Introduction to Mast Cell Activation Syndrome

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Disclosures

I have no conflicts of interest related to this presentation.

Objectives

- Recognize signs and symptoms of mast cell activation syndrome (MCAS).
- Gain awareness of peri-operative management of patients with MCAS.

Overview

- Introduction
- Diagnostic criteria
- Pathogenesis
- Treatment
- Peri-operative recommendations

Nomenclature of mast cell disorders

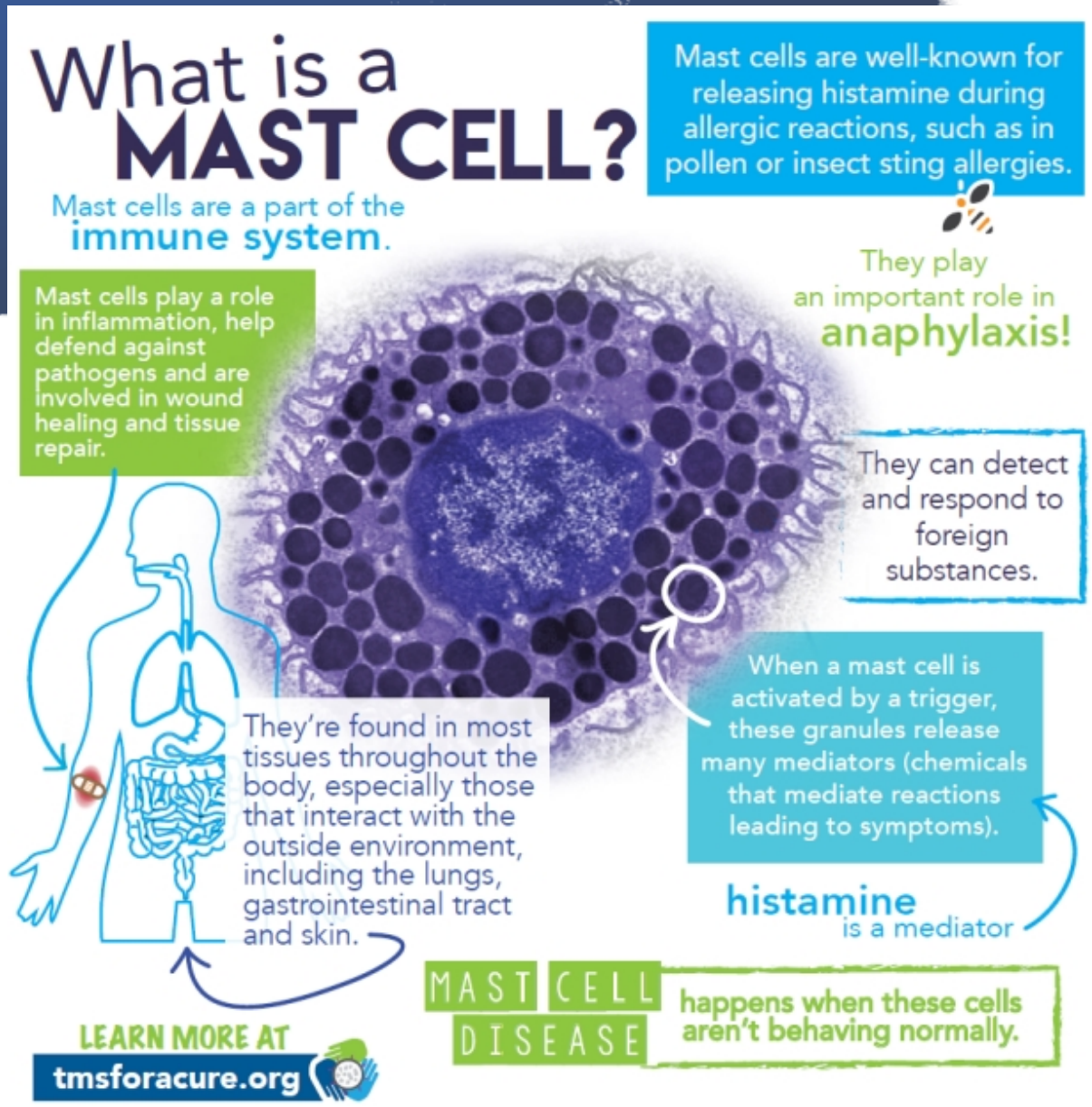
Clonal mast cell disorders	Non-clonal mast cell disorders
-Include: -Systemic mastocytosis -Monoclonal mast cell activation syndrome -Defined by: -Elevation in serum tryptase -Presence of KIT D816v mutation -atypical density and morphology of mast cells in bone marrow or other extracutaneous site -mast cell expression of CD2 or CD25	-more useful to identify by the specific condition rather than a “mast cell disorder” -Include: -Environmental allergies presenting as rhinitis, sinusitis, asthma -Food allergies -Chronic urticaria -(Idiopathic) Mast cell activation syndrome -others

(Idiopathic) Mast cell activation syndrome

- A wide range of conditions that are driven by aberrant mast cell mediator release
- A condition of “dysfunctional” mast cells, which (so far) are not defined by specific genetic markers

