Mast Cell Activation Disorders

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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

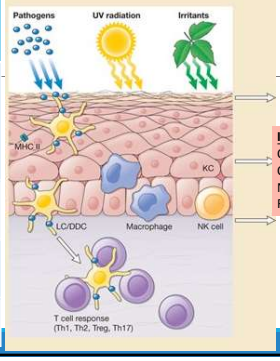
Innate Immune System Components

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

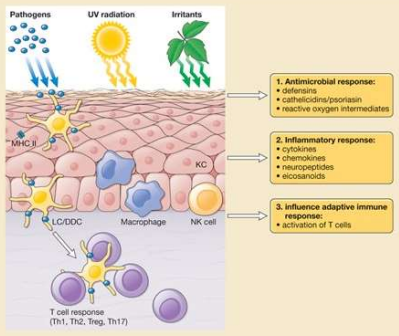


Antimicrobial response
Defensins
Cathelecidins/
Psoriasin
Reactive Oxygen Species

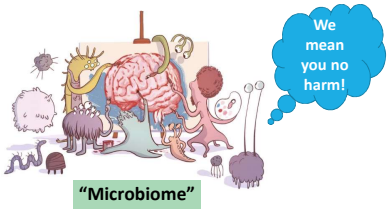
Inflammatory response
Cytokines,
Chemokines
Neuropeptides
Reactive Oxygen Species

Recruiting the adaptive Immune response
T cells, B cells

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

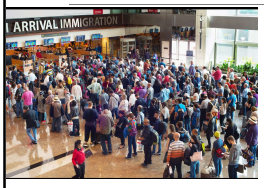


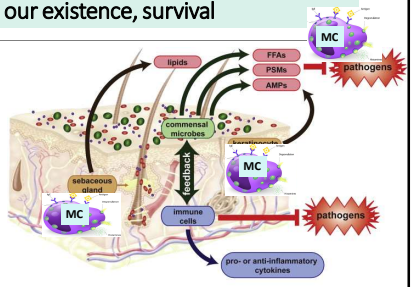
Our Immune system = defense against dangers, such as infectious agents, toxins and trauma…



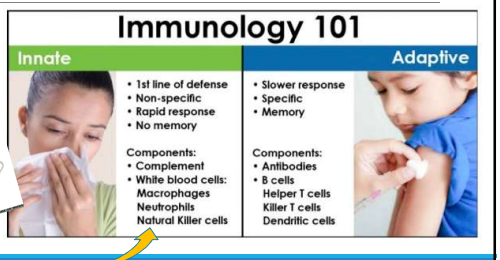
"Microbiome"

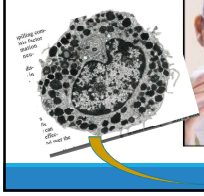
Port of Entry, "vetting" process– to allow entry to entities that support and may enhance our existence, survival





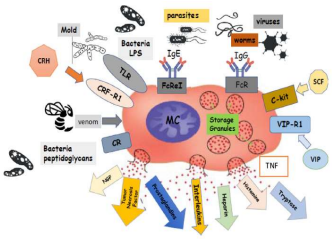
Mast Cells: Beyond Allergy?





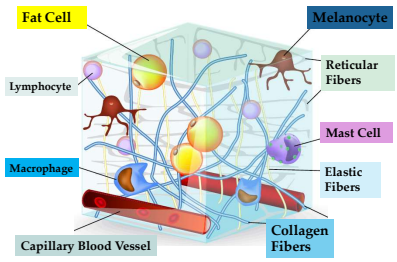
Mast Cell Orders

MAST CELL BIOLOGY 101



Mast Cell Orders:

Surveillance. Protection. Coordinate Response and Repair.



POLICE
PROTECT AND SERVE

NEIGHBOURHOOD WATCH

CERT
COMMUNITY EMERGENCY RESPONSE TEAM

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.

