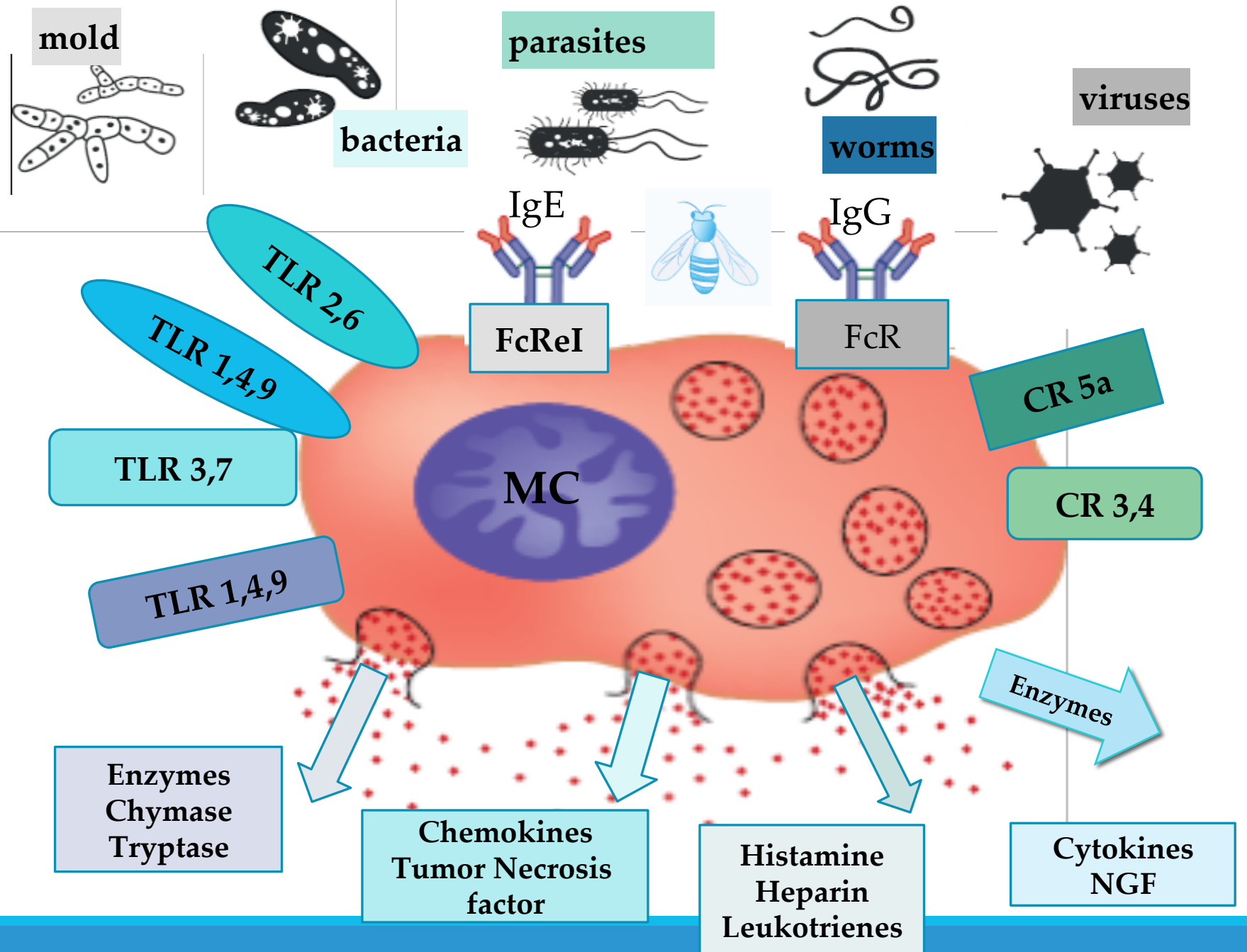
Officer
Sees
This...



And then
does
this...



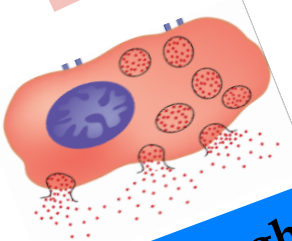
Armed with invariant sensors, Mast Cells are hardwired to recognize and then react with a defined set of chemical and physical responses, in order to contain "usual suspects", pathogens and harmful substances.



911... what's your emergency?

Depending on the nature and severity of the danger, mast cells, will respond with a defined set of mediators, calling for appropriate help.

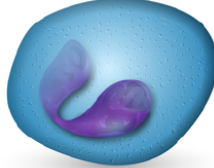
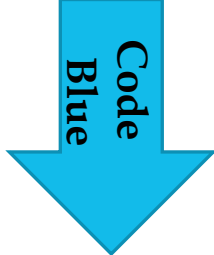
Mast Cell Recognizes This...



And, through chemical mediators and receptors, will call for...

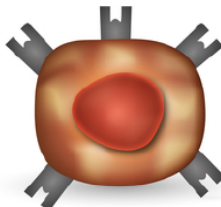
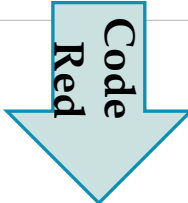
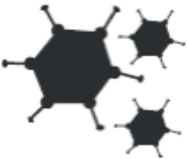
Mast Cells act as the local Peace Keepers, maintaining homeostasis in the surrounding microenvironment.

parasite



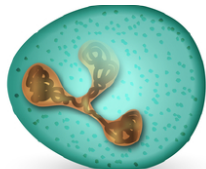
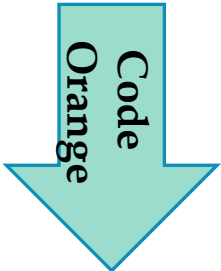
Eosinophil

virus



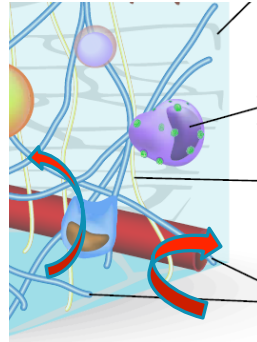
T Cell

bacteria



Neutrophil

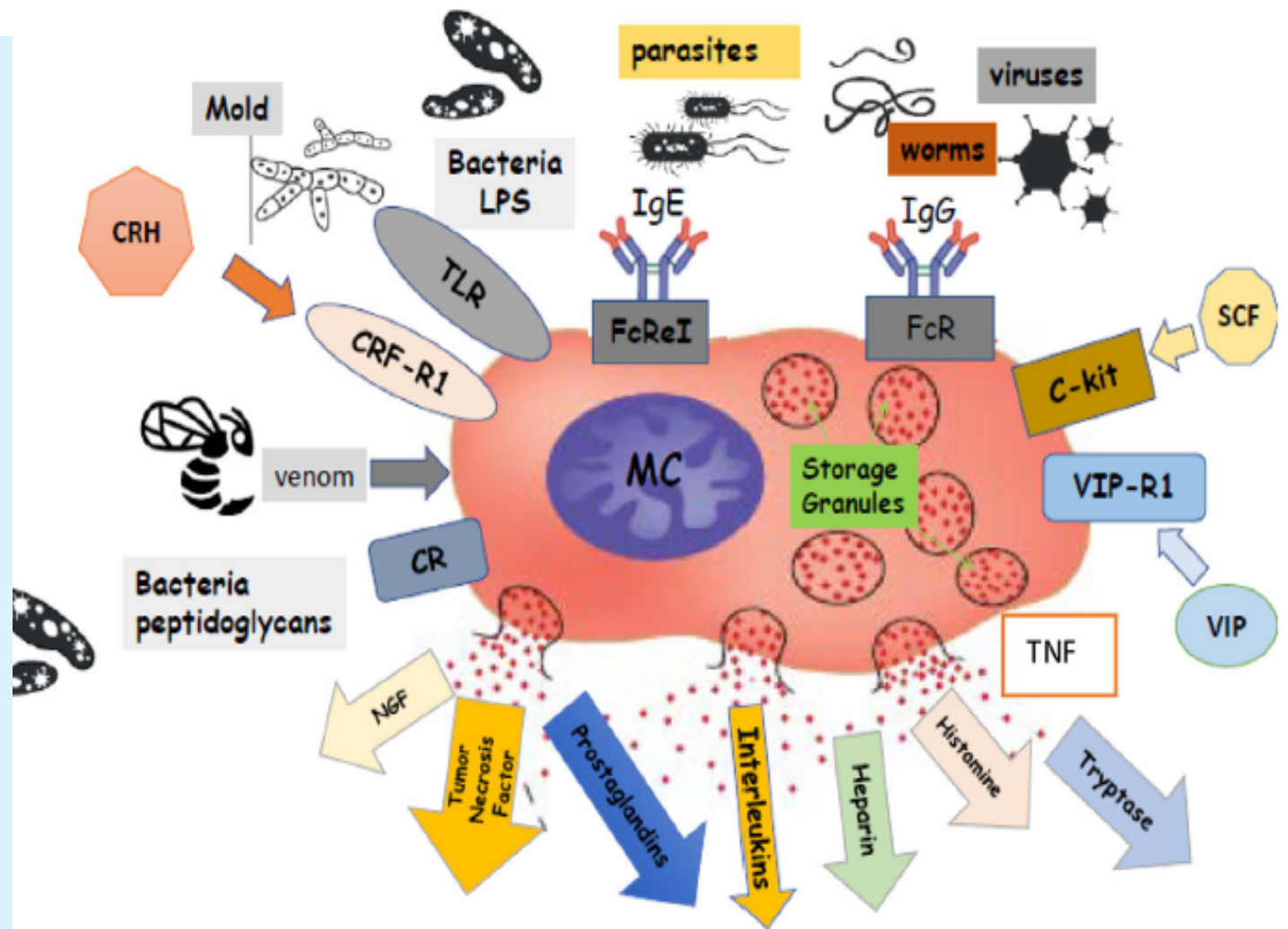
Insect sting



Vascular leakage
-> Serum Proteins
-> Swelling, Itch

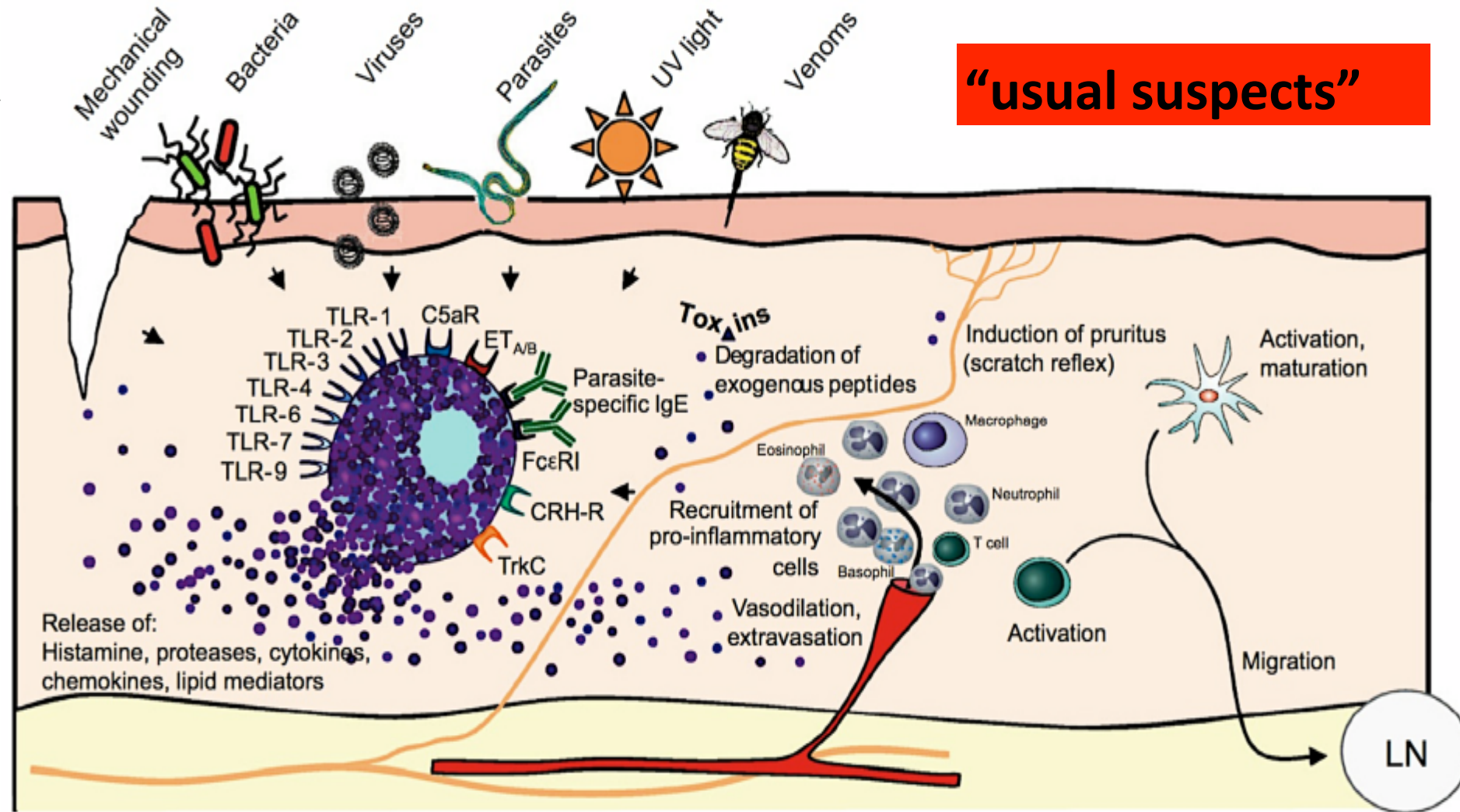
MAST CELL (MC) 101

- MCs are found in most parts of the body are well known for role in allergic/anaphylactic reactions
- MCs are now recognized to play a role in a number of inflammatory diseases in the skin, respiratory tract, joints, Gastrointestinal tract, nervous system, bladder
- MCs contain > 500 secretory granules and can de novo synthesize and release mediators following stimulation, via **degranulation or differential, piecemeal release**

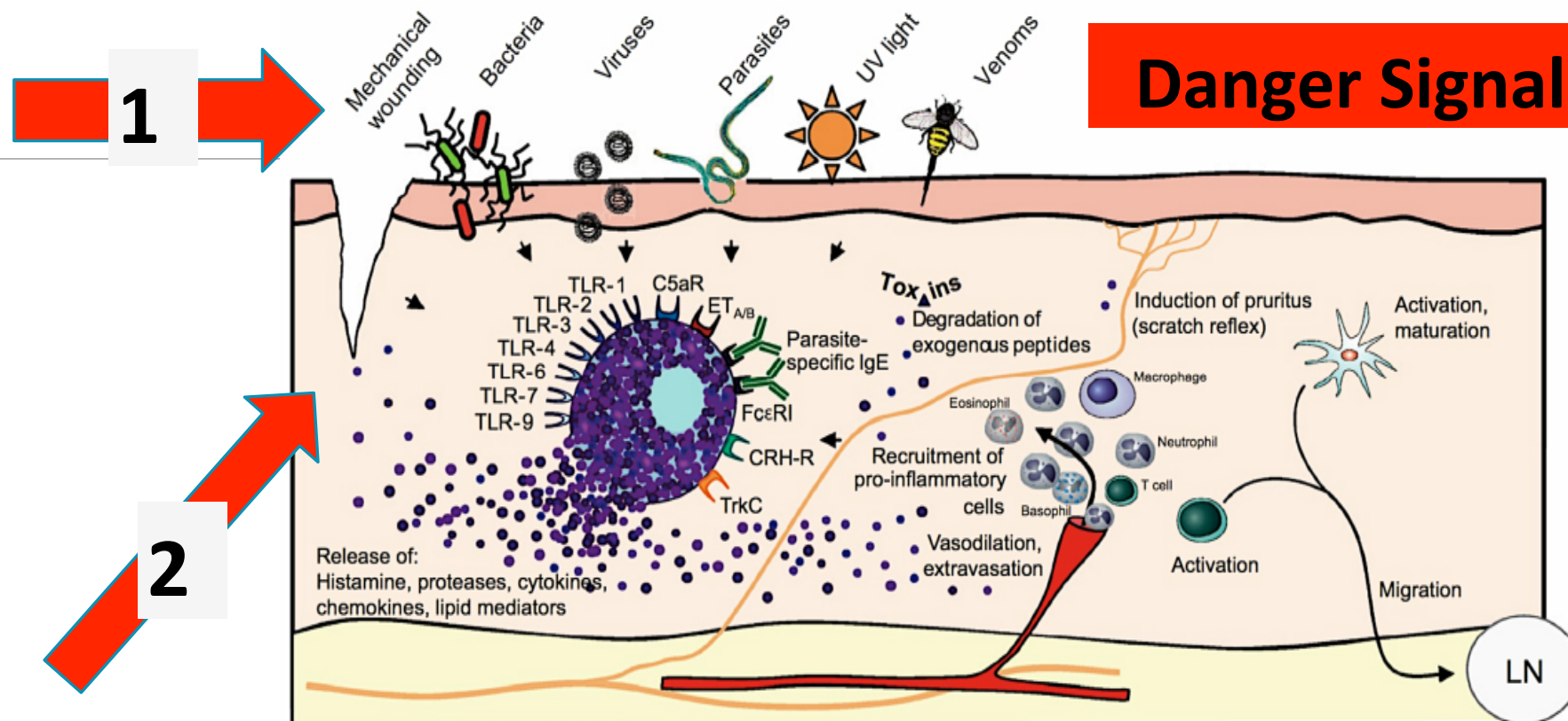


arachidonic acid products, biogenic amines, chemo-attractants, cytokines, growth factors, neuropeptides, proteoglycans, and proteolytic enzymes

Mast Cells=
Border Patrol,
recognizing
and
responding to
clear and
present
dangers



Danger Signals



(1) Infectious, nonself threats, that have as **pattern recognition receptors (PRRs)** and are recognized by evolutionarily conserved membrane-bound Toll-like receptors (TLRs), on MCs