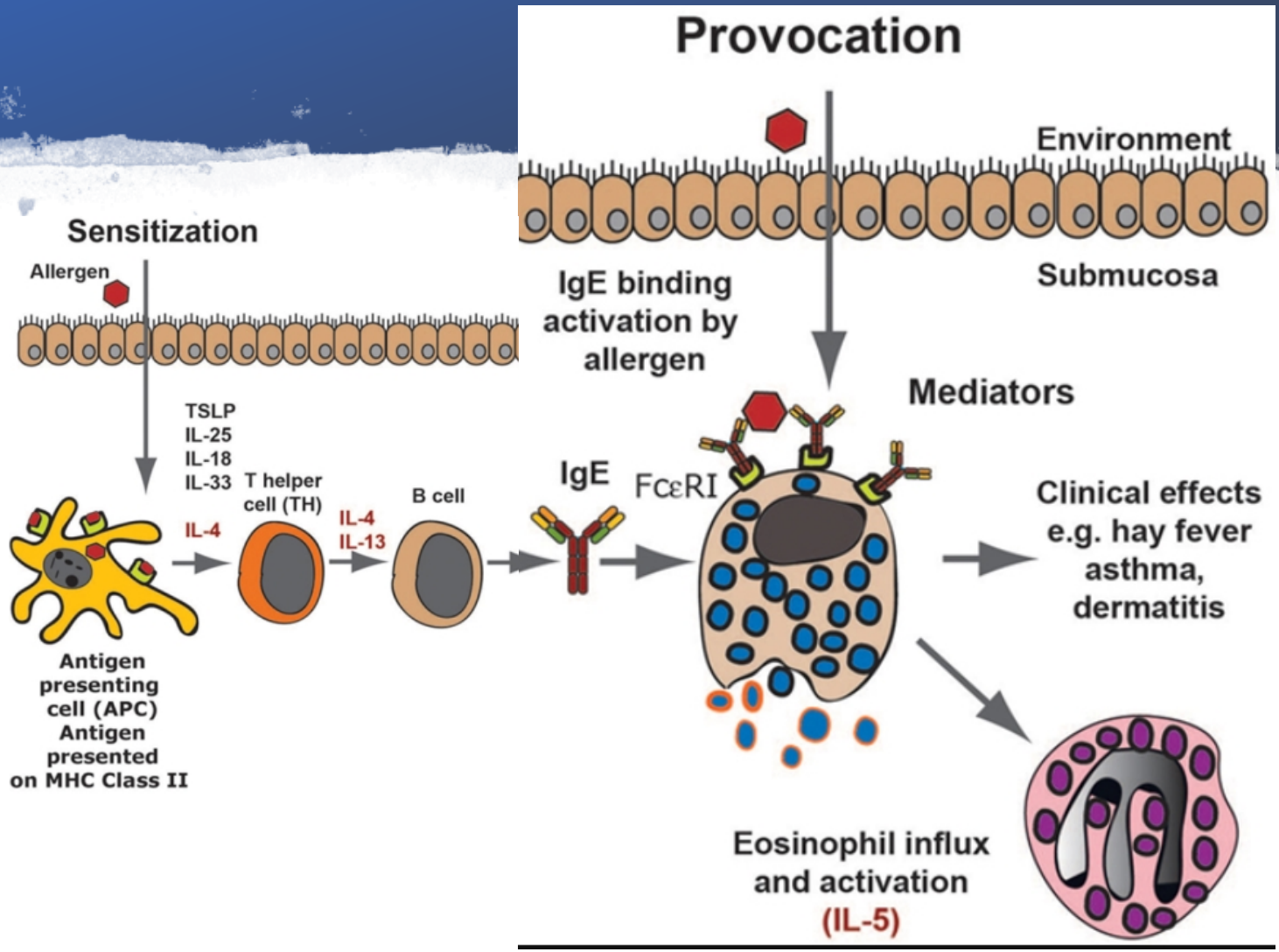
Introduction to mast cells

- Mast cells are antigen presenting cells, part of the innate immune system
- Normal function includes:
  - Sensing danger (not just foreign)
  - Sounding alarm to the rest of the immune system



Courtesy of The Mast Cell Disease Society tmsforacure.org

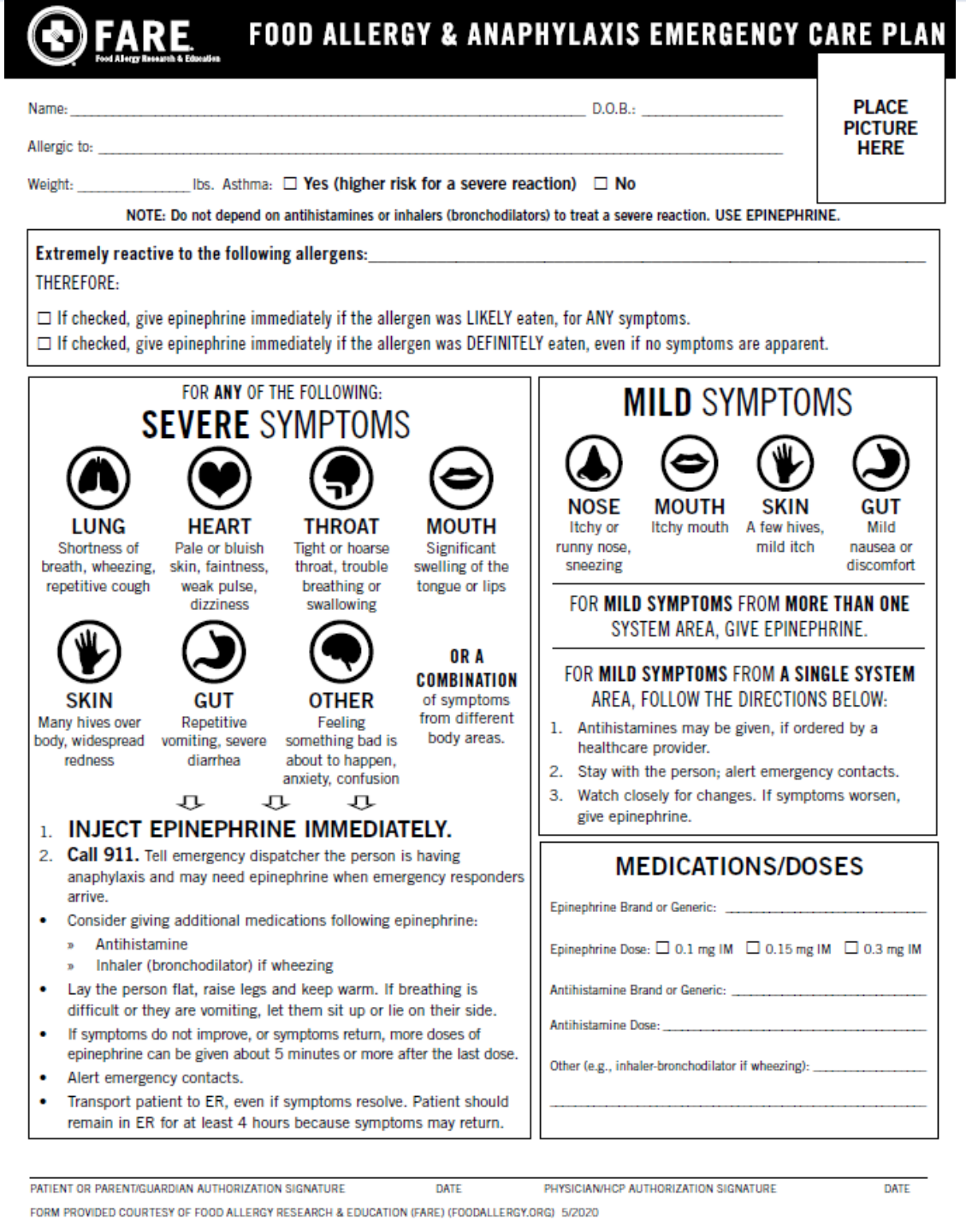
IgE-mediated mast cell activation



Hellman LT, Akula S, Thorpe M, Fu Zhirong. Tracing the origins of IgE, Mast Cells, and Allergies by Studies of Wild Animals. Front. Immunol., 19 December 2017

IgE-mediated food allergies

- History is consistent with positive IgE or skin prick test to the food
- Reaction is reproducible and independent of the preparation of the food and dose (for the most part)
- Treatment is strict avoidance, emergency plan including use of epinephrine autoinjector



FARE Food Allergy Research & Education

FOOD ALLERGY & ANAPHYLAXIS EMERGENCY CARE PLAN

Name: _____ D.O.B.: _____

Allergic to: _____

Weight: _____ lbs. Asthma: ☐ **Yes (higher risk for a severe reaction)** ☐ **No**

PLACE PICTURE HERE

NOTE: Do not depend on antihistamines or inhalers (bronchodilators) to treat a severe reaction. USE EPINEPHRINE.