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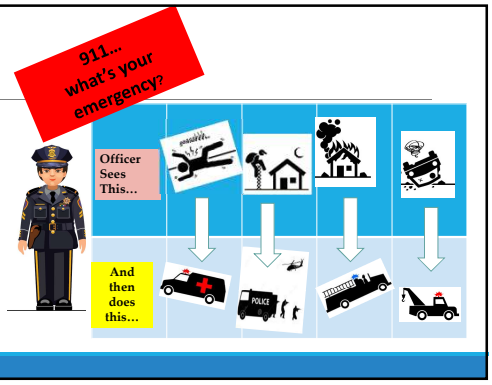
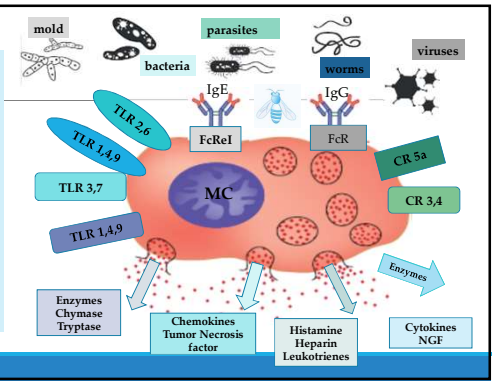
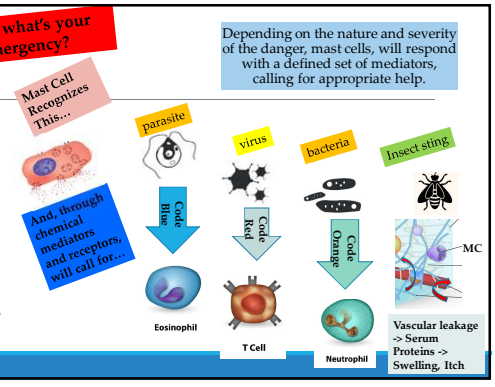


Armed with invariant sensors, Mast Cells are hardwired to recognize and then react with a defined set of chemical and physical responses, in order to contain "usual suspects", pathogens and harmful substances.

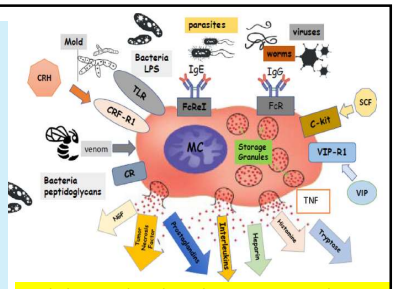


Mast Cells act as the local Peace Keepers, maintaining homeostasis in the surrounding microenvironment.



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**

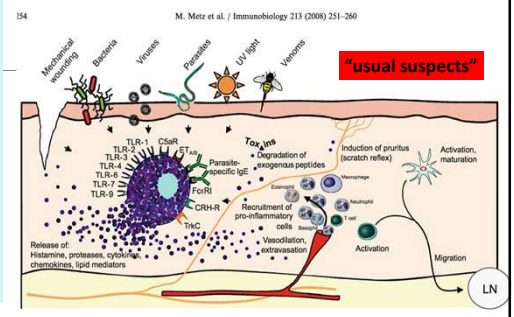


arachidonic acid products, biogenic amines, chemo-attractants, cytokines, growth factors, neuropeptides, proteoglycans, and proteolytic enzymes

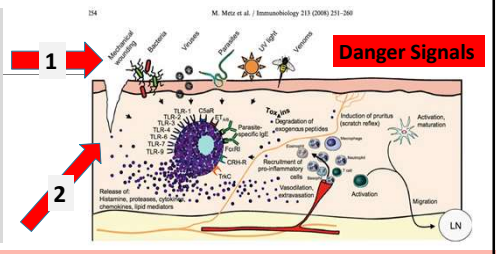
Theoharides, & Bielory, Annals Allergy, Asthma & Immunology, 2003

