

Mast Cell Activation (MCA) and Mast Cell Activation Disease (MCAD)

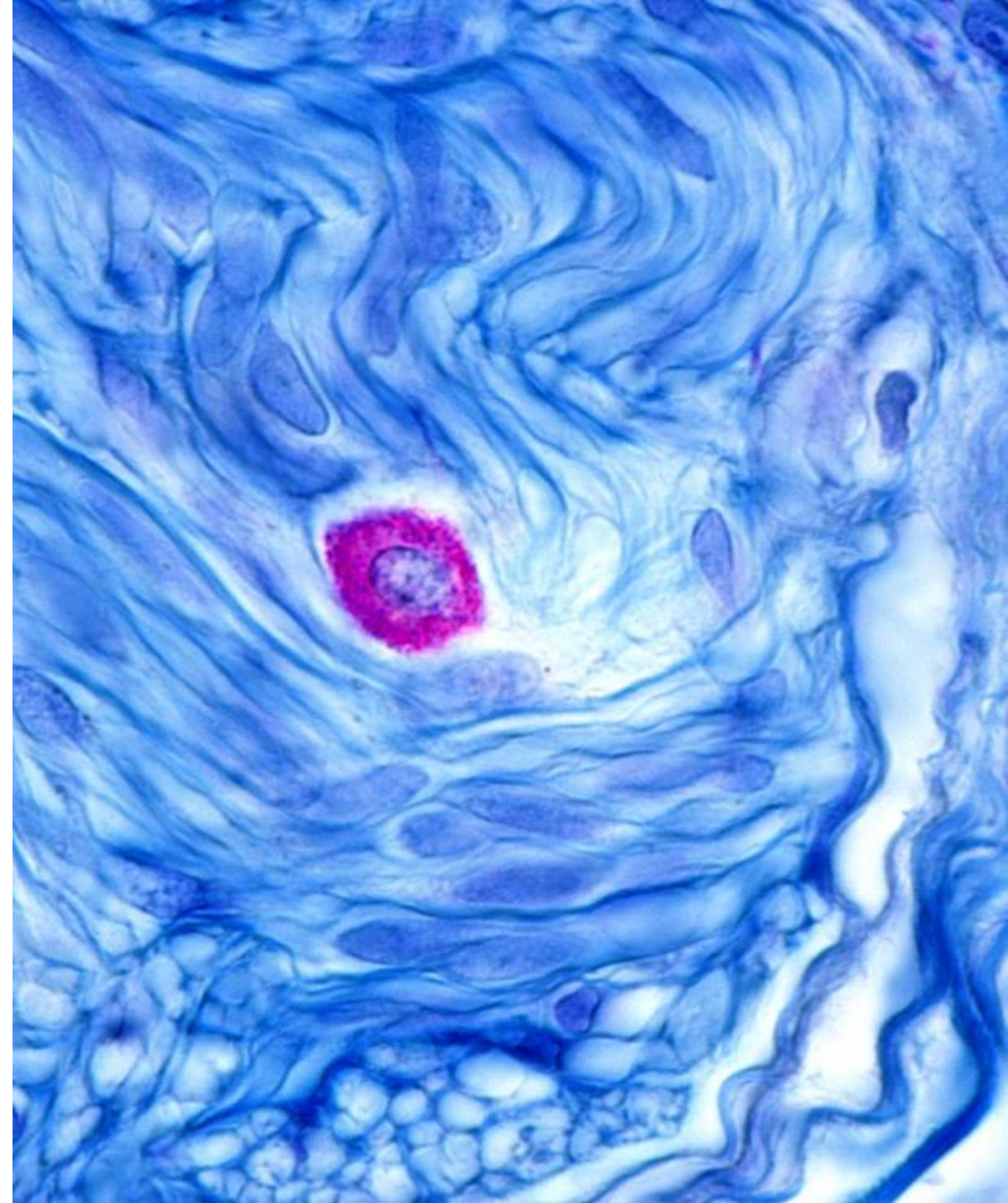
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MEDICINE, DEPARTMENT OF MEDICINE

DIVISION OF ALLERGY & IMMUNOLOGY

ATTENDING PHYSICIAN, CHIARI/EDS CENTER
AT MT SINAI-SOUTH NASSAU

CONSULTING PHYSICIAN, CLINICAL
PARADIGMS COMPREHENSIVE ALLERGY &
ASTHMA CARE



Disclosures

Blueprint Medicines, Speaker
Ehlers Danlos Research Foundation, Grant

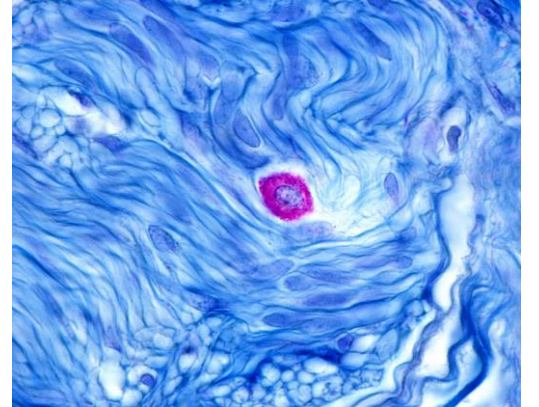


Journal of **Innate
Immunity**

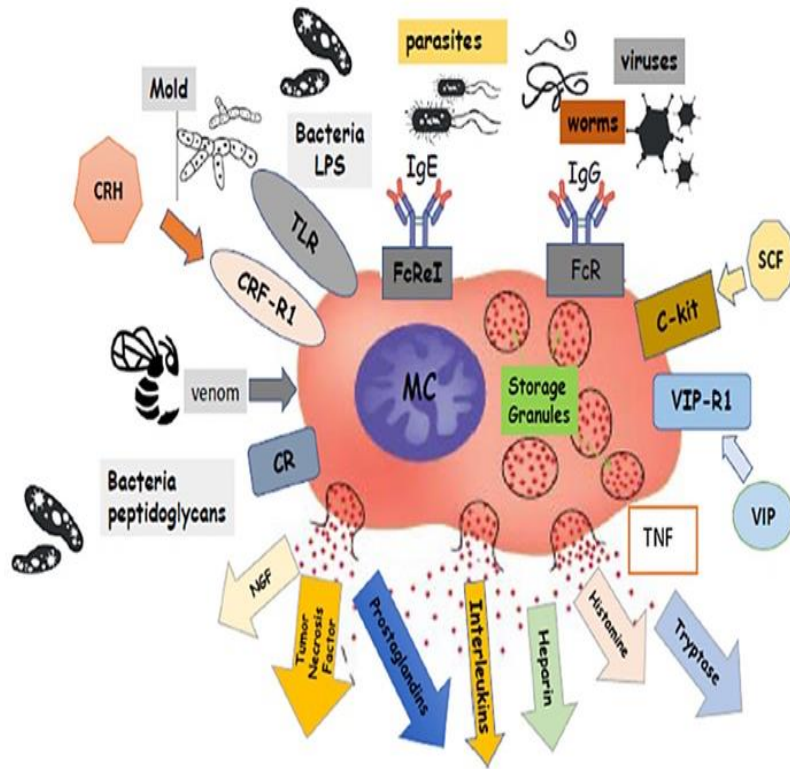
J Innate Immun 2016;8:111–120
DOI: 10.1159/000443526

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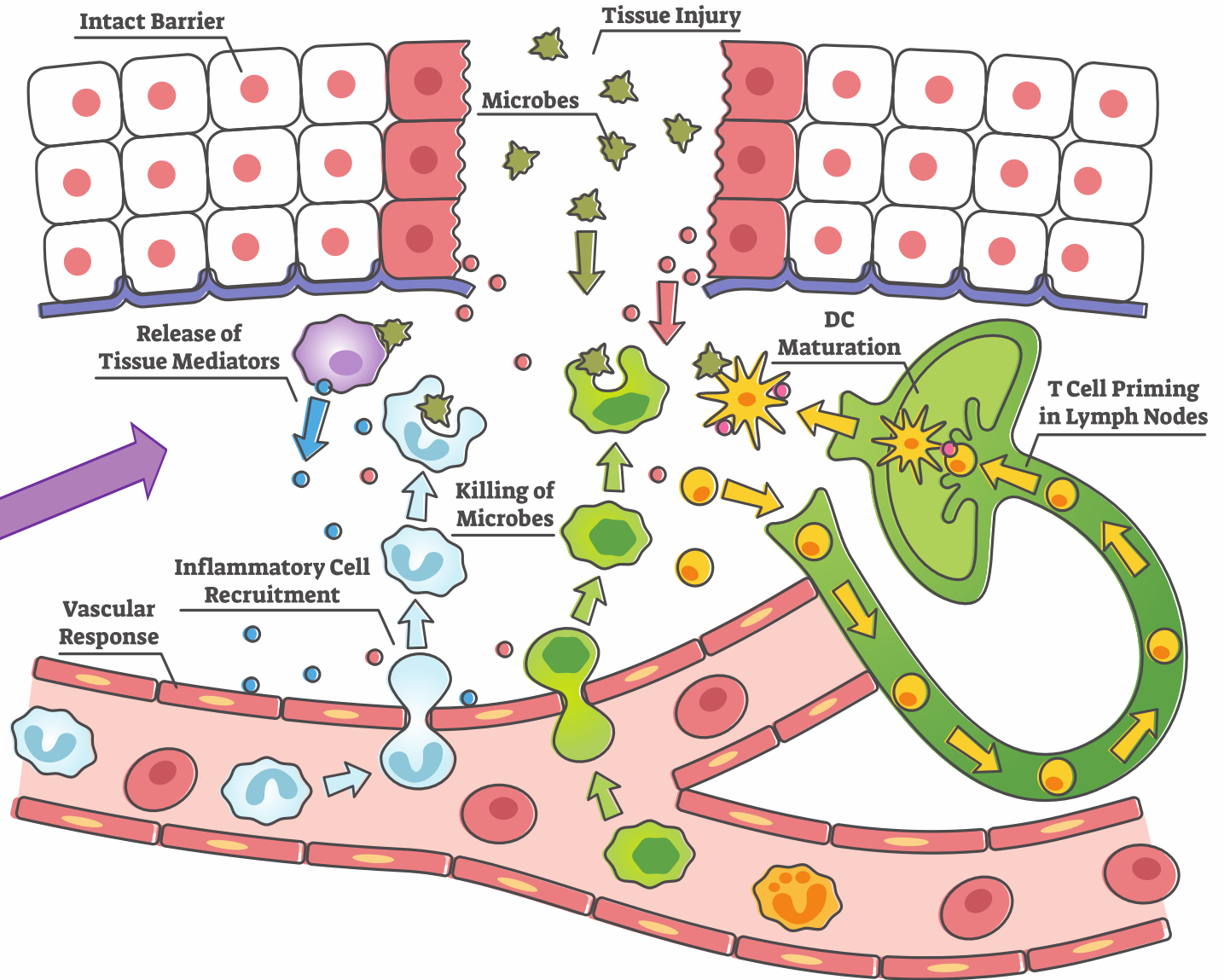
**Paul Ehrlich (1854–1915) and His
Contributions to the Foundation and
Birth of Translational Medicine**



Inflammation, Mast Cell Activation and Our Health



INJURY INFLAMMATION





January 12, 1989

Scientists Find How Allergic Reaction Works

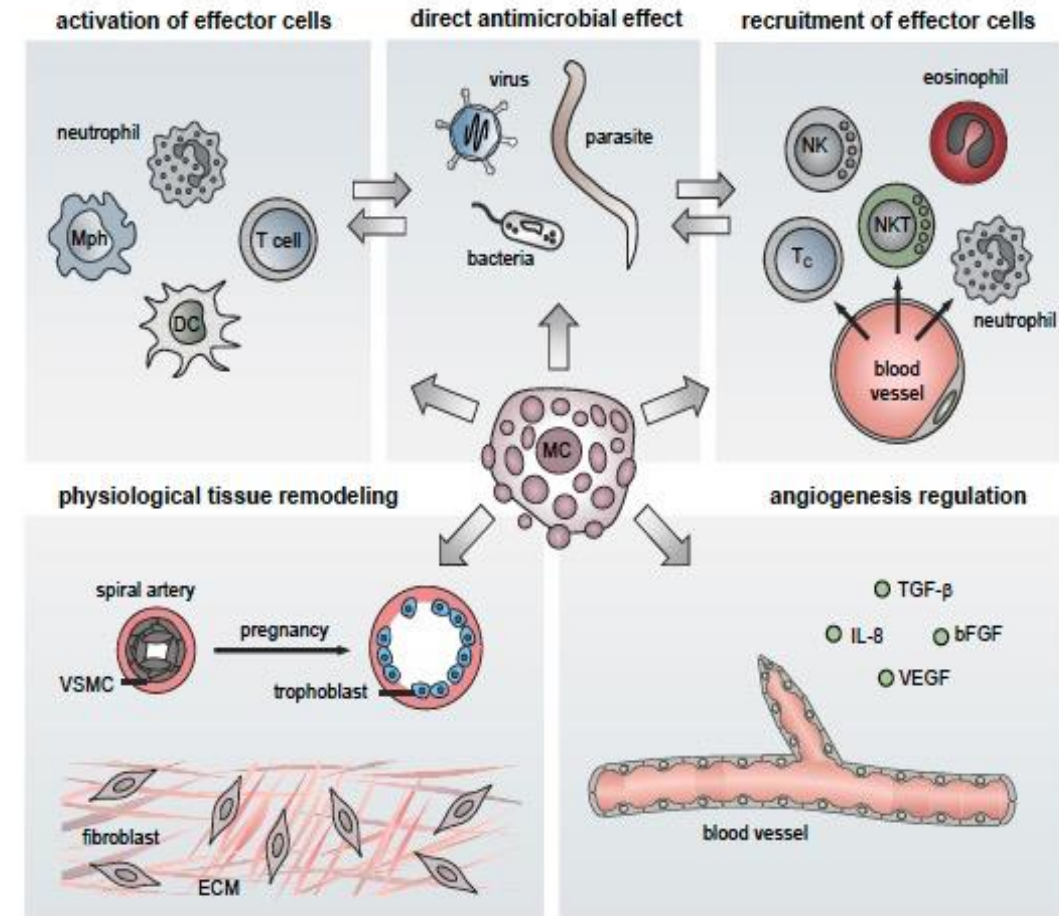
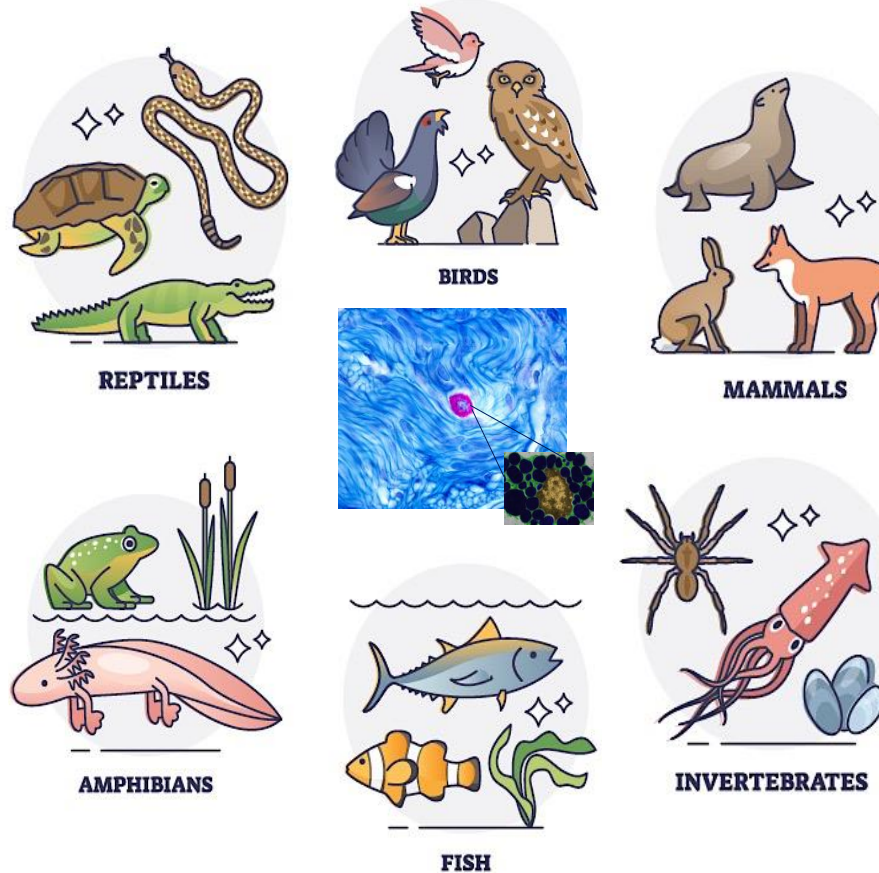
By HAROLD M. SCHMECK Jr.