Extremely reactive to the following allergens: _____

THEREFORE:

☐ If checked, give epinephrine immediately if the allergen was LIKELY eaten, for ANY symptoms.

☐ If checked, give epinephrine immediately if the allergen was DEFINITELY eaten, even if no symptoms are apparent.

FOR **ANY** OF THE FOLLOWING:

SEVERE SYMPTOMS

LUNG — Shortness of breath, wheezing, repetitive cough

HEART — Pale or bluish skin, faintness, weak pulse, dizziness

THROAT — Tight or hoarse throat, trouble breathing or swallowing

MOUTH — Significant swelling of the tongue or lips

SKIN — Many hives over body, widespread redness

GUT — Repetitive vomiting, severe diarrhea

OTHER — Feeling something bad is about to happen, anxiety, confusion

OR A COMBINATION of symptoms from different body areas.

1. **INJECT EPINEPHRINE IMMEDIATELY.**
2. **Call 911.** Tell emergency dispatcher the person is having anaphylaxis and may need epinephrine when emergency responders arrive.

- Consider giving additional medications following epinephrine:
  - Antihistamine
  - Inhaler (bronchodilator) if wheezing
- Lay the person flat, raise legs and keep warm. If breathing is difficult or they are vomiting, let them sit up or lie on their side.
- If symptoms do not improve, or symptoms return, more doses of epinephrine can be given about 5 minutes or more after the last dose.
- Alert emergency contacts.
- Transport patient to ER, even if symptoms resolve. Patient should remain in ER for at least 4 hours because symptoms may return.

MILD SYMPTOMS

NOSE — Itchy or runny nose, sneezing

MOUTH — Itchy mouth

SKIN — A few hives, mild itch

GUT — Mild nausea or discomfort

FOR **MILD SYMPTOMS** FROM **MORE THAN ONE** SYSTEM AREA, GIVE EPINEPHRINE.

FOR **MILD SYMPTOMS** FROM **A SINGLE SYSTEM** AREA, FOLLOW THE DIRECTIONS BELOW:

1. Antihistamines may be given, if ordered by a healthcare provider.
2. Stay with the person; alert emergency contacts.
3. Watch closely for changes. If symptoms worsen, give epinephrine.

MEDICATIONS/DOSES

Epinephrine Brand or Generic: _____

Epinephrine Dose: ☐ 0.1 mg IM ☐ 0.15 mg IM ☐ 0.3 mg IM

Antihistamine Brand or Generic: _____

Antihistamine Dose: _____

Other (e.g., inhaler-bronchodilator if wheezing): _____

_____

PATIENT OR PARENT/GUARDIAN AUTHORIZATION SIGNATURE DATE PHYSICIAN/HCP AUTHORIZATION SIGNATURE DATE

FORM PROVIDED COURTESY OF FOOD ALLERGY RESEARCH & EDUCATION (FARE) (FOODALLERGY.ORG) 5/2020

Non-IgE-mediated mast cell activation

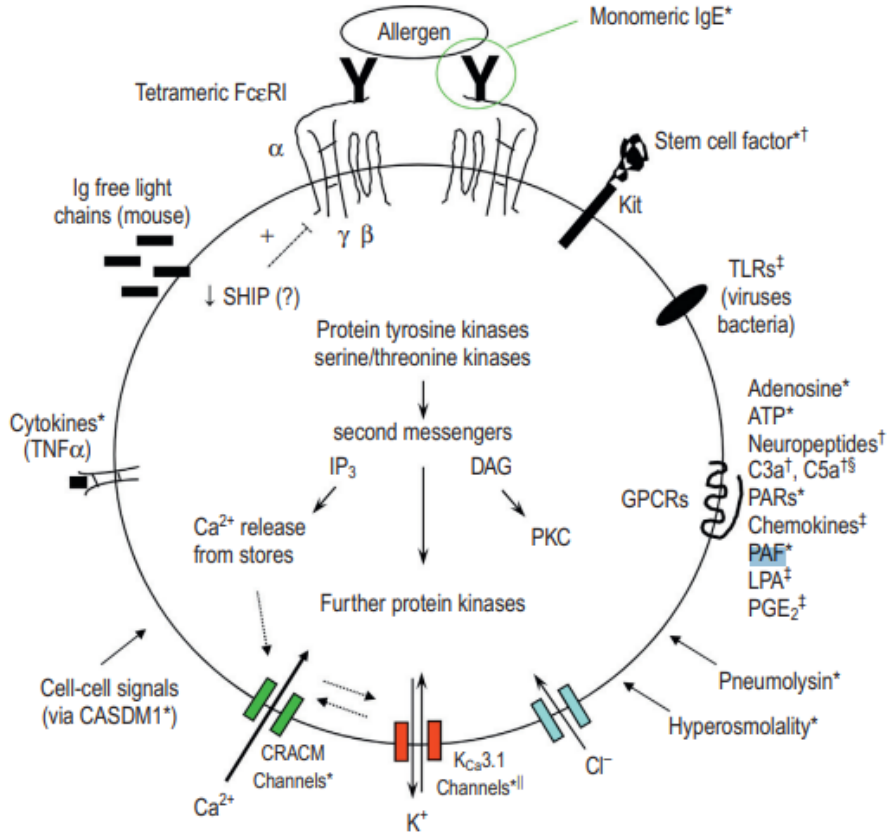


Figure 14-4 Many non–IgE-dependent pathways exist for the activation of human mast cells and are likely to contribute to mast cell activation in chronic diseases such as asthma, rheumatoid arthritis, and pulmonary fibrosis.
*HLMC.
†HSMC.
‡HCBMC.
§MC_{TC} subset of HLMC.
||HPBMC.