Mast Cells=

Border Patrol, recognizing and responding to clear and present dangers



(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

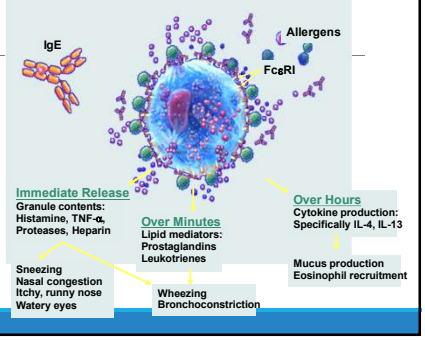


(2) Endogenous, self alarm signals, indicating danger:
breakdown products of hyaluron (made when vessels are damaged).
mammalian DNA, RNA, heat shock proteins (Hsps), interferon a, (an inducible protein often made by virus-infected cells), interleukin-1beta, CD40-L (a surface molecule on activated platelets and activated T cells), and

Dark Side of Mast Cell Activation

Mast Cells are best known for "Allergies"

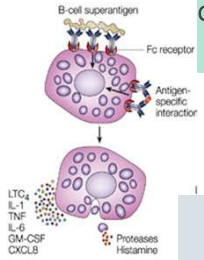
Allergen-IGE-IgE Receptor Mast Cell Activation



IG- IG Receptor on MCs

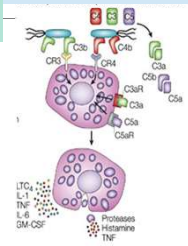
CMC Activation after Complement or IGG bound pathogens,

Complement Coated Pathogen- C' Receptor on MCs



MC release
- Tryptase (proteases)
- Histamine

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



Nature Reviews | Immunology

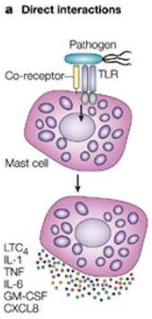
Mast Cell responses to pathogens. Jean Marshall, Nature Reviews Immunology, 2004(4): 787-799

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

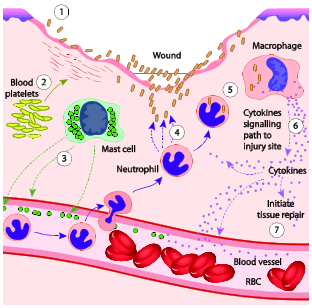


Mast Cell responses to pathogens. Jean Marshall Nature Reviews Immunology, 2004 (4): 787-799

Mast Cells as "Local Peace Keepers"

Mast Cells:

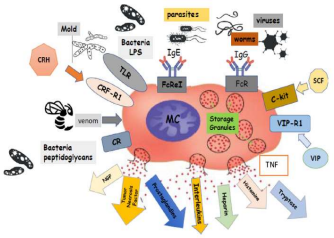
Defense and tissue repair



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

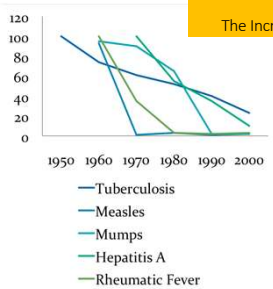
Mast Cell Disorders

MAST CELL ACTIVATION DISORDERS 101



Golden age of medicine = Age of immune dysregulation?

The Increased Burden of Autoimmune and Allergic Disorders



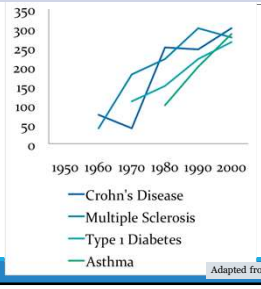
The middle of the 20th century has often been described as a golden age of medicine: scientific advancement and miraculous medical breakthroughs:

- 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

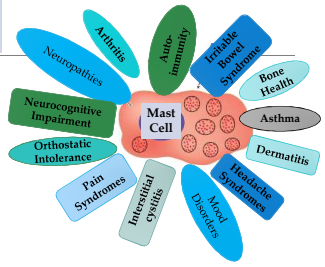
Adapted from Bach, NEJM 2002

"Searching for a Golden Age" University of Pennsylvania

Epidemic of Hypersensitivity Disorders: Role of Mast Cell Dysregulation?