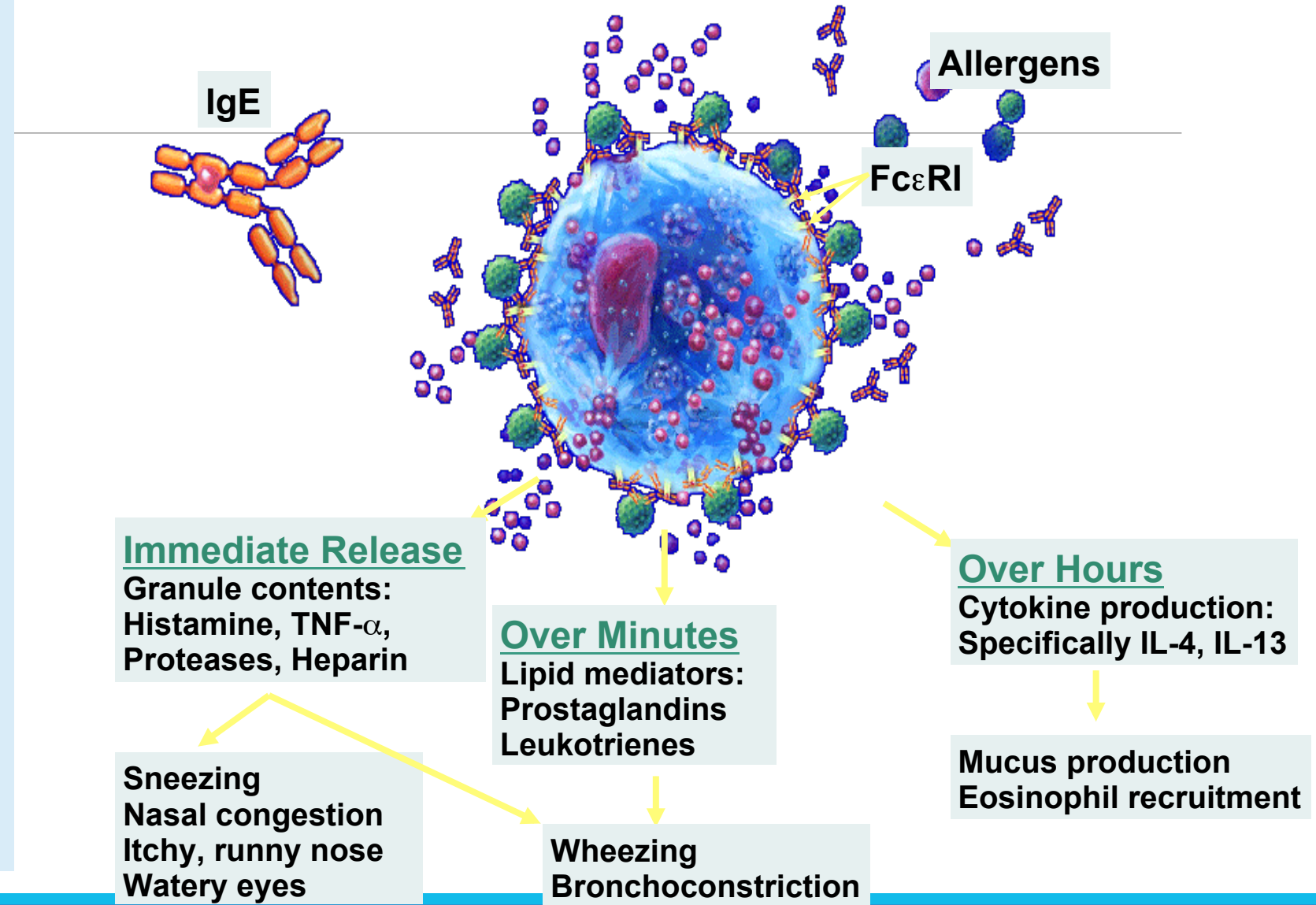
(2) Endogenous, self alarm signals, indicating danger:

breakdown products of hyaluron (made when vessels are damaged). mammalian DNA, RNA, heat shock proteins (Hsps), interferon α , (an inducible protein often made by virus-infected cells), interleukin-1 β , CD40-L (a surface molecule on activated platelets and activated T cells), and

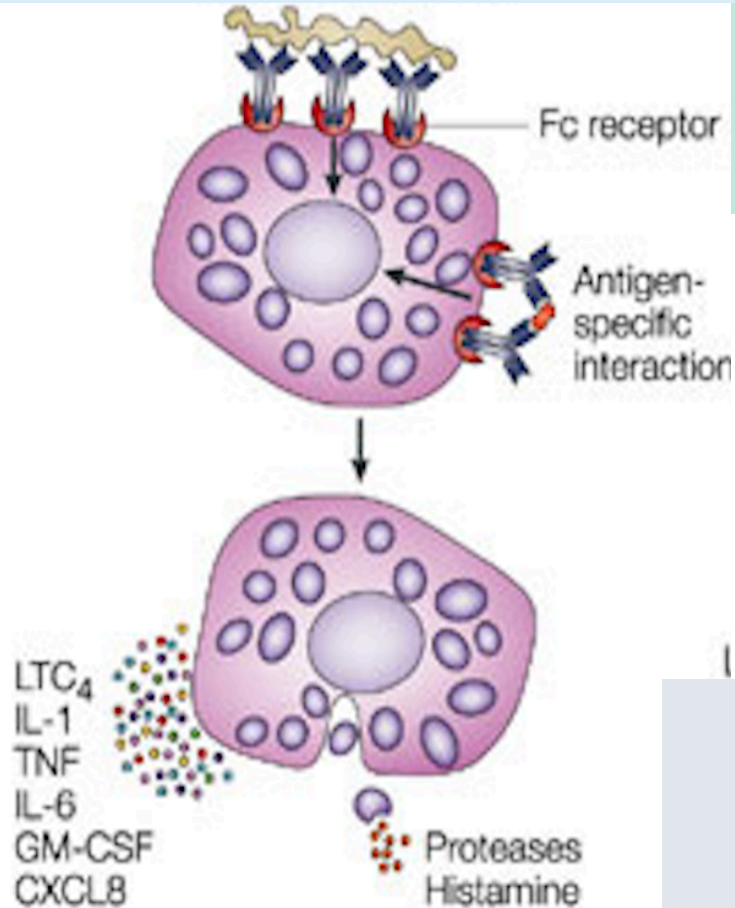
Dark Side of Mast Cell Activation

Mast Cells are best known for “Allergies”

Allergen-IgE-IgE Receptor
Mast Cell Activation



IG- IG Receptor on MCs



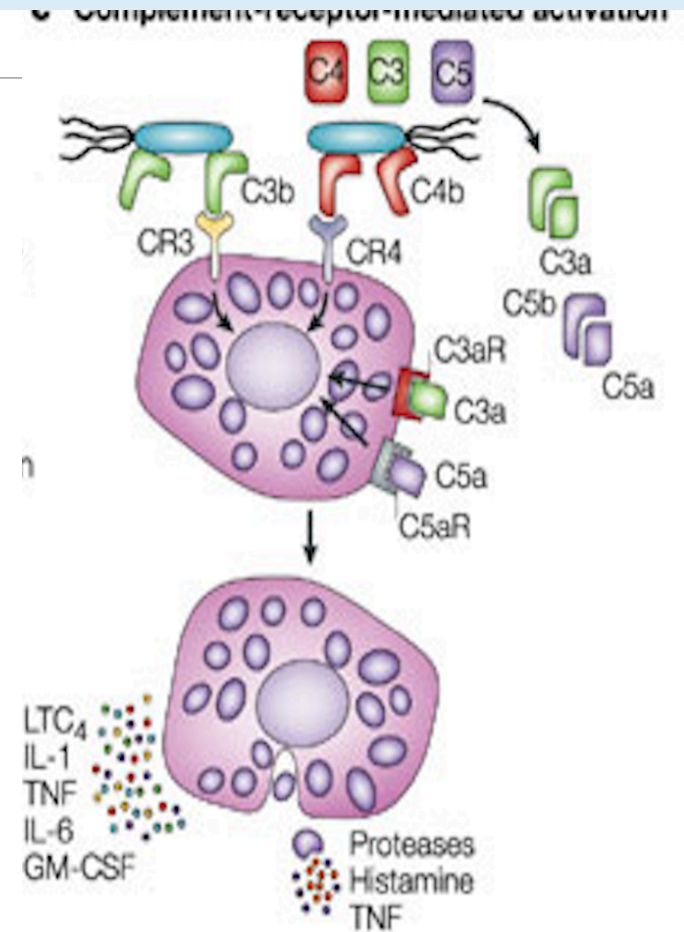
CMC Activation after Complement or IGG bound pathogens,

MC release

- Tryptase (proteases)
- Histamine

Leukotrienes, Interleukin-1, Interleukin- 6, CXCL8, GM-CSF Tumor Necrosis Factor

Complement Coated Pathogen- C' Receptor on MCs



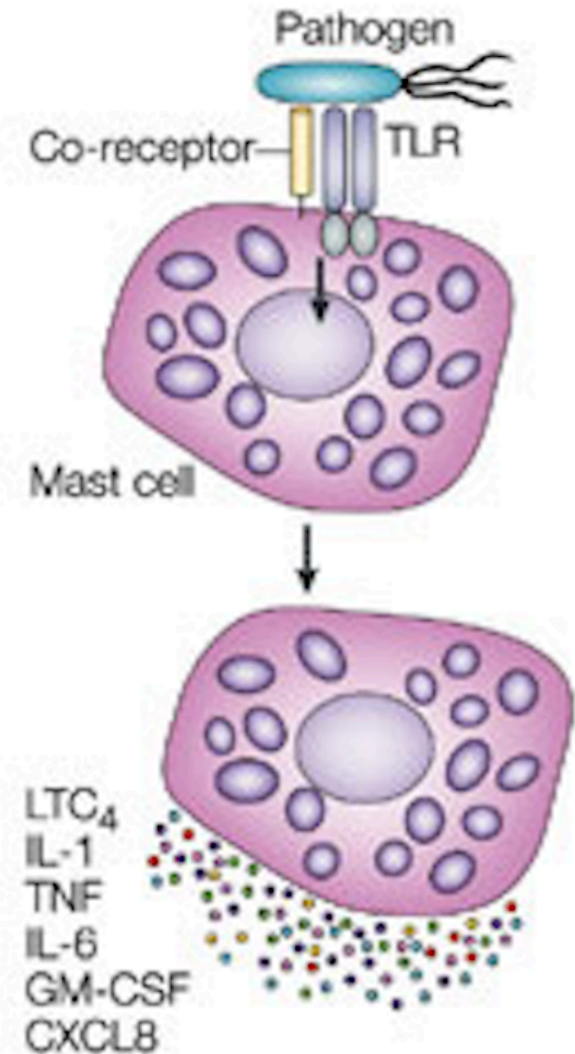
TLR-pathogen mediated Mast Cell Activation

Toll Like Receptors on Mast Cells bind pathogens PRRs for components of bacteria and fungi

- No Release of Proteases (tryptase)
- No Histamine Release

Leukotrienes, Interleukin-1,
Interleukin- 6, CXCL8, GM-CSF
Tumor Necrosis Factor

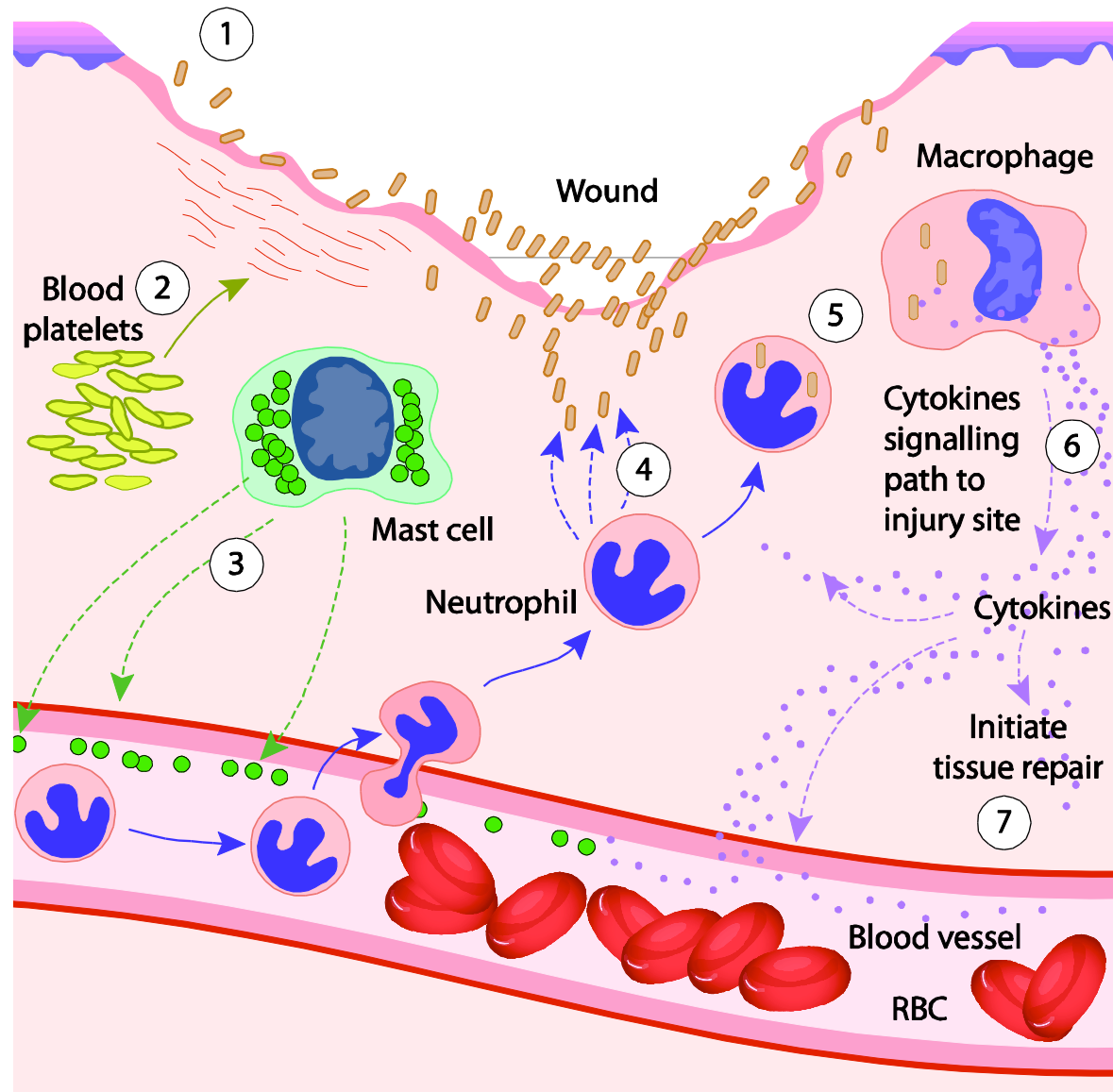
a Direct interactions



Mast Cell responses to pathogens. Jean Marshall
Nature Reviews Immunology, 2004 (4): 787-799

Mast Cells as “Local Peace Keepers”

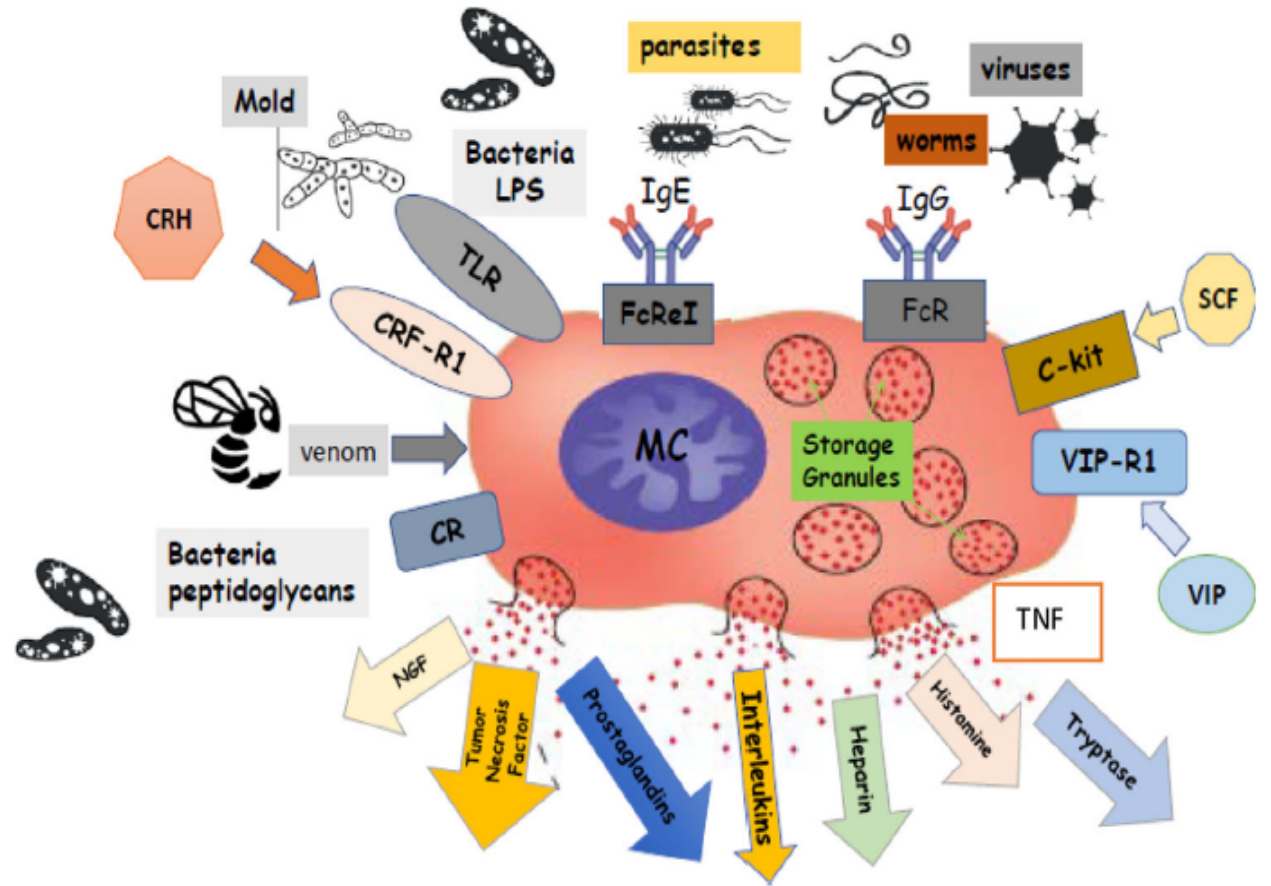
Mast Cells:
Defense
and tissue
repair



1. Bacteria and other pathogens enter wound
2. Platelets from blood release blood-clotting proteins at wound site
3. Mast cells secrete factors that mediate vasodilation and vascular constriction. Delivery of blood, plasma, and cells to injured area increases
4. Neutrophils secrete factors that kill and degrade pathogens
5. Neutrophils and macrophages remove pathogens by phagocytosis
6. Macrophages secrete hormones called cytokines that attract immune system cells to the site and activate cells involved in tissue repair
7. Inflammatory response continues until the foreign material is eliminated and the wound is repaired

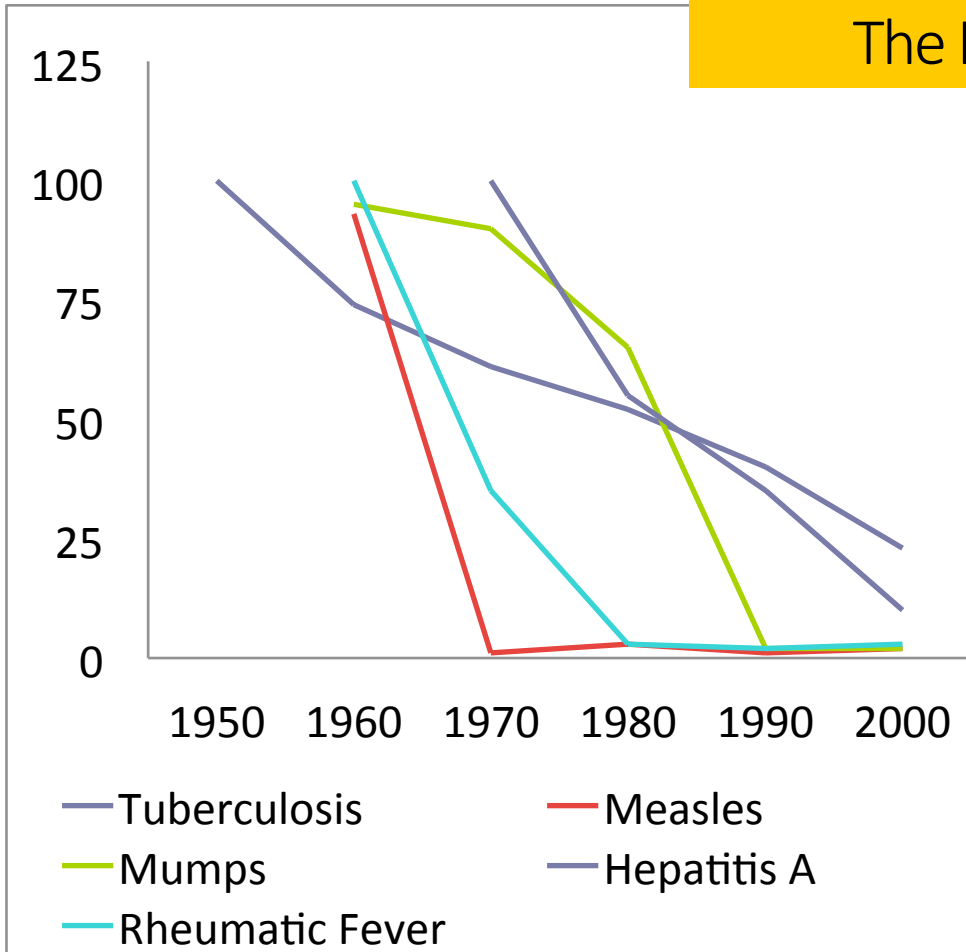
Mast Cell Disorders

MAST CELL ACTIVATION DISORDERS
101



Golden age of medicine = Age of immune dysregulation?