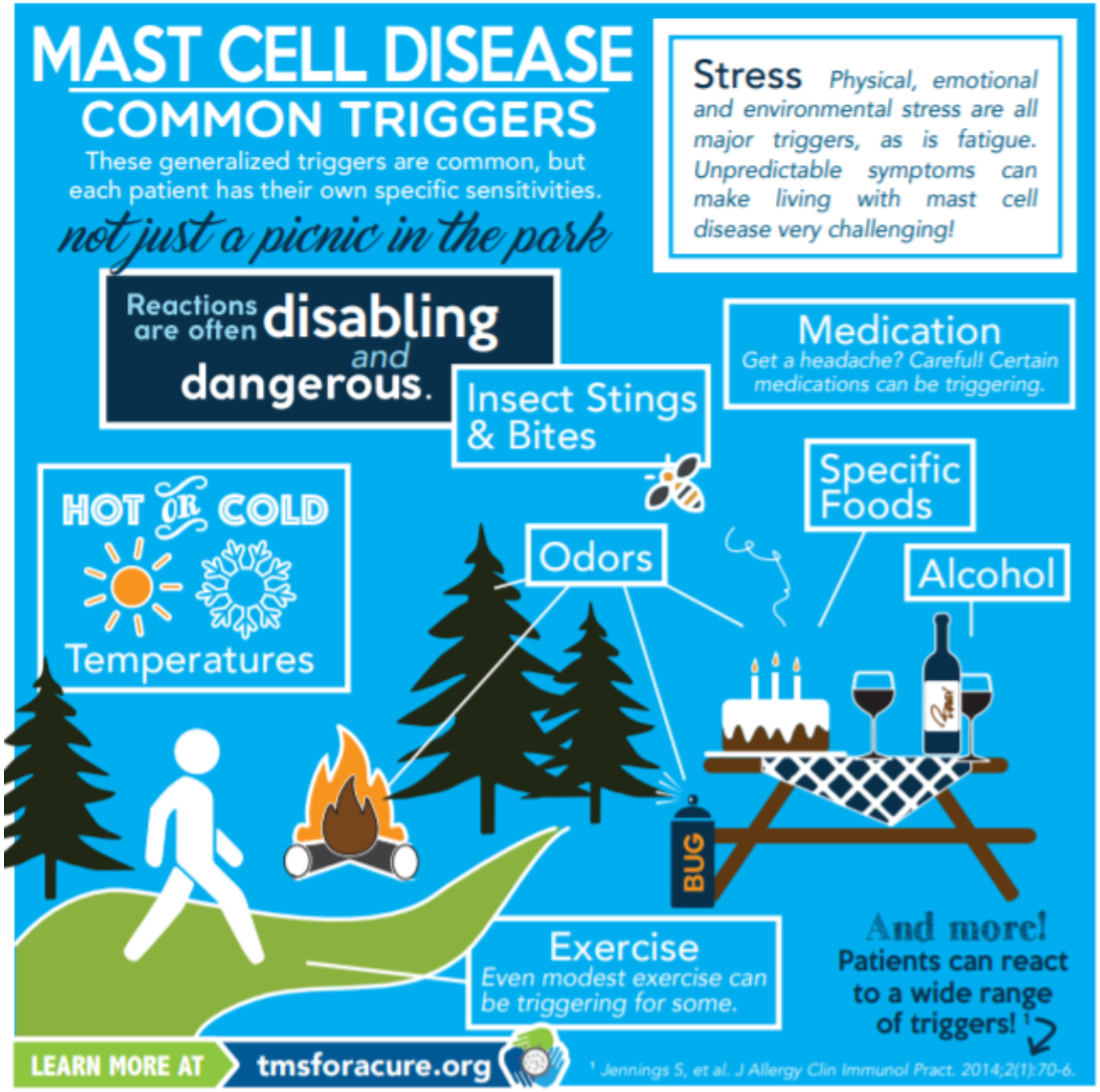
Bradding P, Saito H. "Biology of Mast Cells and Their Mediators." Middleton's allergy:principles and practice, Elsevier/Saunders, 2014. p236

Main receptor types:
-G protein-coupled receptors
-Toll-like receptors
-growth factor receptors

Beyond IgE

Mast cells also can be triggered by:

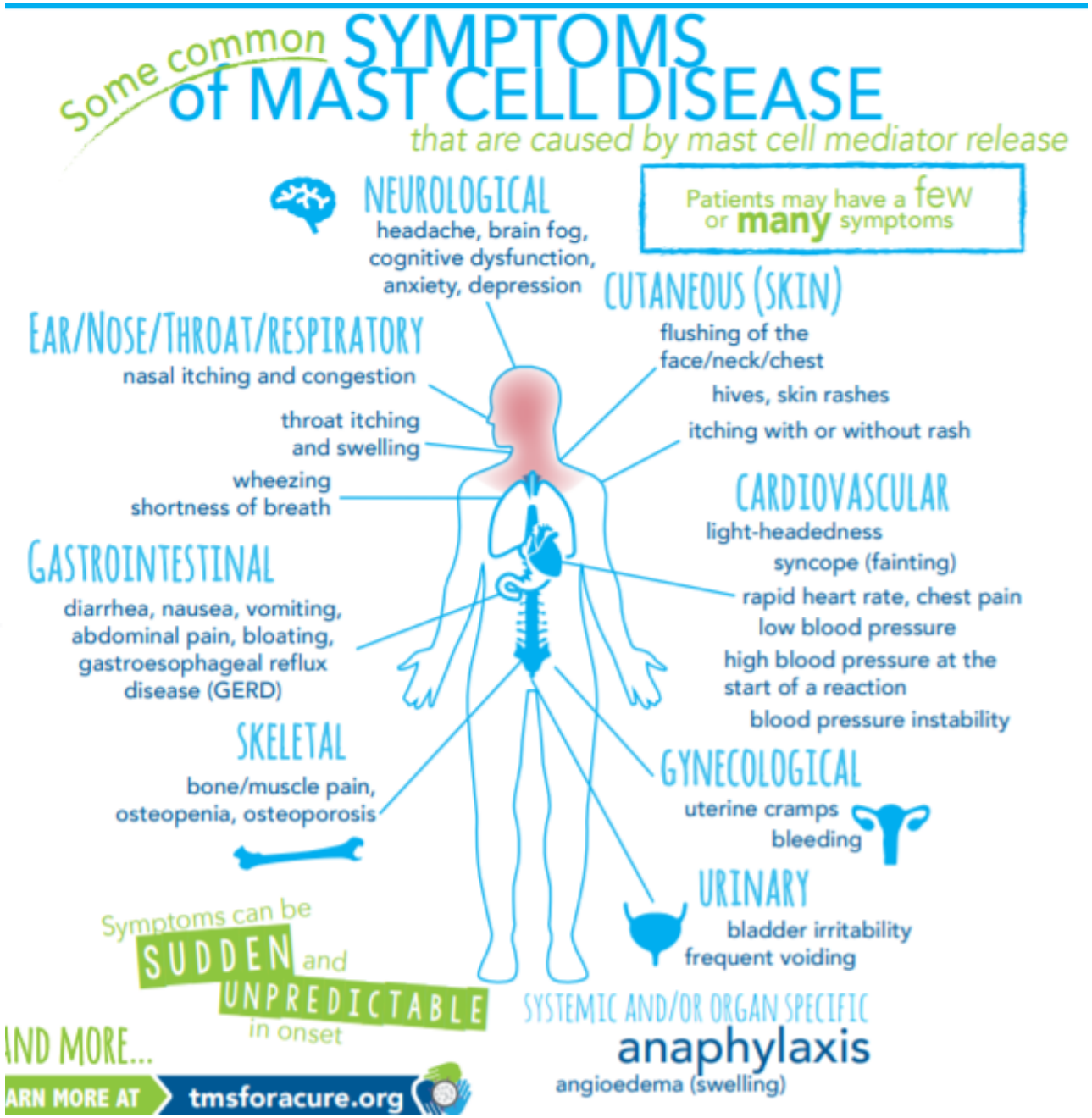
- Physical stimuli:
  - Pressure
  - Temperature
  - Vibration
- Triggers can be inconsistent, additive
- Treatment can raise the threshold for mast cell activation and allow greater tolerance for triggers



Courtesy of The Mast Cell Disease Society tmsforacure.org

Manifestations

- Diverse spectrum of symptoms, severity, age of onset
- Associated with:
  - Connective tissue disorders, including Ehlers-Danlos
  - Dysautonomia



Courtesy of The Mast Cell Disease Society tmsforacure.org

“The Pentad”

- Mast cell activation syndrome
- Dysautonomia
- Connective tissue disorder
- Gastroparesis (GI dysmotility)
- Autoimmunity (immune dysregulation)

When to suspect MCAS?