The New York Times



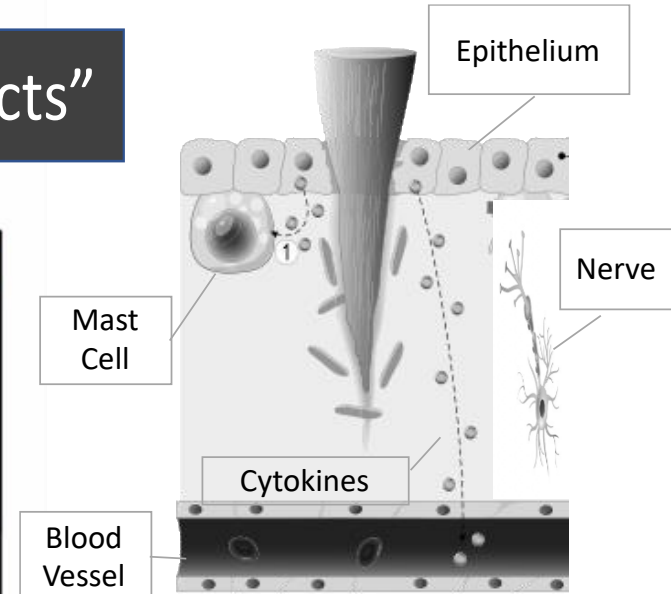
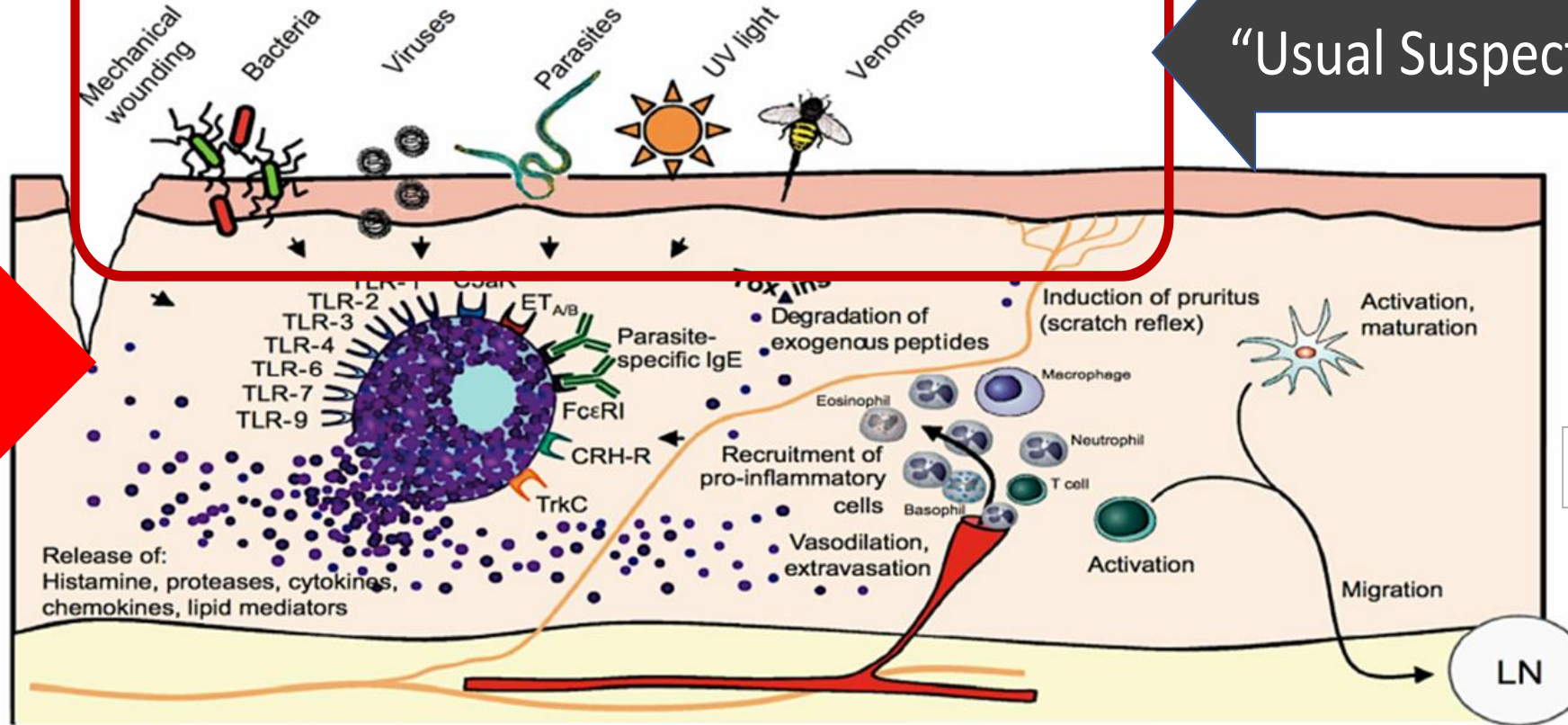
Mast Cells Show Their Might:

Once dismissed as “allergy cells”, mast cells have proven crucial for immunity. Science 317 (3), 2007



DANGER
ZONAL

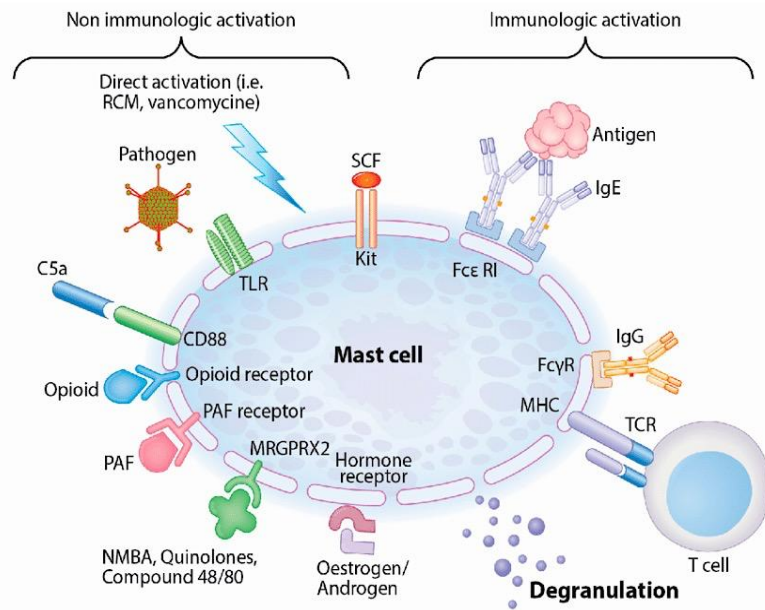
“Usual Suspects”



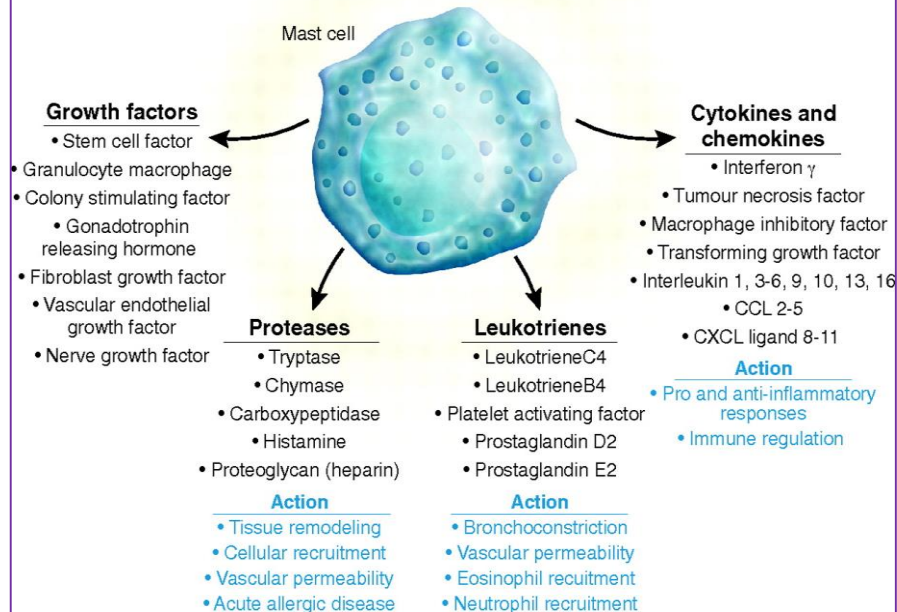
The Triad

Border Patrol = Tissue Surveillance, Defense, Repair
the triad, connective tissues and associated mast cells + nerves

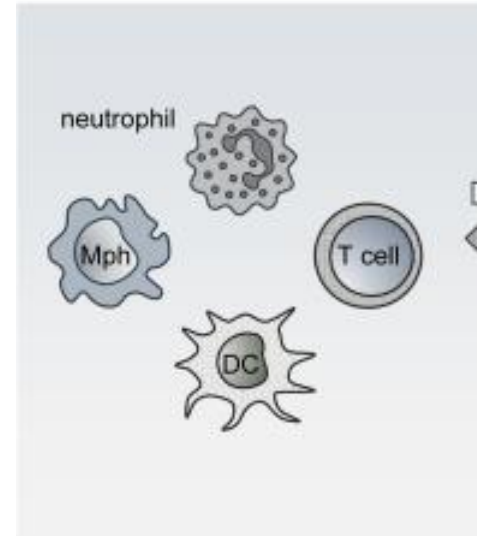
Mast Cells: Our Health Surveillance. Response. Repair.