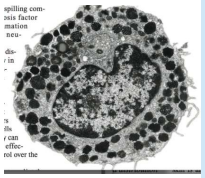


Adapted from Bach, New Eng J Med 2002

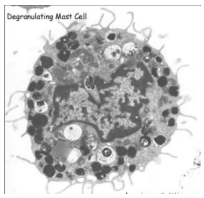


Adapted from Theoharides, NEJM 2015

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 of 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*

Mast Cell Activation Disorder: Signs and Symptoms

MASTOCYTOSIS

(ESCRIBANO ET AL, JACI 124:514)

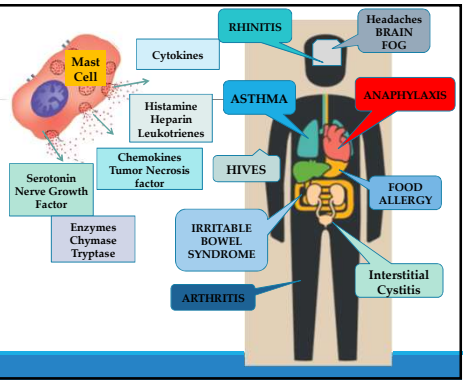
Skin Lesions	90%
Pruritis	82%
Flushing	56%
Diarrhea	35%
Abdominal Cramping	30%
Neuropsychiatric Symptoms	**23%**
Anaphylaxis	23%
Peptic Symptoms	20%
Osteoporosis	18%
Hepatomegaly	12%
Splenomegaly	8%

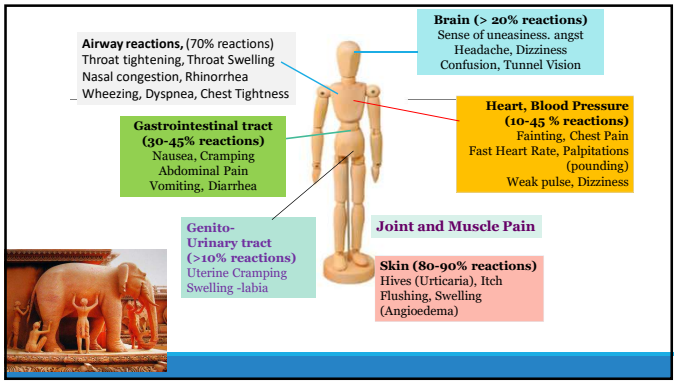
Abdominal Pain	94%
Dermatographism	89%
Flushing	89%
Headache	83%
Neuropsychiatric	**67%**
Diarrhea	67%
Rhinitis (Naso-ocular)	39%
Asthma	39%
Anaphylaxis	17%

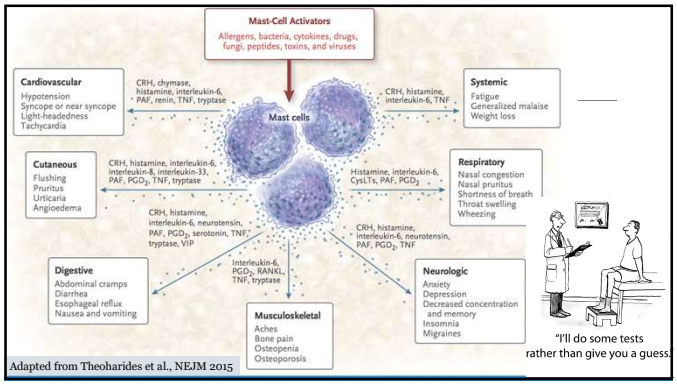
NONCLONAL MAST CELL ACTIVATION DISORDERS

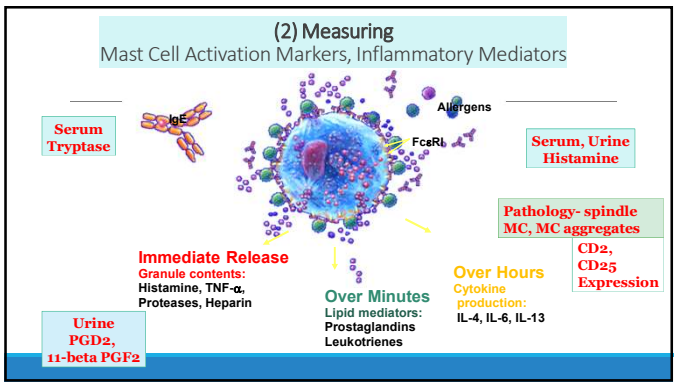
HAMILTON, J ALLERGY CLIN IMMUNOL 128;147