- I suspect in the presence of:
  - Idiopathic urticaria, flushing, pruritus
  - Multiple drug allergies
  - “Atypical” reactions to foods and medications (i.e. “corn makes my joints hurt” “fragrance causes GI symptoms”)
  - Autoimmunity + allergic conditions
  - “undifferentiated connective tissue disorder”
  - “functional” disorders: chronic fatigue, irritable bowel, interstitial cystitis, fibromyalgia, dysfunctional uterine bleeding + allergic conditions
  - Chronic pain + allergic conditions
- Often a significant family history, although presentation may differ from that of the patient

Physical exam findings

- Facial flushing, erythema of face, upper chest
- Dermatographism, mottled skin appearance
- Joint hypermobility
- Erythematous or purpuric hands and feet
- Deep inspiration for lung exam elicits dizziness

Laboratory testing

- Blood:
  - Tryptase
  - Histamine
  - Prostaglandin D2
- 24-hour urine metabolites:
  - n-methyl-histamine
  - leukotriene E4
  - 2,3-dinor-11Beta-prostaglandin F2 alpha
- Other labs I often order:
  - IgE respiratory, food, latex
  - IgA, IgG, IgM, tetanus, diphtheria, strep pneumo Ab titers
  - T, B, NK cell counts
  - If not done recently:
    - CBC with diff, CMP, TSH, HbA1c, vitamin D
    - If on highly restricted diet: B1, B2, B6, B12, C, iron

Diagnostic criteria for MCAS

AAAAI Mast Cell Disorders Committee Work Group Report 2019	Global "Consensus-2" criteria
-Recurrent, acute episodes when 2 or more organ systems involved (cardiovascular, respiratory, dermatologic, gastrointestinal) are involved -associated acute increases in levels of mast cell mediators above baseline on 2 or more occasions -Response to anti-mediator therapy	-Major + >=1 minor -Major criterion: Clinical symptoms that affect 2 or more systems -Minor criteria: -Evidence of above-normal levels of mast cell mediators -Symptomatic response to mast cell stabilizers or inhibitors of mast cell mediators -Pathology findings
Weiler, Catherine R. et al. AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management Journal of Allergy and Clinical Immunology, Volume 144, Issue 4, 883 - 896	Afrin et al. Diagnosis of mast cell activation syndrome: a global "consensus-2." Diagnosis Ahead of Publication; Published online: 22 Apr 2020.

“Broadly accepted characteristics” of MCAS

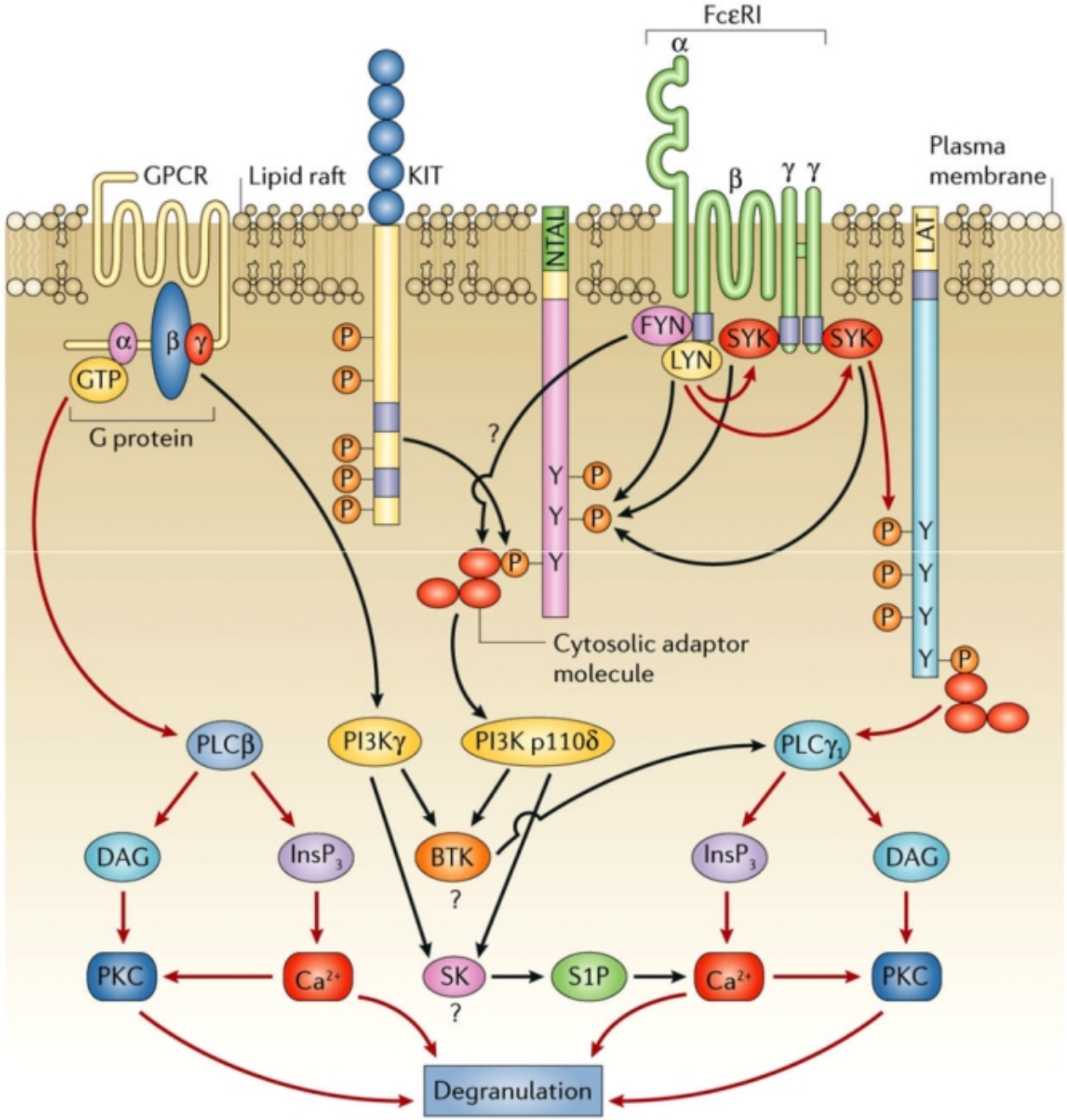
- An MCAS patient must have signs/symptoms of aberrant MCA in *multiple* organ systems
- An MCAS patient must (with reasonable confidence) *not* have some other disease accounting better than MCA for the full range and duration of the observed symptoms/signs”

Afrin et al 2020

(Attempts at) Pathogenesis

Pathways for Mast Cell Activation

- C3a and others can induce mast cell activation independently of antigen
- Agents can also alter the threshold of mast cell activation
- Theoretically, then variants in genes encoding for receptors and downstream signaling molecules potentially influence threshold for mast cell activation



Immunol Res. 2009 ; 43(1-3): 15–24. doi:10.1007/s12026-008-8046-9.