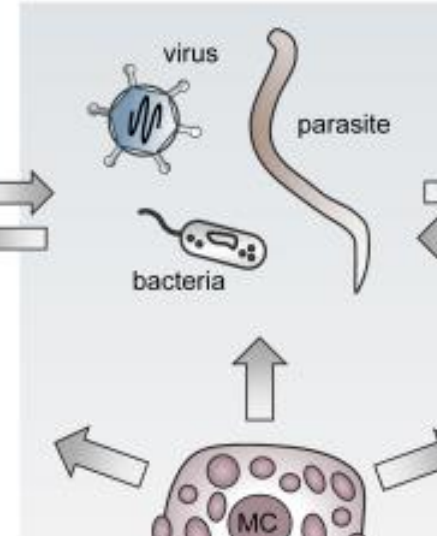
MEDIATOR RELEASE AND PHYSIOLOGICAL REACTIONS OF MAST CELL DEGRANULATION



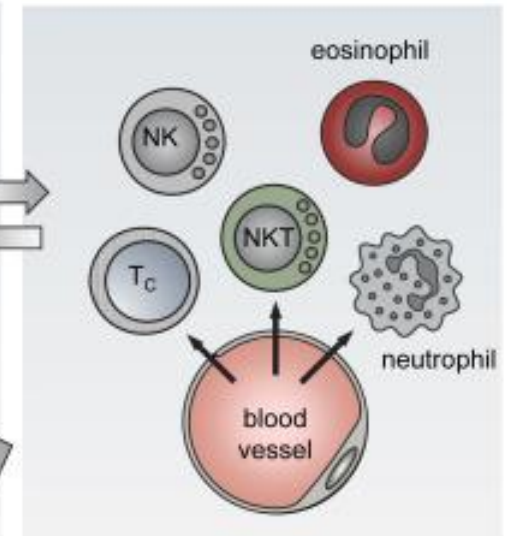
activation of effector cells



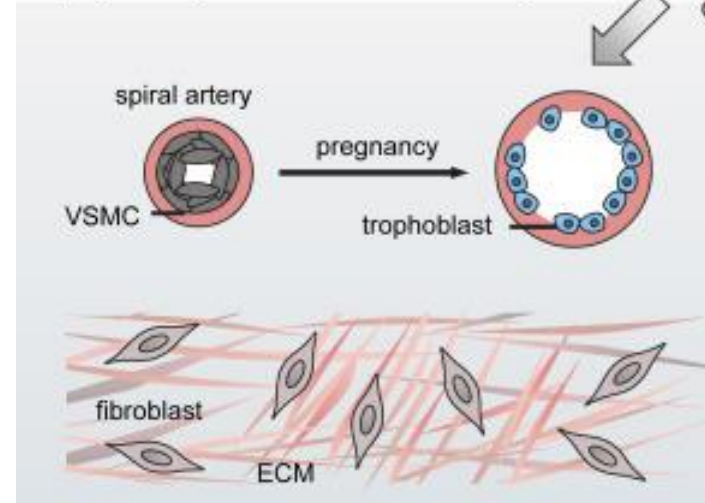
direct antimicrobial effect



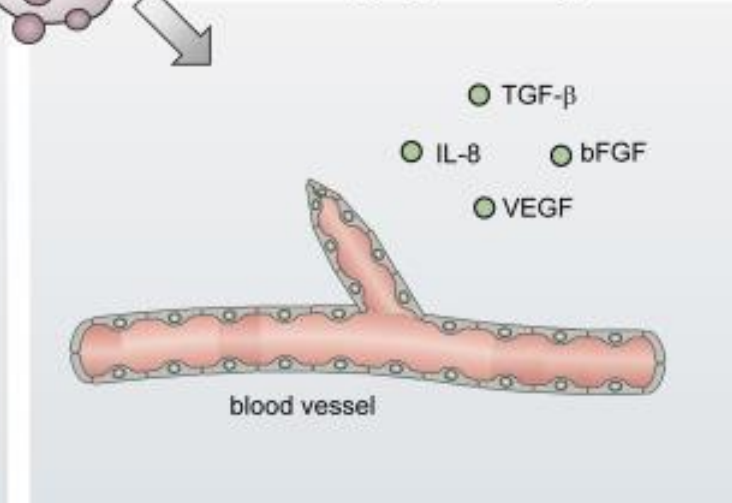
recruitment of effector cells



physiological tissue remodeling



angiogenesis regulation



Mast Cell Activation (MCA) in Disease: MCs Breakin' Bad

The New England Journal of Medicine

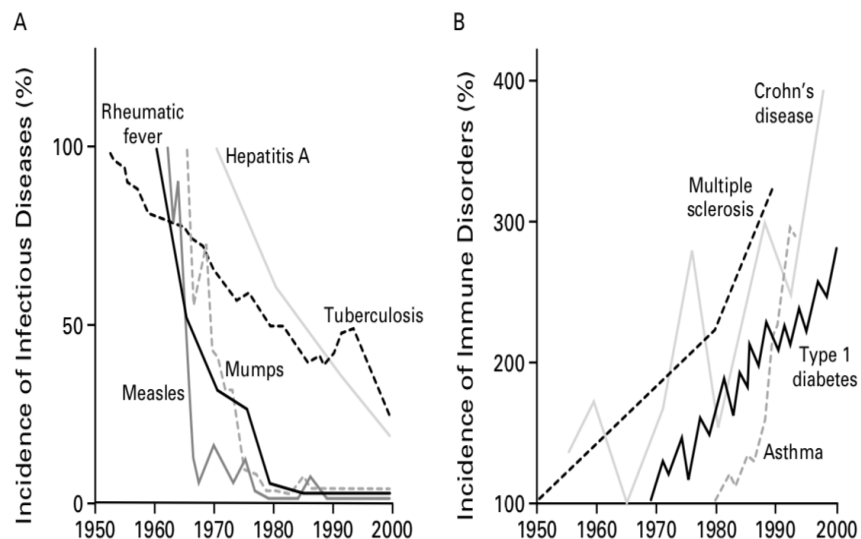


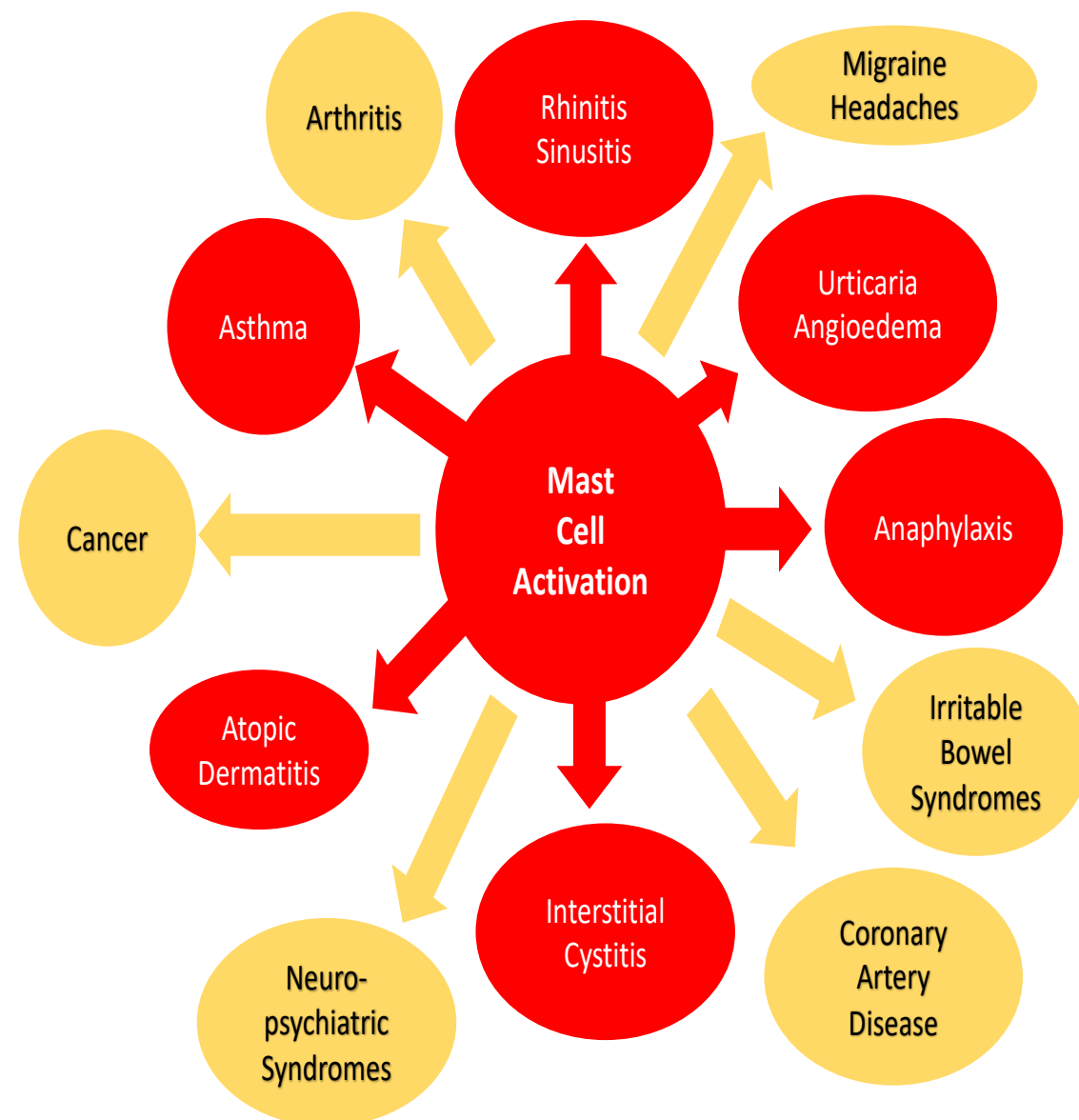
Figure 1. Inverse Relation between the Incidence of Prototypical Infectious Diseases (Panel A) and the Incidence of Immune Disorders (Panel B) from 1950 to 2000.



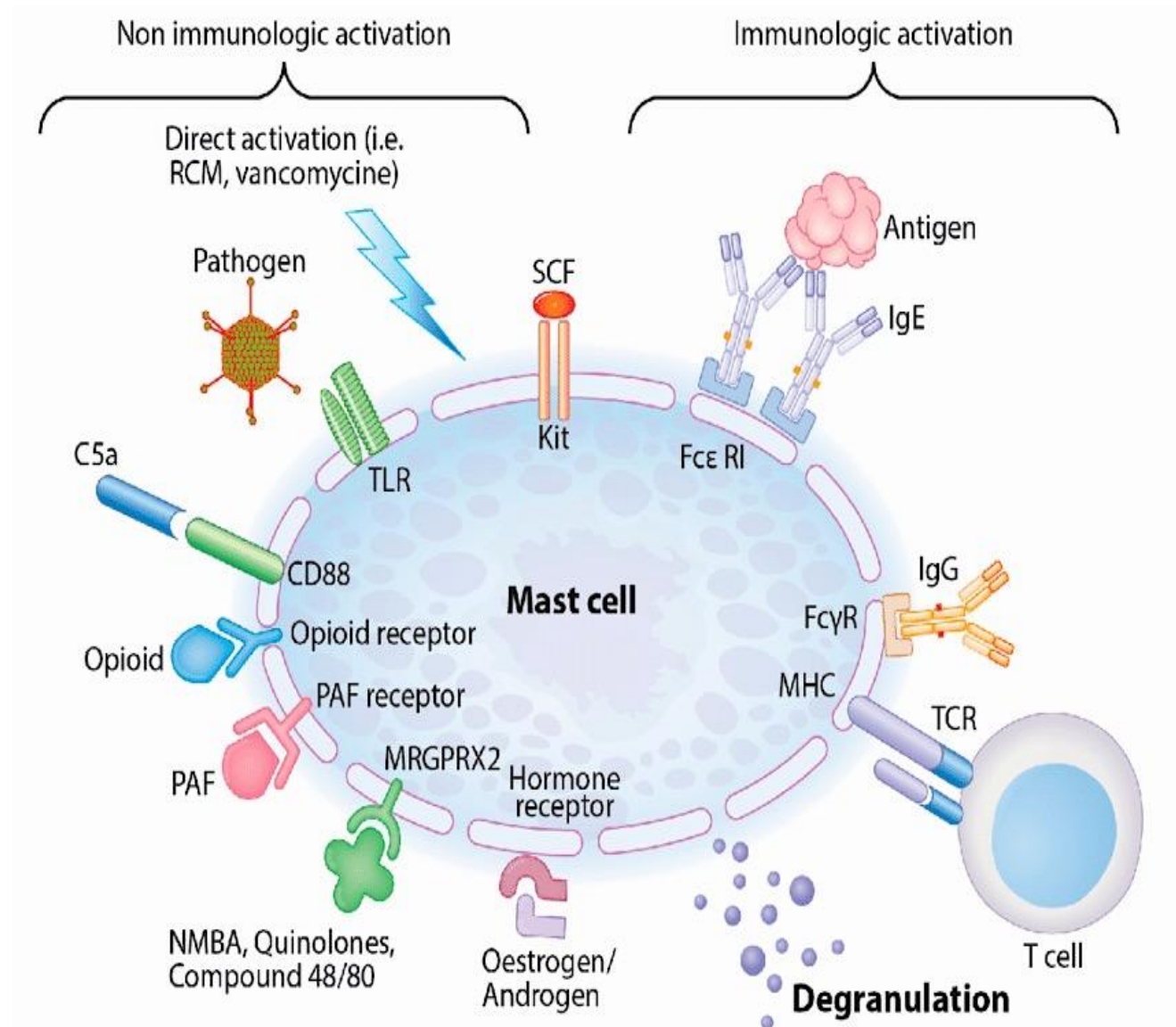
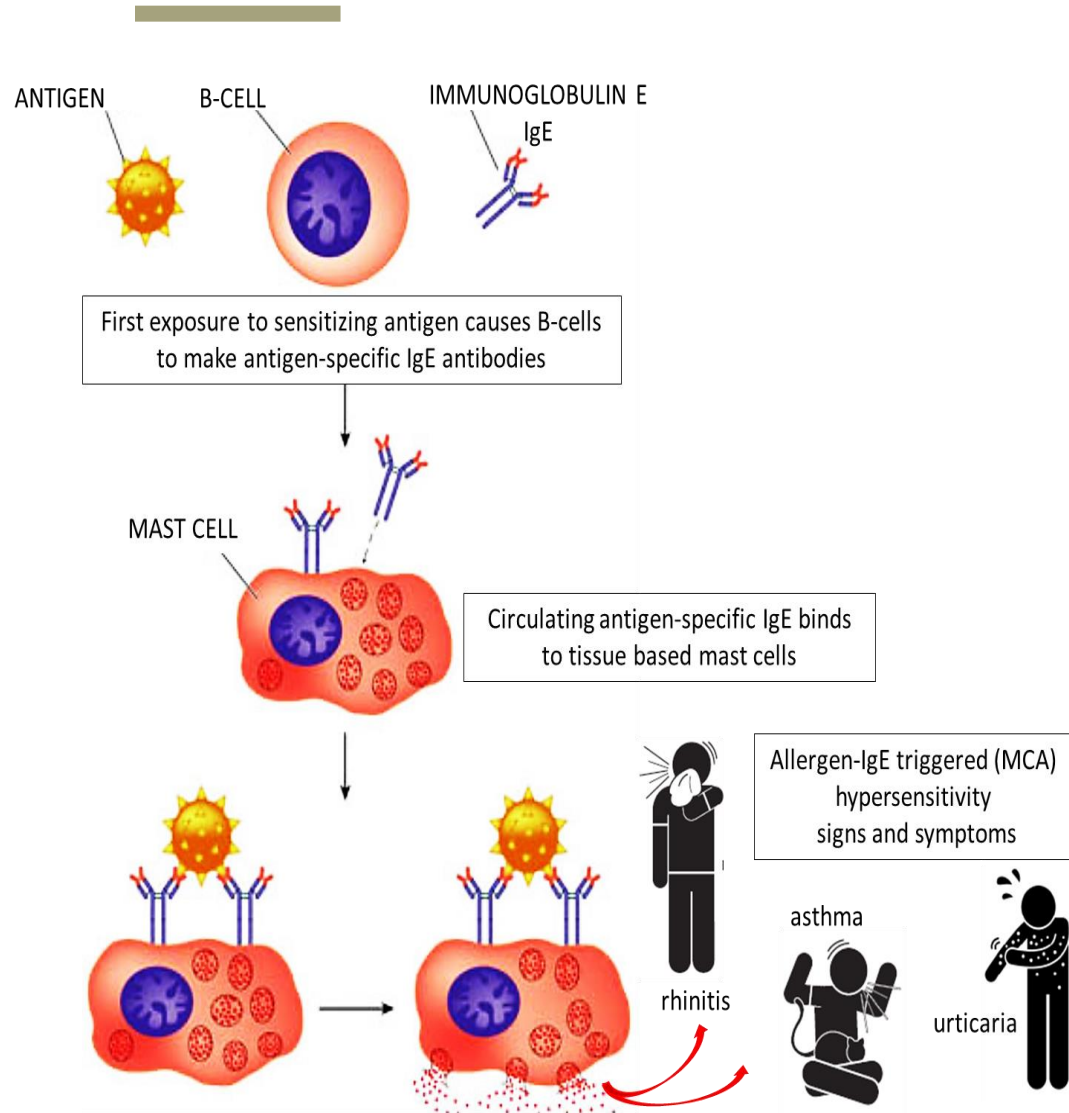
Mast Cell Activation (MCA) involved in several inflammatory disorders