- **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**

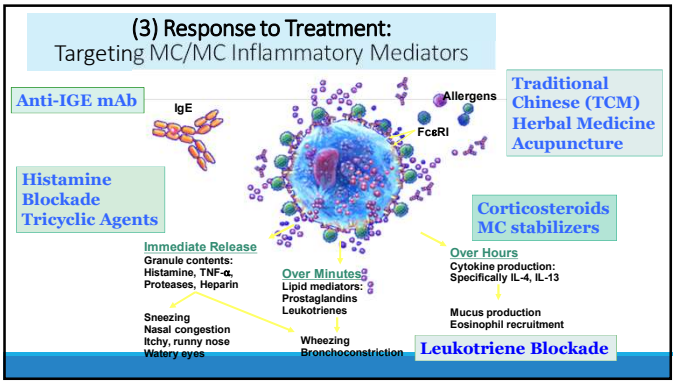



Airway reactions, (70% reactions)
Throat tightening, Throat Swelling
Nasal congestion, Rhinorrhea
Wheezing, Dyspnea, Chest Tightness
Brain (> 20% reactions)
Sense of uneasiness. angst
Headache, Dizziness
Confusion, Tunnel Vision
Heart, Blood Pressure
(10-45 % reactions)
Fainting, Chest Pain
Fast Heart Rate, Palpitations
(pounding)
Weak pulse, Dizziness
Gastrointestinal tract
(30-45% reactions)
Nausea, Cramping
Abdominal Pain
Vomiting, Diarrhea
Genito-
Urinary tract
(>10% reactions)
Uterine Cramping
Swelling -labia
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
Mast cells
Cardiovascular
Hypotension
Syncope or near syncope
Light-headedness
Tachycardia
CRH, chymase, histamine, interleukin-6, PAF, renin, TNF, tryptase
Systemic
Fatigue
Generalized malaise
Weight loss
CRH, histamine, interleukin-6, TNF
Cutaneous
Flushing
Pruritus
Urticaria
Angioedema
CRH, histamine, interleukin-6, interleukin-8, interleukin-33, PAF, PGD2, TNF, tryptase
Respiratory
Nasal congestion
Nasal pruritus
Shortness of breath
Throat swelling
Wheezing
Histamine, interleukin-6, CysLTs, PAF, PGD2
CRH, histamine, interleukin-6, neurotensin, PAF, PGD2, serotonin, TNF, tryptase, VIP
CRH, histamine, interleukin-6, neurotensin, PAF, PGD2, TNF
Digestive
Abdominal cramps
Diarrhea
Esophageal reflux
Nausea and vomiting
Interleukin-6, PGD2, RANKL, TNF, tryptase
Neurologic
Anxiety
Depression
Decreased concentration and memory
Insomnia
Migraines
Musculoskeletal
Aches
Bone pain
Osteopenia
Osteoporosis
"I'll do some tests rather than give you a guess."
Adapted from Theoharides et al., NEJM 2015


(2) Measuring
Mast Cell Activation Markers, Inflammatory Mediators
Serum Tryptase
IgE
Allergens
FcεRI
Serum, Urine Histamine
Pathology- spindle MC, MC aggregates
CD2, CD25 Expression
Immediate Release
Granule contents:
Histamine, TNF-α, Proteases, Heparin
Over Minutes
Lipid mediators:
Prostaglandins
Leukotrienes
Over Hours
Cytokine production:
IL-4, IL-6, IL-13
Urine PGD2, 11-beta PGF2