An amplified signal

- Variants in these genes are often found when I request whole genome sequencing with analysis performed by Dr. Richard Boles:
  - Calcium channels: CACNA1A, CACNA1S, RYR2
  - Sodium channels: SCN1A, SCN2A, SCN4A, SCN9A, SCN10A, SCN11A
- These all result in “overactivity” or “lack of filter” or “amplified signal” that often present with:
  - Pain
  - migraine
  - Fatigue
  - Visceral hyperalgesia, gastrointestinal symptoms
  - Excessive/inappropriate “fight or flight” response (dysautonomia)

MRGPRX2 Receptor

- Expressed on surface of human skin mast cells, synovial mast cells
- Can be activated by:
  - Neuropeptide substance P
  - vancomycin
  - Morphine
  - Cationic agents (atracurium, icatibant)
- Evidence for upregulation of MRGPRX2 receptor in patients with chronic urticaria

Fujisawa D, Kashiwakura J, Kita H, et al. Expression of Mas-related gene X2 on mast cells is upregulated in the skin of patients with severe chronic urticaria. *J Allergy Clin Immunol*. 2014;134(3):622-633.e9.
Varricchi G et al. Heterogeneity of Human Mast cells with respect to MRGPRX2 Receptor expression and function. Front. Cell. Neurosci., 03 July 2019

MCAS and autoimmunity

- Autoantibodies to G-protein coupled adrenergic receptors and muscarinic acetylcholine receptors are associated with postural orthostatic tachycardia syndrome (POTS).
  - In a study of 55 patients with POTS, 50 had presence of autoantibodies to adrenergic or muscarinic receptors.
- Mast cells express adrenergic and muscarinic receptors which could also be activated by autoantibodies
- Patients with chronic urticaria often have IgG antibodies to high affinity IgE receptor (FC□R1) which can potentially induce mast cell activation

Gunning WT 3rd, Kvale H, Kramer PM, Karabin BL, Grubb BP. Postural Orthostatic Tachycardia Syndrome Is Associated With Elevated G-Protein Coupled Receptor Autoantibodies. J Am Heart Assoc. 2019;8(18):e013602. doi:10.1161/JAHA.119.013602

Mechanisms for the Pentad

- Mast cell proteases may induce abnormal remodeling of the extracellular matrix
- Weakened barrier function may allow for abnormal penetration of antigen, mast cell activation and downstream effects (akin to “leaky skin” and food allergy)
- Extra cellular matrix stretch induces mast cell degranulation
- Genes associated with connective tissue disorders commonly seen when whole genome sequencing is performed in my patients:
    - TNXB encodes for tenascin
    - COL genes encoding for collagen types

Doherty TA, White AA. Postural orthostatic tachycardia syndrome and the potential role of mast cell activation. Autonomic Neuroscience. 215. Dec 2018. 83-88.

Mechanisms for the Pentad

- Mast cells are located in close proximity to blood vessels and nerve endings
- Mast cells can form membrane-membrane contact with nerve cells in vivo
- Mast cells can release mediators that can acutely modulate nerve function and be responsible for symptoms of tachy/brady-cardia, hyper-/hypo-tension
- Mast cell mediators may alter excitability of a nerve and vice versa
  - LTD4 acting at CyLT1 does not singularly activate the nerve, but makes the trigeminal nerve more susceptible to activation by other stimuli
  - Platelet-activating factor (PAF) stimulates histamine release from mast cells in intact human skin but not in dispersed human skin mast cells in vitro. This suggests indirect activation of mast cells via local nerve cells by PAF.

Mechanisms for the Pentad

- After allergic stimulation, nerves can undergo phenotypic changes which may be responsible for longer-term effects that persist after resolution of mast cell mediators
- Mast cell mediators can stimulate receptors expressed on afferent nerve terminals. These neurons can then send signals to the central nervous system and release neuromodulators which then further stimulate mast cell activation
- Mast cells can also recruit other immune cells (neutrophils, eosinophils, macrophages, T cells), which release pro-nociceptive mediators and promote inflammation

Doherty TA, White AA. Postural orthostatic tachycardia syndrome and the potential role of mast cell activation. Autonomic Neuroscience. 215. Dec 2018. 83-88.

MCAS and multiple sclerosis

- Mast cells release cytokines and chemokines which recruit and activate T cells and macrophages
- Mast cells present myelin antigen to T cells
- Mast cells disrupt the blood brain barrier allowing T cells to infiltrate and target myelin basic protein
- In vitro, mast cell proteases degrade myelin protein
- Myelin stimulates mast cell degranulation directly
- Mast cells may be a therapeutic target for multiple sclerosis

Xu Y, Chen G. Mast cell and autoimmune diseases. Mediators Inflamm. 2015;2015:246126. doi:10.1155/2015/246126

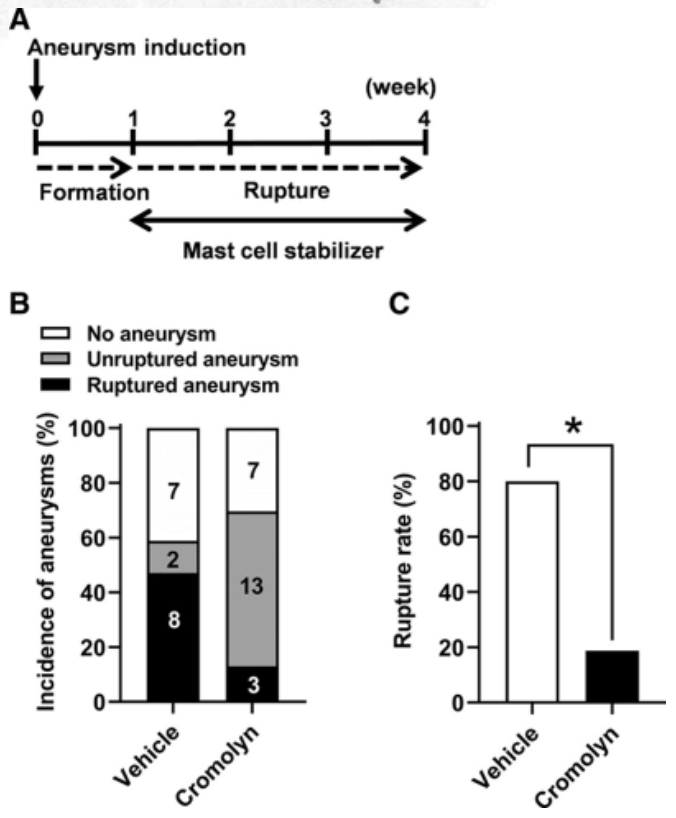
MCAS and intracranial aneurysm

- Mast cells have been detected in human intracranial aneurysm tissues and their presence was associated with intramural microhemorrhage and wall degeneration.
- Intracranial aneurysms were induced in mice by using a combination of induced systemic hypertension and single injection of elastase into the CSF. Aneurysm formation and rupture were assessed over 3 weeks.
- Roles of mast cells were assessed using cromolyn (mast cell stabilizer), CD48/80 (mast cell activator), and mice that are genetically lacking mature mast cells.