The Increased Burden of Autoimmune and Allergic Disorders

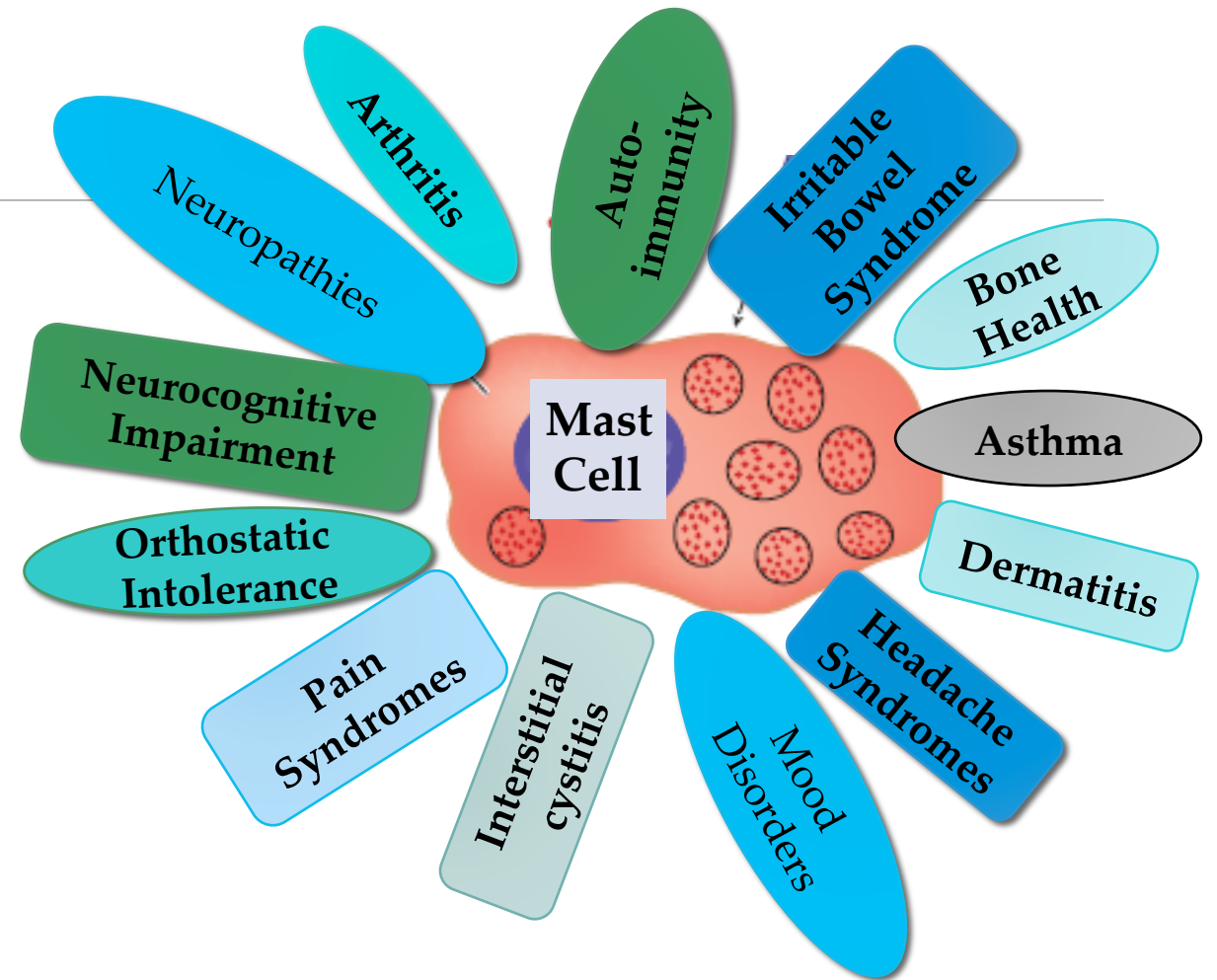
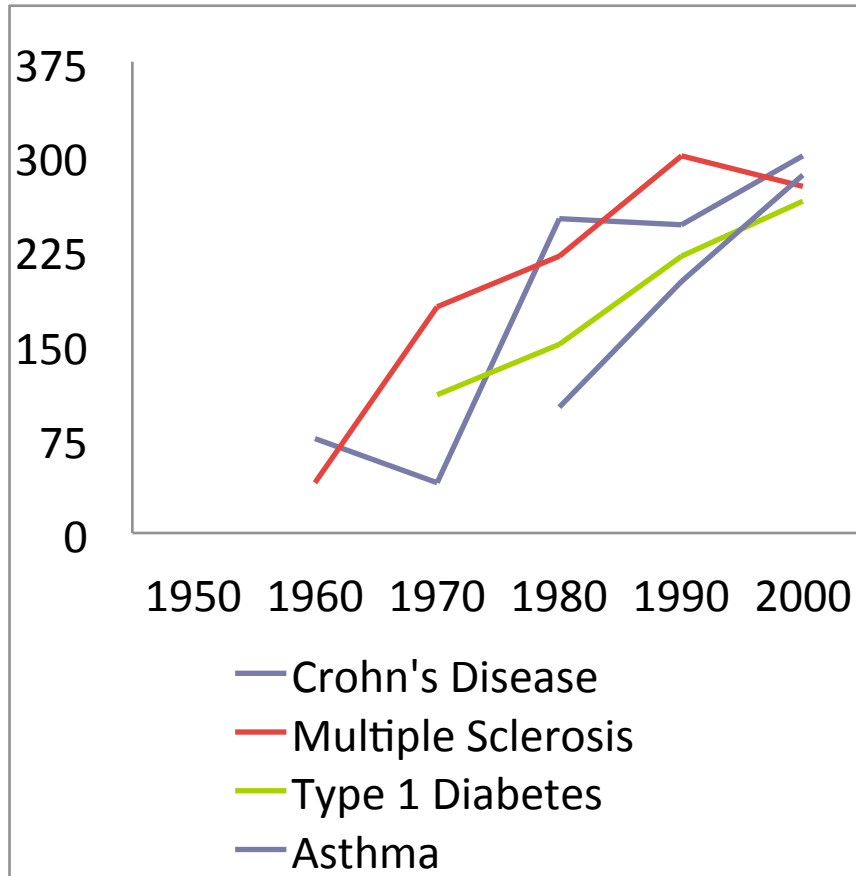


The middle of the 20th century has often been described as a golden age of medicine: scientific advancement and miraculous medical breakthroughs:

- the bacteriological revolution
- the flowering of scientific research and pharmaceutical development that is associated with World War I
- changes in medical education and public health

“Searching for a Golden Age”
University of Pennsylvania

Epidemic of Hypersensitivity Disorders: Role of Mast Cell Dysregulation?

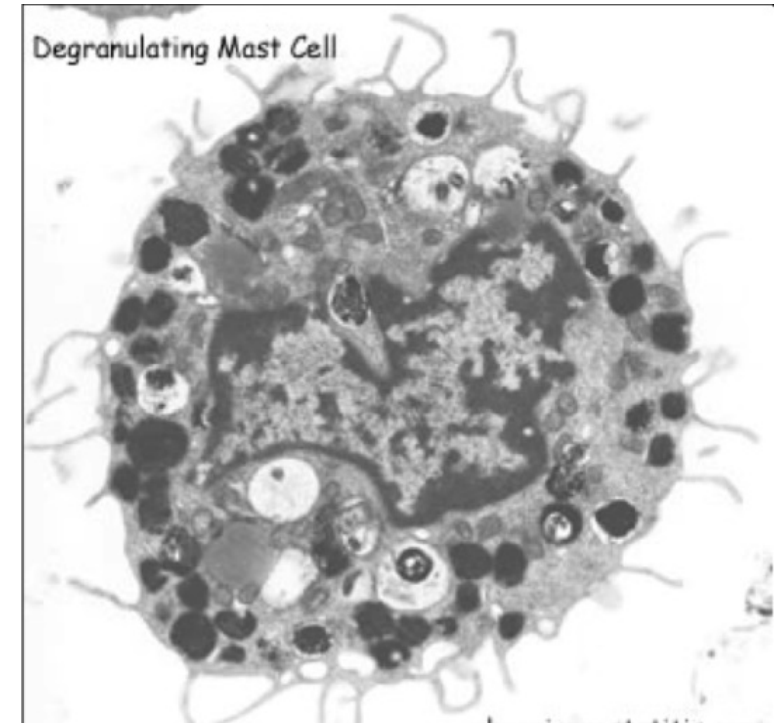
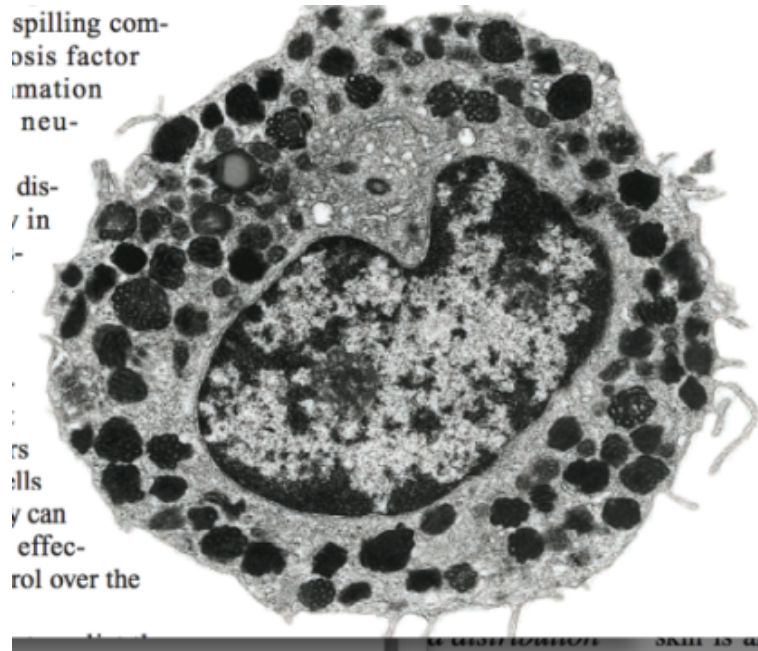


Adapted from Theoharides, NEJM 2015

Adapted from Bach, New Eng J Med 2002

Mast Cell Activation Syndrome (MCAS): a collection of disorders characterized by...

- ❖ Accumulation of pathological mast cells in potentially any or all organs and tissues
- ❖ Aberrant release of variable subsets of mast cell mediators, leading to one or more symptoms (suggestive of systemic mast cell degranulation)



Proposed Diagnostic Criteria for Mast Cell Activation Disorders

- (1) Episodic Signs & Symptoms Consistent with Mast Cell (MC) Activation, affecting 2 or more organ systems
- (2) Response to therapy – decrease in frequency, severity or resolution of symptoms with anti-MC mediator therapies or MC stabilizers
- (3) Evidence of an increase in validated urinary or serum markers of MC activation; increased burden of tissue mast cells (CD117) or chronically activated mast cells (CD117+ and CD25+/CD2+/CD30+)

Proposed Criteria for MCAS Diagnosis:

Rule out Primary MCAS and Secondary Causes of MC activation,
clinical entities that mimic MC activation

Cardiac conditions: Coronary hypersensitivity (the Kounis syndrome)* Postural orthostatic tachycardia syndrome

Endocrine conditions: Fibromyalgia Parathyroid tumor Pheochromocytoma Carcinoid syndrome

Digestive conditions Adverse reaction to food* Eosinophilic esophagitis* Eosinophilic gastroenteritis* Gastroesophageal reflux disease; Gluten enteropathy; Irritable bowel syndrome; Vasoactive intestinal peptide–secreting tumor

Immunologic conditions: Autoinflammatory disorders such as deficiency of inter-leukin-1–receptor antagonist*; Familial hyper-IgE syndrome Vasculitis*

Neurologic and psychiatric conditions Anxiety; Chronic fatigue syndrome Depression; Headaches; Mixed organic brain syndrome; Somatization disorder; Autonomic dysfunction; Multiple sclerosis

Skin conditions : Angioedema* Atopic dermatitis* Chronic urticaria* Scleroderma*

MASTOCYTOSIS

(ESCRIBANO ET AL, JACI 124:514)

Mast Cell Activation Disorder: Signs and Symptoms

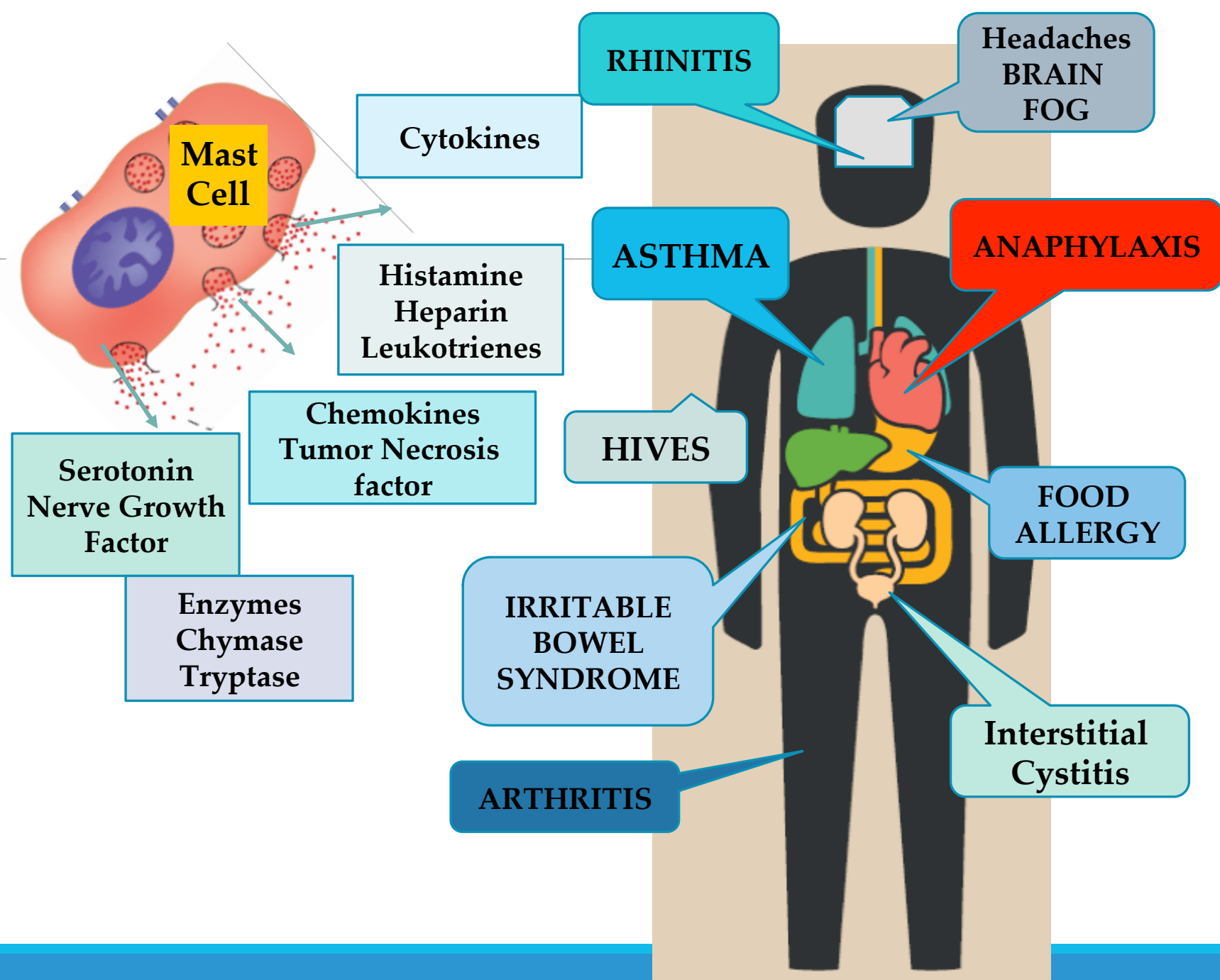
| Skin Lesions | 90% |
|----------------------------------|------------|
| Pruritis | 82% |
| Flushing | 56% |
| Diarrhea | 35% |
| Abdominal Cramping | 30% |
| Neuropsychiatric Symptoms | 23% |
| Anaphylaxis | 23% |
| Peptic Symptoms | 20% |
| Osteoporosis | 18% |
| Hepatomegaly | 12% |
| Splenomegaly | 8% |

| Abdominal Pain | 94% |
|-------------------------|------------|
| Dermatographism | 89% |
| Flushing | 89% |
| Headache | 83% |
| Neuropsychiatric | 67% |
| Diarrhea | 67% |
| Rhinitis (Naso-ocular) | 39% |
| Asthma | 39% |
| Anaphylaxis | 17% |

NONCLONAL MAST CELL ACTIVATION DISORDERS

HAMILTON, J ALLERGY
CLIN IMMUNOL 128;147

- **Mast cells** are found in most parts of the body
- **Mast cells** have a role in allergic/anaphylactic reactions as well as other inflammatory diseases in the skin, respiratory tract, joints, gastrointestinal tract, nervous system, bladder
- **Mast cell mediated disorders worsen with stress**



Airway reactions, (70% reactions)
Throat tightening, Throat Swelling
Nasal congestion, Rhinorrhea
Wheezing, Dyspnea, Chest Tightness