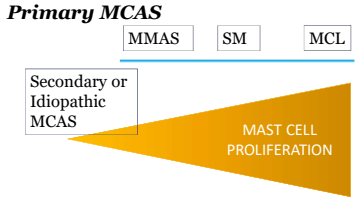
(3) Response to Treatment: Targeting MC/MC Inflammatory Mediators



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

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

adapted from Akin et al, JACI

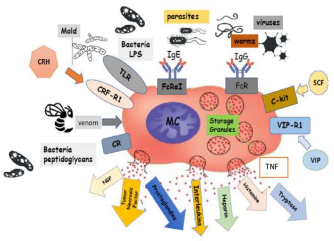


**Decreased likelihood MMAS, SM or MCL by bone marrow MC aggregates diminishes significantly in those with tryptase < 20 ng/mL

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) ▪ Hyper-tryptasemia (tryptase mutation-autosomal dominant)
Idiopathic	A. Anaphylaxis B. Angioedema C. Urticaria

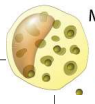
Mast Cell Disorders

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.jrheum.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

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.

HOMIK , J Rheumatol 2011;38;1225-1227

Mast Cell Activation Disorders Guidelines to Diagnosis and Treatment

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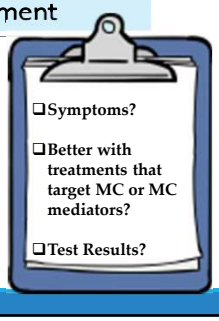
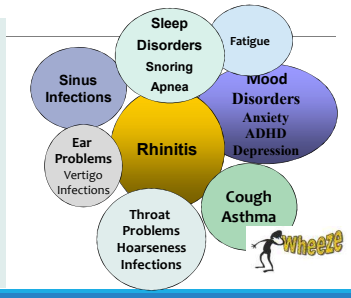


Common MC -Mediated Disorder: Rhinitis

- 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



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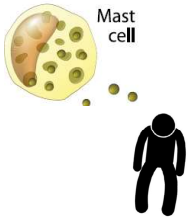


MCAD/MCAS Treatment: Targeting MCs or MC derived Inflammatory Mediators

Corticosteroids
MC stabilizers
Cytokine Antagonists

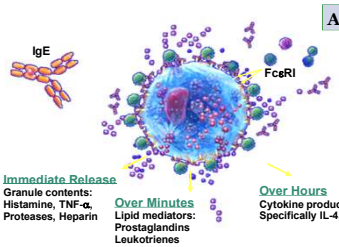
Anti-IGE mAb

Histamine Blockade
Tricyclic Agents

Leukotriene Blockade
Cyclooxygenase Inhibitors

Nutraceuticals
DAO supplement
Vitamin C
Quercetin
Stinging Nettle
Butterbur

Traditional Chinese (TCM)
Herbal Medicine
Acupuncture



Theoharides et al, NEJM 2015; Engler et al, J Allergy Clin Immunol,2009;

NEWS

Mast Cells Show Their Might

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

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 neutralize 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 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 Yukihiko Kitamura of Osaka University Medical School in Japan and colleagues determined that the genetic defect responsible for the color change also short-circuits mast-cell development. Led by Kitamura and pathologist Stephen Galli of Stanford University in Palo Alto, California,

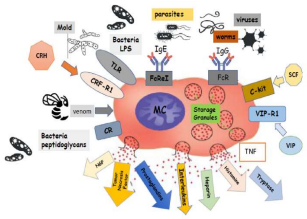
Standing guard. Mast cells from the umbilical cord.

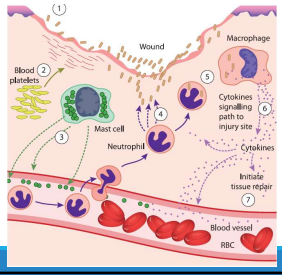
Published by AAAS

hey are the most reviled cells in the body. Their meddling makes our skin itch, our eyes swell, and our noses stream; the ce
That could be a big mistake.