Hajime Furukawa. Stroke. Mast Cell Promotes the Development of Intracranial Aneurysm Rupture, Volume: 51, Issue: 11, Pages: 3332-3339, DOI: (10.1161/STROKEAHA.120.030834)

MCAS and intracranial aneurysm

- There was no difference in incidence of aneurysm formation between the mice treated with cromolyn vs. vehicle.
- Mice treated with cromolyn after aneurysmal formulation had significantly reduced rupture rate (80% vs. 19%; n = 10 vs n = 16 $p<0.05$)
- Mice treated with cromolyn had significant reduced expression of tryptase compared to vehicle-treated group



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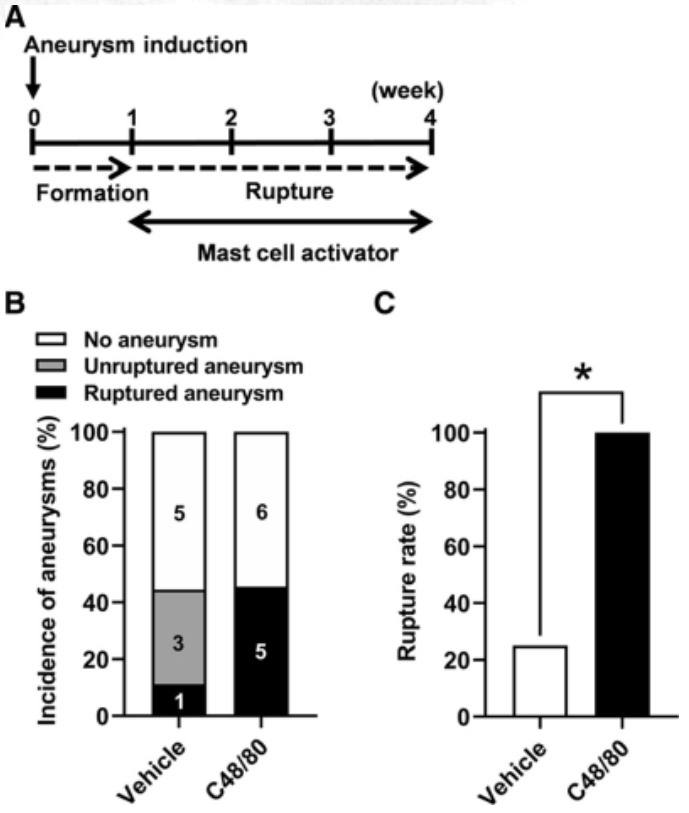
MCAS and intracranial aneurysm

- Mice treated with compound 48/80 (promotes mast cell activation and degranulation) did not have increased incidence of intracranial aneurysm compared to those treated with vehicle, but it significantly increased rupture rate (25% vs. 100%; n=4 vs. n=5; $p<0.05$)
- Dose-dependent effect of C48/80 was also demonstrated.
- PCR quantification of the mRNA of inflammatory cytokines and enzymes with mast cell origin (angiotensin II type I receptor, interleukin-6, matrix metallopeptidase 9, tumor necrosis factor-α, cathepsin G, chymase, and tryptase) did not show significant difference between vehicle-treated and CD48/80-treated mice.



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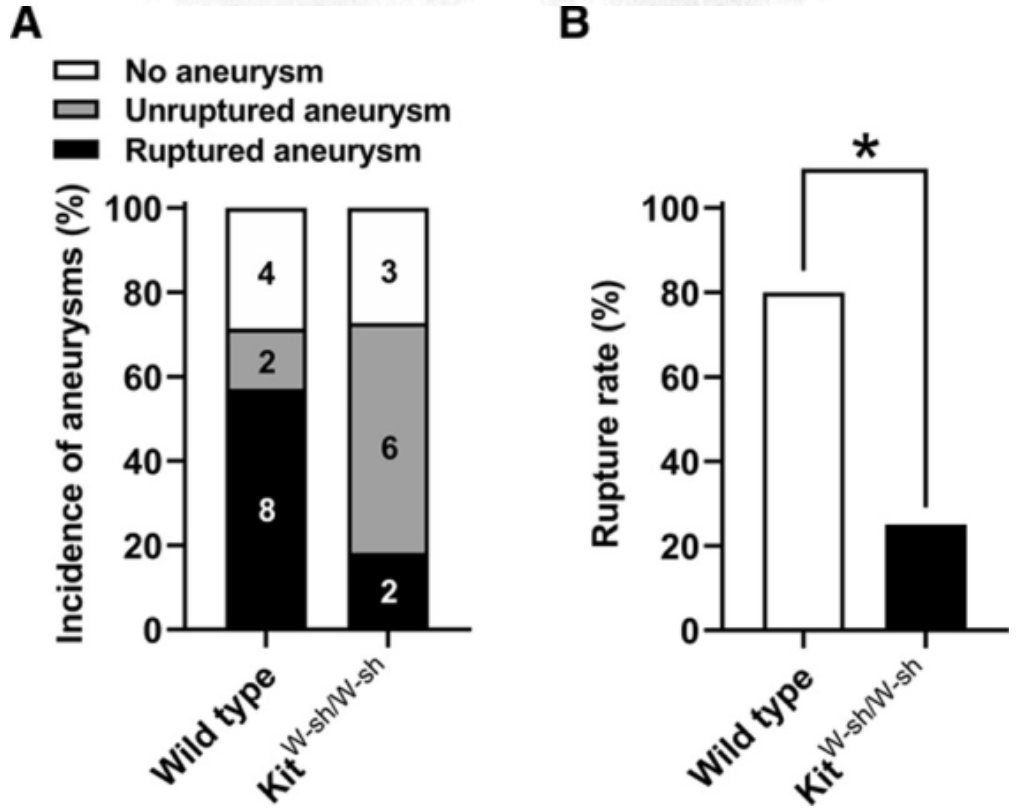
MCAS and intracranial aneurysm

- KitW-sh/W-sh mice genetically lack mature mast cells. These cells had no significant difference in incidence of aneurysm compared to wild-type mice. They had a significantly lower rate of aneurysm rupture compared to wild-type mice.