**Gastrointestinal tract
(30-45% reactions)**
Nausea, Cramping
Abdominal Pain
Vomiting, Diarrhea

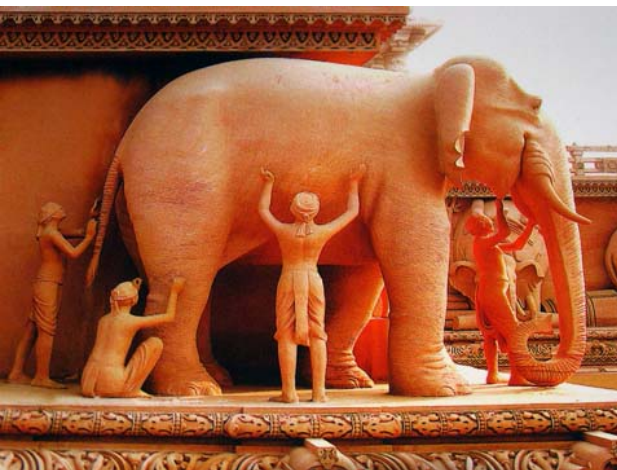
**Genito-
Urinary tract
(>10% reactions)**
Uterine Cramping
Swelling -labia

Brain (> 20% reactions)
Sense of uneasiness, angst
Headache, Dizziness
Confusion, Tunnel Vision

**Heart, Blood Pressure
(10-45 % reactions)**
Fainting, Chest Pain
Fast Heart Rate, Palpitations
(pounding)
Weak pulse, Dizziness

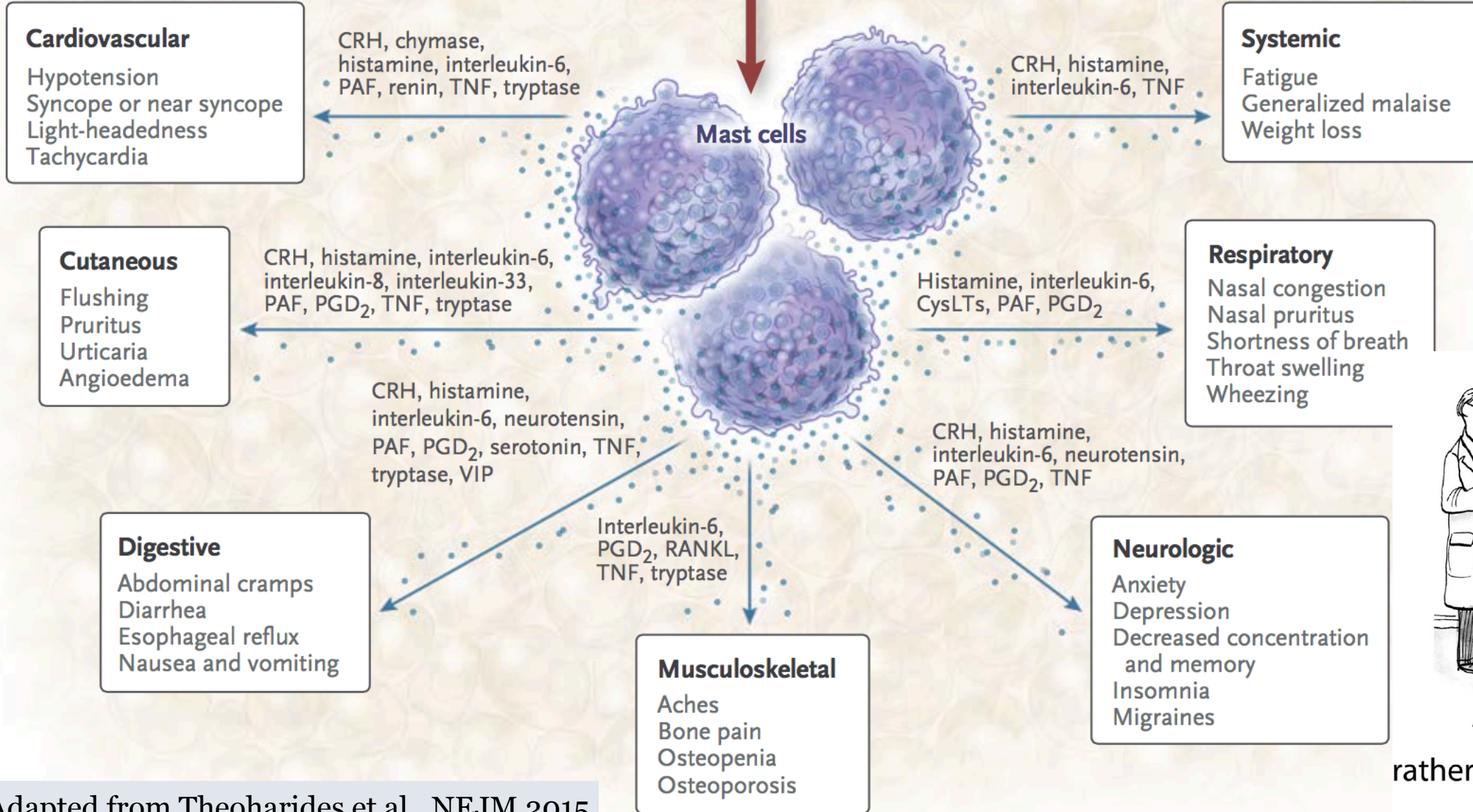
Joint and Muscle Pain

Skin (80-90% reactions)
Hives (Urticaria), Itch
Flushing, Swelling
(Angioedema)



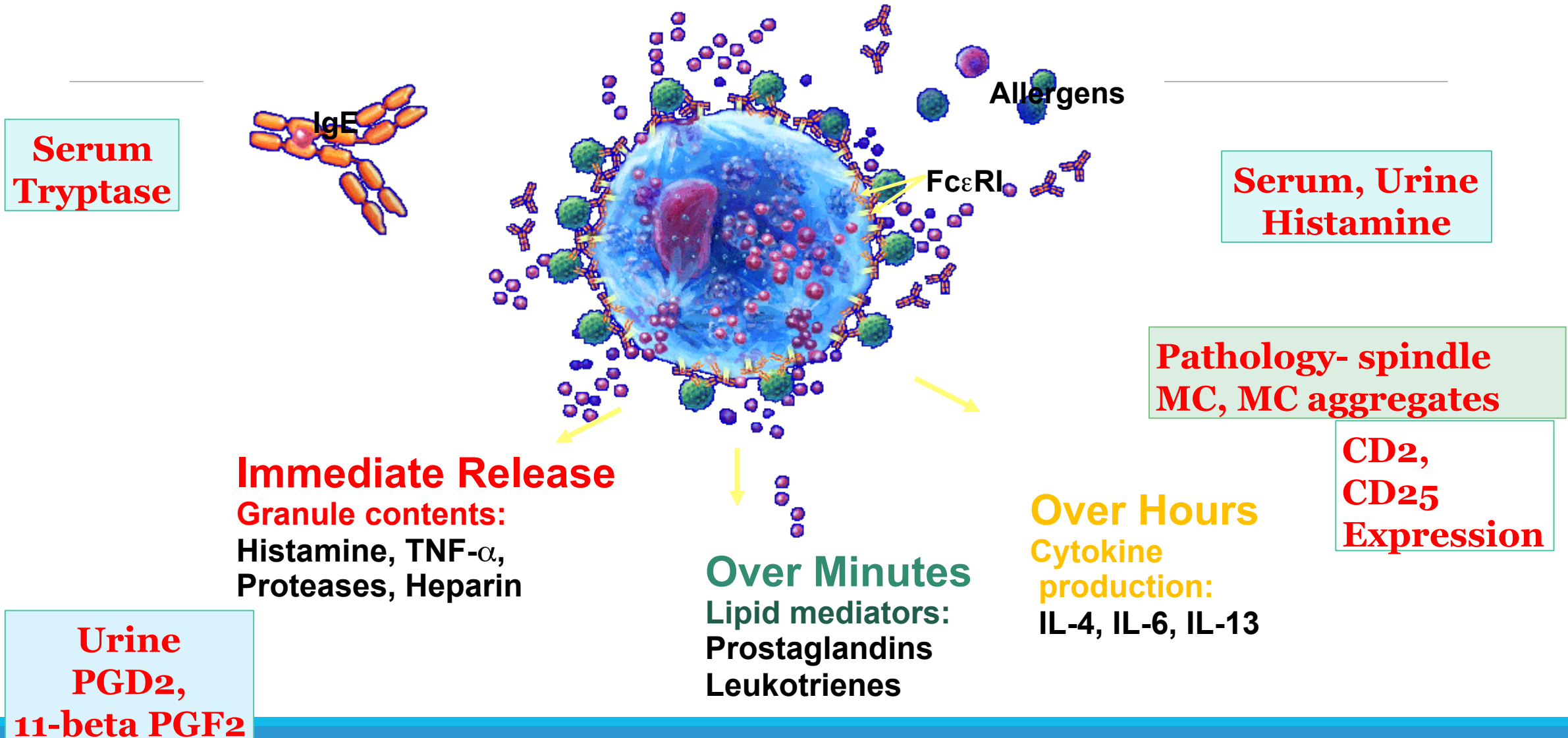
Mast-Cell Activators

Allergens, bacteria, cytokines, drugs, fungi, peptides, toxins, and viruses



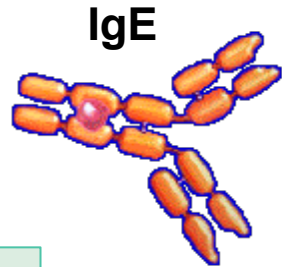
"I'll do some tests rather than give you a guess."

(2) Measuring Mast Cell Activation Markers, Inflammatory Mediators



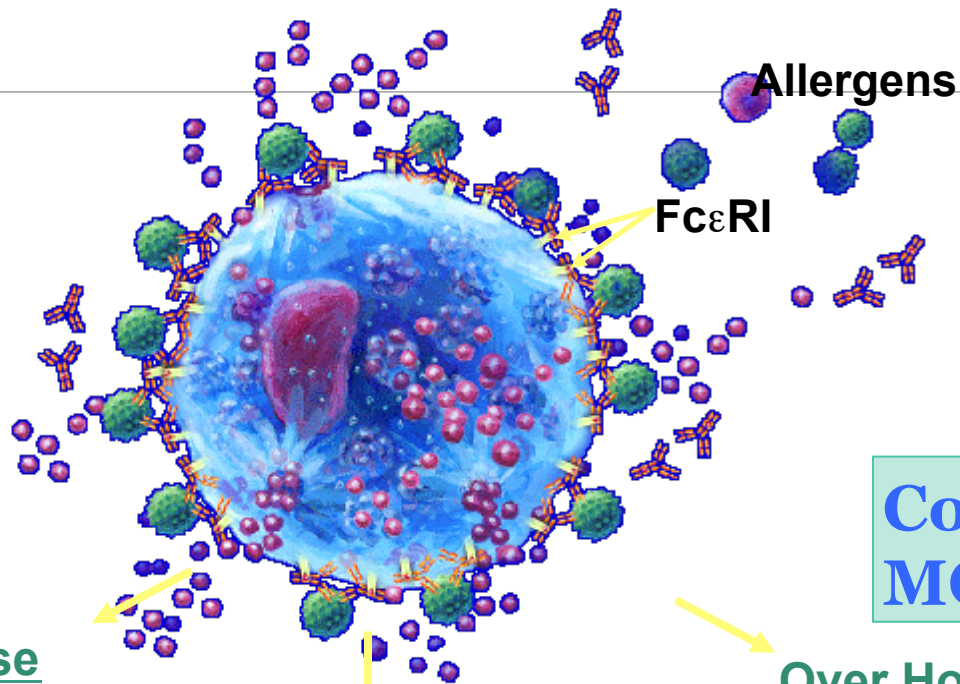
(3) Response to Treatment: Targeting MC/MC Inflammatory Mediators

Anti-IGE mAb



**Traditional Chinese (TCM) Herbal Medicine
Acupuncture**

**Histamine Blockade
Tricyclic Agents**



**Corticosteroids
MC stabilizers**

Immediate Release
Granule contents:
Histamine, TNF- α ,
Proteases, Heparin

Sneezing
Nasal congestion
Itchy, runny nose
Watery eyes

Over Minutes
Lipid mediators:
Prostaglandins
Leukotrienes

Wheezing
Bronchoconstriction

Over Hours
Cytokine production:
Specifically IL-4, IL-13

Mucus production
Eosinophil recruitment

Leukotriene Blockade

Spectrum of Mast Cell Disorders: clonal (c-kit pathway) vs nonclonal

adapted from Akin et al, JACI

1. Typical MC mediated clinical symptoms
2. Increase (transient/sustained) tryptase**
3. Response to anti-MC/MC-mediator treatment(s)

Primary MCAS

MMAS

SM

MCL

Secondary or
Idiopathic
MCAS

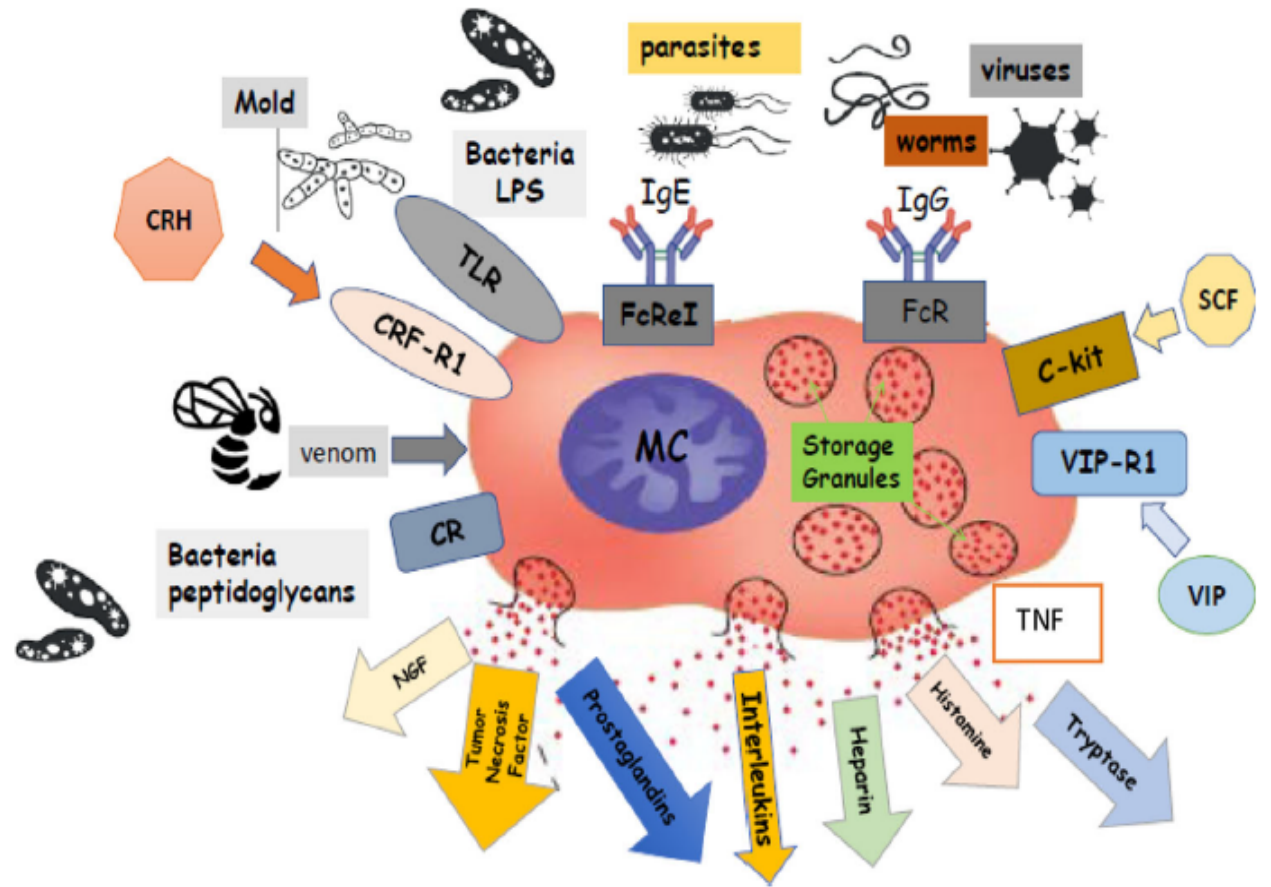
MAST CELL
PROLIFERATION

**Decreased likelihood MMAS, SM or MCL by bone marrow MC aggregates diminishes significantly in those with tryptase < 20 ng/mL

| | |
|---------------------------------|--|
| | |
| Primary (c-kit mutation) | Symptoms Associated with monoclonal mast cell population A. Mastocytosis B. Monoclonal Mast Cell Activation Syndrome (MMAS) |
| Secondary | A. Allergic (IGE mediated) Disorders B. MC activation associated with chronic inflammatory/ neoplastic disorders C. Physical Urticarias D. Chronic Autoimmune Urticaria |
| | Mast Cell Activation Syndrome (MCAS) <ul style="list-style-type: none">▪ Hyper-tryptasemia (tryptase mutation-autosomal dominant) |
| Idiopathic | A. Anaphylaxis B. Angioedema C. Urticaria |

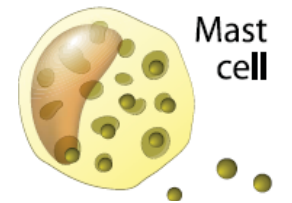
Mast Cell Disorders

TREATMENT STRATEGIES



Mast Cell Activation Disorders Guidelines to Diagnosis and Treatment

1. Accurate, “Best Working” Diagnosis
2. Assess severity
3. Education for partnership in Care
4. Treatment/Management
5. Return to review and reflect on diagnosis and treatment- are you or are you not better

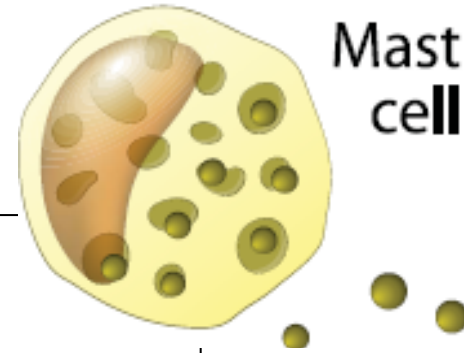


Mast cell activation syndrome is easily treated, if it's recognized

Last Updated: 2011-06-10 19:15:17 -0400 (Reuters Health)

By Anne Harding

NEW YORK (Reuters Health) - Patients with mast cell activation syndrome (MCAS) frequently go for years without an accurate diagnosis, but once diagnosed and treated, their response is likely to be "excellent," according to a new report.