COMMUNITY EMERGENCY RESPONSE TEAM

Mast Cells: Defense and Wound Repair





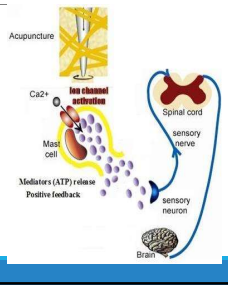
Acupuncture & MCAS treatment:

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



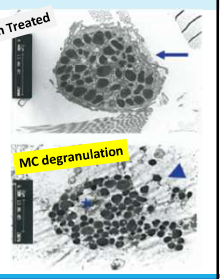
Acupuncture & MCAS treatment: Role of mast cells in acupuncture effect: a pilot study

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.



Better Health = Mast Cell suppression ???

MCAD/MCAS Treatment:
Targeting MCs or
MC derived Inflammatory Mediators

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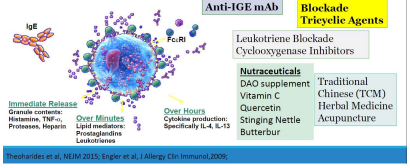
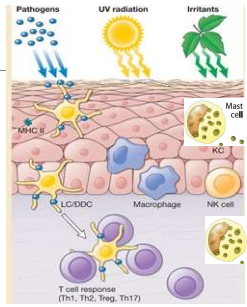


Theoharides et al, NEJM 2015; Engler et al, J Allergy Clin Immunol.2009;

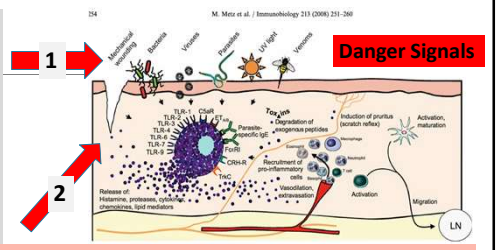
Treatment of Hypersensitivity Disorders

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



(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



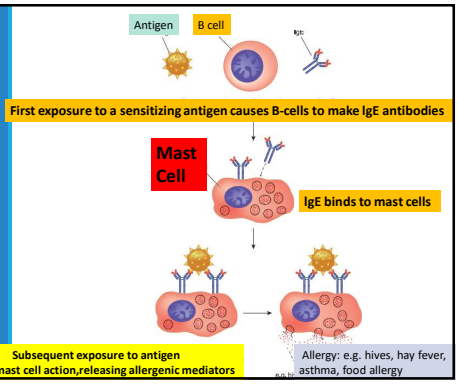
(2) Endogenous, self alarm signals, indicating danger:
breakdown products of hyaluron (made when vessels are damaged).
mammalian DNA, RNA, heat shock proteins (Hsps), interferon a, (an inducible protein often made by virus-infected cells), interleukin-1beta, CD40-L (a surface molecule on activated platelets and activated T cells), and

Primary (c-kit mutation)	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) ▪ **Hyper-tryptasemia (tryptase mutation-autosomal dominant)**
Idiopathic	A. Anaphylaxis B. Angioedema C. Urticaria

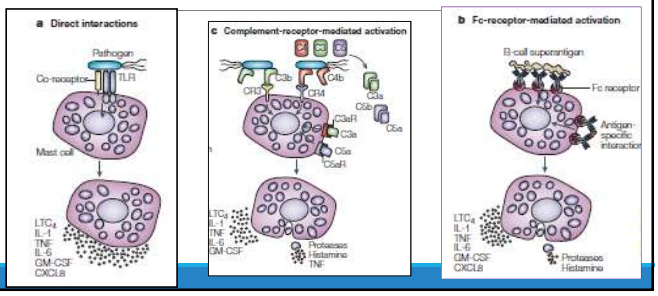
Mast Cell Activation Syndrome (MCAS) Endotypes: from Clinical Phenotypes to Molecular Approaches

Allergic Reactions

Allergen-IGE-IGE receptor tirggered Mast Cell Activation



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

Clinical Allergy, 1977, Volume 7, page 203

Letter to the Editor

Atopy in Connective Tissue Disorders

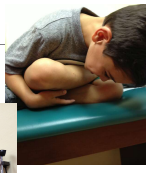
An early observation of a possible relationship between connective tissue and mast cells

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.