Strong Evidence

Some evidence

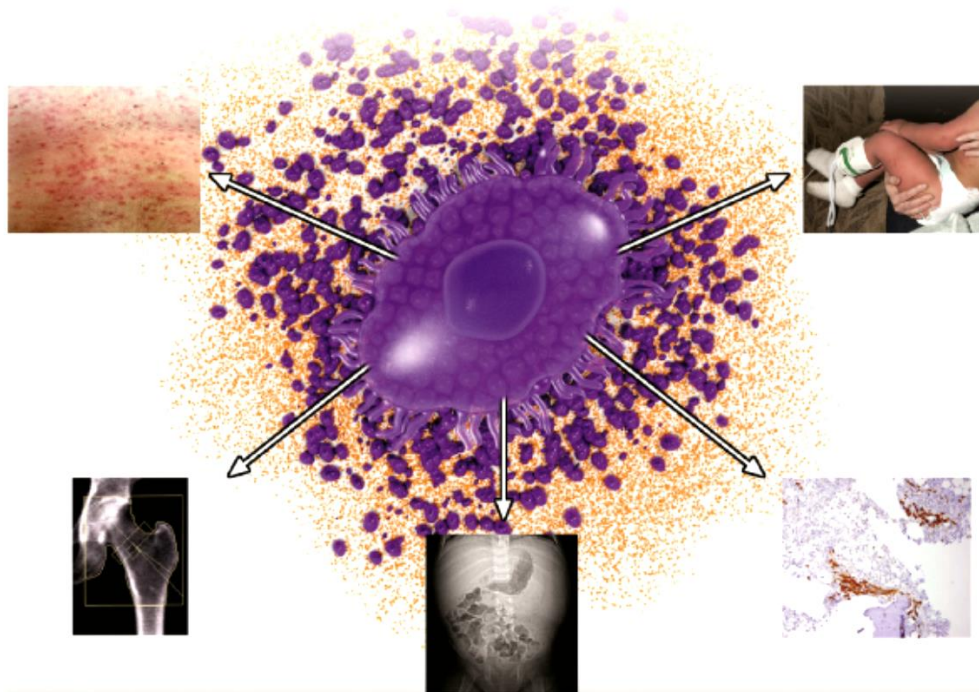


Mast Cell Activation Disease: More than Allergies



The Journal of Allergy and Clinical Immunology:

In Practice



Mast Cell Disorders

AN OFFICIAL JOURNAL OF



American Academy of
Allergy Asthma
& Immunology

CLINICAL MANAGEMENT REVIEW
Mast Cell Activation Syndrome and
Mastocytosis: Initial Treatment Options and
Long-Term Management

CLINICAL COMMENTARY REVIEW
Doctor, I Think I Am Suffering from MCAS:
Differential Diagnosis and Separating Facts
from Fiction

GRAND ROUNDS REVIEW
Insect Sting Anaphylaxis—Or Mastocytosis—Or
Something Else?

SPECIAL ARTICLE
Proposed Diagnostic Algorithm for Patients
with Suspected Mast Cell Activation Syndrome

CONTROVERSIES IN ALLERGY
Controversies in Allergy: Is a Bone Marrow
Biopsy Optional or Essential in the Evaluation of
the Patient with a Suspected Mast Cell Disorder?

THEME EDITORIAL
The Many Faces of Mast Cell Disorders—A
House of Mirrors?


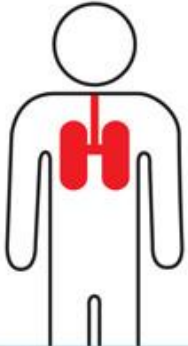



Mast Cell Activation Syndrome

“Mast cells = breaking bad”

When symptoms are

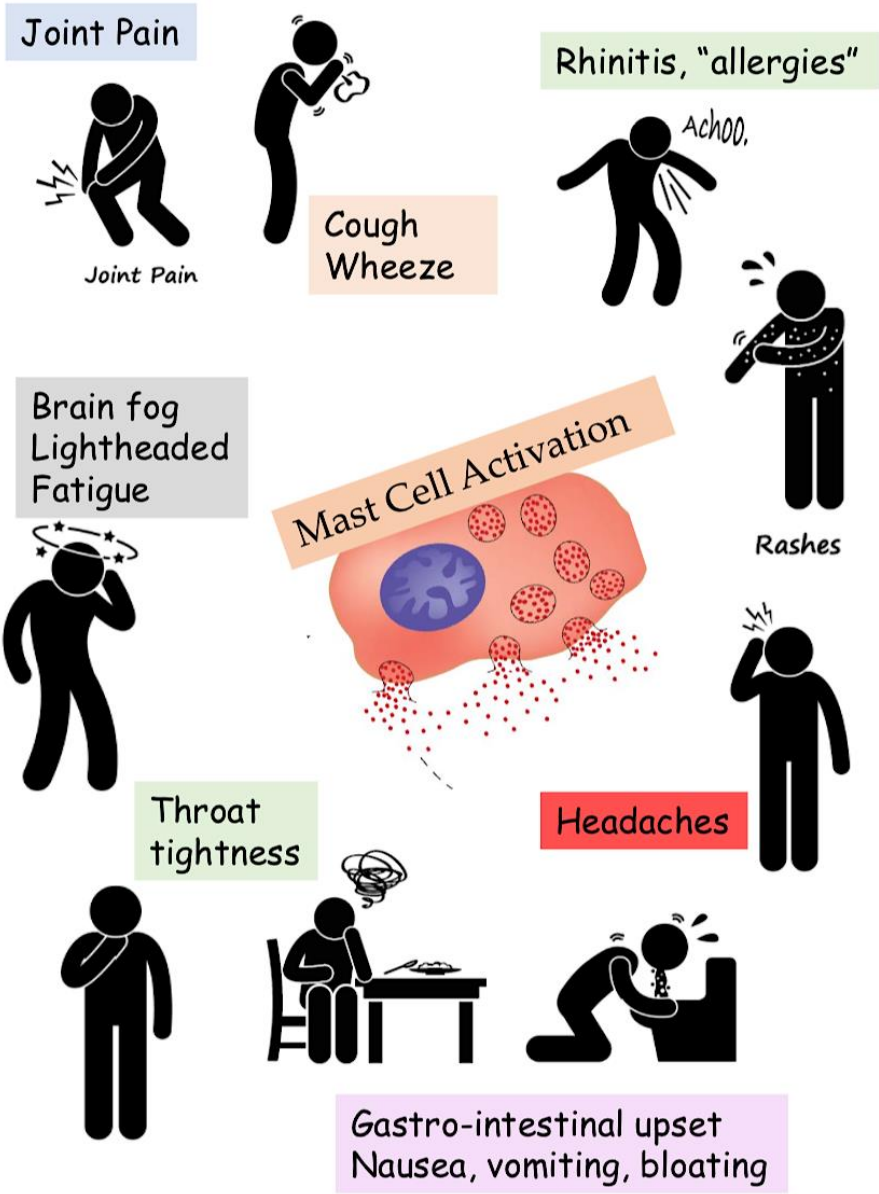
- recurrent,
- accompanied by an increase in mast cell–derived mediators in biological fluids, and
- responsive to treatment with mast cell–stabilizing or mediator–targeting drugs,

the diagnosis of mast cell activation syndrome (MCAS) is appropriate.

				
SKIN	RESPIRATORY	GASTROINTESTINAL	CARDIOVASCULAR	NEUROLOGICAL
hives, swelling, itching, warmth, redness	coughing, wheezing, shortness of breath, chest pain or tightness, throat tightness, trouble swallowing, hoarse voice, nasal	nausea, stomach pain or cramps, vomiting, diarrhea	dizziness/ lightheadedness, pale/blue colour, weak pulse, fainting, shock, loss of consciousness	anxiety, feeling of "impending doom" (feeling that something really bad is about to happen), headache

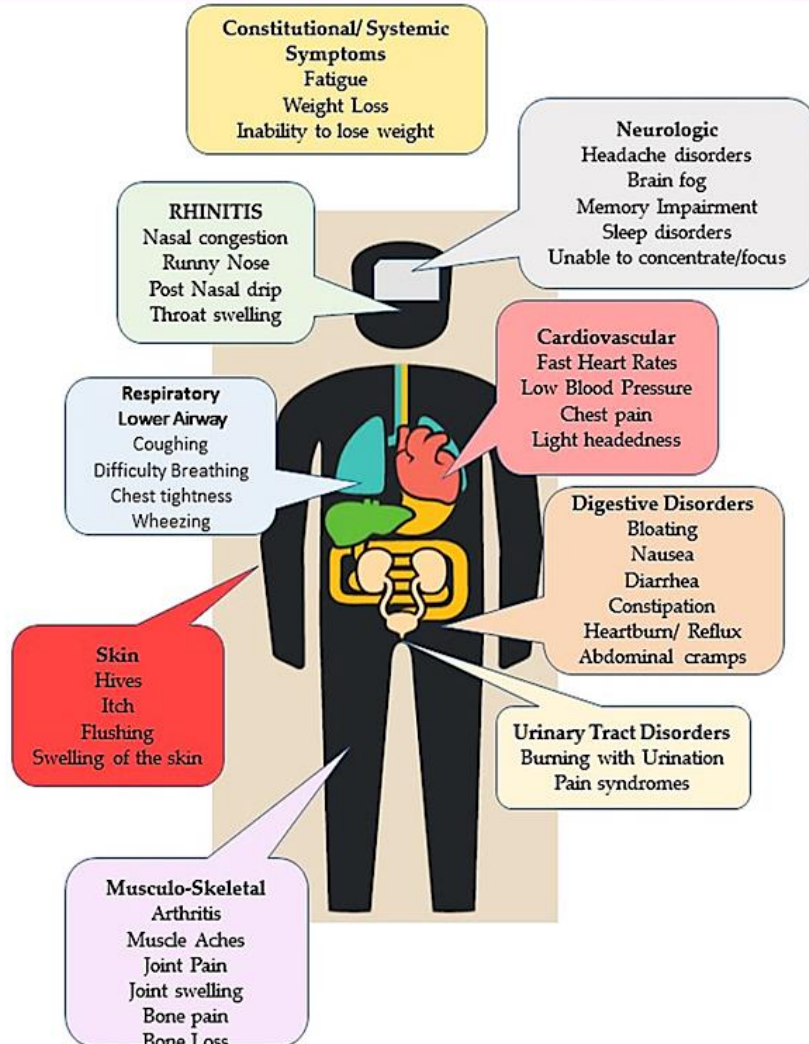
Mast Cell Activation Disease
is common.

MCAS (Anaphylaxis) less so .



MCA in 2 or more organ systems?

Mast Cell Activation Disorders



Mast cell activation syndrome: Proposed diagnostic criteria

Cem Akin, MD, PhD,^{a*} Peter Valent, MD,^b and Dean D. Metcalfe, MD^c *Ann Arbor, Mich, Vienna, Austria, and Bethesda, Md*

Better with anti-MC/MC mediator medications?