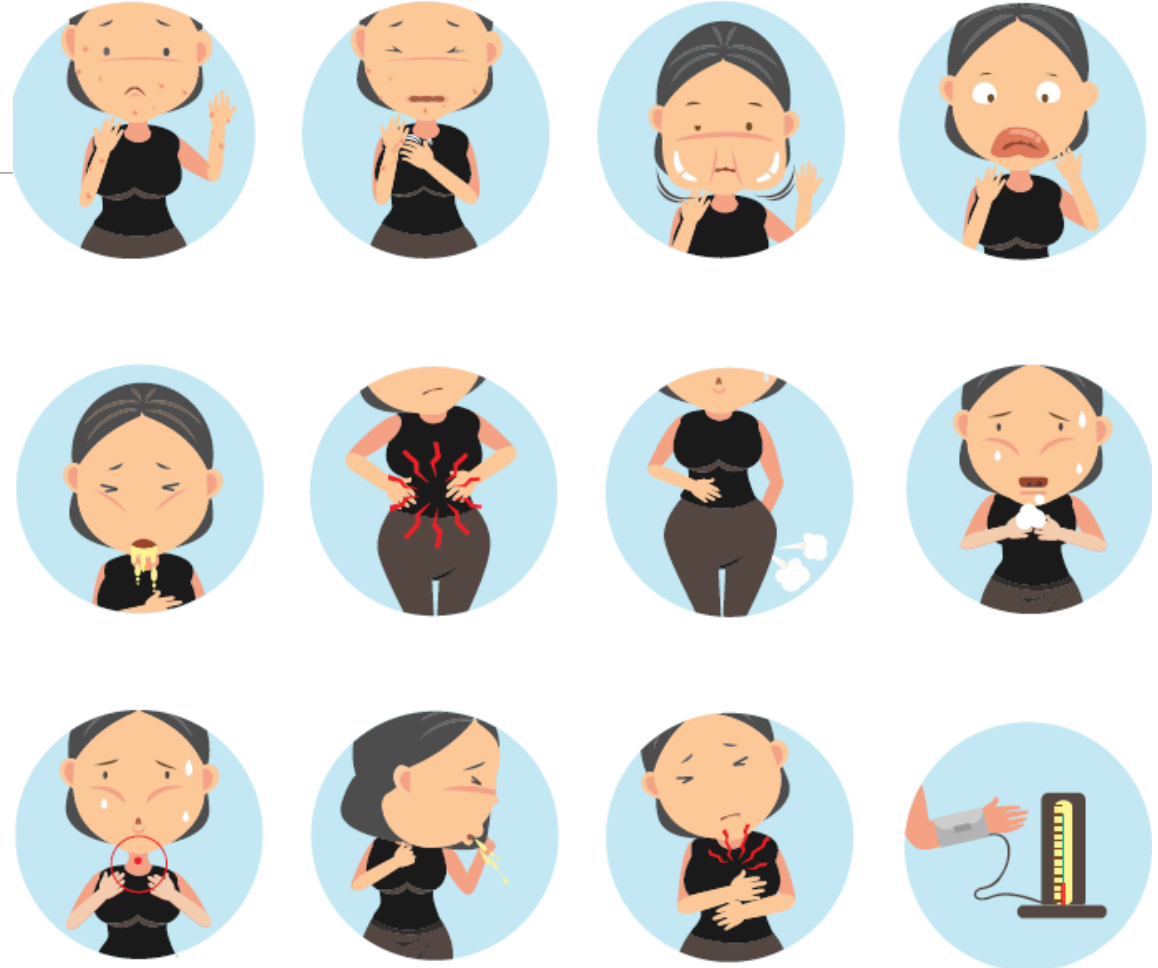
Who's Holding Up the Queue? Delay in diagnosis and treatment of MCAD

HOMIK <http://www.irheum.org/content/38/7/1225> J Rheumatol 2011;38;1225-1227

Allergy (Immune mediated) disorders now cause problems of increased complexity and commonly involves several organ systems, so patients are often referred to a succession of different specialists, resulting only in confusion.

Allergy: the unmet need,
Royal College of Physicians, 2006

ALLERGY SYMPTOMS



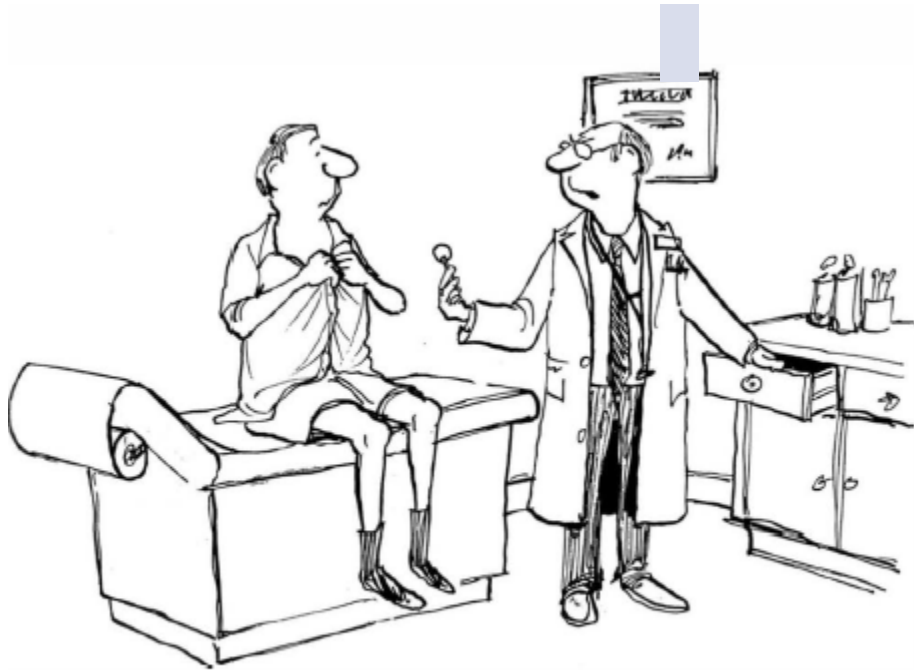
Paging ZocDoc for the future of medicine

ZocDoc, turning health care into a one-click experience, upends traditional medical practice.

<http://www.usatoday.com/story/money/business/2012/12/30/michael-wolfe-zocdoc-an-omen-of-big-changes-in-health-care/1799511/>

Knowledge of good allergy management in practice is therefore minimal or non-existent.

Allergy: the unmet need, Royal College of Physicians, 2003



You're fine, take the lollipop!

1. Patient awareness

“Do I have a problem that warrants medical care”

2. General Practitioner Awareness

Allergy barely features in the undergraduate medical curriculum

“Does this patient have an inflammatory disorder that warrants specialist attention”

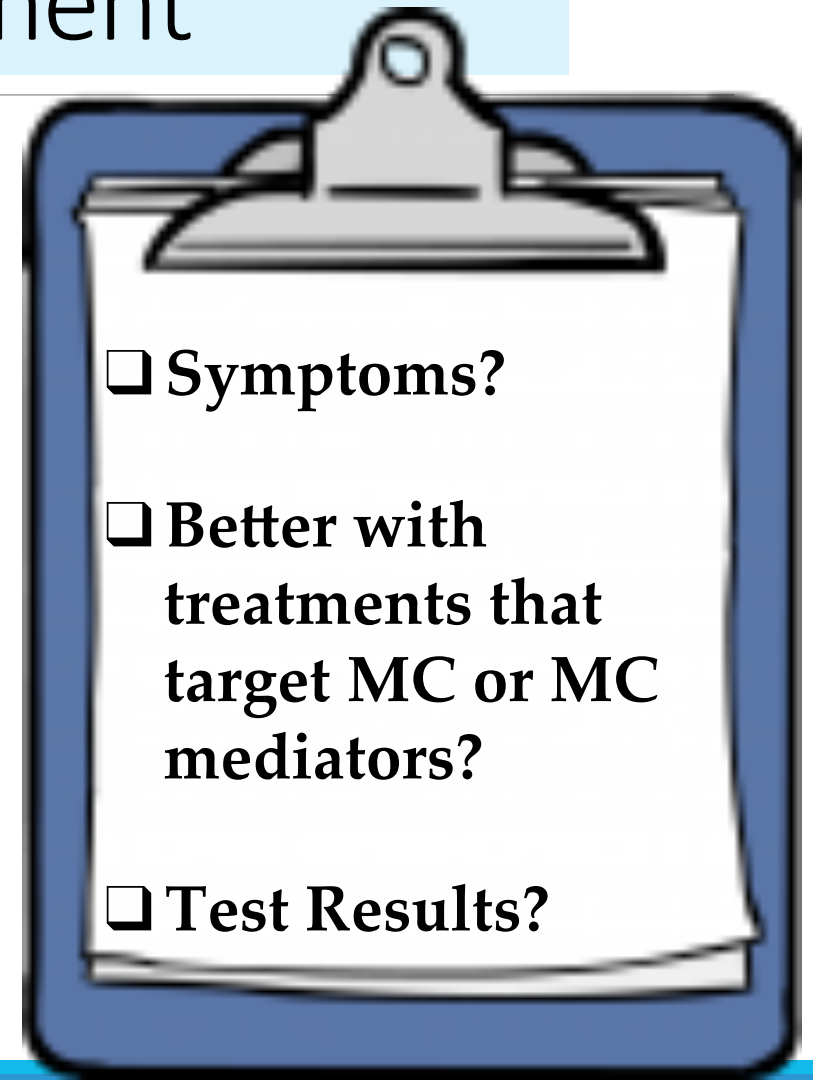
3. Specialist Awareness

lack of specialists in academic medical centers and communities means virtually no clinical training is available.

Mast Cell Activation Disorders

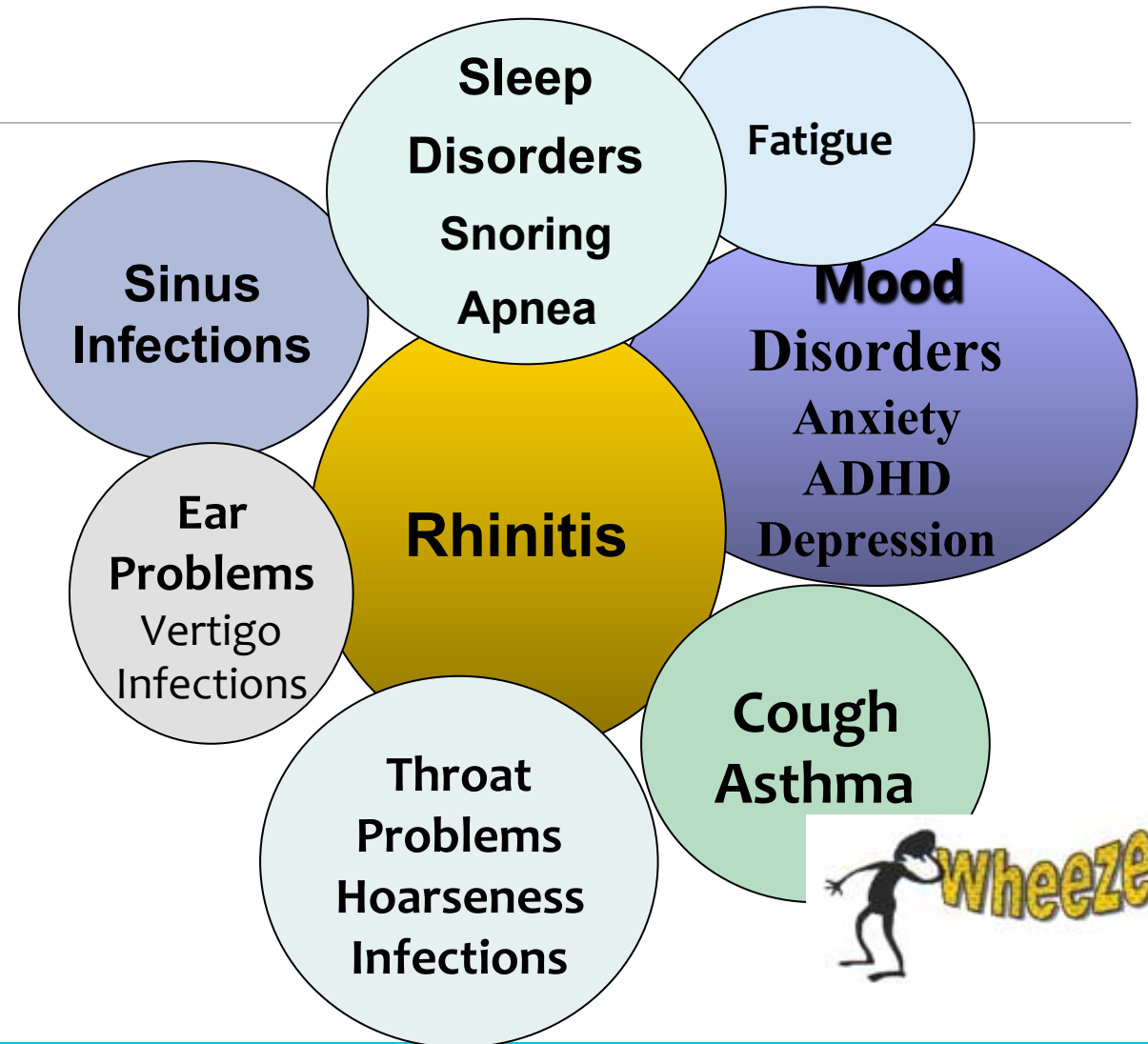
Guidelines to Diagnosis and Treatment

- 1. Accurate, “Best Working” Diagnosis**
- 2. Assess severity**
- 3. Education for partnership in Care**
4. Treatment/Management
5. Return to review and reflect on diagnosis and treatment- are you or are you not better



Common MC -Mediated Disorder: Rhinitis

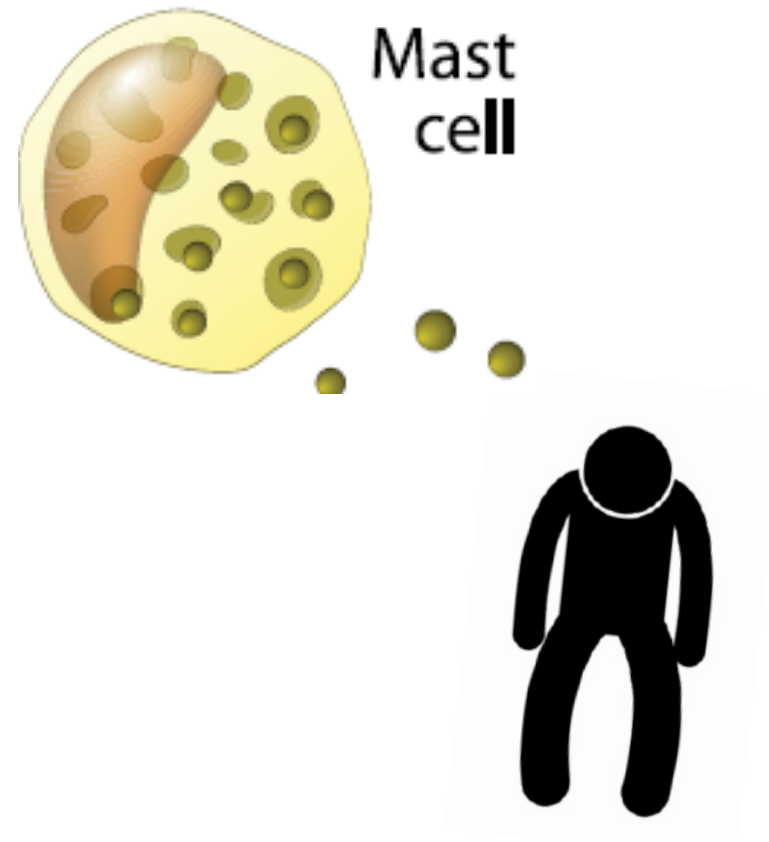
- Sneezing, Itching: Nose, eyes, ears, palate
- Runny nose, Postnasal drip, back drip
- Congestion, Headache, Facial Pain, Dental pain
- Lose sense of smell, taste
- Headache, Earache
- Tearing, Red eyes, Eye swelling
- Fatigue
- Snoring, Poor sleep, Drowsiness, Malaise
- Sore throat, hoarseness. Mouth breathing
- Acute or chronic sinusitis; Otitis media
- Sleep disturbance or apnea



Mast Cell Activation Disorders

Guidelines to Diagnosis and Treatment

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- 4. Treatment/Management**
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MCAD/MCAS Treatment: Targeting MCs or MC derived Inflammatory Mediators

Corticosteroids
MC stabilizers
Cytokine Antagonists

**Histamine
Blockade
Tricyclic Agents**

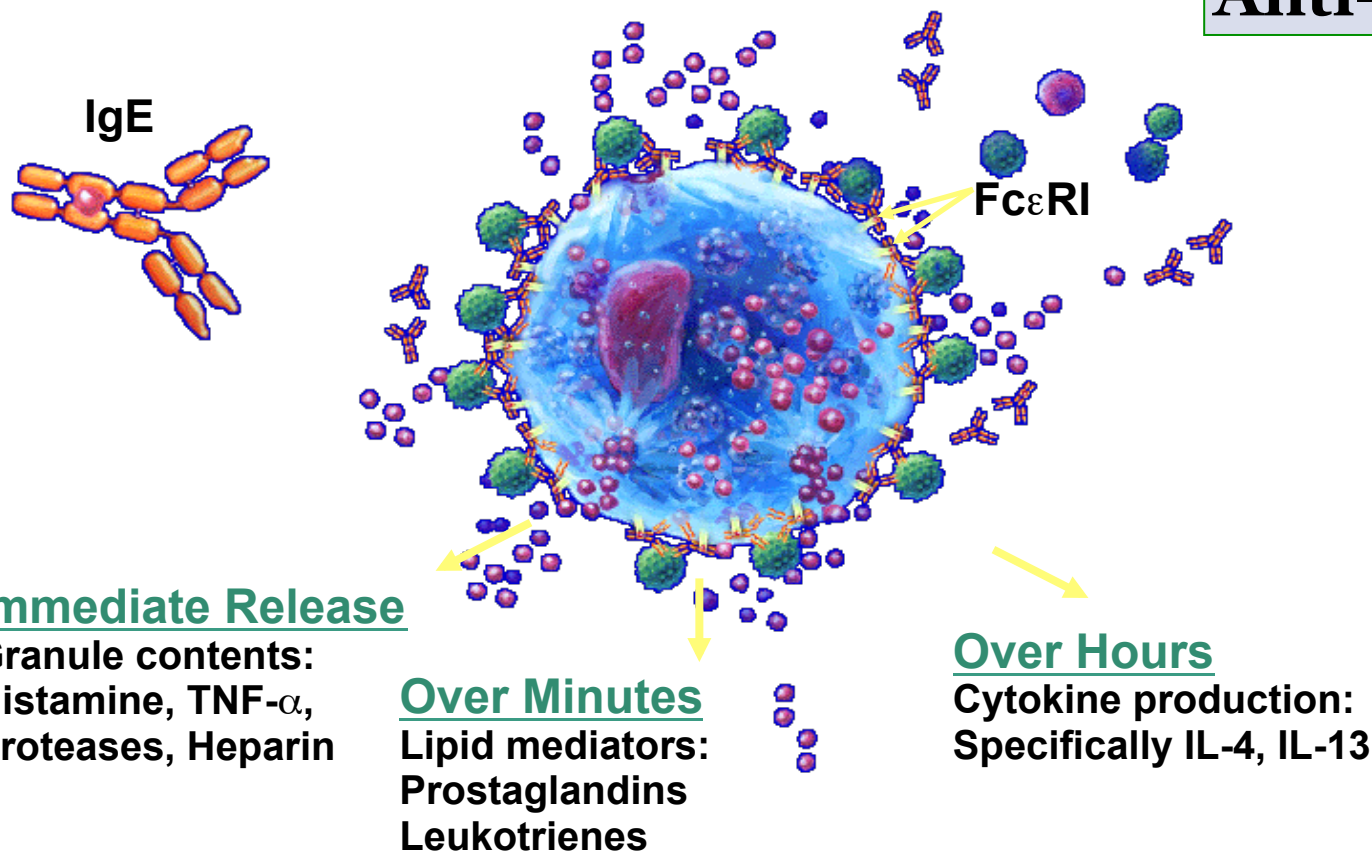
Anti-IGE mAb

Leukotriene Blockade
Cyclooxygenase Inhibitors

Nutraceuticals

DAO supplement
Vitamin C
Quercetin
Stinging Nettle
Butterbur

Traditional
Chinese (TCM)
Herbal Medicine
Acupuncture



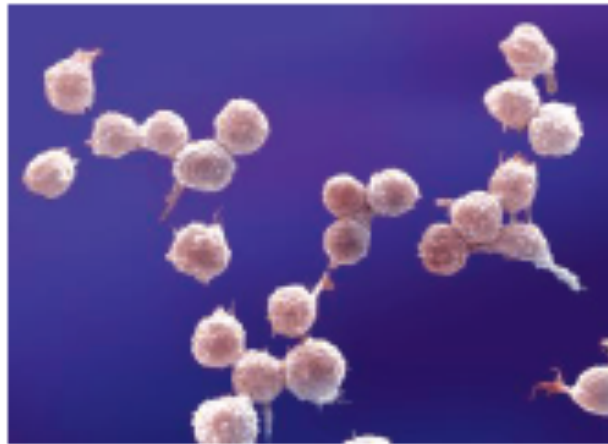
Mast Cells Show Their Might

They are the most reviled cells in the body. Their meddling makes our skin itch, our eyes swell, and our noses stream; the cells even provoke suffocating asthma attacks that kill thousands of people every year. In fact, these villains, known as mast cells, are responsible for so much suffering that some researchers have proposed eradicating them.