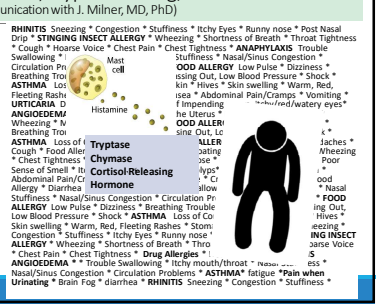
One Gene Mutation Links Three Mysterious, Debilitating Diseases:

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."

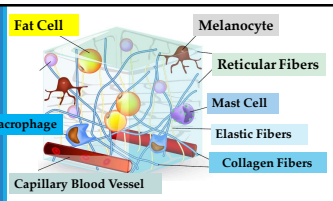
-Kate Horowitz, Mental Floss, October 2016



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

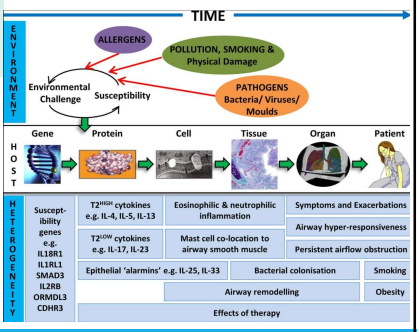
Jonathan J Lyons[1], Xiaomin Yu[1], Jason D Hughes[2], Quang T Le[3], Ali Jamil[1], Yun Bai[1], Nancy Ho[4], Ming Zhao[5], Yihui Liu[1], Michael P O'Connell[1], Neil N Trivedi[6,7], Celeste Nelson[1], Thomas DiMaggio[1], Nina Jones[8], Helen Matthews[9], Katie L Lewis[10], Andrew J Oler[11], Ryan J Carlson[1], Peter D Arkwright[12], Celine Hong[10], Sherene Agama[1], Todd M Wilson[1], Sofie Tucker[1], Yu Zhang[13], Joshua J McElwee[2], Maryland Pao[14], Sarah C Glover[15], Marc E Rothenberg[16], Robert J Hohman[5], Kelly D Stone[1], George H Caughey[6,7], Theo Heller[4], Dean D Metcalfe[1], Leslie G Biesecker[10], Lawrence B Schwartz[5] & Joshua D Milner[1]

Mast Cell Activation Syndrome (MCAS) Endotypes

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

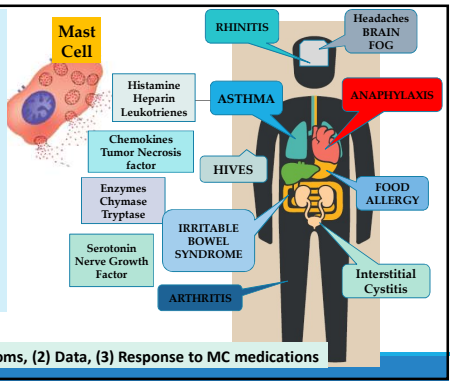
Criteria for defining MCAS endotypes on the basis of their phenotypes and putative pathophysiology.

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.

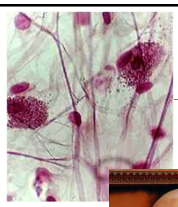


Mast cells

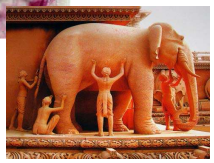
- are found in most parts of the body
- have a role in allergic/anaphylactic reactions and other inflammatory diseases in the skin, respiratory tract, joints, gastrointestinal tract, nervous system, bladder
- **worsen with stress**



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



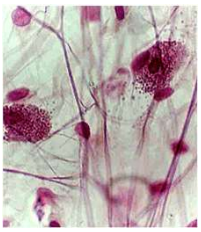
Key to MCAD treatment: Early Diagnosis, Education to reduce stress



You're fine, take the lollioP!

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