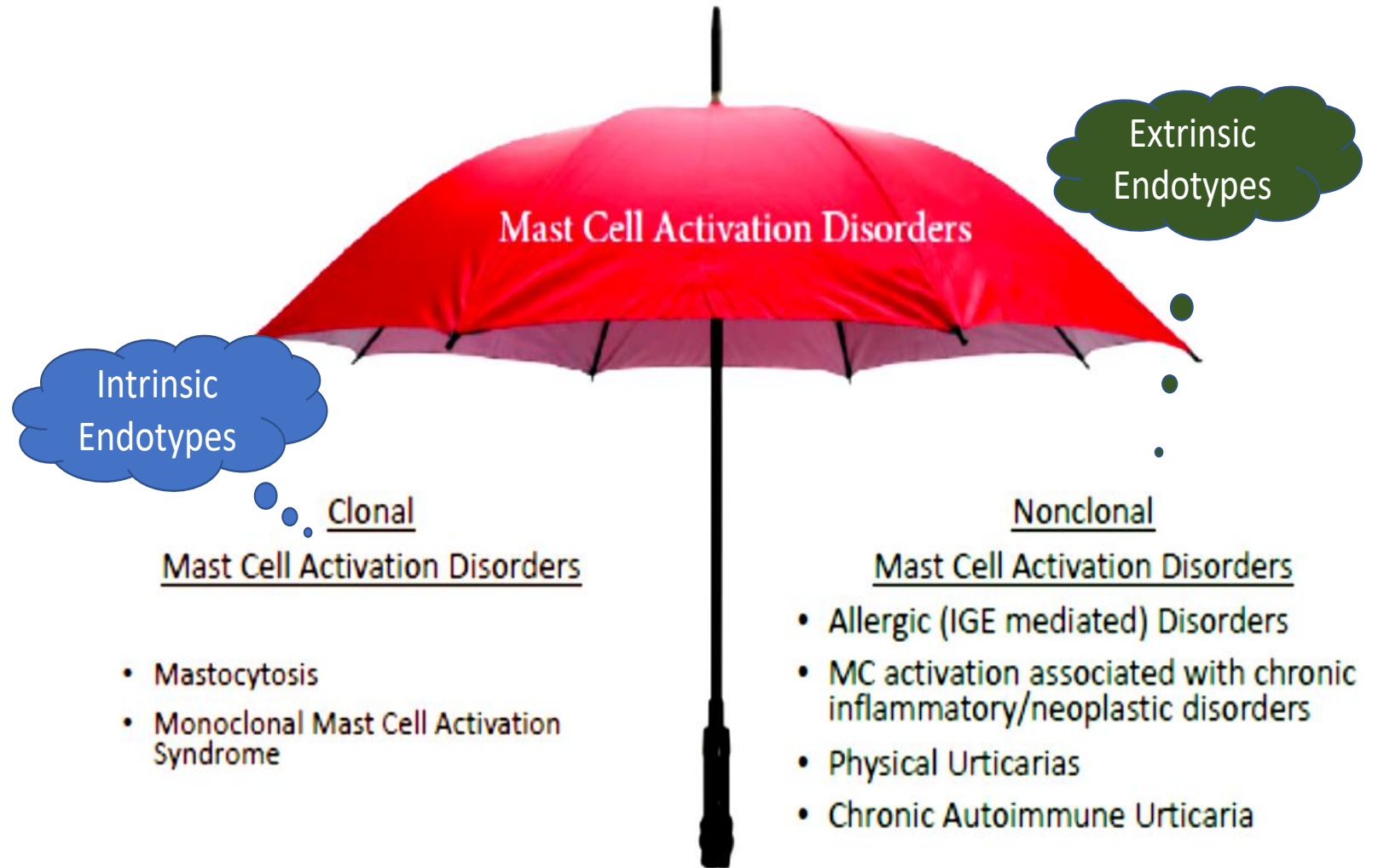
- Histamine Blockade
- Leukotriene Antagonists
- Cromones
- Omalizumab
- Ketotifen

MCA events associated w/ validated MCA markers

- Tryptase
- Urine Methylhistamine
- Urine Prostaglandin D2
- Urine 11- Beta Prostaglandin F2alpha
- C kit mutation- tissue, peripheral blood
- CD25+ MC in biopsies
- Clustered MC in biopsies

Diagnosis: MCAS Checklist

- ✓ Symptoms?
- ✓ Better with treatments that target MC or MC mediators?
- ✓ Test Results?



Hypertryptasemia – Mast Cells that have increased copies of the tryptase gene, patients exhibit MCAS signs and Symptoms

Idiopathic – Idiopathic anaphylaxis, Idiopathic Urticaria

Allergen testing
Celiac Panel
EGD/
Colonoscopy

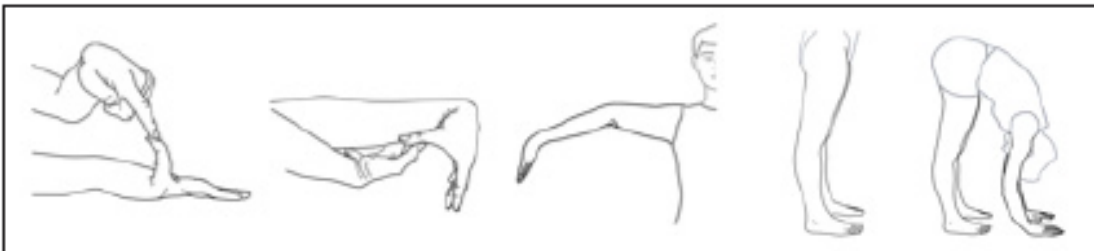
**PIDD
evaluation**
Primary
Immune
Deficiency
Disorder

- Some food (wheat/gluten, peanuts, eggs, nuts and shellfish, milk*, egg*, soy*)
- Medications
- Airborne Allergens
- Insect stings or bites
- Autoimmune Disorders
- Infections
- Physical stimuli, such as pressure, cold, heat, exercise or sun exposure

**Allergen
testing**

Rheumatology Panel
ANA, RF, ANCA, Thyroid
Abs
Neuonal Abs
PIDD evaluation

**Connective Tissue
Disorder EDS Screen**



If 5 of 9 are present with a sensitivity of 99.6% and a specificity of 98% there is a form of EDS present:

- Peri-arthritis (more than 1 joint more than 3 months)
- Fatigue (chronic, disabling more than 6 months)
- motor dysproprioception (the door sign)
- joint instability (subluxations, dislocations often autoreducing)
- skin fragility (atrophic scarring, delayed wound healing)
- Hypermobility (pos Beighton / 5 point historic questionnaire / pos glomerulo-humeral abduction above 95 degrees),
- gastro-esophageal reflux (treated)
- Ecchymosis (spontaneous)
- Hyperacusis (fragility to sounds below 50 decibel)
- Hamonet C., *et al.* "Ehlers-Danlos Syndrome (EDS) - Contribution to Clinical Diagnosis - A Prospective Study of 853 Patients". *EC Neurology* 10.6 (2018).

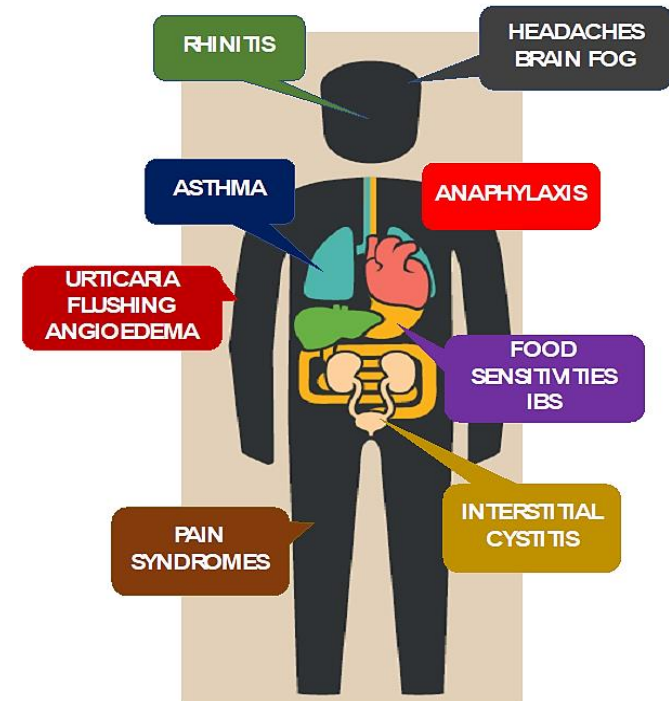
56 yo male, 1st seen in 2015 at JHMI and NIAID

- 1st evaluated for insect venom allergy, after a brown wasp sting caused flushing and lightheadedness. (brother also has venom allergy), tryptase 14 ng/ml
- h/o cat allergy and IGE- Yellow jacket; Had anaphylaxis to VIT, then lost to f/u
- In 2017: syncopal episodes with nausea, lightheadedness, concentration problems; repeat VIT was not tolerated
- @ NIH, noted to have syncopal episodes between 2-4 AM, after steak meal, detected alpha gal- IgE +ve (h/o tick bites)
- Underwent BM biopsy = +ve for KIT D816V = indolent systemic mastocytosis
- Duplication of alphas tryptase gene = Hyper alpha typtasemia (HAT)

Grand Rounds Review

Insect Sting Anaphylaxis—Or Mastocytosis—Or Something Else?

David B.K. Golden, MD^a, and Melody C. Carter, MD^b Baltimore and Bethesda, Md



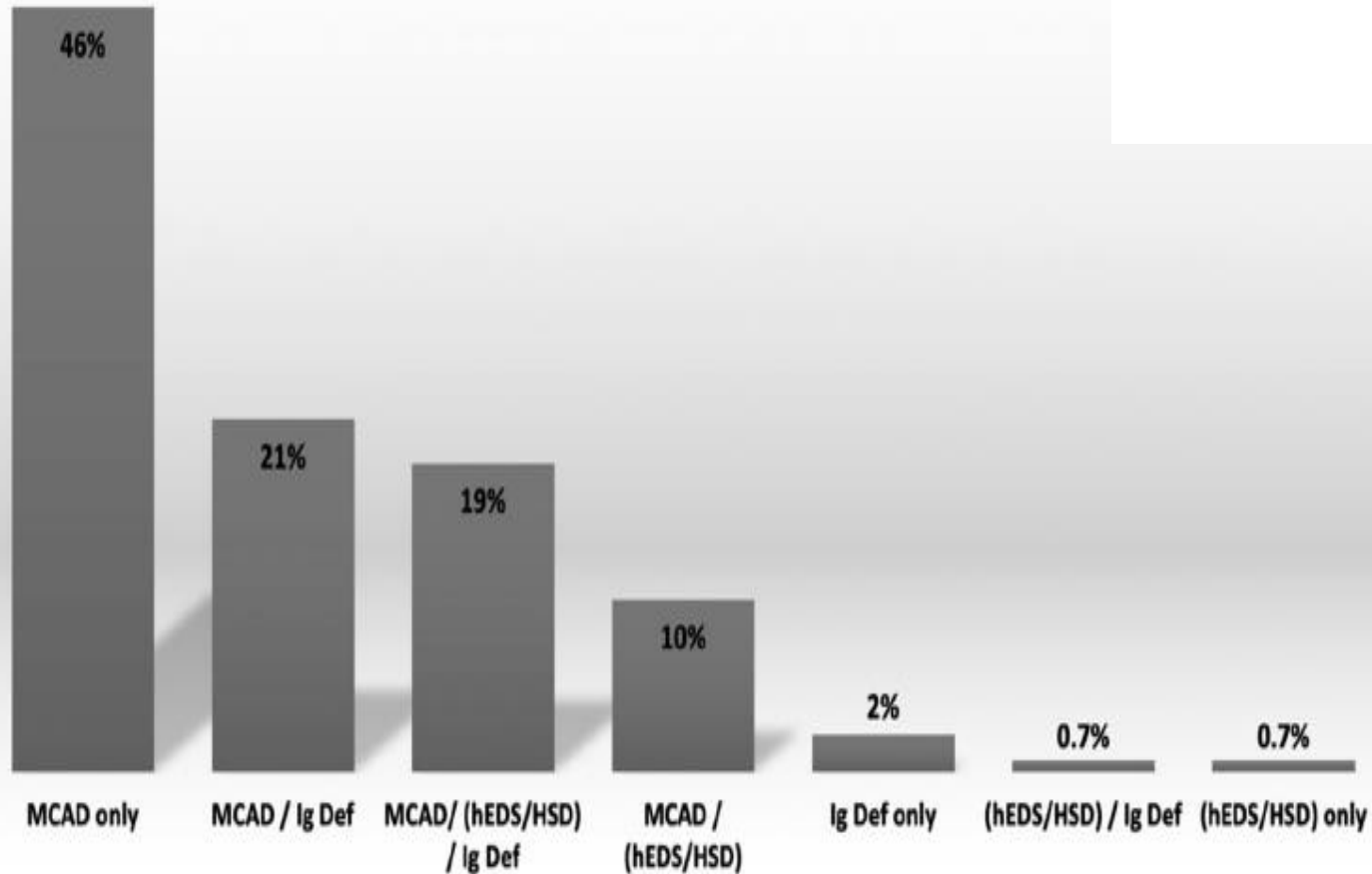
Flavors of MCAD

TABLE I. Chronology of patient history and results of evaluation

Year	Venom sting reaction	Anaphylaxis trigger	Venom-specific IgE	Specific IgE (kU/L)	Serum tryptase (ng/mL)	PB KIT ASqPCR	BM KIT ASqPCR
1998	Local reaction						
2008	Anaphylaxis	Venom					
2014	Large local reaction						
2015			YJ-2.53 kU/L		14		
2017		Idiopathic			26		
2018		Idiopathic		Alpha-gal-19.2, B-2.24, L-0.36, P-0.95	27.1	0.059	0.068

ASqPCR, Allele-specific quantitative PCR; B, beef; BM, bone marrow; L, lamb; P, pork; PB, peripheral blood; YJ-yellow jacket.

Frequencies of Diagnoses

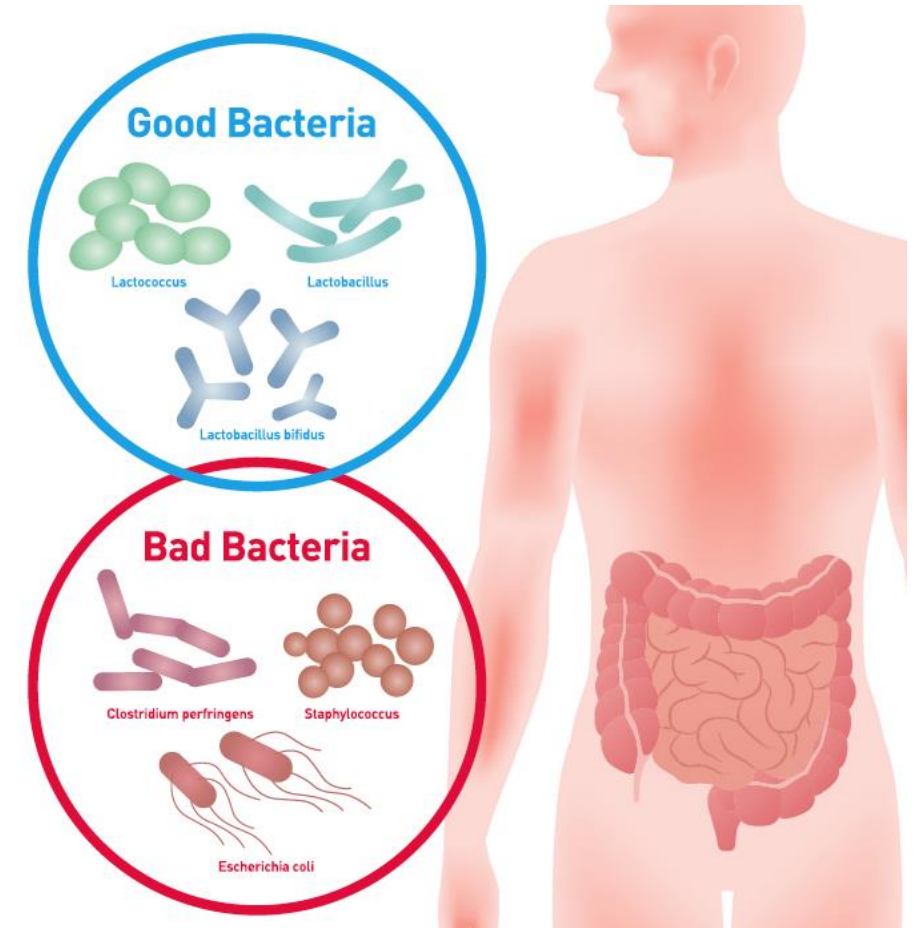


Airway inflammation and dysbiosis in antibody deficiency despite the presence of IgG

Anna Schnell, PhD,^{a,b} Mehmet Davrandi, PhD,^{c,d} Moritz Saxenhofer, PhD,^{a,b} Clara Lebreiro, BSc,^{c,d} Stefania Grotzer, PhD,^{a,b} Fernando Moreira, BSc,^e Maria Hauswald, PhD,^{a,b} Carolin Witte, PhD,^{a,b} Lisa Le...