That could be a big mistake. Over the past decade or so, the reputation of these immune cells has been turned around. Researchers have learned that mast cells are vital sentinels that orchestrate counterattacks on invading bacteria and viruses. The cells link the innate immune system, which deploys a standard set of defenses, with the adaptive immune system, which customizes the body's weapons to a specific attacker. Mast cells even neu-

tralize toxins from snakebites and bee stings (*Science*, 28 July 2006, p. 427).

However, mast cells turn out to be fickle allies. Extending the cells' disease connections far beyond allergic reactions, recent studies put them at the center of multiple



Standing guard. Mast cells from the umbilical cord.

Once dismissed as "allergy cells," mast cells have proven crucial for immunity. But they've also shown a dark side

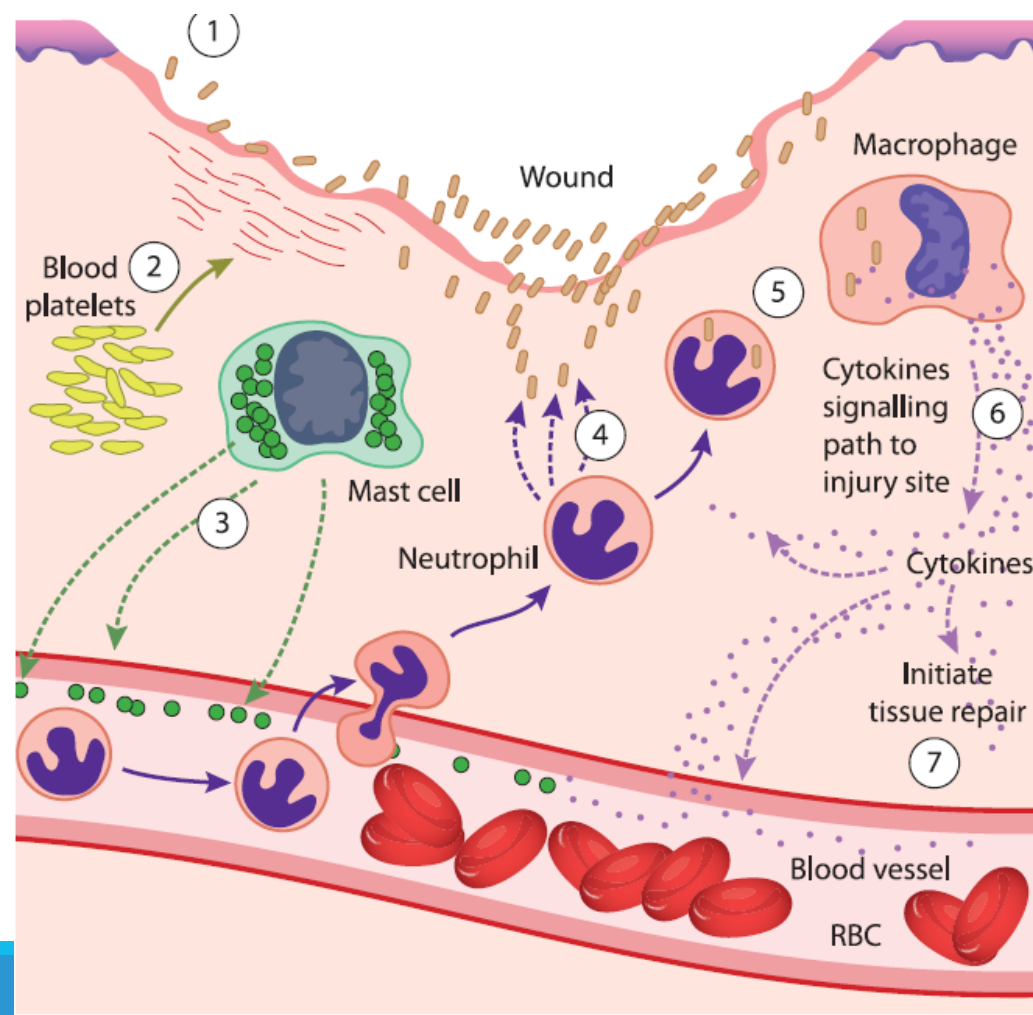
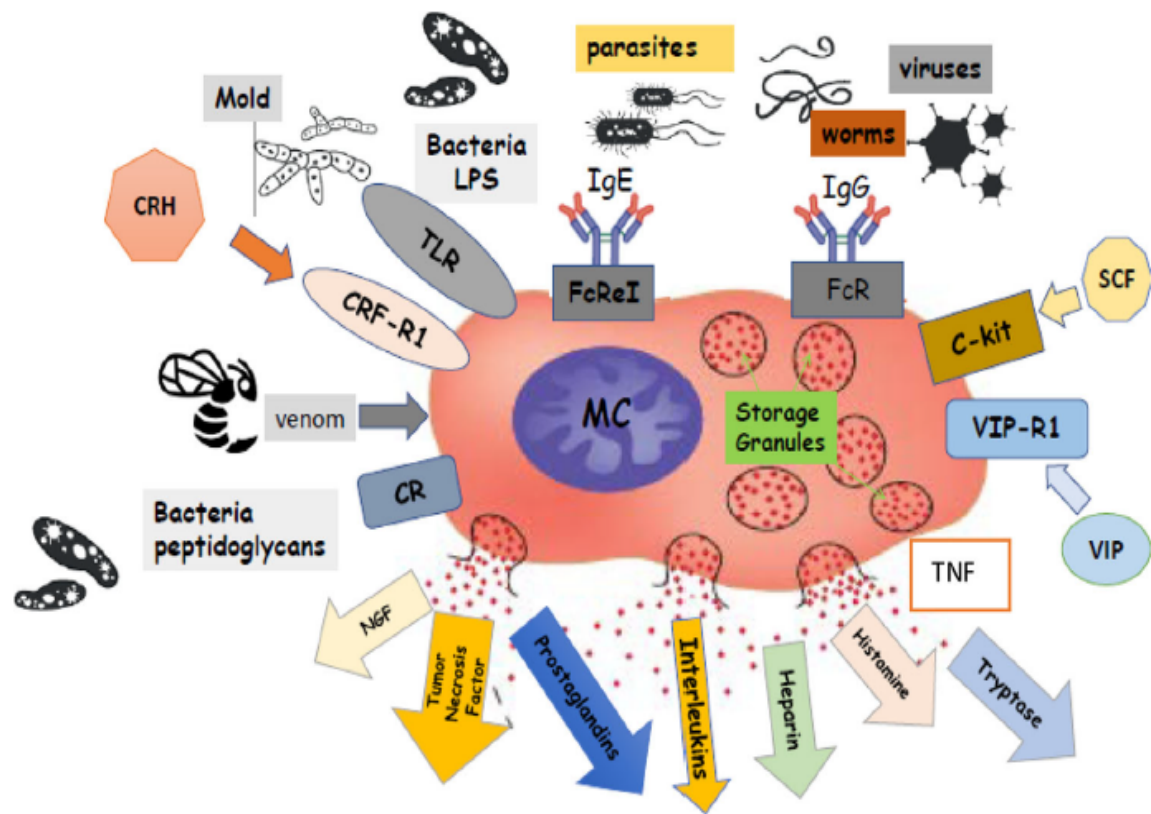
sclerosis, rheumatoid arthritis, cancer, and atherosclerosis. "What this research tells you is that mast cells are key to a lot of biological processes," says immunologist Dean Metcalfe of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland.

The catalyst for many of these discoveries was the identification of mutant mice that lack mast cells. A white-spotted coat on one of these rodents first attracted geneticists' attention in 1937. But it wasn't until the late 1970s that Yukihiro Kitamura of Osaka University Medical School in Japan and colleagues determined that the genetic defect responsible for the color change also short-circuited mast-cell development. Led by Kitamura and pathologist Stephen Galli of Stanford University in Palo Alto, California,

CREDIT: FRED HOESLY/SHUTTERSTOCK



Mast Cells: Defense and Wound Repair

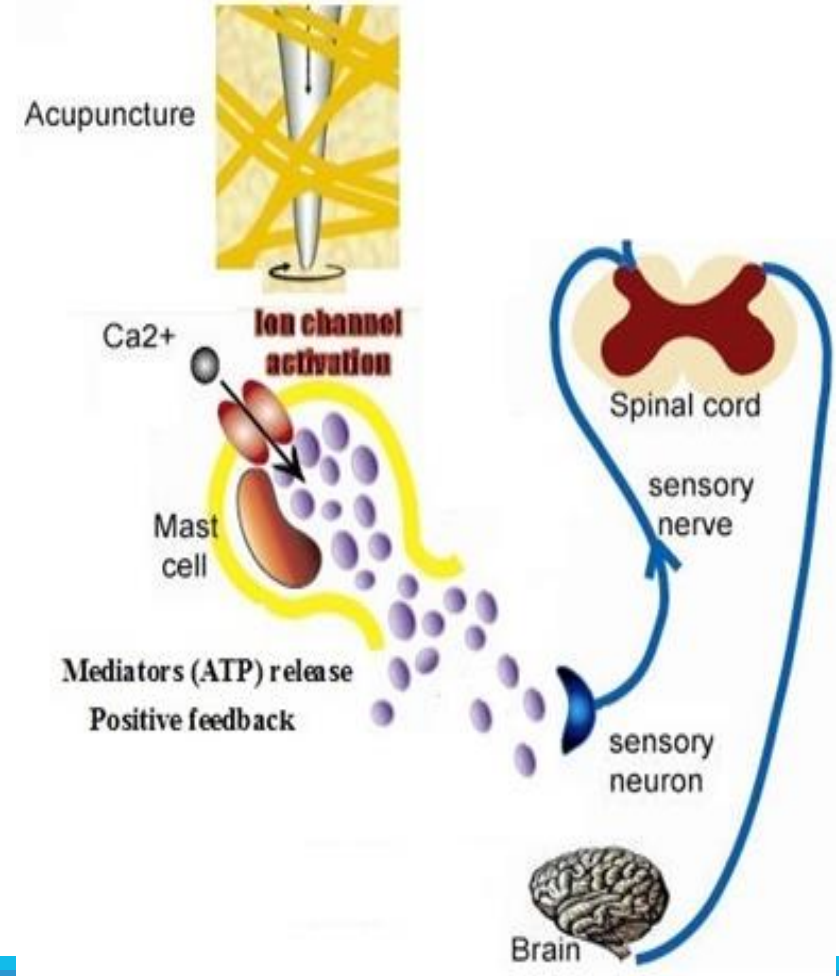


Acupuncture & MCAS treatment: Role of mast cells in acupuncture effect: a pilot study

Di Zhang, PhD et al, EXPLORE May/June 2008

MCs are common at sites that are in close contact with the external environment (skin, gastrointestinal tract and airways), they are distributed in virtually all organs and vascularized tissues

Mast cells are found abundant at sites of acupoints



Acupuncture & MCAS treatment: Role of mast cells in acupuncture effect: a pilot study

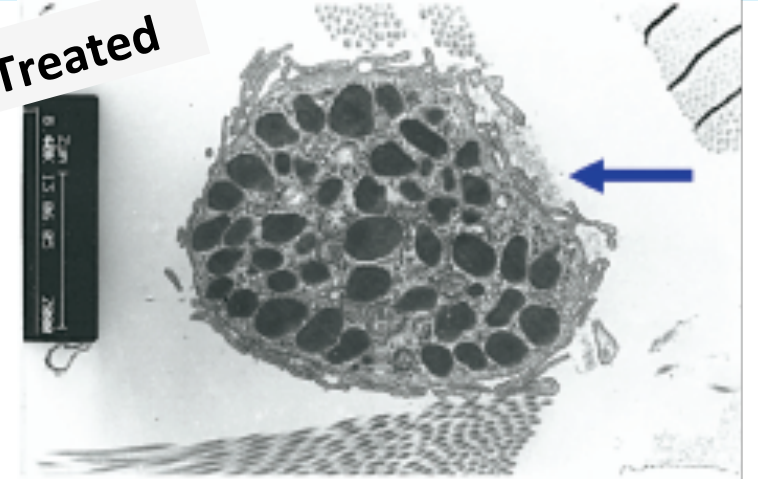
Di Zhang, PhD et al, EXPLORE May/June 2008

Impact of manual stimulation by an acupuncture needle on anesthesia

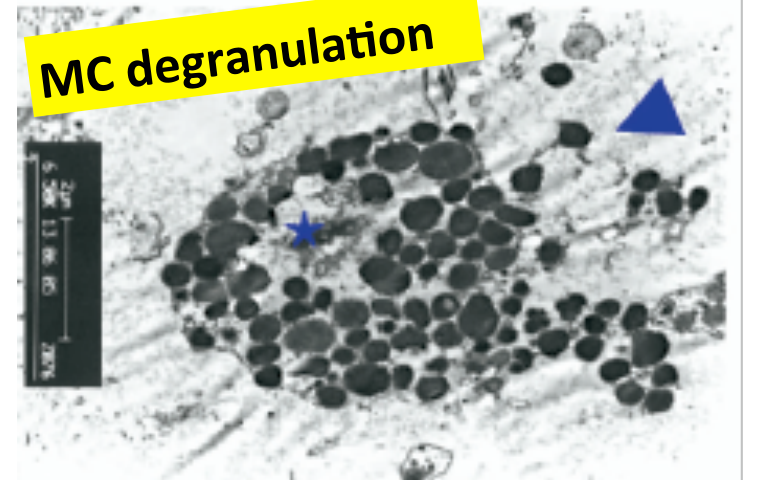
Acupuncture:

- Increased the density of mast cells
- Increase in MC degranulation
- Pretreatment of the acupuncture point with disodium chromoglycate not only counteracted the phenomenon of degranulation but also reduced analgesic effect of acupuncture.

Sham Treated



MC degranulation



Better Health = Mast Cell suppression ???

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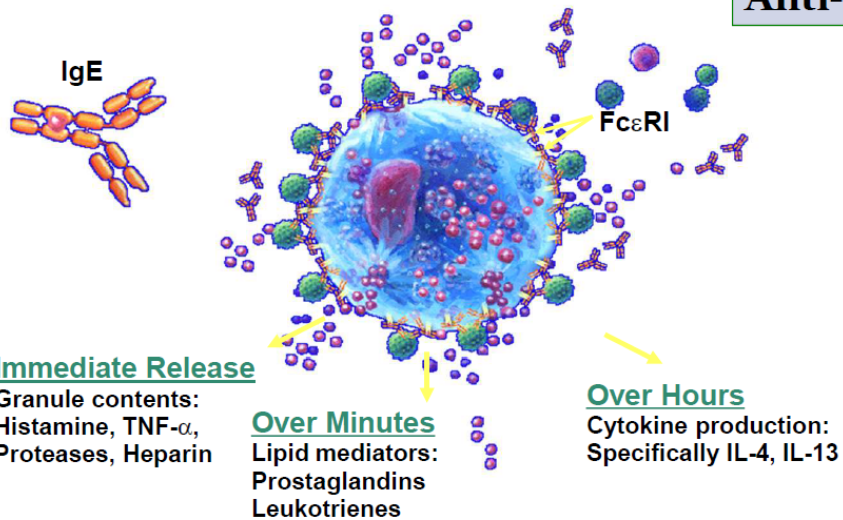
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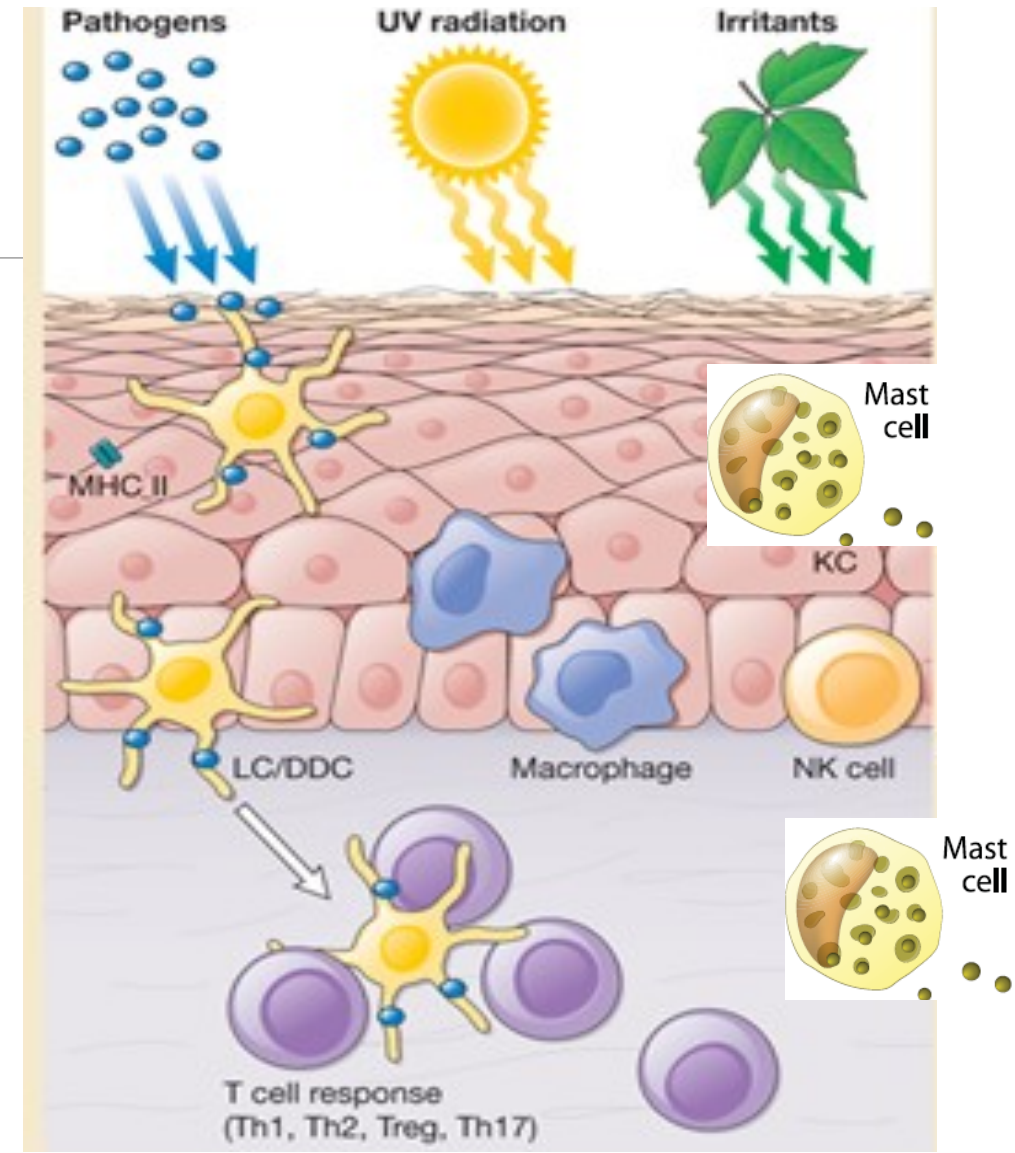
Traditional
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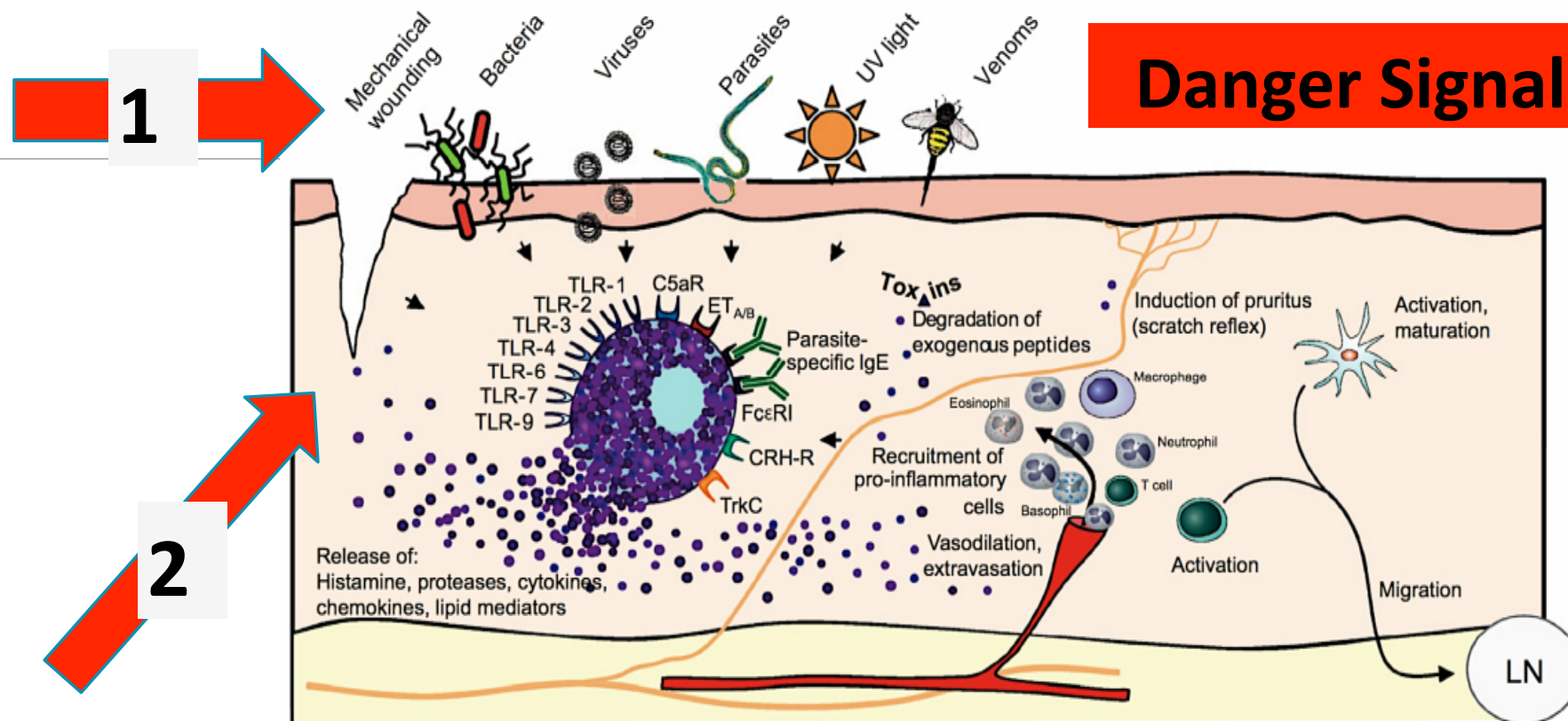
Treatment of Hypersensitivity Disorders

Like most immunologists, I had thought that immunity is controlled by the cells of the “adaptive” immune system (lymphocytes) or the more ancient “innate” immune system (such as macrophages, dendritic cells, and the complement system).

- Polly Matzinger, Science 2002



Danger Signals



(1) Infectious, non-self threats, that have as **pattern recognition receptors (PRRs)** and are recognized by evolutionarily conserved membrane-bound Toll-like receptors (TLRs), on MCs

(2) Endogenous, self alarm signals, indicating danger:

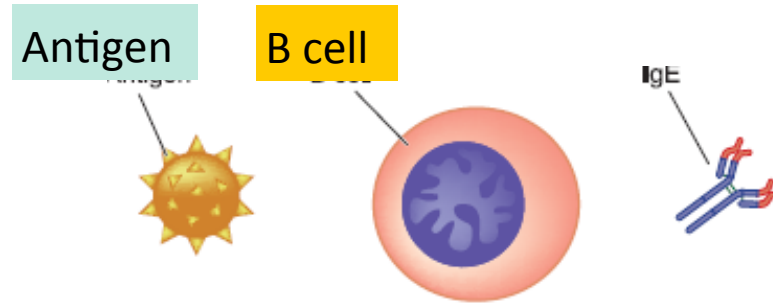
breakdown products of hyaluron (made when vessels are damaged), mammalian DNA, RNA, heat shock proteins (Hsps), interferon α , (an inducible protein often made by virus-infected cells), interleukin-1 β , CD40-L (a surface molecule on activated platelets and activated T cells), and

| | |
|---------------------------------|---|
| | |
| Primary (c-kit mutation) | <ul style="list-style-type: none"> A. Mastocytosis B. Monoclonal Mast Cell Activation Syndrome (MMAS) |
| Secondary | <ul style="list-style-type: none"> A. Allergic (IGE mediated) Disorders B. MC activation associated with chronic inflammatory/neoplastic disorders C. Physical Urticarias D. Chronic Autoimmune Urticaria |
| | <p>Mast Cell Activation Syndrome (MCAS)</p> <ul style="list-style-type: none"> ▪ Hyper-tryptasemia (tryptase mutation-autosomal dominant) |
| Idiopathic | <ul style="list-style-type: none"> A. Anaphylaxis B. Angioedema C. Urticaria |

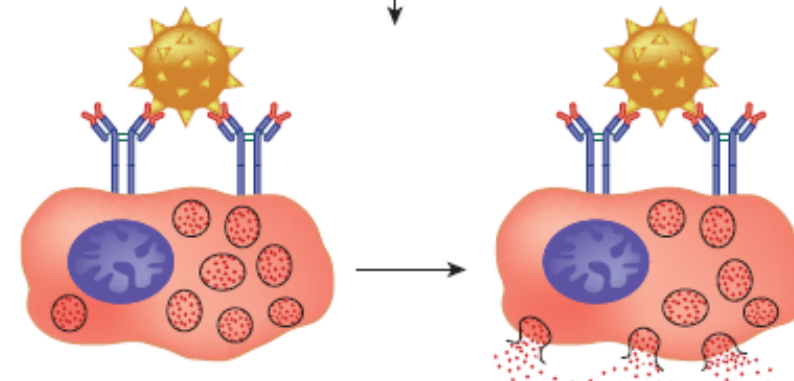
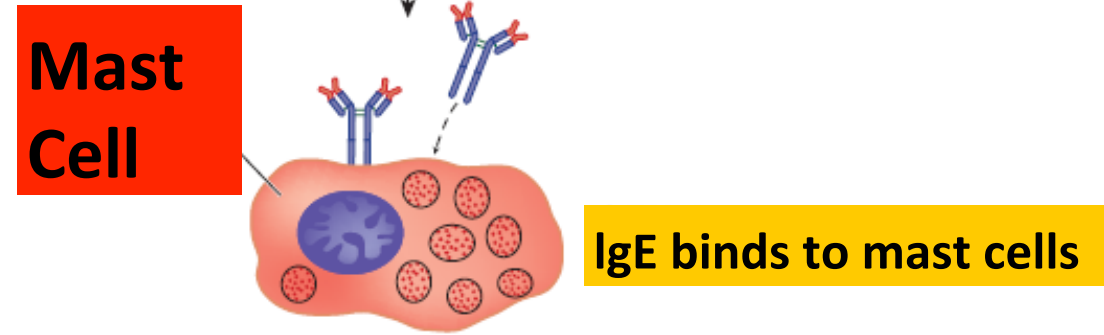
Mast Cell Activation Syndrome (MCAS)
Endotypes:
 from
 Clinical Phenotypes to
 Molecular Approaches

Allergic Reactions

Allergen-IgE-
IgE receptor
triggered Mast
Cell
Activation



First exposure to a sensitizing antigen causes B-cells to make IgE antibodies



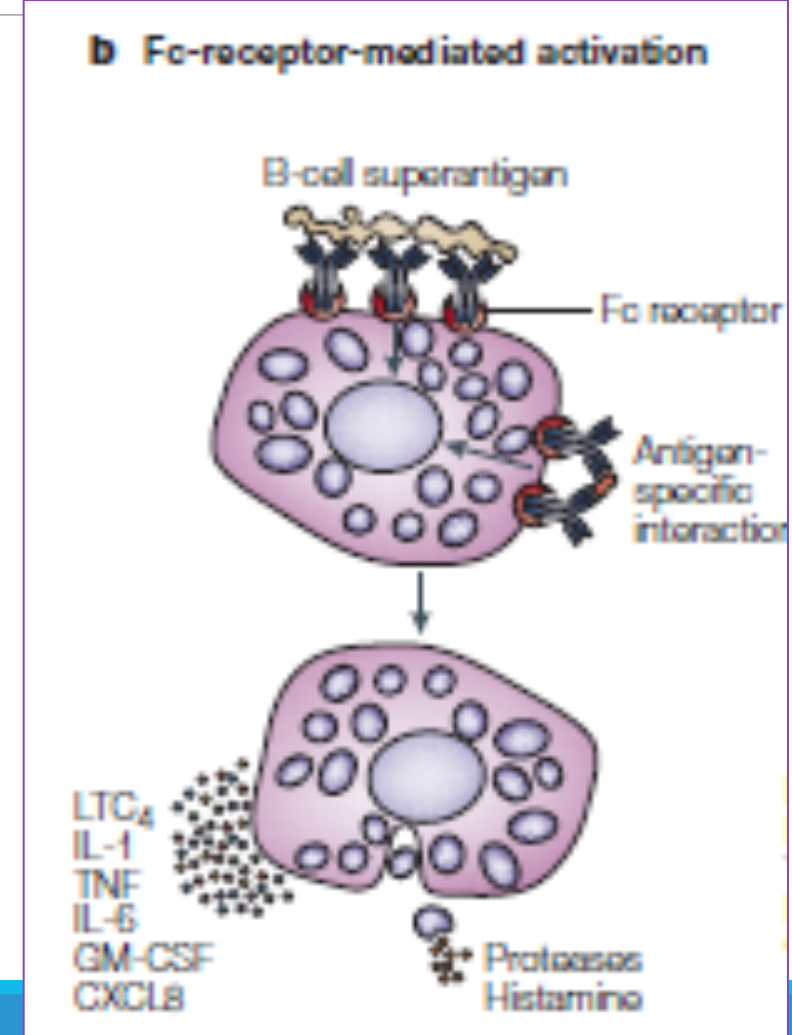
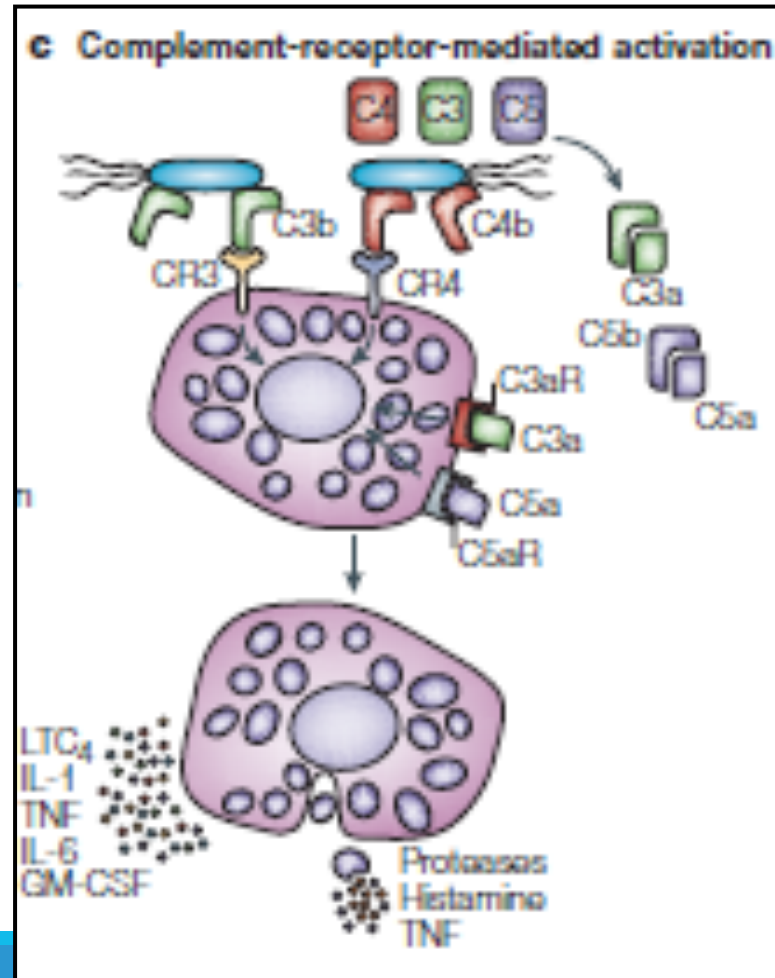
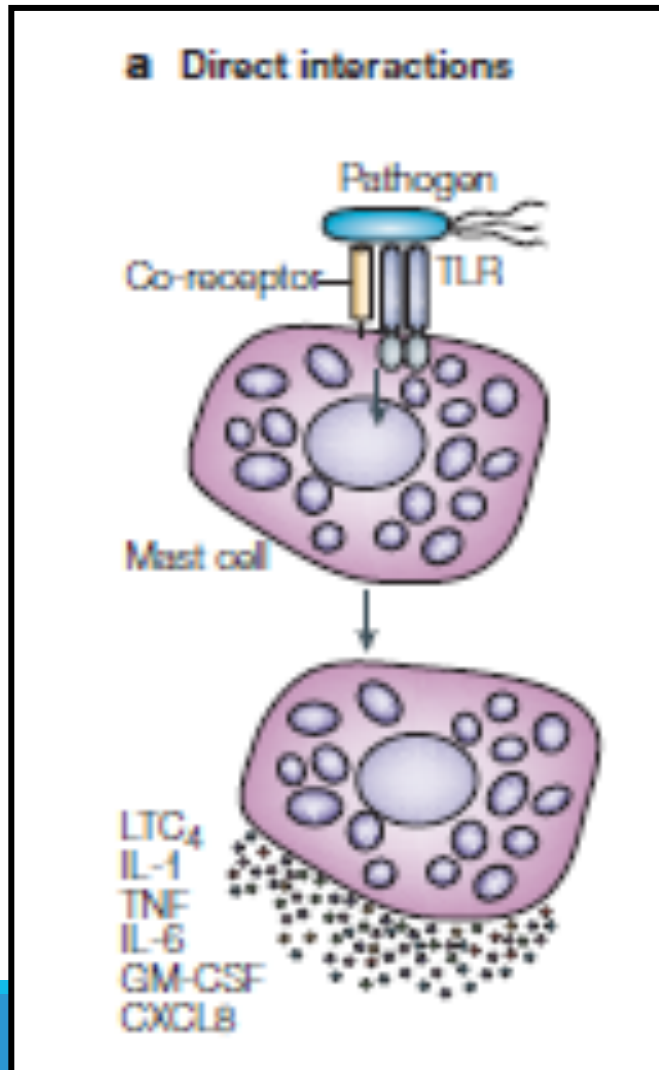
Subsequent exposure to antigen
causes mast cell action, releasing allergenic mediators

Allergy: e.g. hives, hay fever,
asthma, food allergy

e.g. hi

While the cause of the condition isn't clear... "we have some clues that it might be something to do with the signaling that goes on at the mast cell surface." -

Dr. Matthew J. Hamilton of Brigham and Women's Hospital, Boston, 2011



| | |
|---------------------------------|---|
| | |
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Mast Cell Activation Syndrome (MCAS) Endotypes:
 from
 Clinical Phenotypes to Molecular Approaches

Letter to the Editor

Atopy in Connective Tissue Disorders

An early
observation of a
possible
relationship
between
connective tissue
and mast cells

MCAS and EDS: Objective Data

5 patients were tested for objective evidence of mast cell activation, including

- serum tryptase levels were normal
- Serum IGE < 20 kiu/ml (3-20)
- 24 hour urine histamine collections were unremarkable.

All Ehlers Danlos Syndrome patients appear to display non-IgE mediated allergic disease controlled by anti-mediator therapy and avoidance of triggers.



One Gene Mutation Links Three Mysterious, Debilitating Diseases: Hypertryptasemia, tryptase > 9 ng/ml

(personal communication with J. Milner, MD, PhD)

“On a good day, my shoulders, knees, and hips will dislocate two to five times apiece. The slightest bump into a table or door will bloom new bruises on my arms and legs or tear a gash in the thin skin on my hands. My blood pressure will plummet each time I stand, making me feel woozy, nauseated, and weak. I’ll have trouble focusing and remembering words. I’ll run my errands from underneath an umbrella to prevent an allergic reaction to the Sun.”