The Causes of Intestinal Dysbiosis: A Review

Jason A. Hawrelak, BNat (Hons), PhD Candidate and
Stephen P. Myers, PhD, BMed, ND



Hereditary Alpha Tryptasemia (HaT)

SCIENCE

One Gene Mutation Links Three Mysterious, Debilitating Diseases



By Kate Horowitz
Oct 17, 2016



12/10/16

POTS
EDS
IBS

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,

HaT affects =
7% of Western European Descent

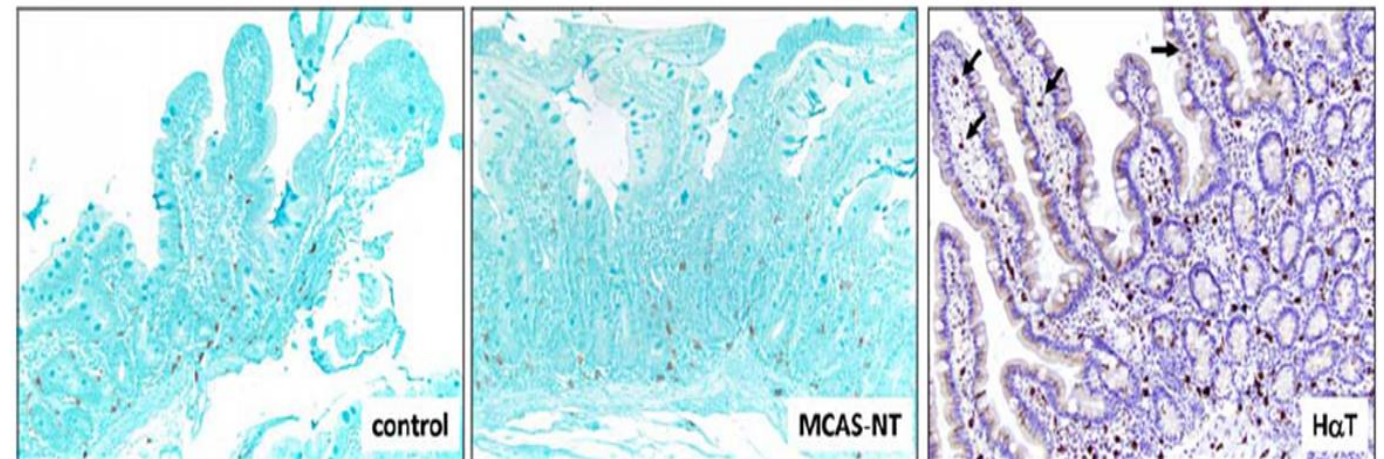
Distinct Small Intestine Mast Cell Histologic Changes in Patients With Hereditary Alpha-tryptasemia and Mast Cell Activation Syndrome

Patient Study Groups

- with HaT (baseline serum tryptase > 8 ng/mL, and a **confirmatory** increased copy number of the TPSAB1 gene based on a DNA test
- MCAS-NT (MCAS- normal serum tryptase
 - had signs and symptoms of MC activation,
 - response to medications that block MCs or MC mediators
 - at least 1 documented elevated MC mediator during symptomatic episode
- GI-control patients did not have evidence of an **inflammatory** condition or clinical manifestations to suggest MCAS

Tissue Staining and Histology Analysis

- Stain for CD117, to highlight MCs in the biopsy sections
- MC morphology (round or spindle), and
- MC locations (with at least 3 MCs/HPF) within the intestinal mucosa and submucosa



hives, flushing



itching



facial swelling



lip swelling



nausea
vomiting



abdominal pain
bloating



gassiness,
flatulence
diarrhea



chest tightness,
coughing



throat
closing



throat/nose congestion
mucus in the back of
the throat



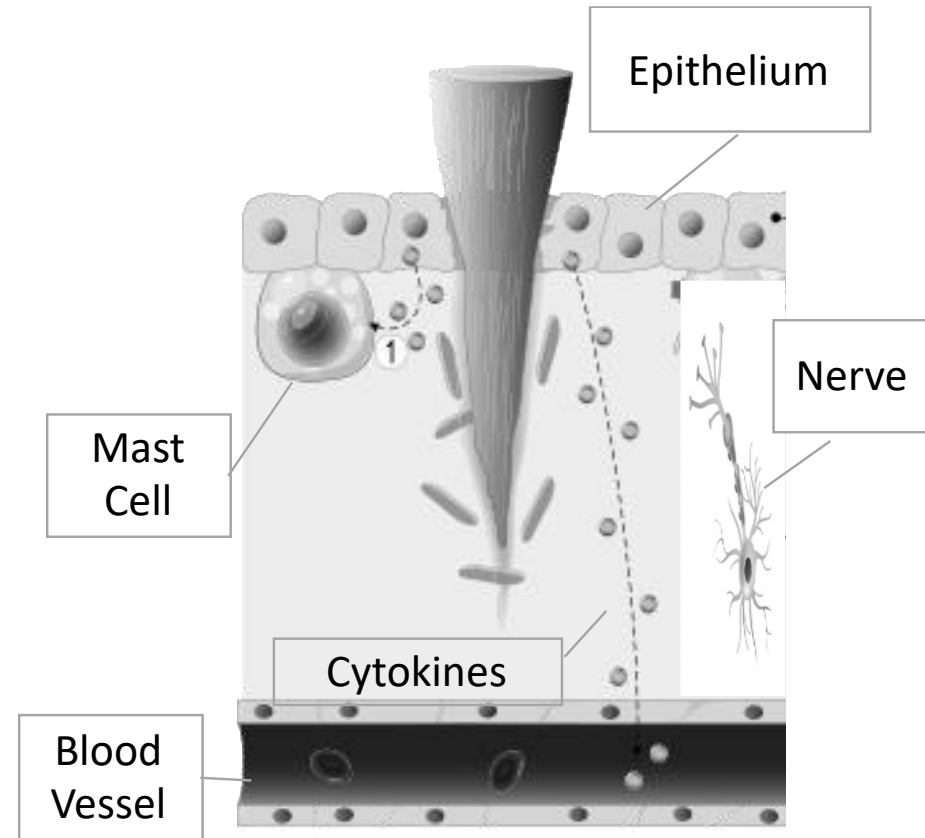
chest pain



low blood pressure
fast heart rate



MCAD Treatment





The Mastocytosis Society, Inc.

www.tmsforacure.org

QUICK REFERENCE GUIDE: MEDICATIONS TO USE AND AVOID IN PATIENTS WITH MAST CELL DISEASE IN EMERGENCY SITUATIONS

Please note: Some of the Drugs to Avoid may be given if absolutely necessary, if given with a prep to stabilize mast cells. Please refer to one of our mast cell experts for instructions.

Medication Type	AVOID THESE DRUGS	Drugs that are typically tolerated
General Drugs	Alcohol Amphotericin B Anticholinergic drugs Dextran Dextromethorphan Ethanol Polymyxin B Quinine Vancomycin IV Alpha-adrenergic blockers Beta-adrenergic blockers	
Pain Medications	Opioid narcotics (may be tolerated by some individuals) Toradol Non-steroidal anti-inflammatory drugs (unless the patient is already taking a drug from this class)	Fentanyl (may require adjunct treatment with Zofran) Tramadol
Muscle Relaxants	Atracurium Doxacurium D-tubocurarine Metocurine Mivacurium Succinylcholine	Pancuronium vecuronium
Local Anesthetics	Benzocaine Chloroprocaine Procaine Tetracaine	Bupivacaine Lidocaine Mepivacaine Prilocaine Levobupivacaine Ropivacaine
Intraoperative Induction Meds		Ketamine Midazolam Propofol
Inhaled Anesthetics		Sevoflurane

Clinical Management Review

Mast Cell Activation Syndrome and Mastocytosis: Initial Treatment Options and Long-Term Management

Mariana Castells, MD, PhD^a, and Joseph Butterfield, MD^b Boston, Mass; and Rochester, Minn



Anaphylaxis Emergency Action Plan

Patient Name: _____ Age: _____

Allergies: _____

Asthma ☐ Yes (high risk for severe reaction) ☐ No

Additional health problems besides anaphylaxis: _____

Concurrent medications: _____

	Symptoms of Anaphylaxis
MOUTH	itching, swelling of lips and/or tongue
THROAT*	itching, tightness/closure, hoarseness
SKIN	itching, hives, redness, swelling
GUT	vomiting, diarrhea, cramps
LUNG*	shortness of breath, cough, wheeze
HEART*	weak pulse, dizziness, passing out

Only a few symptoms may be present. Severity of symptoms can change quickly.
*Some symptoms can be life-threatening. ACT FAST!

Emergency Action Steps - DO NOT HESITATE TO GIVE EPINEPHRINE!

1. Inject epinephrine in thigh using (check one): ☐ Adrenaclick (0.15 mg) ☐ Adrenaclick (0.3 mg)

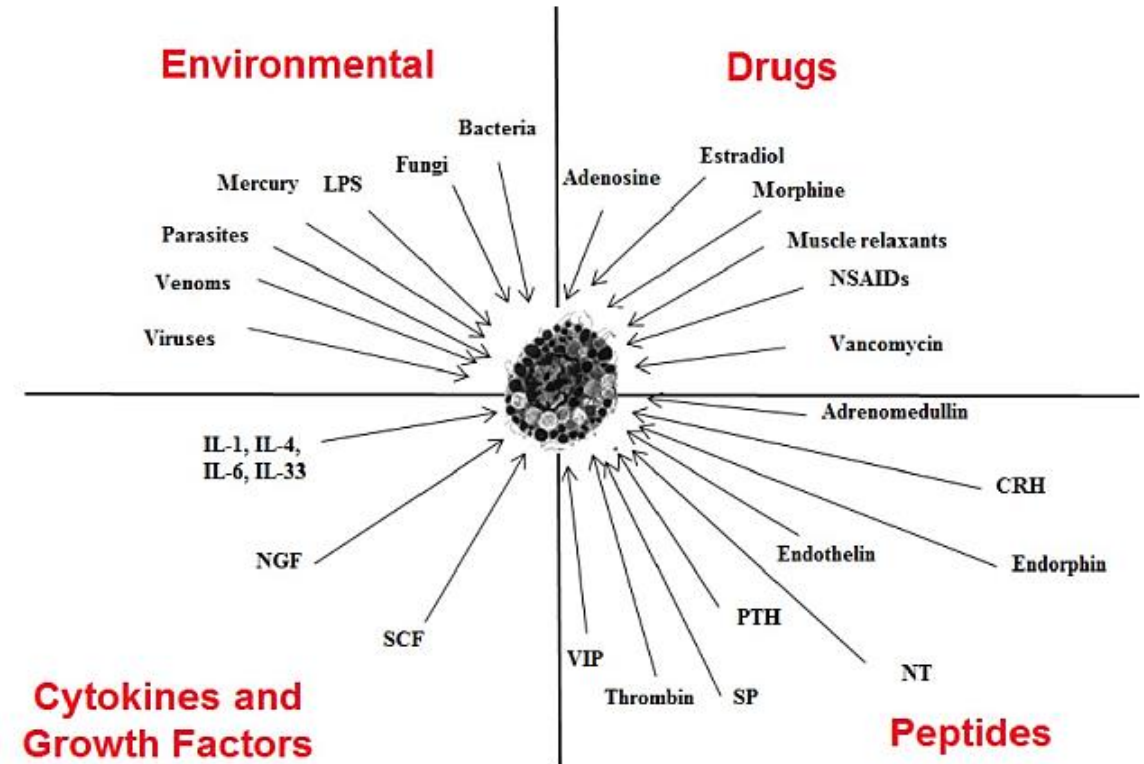
☐ Auvi-Q (0.15 mg) ☐ Auvi-Q (0.3 mg)

☐ EpiPen Jr (0.15 mg) ☐ EpiPen (0.3 mg)

Epinephrine Injection, USP Auto-injector- authorized generic
☐ (0.15 mg) ☐ (0.3 mg)

☐ Other (0.15 mg) ☐ Other (0.3 mg)

Therapeutic Recommendations



Allergen-IgE	Infections	Primary Immune Deficiency	Autoimmune Disorders
Avoidance measures (Diet, Environment) Medications: histamine, Leukotriene blockade Tricyclic agents Ketotifen, Cromolyn Desensitization/Immunotherapy Omalizumab	Lyme, Borrelia Bacterial infections (Strep- ASO/DNAse Ig) EBV, HSV, Hepatitis COVID	Prophylactic Antibiotics Immune Globulin Anti-inflammatory Agents	Anti-inflammatory Agents Immune Globulin

Traditional Chinese medicine for food allergy and eczema

Zixi Wang, Zhen-Zhen Wang, Jan Geliebter, Raj Tiwari, Xiu-Min Li

Ann Allergy Asthma Immunol 126 (2021) 639e654

Z. Wang et al. / Ann Allergy Asthma Immunol 126 (2021) 639–654

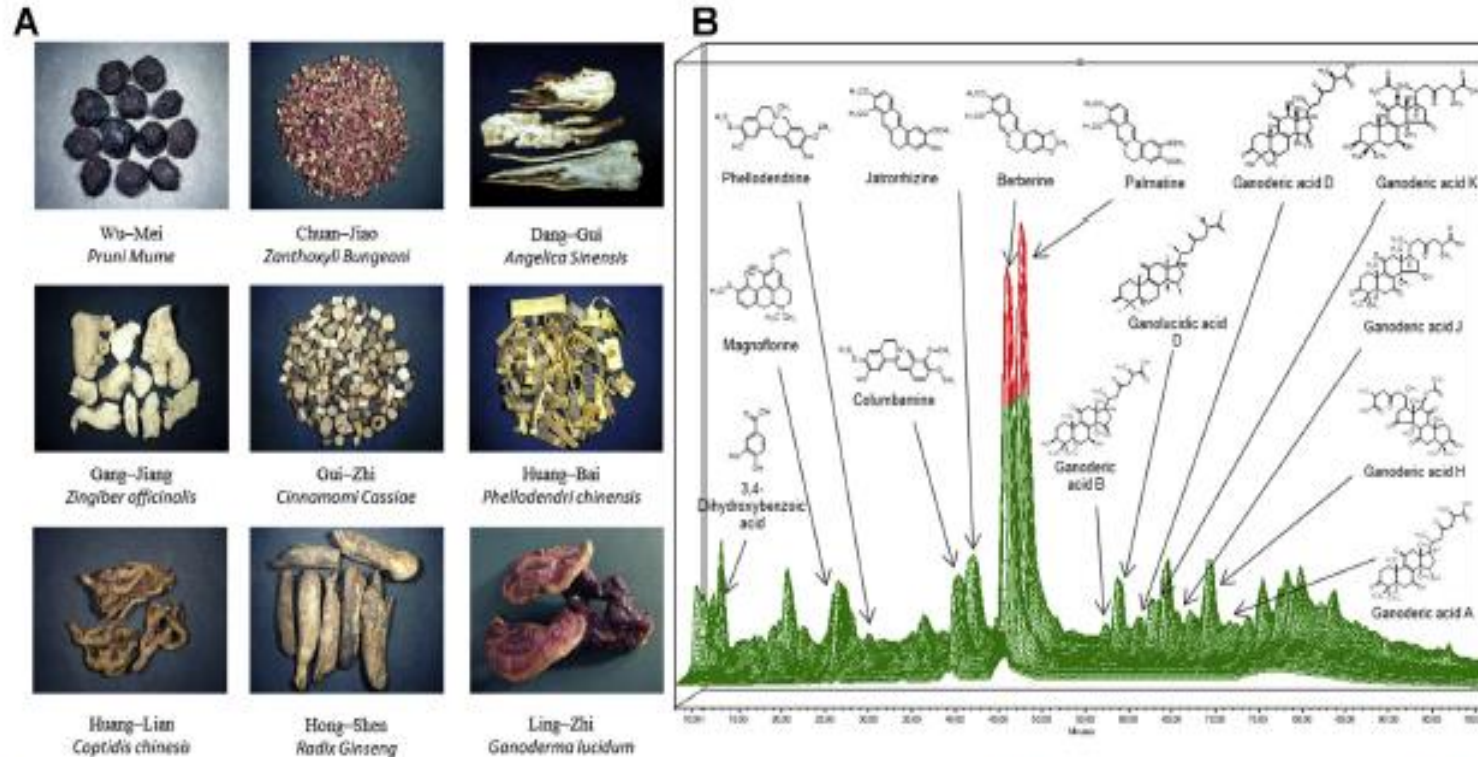
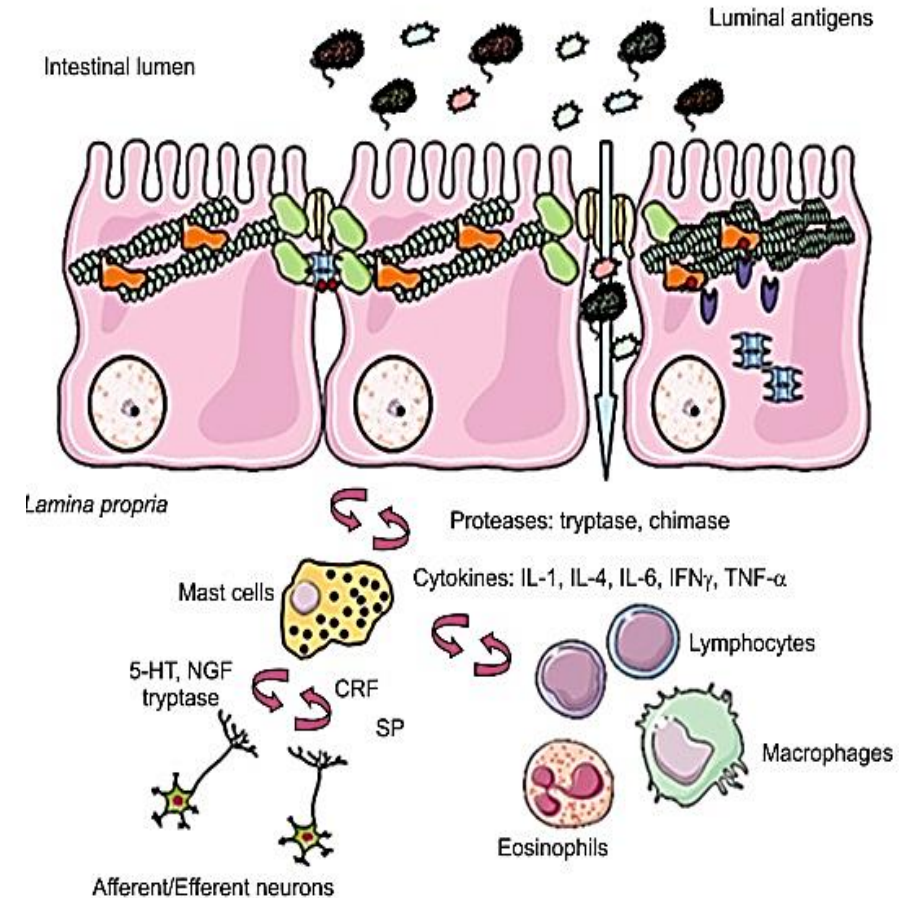


Figure 1. Herbal components of FAHF-2 A, Photographic illustration of 9 herbal constituents of FAHF-2 formula.³⁶ B, 3-Dimensional HPLC fingerprint of FAHF-2.⁴⁰ FAHF-2, Allergy Herbal Formula; HPLC, high-performance liquid chromatography.



Acupuncture/Traditional Chinese Medicine and MCAD

J Allergy Clin Immunol. 2010 December ; 126(6): 1208–17.e3. doi:10.1016/j.jaci.2010.09.013.

Food Allergy Herbal Formula -2 protection against peanut anaphylactic reaction is via inhibition of mast cells and basophils

Ying Song, MD^{1,*}, Chunfeng Qu, Ph.D^{1,*}, Kamal Srivastava, M.Phil¹, Nan Yang, PhD¹, Paula Busse, MD¹, Wei Zhao, MD, PhD², and Xiu-Min Li, MD¹

¹Department of Allergy, Immunology and Rheumatology, National Children's Medical Center, Beijing, China

Lisann et al. *Allergy, Asthma & Clinical Immunology* (2014) 10:66
DOI 10.1186/s13223-014-0066-5



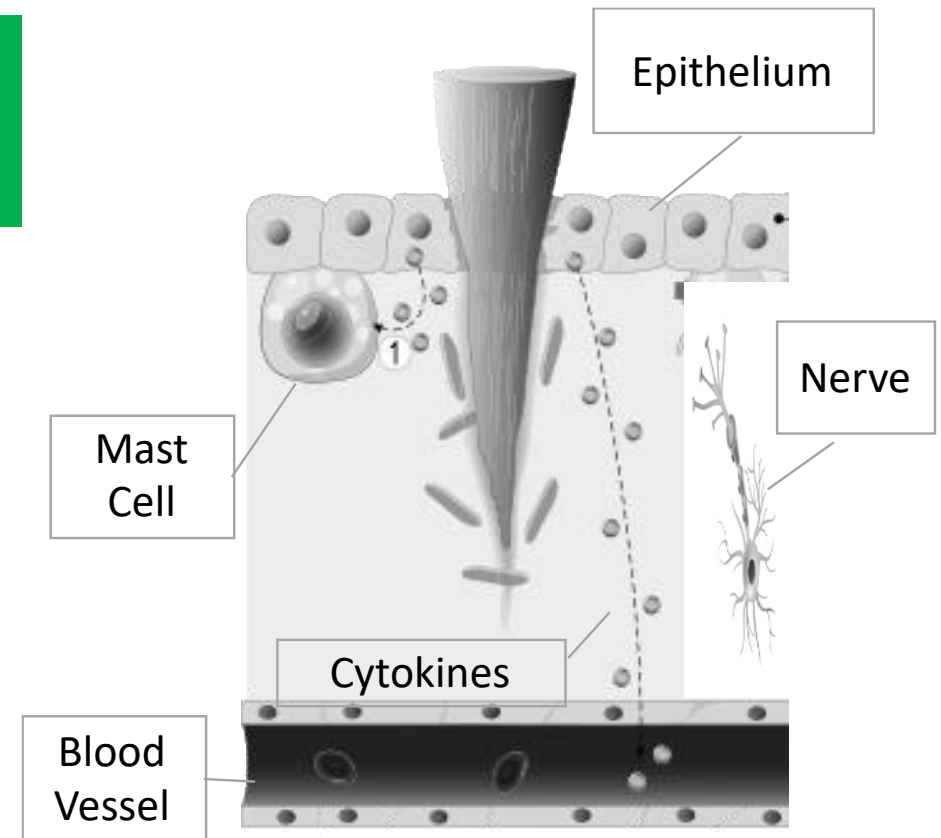
ALLERGY, ASTHMA & CLINICAL
IMMUNOLOGY

CASE REPORT

Open Access

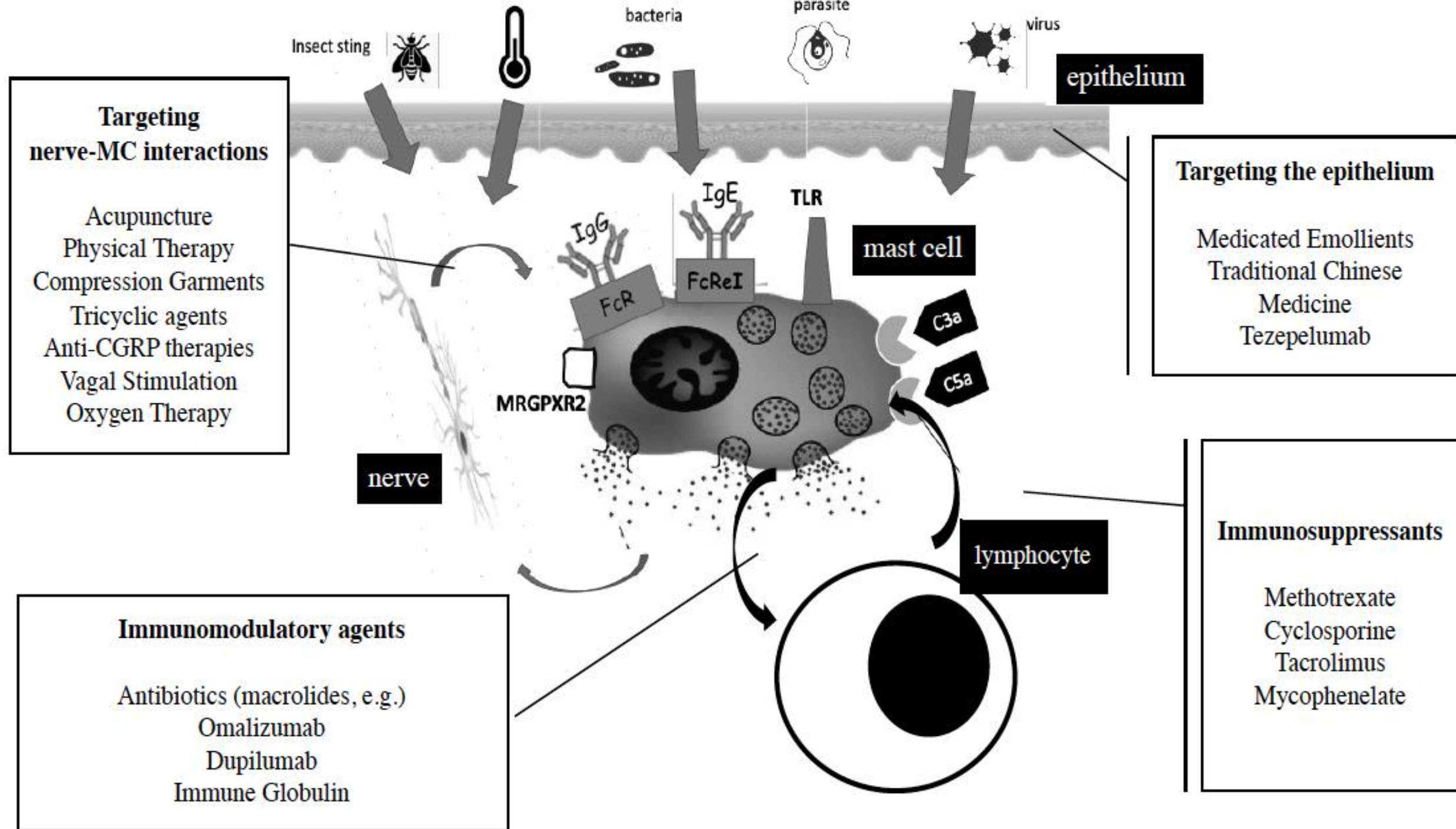
Successful prevention of extremely frequent and severe food anaphylaxis in three children by combined traditional Chinese medicine therapy

Lauren Lisann^{1,2}, Ying Song¹, Julie Wang¹, Paul Ehrlich³, Anne Maitland^{4,5} and Xiu-Min Li^{1*}