-Kate Horowitz, Mental Floss, October 2016

RHINITIS Sneezing * Congestion * Stuffiness * Itchy Eyes * Runny nose * Post Nasal Drip

* **STINGING INSECT ALLERGY** * Wheezing * Shortness of Breath * Throat Tightness * Cough * Hoarse Voice * Chest Pain * Chest Tightness * **ANAPHYLAXIS** Trouble Swallowing * Itchy mouth/throat * Nasal Stuffiness * Nasal/Sinus Congestion * Circulation Problems * **ASTHMA** * fatigue * **Pain when Urinating** * Brain Fog * diarrhea * Breathing Troubles * Lightheadedness/Pain when Urinating * **ANGIOEDEMA** * Stomach Troubles * **RHINITIS** * Sneezing * Congestion * Stuffiness * Wheezing * Muffled Voice * Chest Tightness * Cough * Hives * Skin swelling * Warm, Red, Swelling * Abdominal Pain/Cramps * Vomiting * Impending Danger * itchy/red/watery eyes * Uterus * Fainting * Low Blood Pressure * Shock * Dizziness * Low Pulse * Stomach Issues * Diarrhea * Nausea * Itchy/red/watery eyes *

Tryptase
Chymase
Cortisol Releasing Hormone

Mast cell

Histamine

JOD ALLERGY Low Pulse * Dizziness * Fainting * Hives * Skin swelling * Warm, Red, Swelling * Abdominal Pain/Cramps * Vomiting * Impending Danger * itchy/red/watery eyes *

JOD ALLERG Low Pulse * Dizziness * Fainting * Hives * Skin swelling * Warm, Red, Swelling * Abdominal Pain/Cramps * Vomiting * Impending Danger * itchy/red/watery eyes *

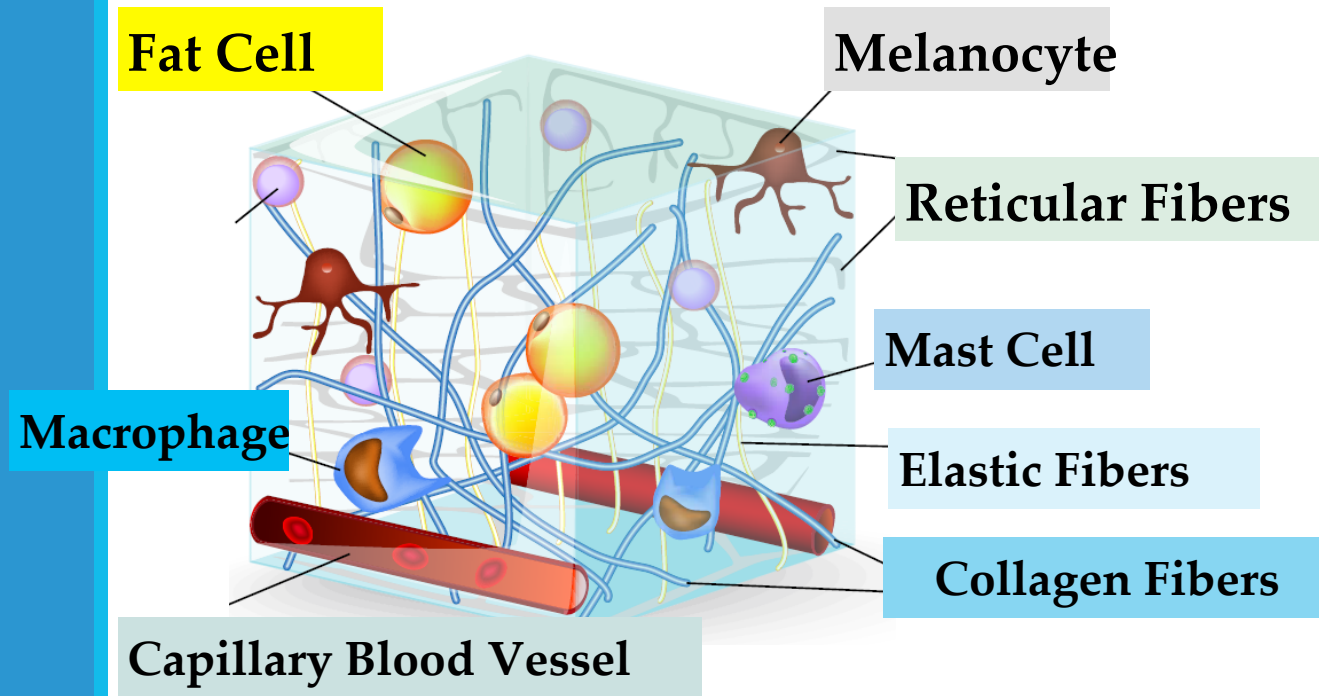
ALLERGIC * Itchy/red/watery eyes *

ALLERGIC * Itchy/red/watery eyes *

Mast Cell Derived Enzyme Mutation and EDS/JHS?

“ Our findings link findings (germline) duplication in *TPSAB1* (the alpha-tryptase gene) with

- Irritable bowel syndrome
- Cutaneous complaints
- Connective Tissue Abnormalities
- Dysautonomia



nature
genetics

Elevated basal serum tryptase identifies a multisystem disorder associated with increased *TPSAB1* copy number

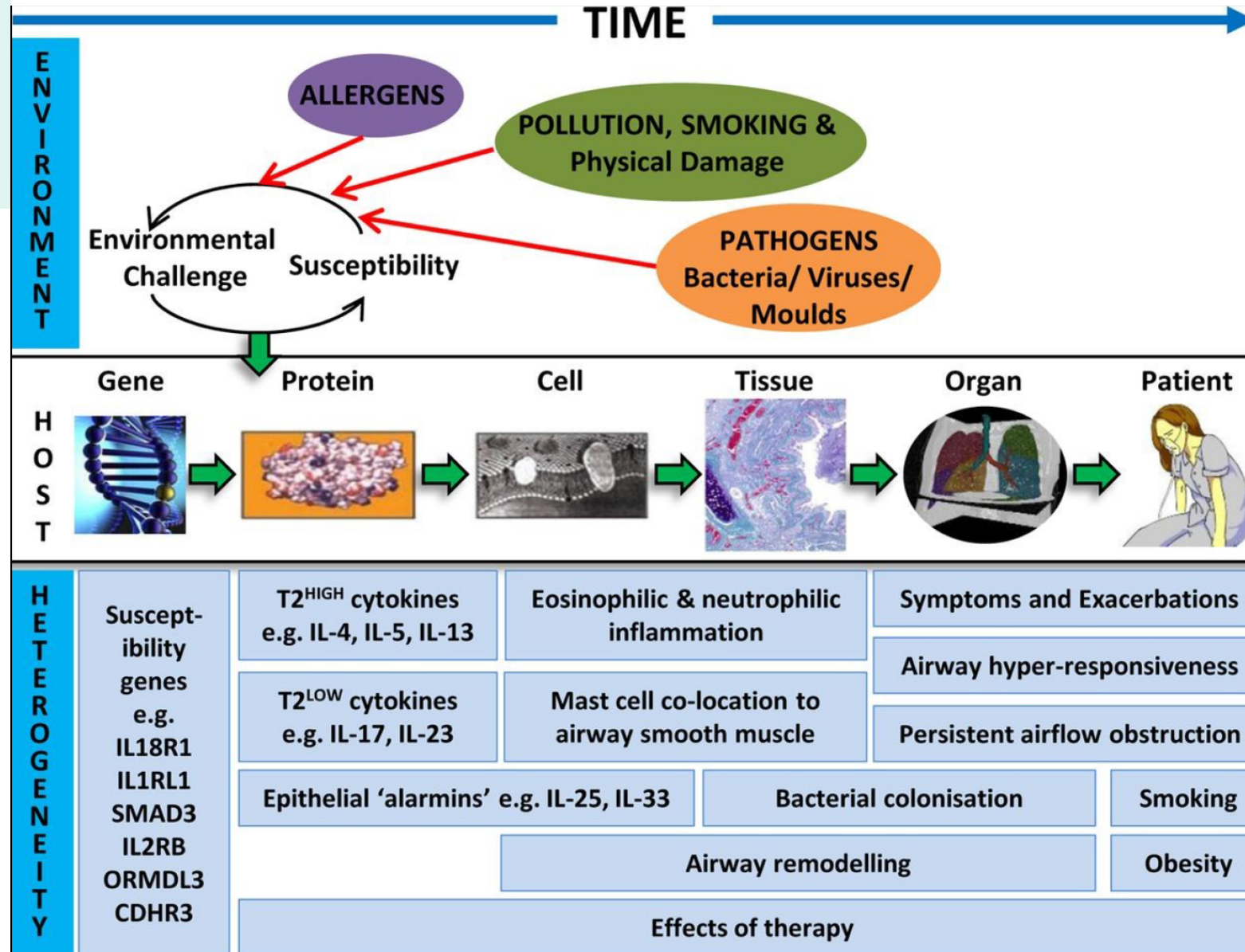
Jonathan J Lyons¹, Xiaomin Yu¹, Jason D Hughes², Quang T Le³, Ali Jamil¹, Yun Bai¹, Nancy Ho⁴, Ming Zhao⁵, Yihui Liu¹, Michael P O'Connell¹, Neil N Trivedi^{6,7}, Celeste Nelson¹, Thomas DiMaggio¹, Nina Jones⁸, Helen Matthews⁹, Katie L Lewis¹⁰, Andrew J Oler¹¹, Ryan J Carlson¹, Peter D Arkwright¹², Celine Hong¹⁰, Sherene Agama¹, Todd M Wilson¹, Sofie Tucker¹, Yu Zhang¹³, Joshua J McElwee², Maryland Pao¹⁴, Sarah C Glover¹⁵, Marc E Rothenberg¹⁶, Robert J Hohman⁵, Kelly D Stone¹, George H Caughey^{6,7}, Theo Heller⁴, Dean D Metcalfe¹, Leslie G Biesecker¹⁰, Lawrence B Schwartz³ & Joshua D Milner¹

Mast Cell Activation Syndrome (MCAS) Endotypes

An “endotype” is a subtype of a condition defined by a distinct pathophysiological mechanism.

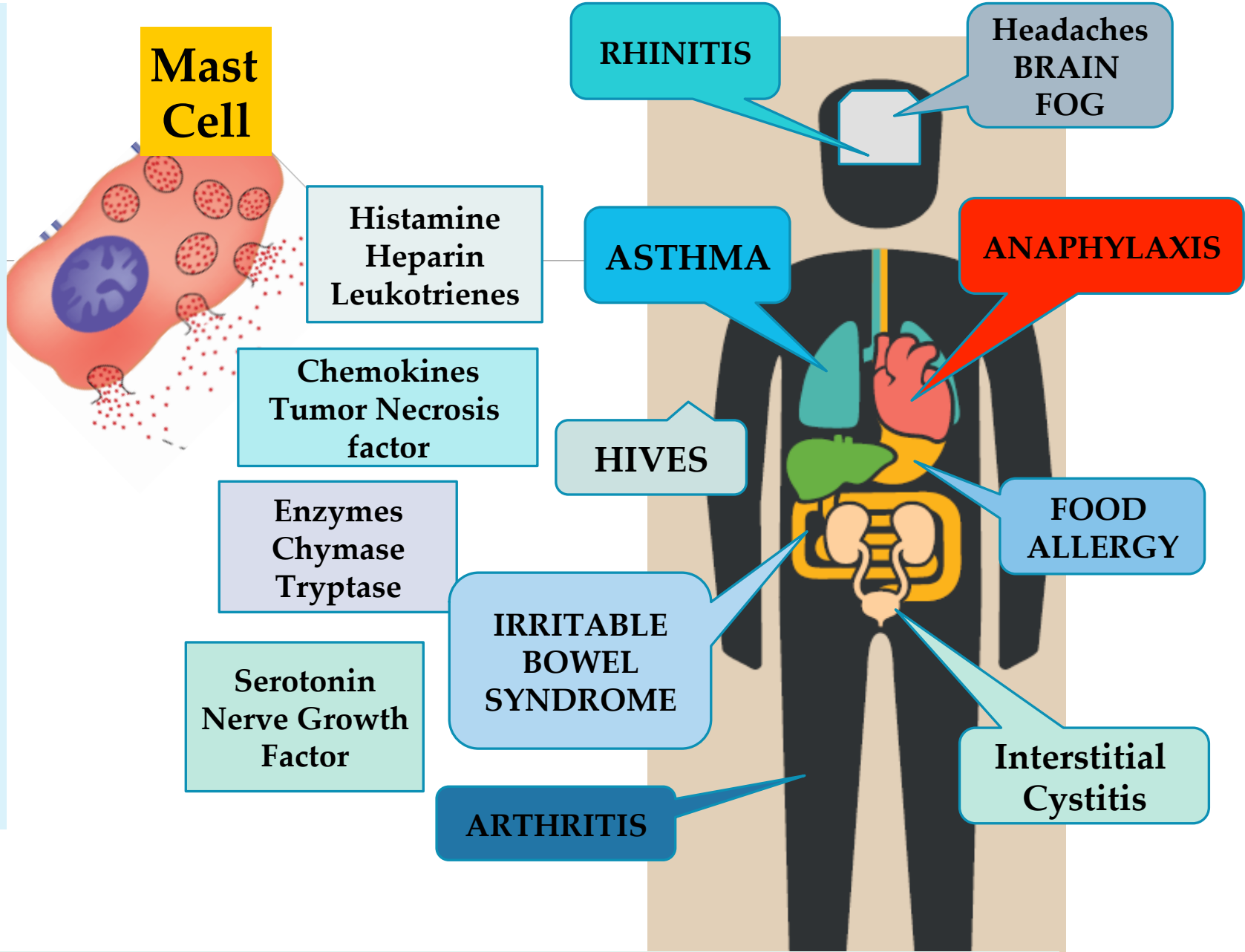
Criteria for defining MCAS endotypes on the basis of their phenotypes and putative pathophysiology.

Using these criteria will help identify MCAS endotypes, which can then be used to design and tailor existing and novel therapies to patients, that would most likely to benefit.

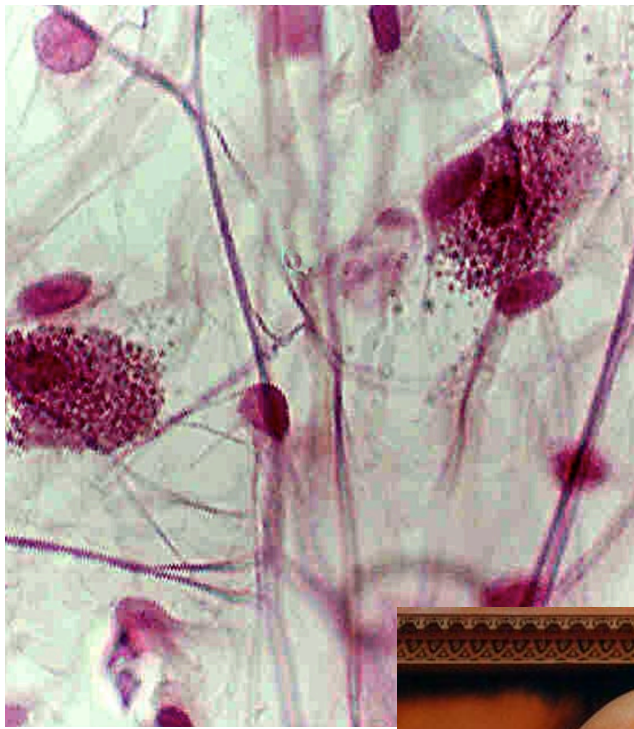


Mast cells

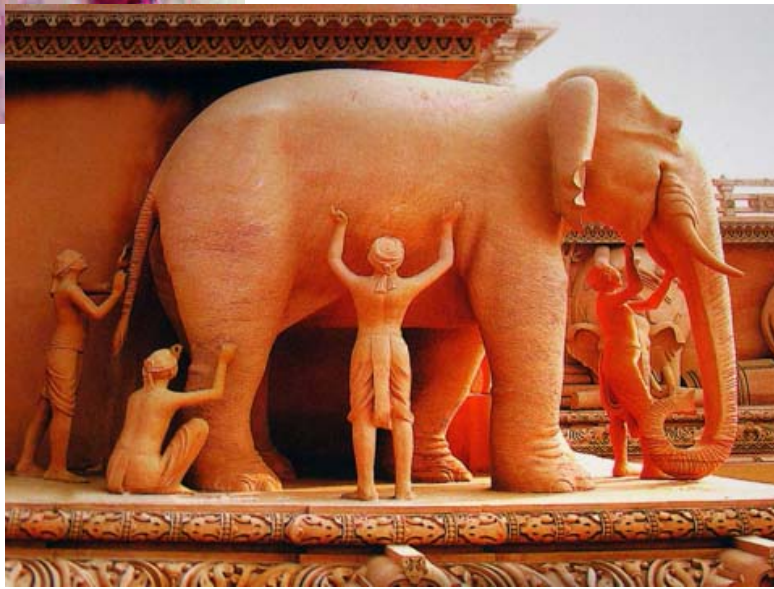
- are found in most parts of the body
- have a role in allergic/anaphylactic reactions and other inflammatory diseases in the skin, respiratory tract, joints, gastrointestinal tract, nervous system, bladder
- worsen with stress



MCAD Diagnosis: (1) Symptoms, (2) Data, (3) Response to MC medications

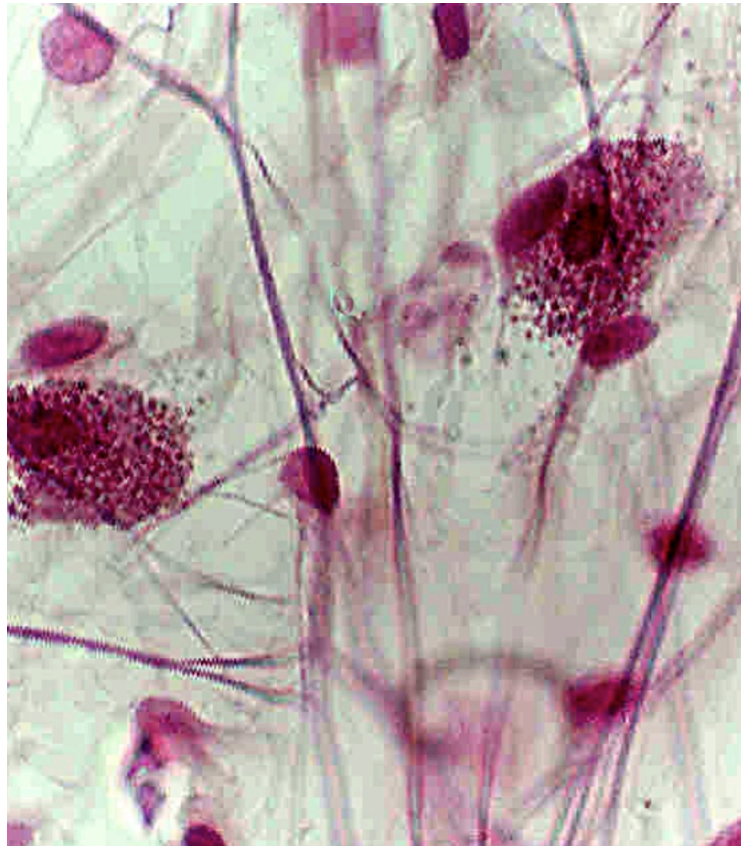


Key to MCAD treatment:
Early Diagnosis, Education
to reduce stress



You're fine, take the lollipop!

Stress Reduction & Regain Tolerance



**Mast
Cells**

I now believe that the ultimate power lies with the tissues. When healthy, tissues induce tolerance. When distressed, they stimulate immunity, and (continuing down this path) they may also determine the effector class of a response.

- Polly Matzinger, Reflections on self: Immunity and beyond. Viewpoint: The Danger Model: A Renewed Sense of Self, Science vol 296, 2002