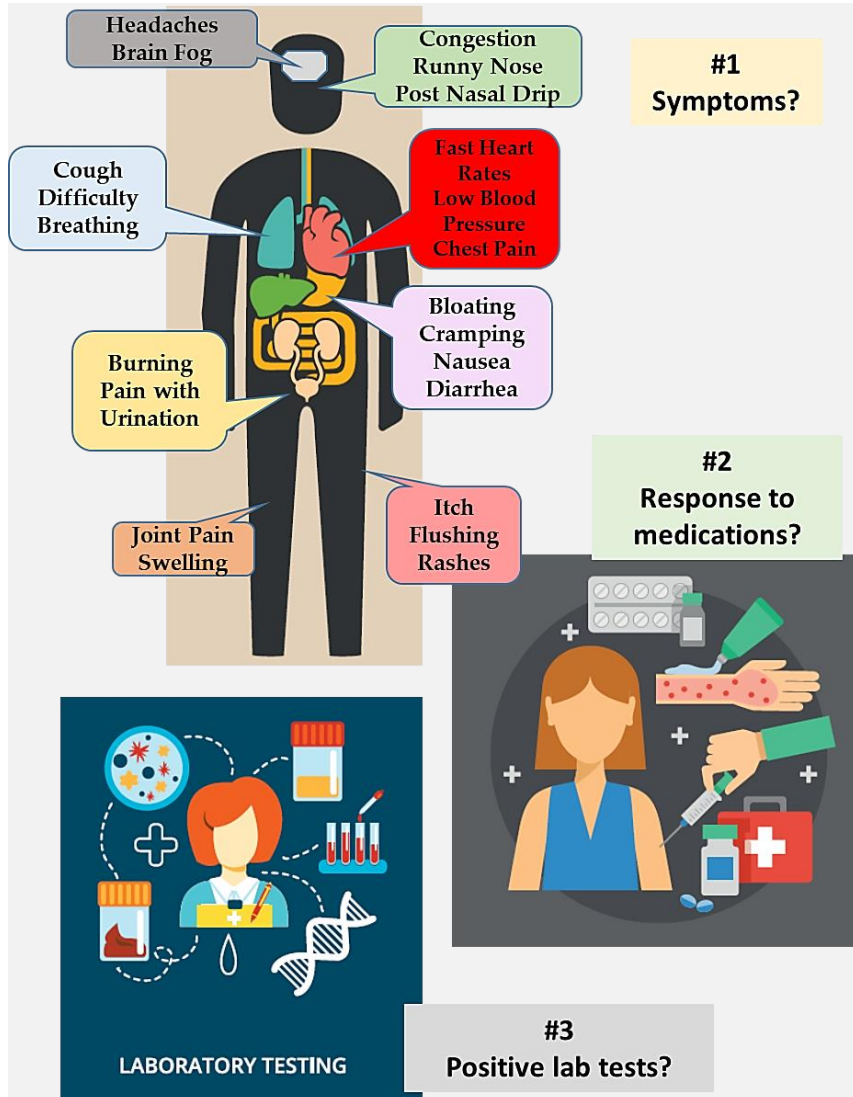


BMJ Open Acupuncture for patients with chronic urticaria: a systematic review protocol

Qin Yao,^{1,2} Yongming Ye,¹ Xiaoxu Liu,^{1,2} Zongshi Qin,^{1,2} Zhishun Liu¹



Treating MCAD...



Cardiac conditions

Coronary hypersensitivity (the Kounis syndrome)*
Postural orthostatic tachycardia syndrome

Endocrine conditions

Fibromyalgia Parathyroid tumor
Pheochromocytoma Carcinoid syndrome

Digestive conditions

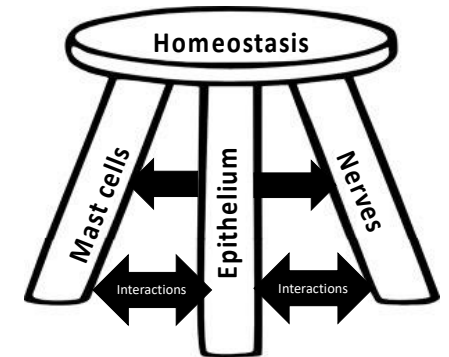
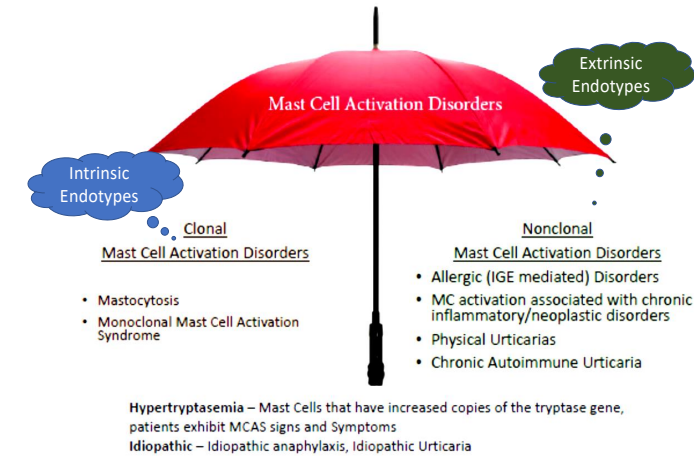
Adverse reaction to food* Eosinophilic esophagitis*
Eosinophilic gastroenteritis* Gastroesophageal reflux disease; Gluten enteropathy; Irritable bowel syndrome; Vasoactive intestinal peptide-secreting tumor

Immunologic conditions

Auto-inflammatory disorders such as deficiency of inter- leukin-1-receptor antagonist*; Familial hyper-IgE syndrome Vasculitis*

Neurologic/psychiatric conditions

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



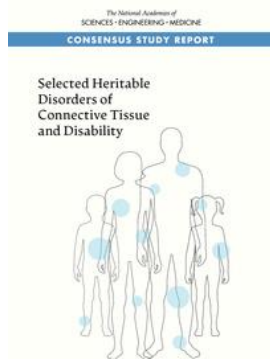
MCAD Phenotypes

Selected Heritable Disorders of Connective Tissue and Disability

The U.S. Social Security Administration has requested the National Academies of Sciences, Engineering, and Medicine establish an ad hoc committee to review certain heritable conditions related to connective tissues, including but not necessarily limited to Ehlers-Danlos syndrome and Marfan syndrome. The Committee will use published evidence and professional experience to develop a report that will examine the diagnosis, treatment, and prognosis of the selected conditions, as well as levels of associated functional limitation, in adults and children in the U.S. population.

 [Provide feedback on this project](#)

Publications



2022

Selected Heritable Disorders of Connective Tissue and Disability

Heritable disorders of connective tissue (HDCTs) are a diverse group of inherited genetic disorders and subtypes. Because connective tissue is found throughout the body, the impairments associated with HDCTs manifest in multiple body systems and may change or vary in severity throughout an affected individual's lifetime. In some cases, these impairments may be severe

RESOURCES

 [Report Highlights](#)

 [Report Conclusions](#)

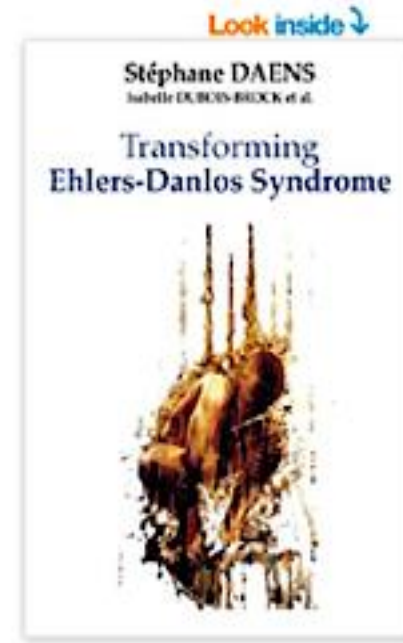
<https://www.nationalacademies.org/our-work/selected-heritable-disorders-of-connective-tissue-and-disability>

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<https://www.nationalacademies.org/our-work/selected-heritable-disorders-of-connective-tissue-and-disability>

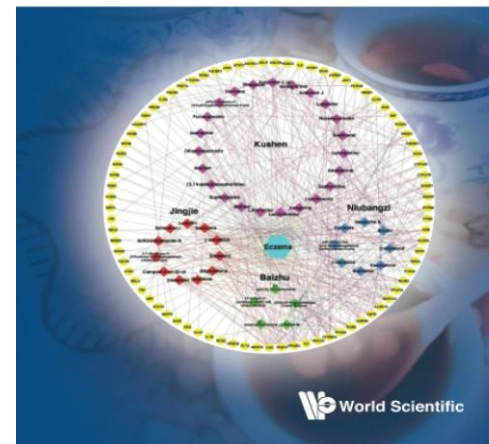
Resources

Mast Cell
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Treating Eczema with Traditional Chinese Medicine

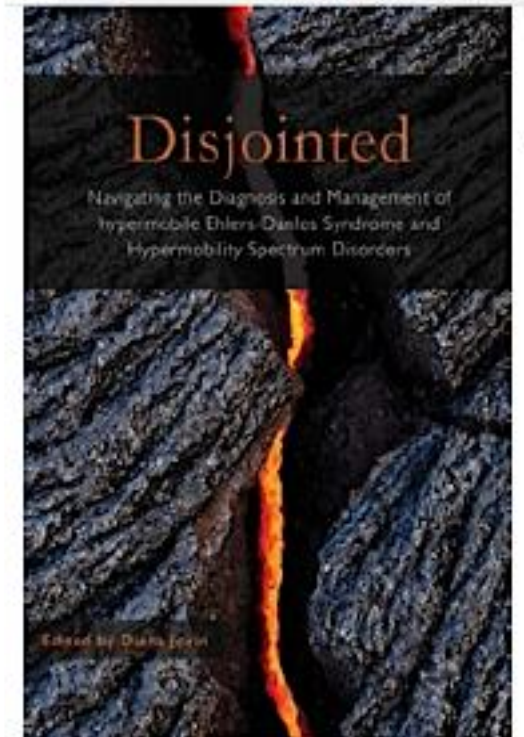
Xiu-Min Li • Henry Ehrlich



Transforming Ehlers-Danlos Syndrome: A Global Vision of the Disease - The Epigenetic Revolution - Emergencies

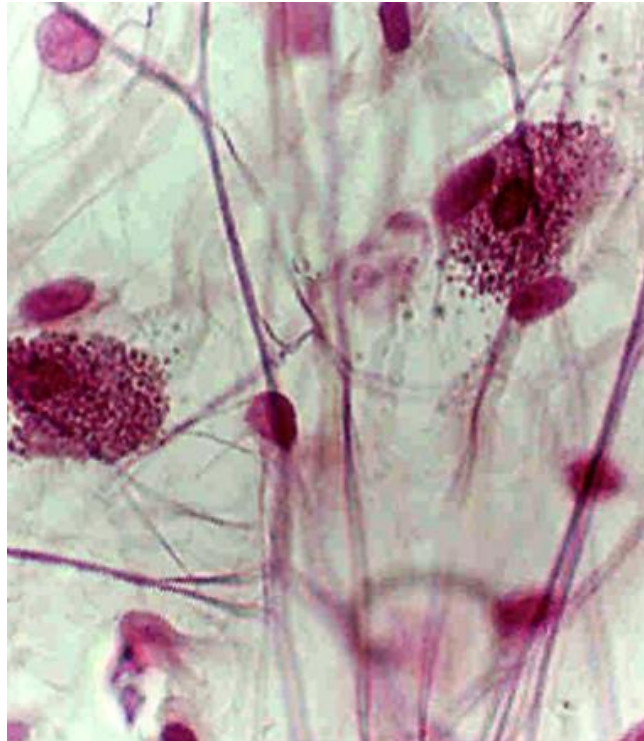
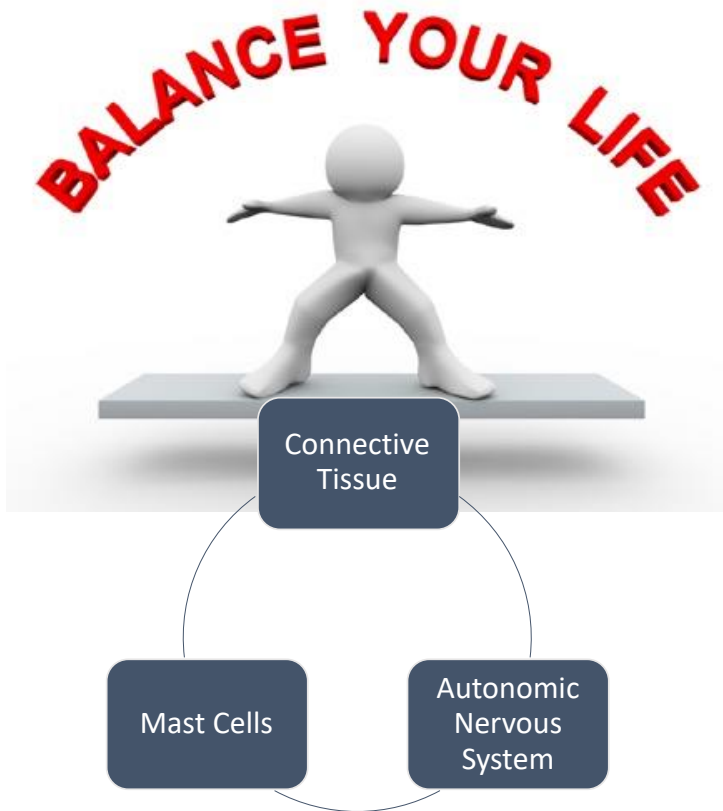
by Stéphane DAENS (Author), Isabelle DUBOIS-BROCK (Author), RAAL (Illustrator), Yannick ATAMBONA (Translator), & 6 more

13 ratings



Gratitude

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- Dr. Xiu-Min Li and her laboratory and colleagues
- Comprehensive Allergy & Asthma Care
- Clinical Paradigms, LLC, Drs. Brock and Pizano
- Ehlers Danlos Society
- Bobby Jones Chiari Syringomyelia Society
- Mt Sinai- South Nassau Hospital- Chiari/EDS center