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MCAS and intracranial aneurysm

- KitW-sh/W-sh mice genetically lack mature mast cells. These cells had no significant difference in incidence of aneurysm compared to wild-type mice. They had a significantly lower rate of aneurysm rupture compared to wild-type mice.
- In summary, presence of mast cells and increased mast cell activation had no effect on formation of aneurysm but increased rate of rupture.
- Authors hypothesize that cytokines and chemokines release by mast cells may be responsible for promotion of aneurysm.

Hajime Furukawa. Stroke. Mast Cell Promotes the Development of Intracranial Aneurysm Rupture, Volume: 51, Issue: 11, Pages: 3332-3339, DOI: (10.1161/STROKEAHA.120.030834)

Treatment

Pharmacologic Therapies

There are no FDA-approved therapies for the indication mast cell activation syndrome.

- Antihistamines (H1 and H2 blockers)
- Anti-leukotrienes (i.e. montelukast, zafirlukast)
- Cromolyn (mast cell stabilizer)
- Ketotifen (mast cell stabilizer, antihistamine)
- Quercetin (mast cell stabilizer)
- Vitamin C (enzymatic cofactor involved in mast cells, skin and endothelial barriers)
- Mitochondrial supplementation (coenzyme 10, magnesium, vitamin B2, C, D, carnitine)

- Higher risk therapies:
  - Omalizumab (anti-IgE IgG)
  - Imatinib (tyrosine kinase inhibitor)
  - IVIG, Immunosuppresion
  - Jak inhibitors?
- Others:
  - Dupilumab
  - Low dose naltrexone

Peri-operative/peri-procedural considerations

- Extrapolated from recommendations for patients with systemic mastocytosis) these medications are recommended as least likely to trigger mast cell release:
  - IV hypnotics: etomidate, propofol, ketamine
  - Neuromuscular blocking agents: succinylcholine, cis-atracurium, pancuronium, vecuronium
  - Analgesics: Fentanyl, acetaminophen
- The following medications are discouraged:
  - IV hypnotics: thiopental
  - Neuromuscular blocking agents: Rapacuronium, Atracurium, Mivacurium
  - Analgesics: Codeine

Hermans et al. Management around invasive procedures in mastocytosis: An update. Ann Allergy Asthma Immunol. 2017 Oct;119(4):304-309. doi: 10.1016/j.anai.2017.07.022. Epub 2017 Aug 31.

Peri-operative/peri-procedural considerations

- Premedication:
  - IV solumedrol 40-80mg
  - IV diphenhydramine 50mg (may potentiate anesthesia)
- IV Hydration at maintenance rate of 120ml/hr or greater
- Increase in baseline medication to assist with management of pain, nausea, additional medications, antibiotics
- MCAS patients tend to be sensitive to opioids and NSAIDs, but most will tolerate specific agents.

Peri operative/peri procedural considerations

- Potential triggers unique to the procedure/test:
  - Antiseptic and its application (rubbing of the skin)
  - Anesthetic and its excipients
  - Trauma (e.g. excision, electrocautery, etc.)
  - Bandage containing adhesive
  - Topical ointment (i.e. antibiotic, petrolatum)
- Potential triggers of the office visit:
  - Fragrances
  - Room temperature
  - Emotional stress

MCAS in summary

- Wide spectrum of presentation, laboratory data, response to therapy
- Probably common
- Treatable, and patients would benefit from good control of disease peri-operatively


Thank you!

References 1

- Afrin LB, Self S, Menk J, Lazarchick J. Characterization of Mast Cell Activation Syndrome. Am J Med Sci. 2017 Mar;353(3):207-215. doi: 10.1016/j.amjms.2016.12.013. Epub 2016 Dec 16. PMID: 28262205; PMCID: PMC5341697.
- Afrin et al. Diagnosis of mast cell activation syndrome: a global “consensus-2.” Diagnosis Ahead of Publication; Published online: 22 Apr 2020.
- Bradding P, Saito H. “Biology of Mast Cells and Their Mediators.” Middleton’s allergy:principles and practice, Elsevier/Saunders, 2014. p236.
- Fujisawa D, Kashiwakura J, Kita H, et al. Expression of Mas-related gene X2 on mast cells is upregulated in the skin of patients with severe chronic urticaria. *J Allergy Clin Immunol*. 2014;134(3):622-633.e9.
- Furukawa H, Wada K, Tada Y, Kuwabara A, Sato Hiroki, Ai J, Lawton MT, Hashimoto T. Mast Cell Promotes the Development of Intracranial Aneurysm Rupture. 6 Oct 2020https://doi.org/10.1161/STROKEAHA.120.030834Stroke. 2020;51:3332–3339
- Gunning WT 3rd, Kvale H, Kramer PM, Karabin BL, Grubb BP. Postural Orthostatic Tachycardia Syndrome Is Associated With Elevated G-Protein Coupled Receptor Autoantibodies. J Am Heart Assoc. 2019;8(18):e013602. doi:10.1161/JAHA.119.013602
- Gilfillan AM, Peavy RD, Metcalf DD. Amplification mechanisms for the enhancement of antigen-ediated last cell activation. *Immunol Res*. 2009 ; 43(1-3): 15–24. doi:10.1007/s12026-008-8046-9.
- Hellman LT, Akula S, Thorpe M, Fu Zhirong. Tracing the origins of IgE, Mast Cells, and Allergies by Studies of Wild Animals. Front. Immunol., 19 December 2017
- Horny HP et al. Mastocytosis. In: WHO classification of tumours of haematopoietic and lymphoid tissues, 4th ed, Lyon 2008.

References 2

- Kim JH, Xi S, Ference EH, Ge M, Liu MM, Wrobel BB. Patient characteristics of suspected mast-cell activation syndrome with sinonasal obstruction: a single institution experience. Int Forum Allergy Rhinol. 2020;10(8):996-1000. doi:10.1002/alr.22558Molderings, G.J., Brettner, S., Homann, J., and Afrin, L.B. Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options. *J Hematol Oncol*. 2011; 4: 10
- Petersen LJ, Church MK, Skov PS. Platelet-activating factor induces histamine release from human skin mast cells in vivo, which is reduced by local nerve blockade. *J Allergy Clin Immunol*. 1997;99(5):640-647. doi:10.1016/s0091-6749(97)70026-5
- Varricchi G et al. Heterogeneity of Human Mast cells with respect to MRGPRX2 Receptor expression and function. Front. Cell. Neurosci., 03 July 2019
- Xu Y, Chen G. Mast cell and autoimmune diseases. Mediators Inflamm. 2015;2015:246126. doi:10.1155/2015/246126
- Zuberbier, T, Abdul Latiff, AH, Abuzakouk, M, et al. The international EAACI/GA²LEN/EuroGuiDerm/APAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2021; 00: 1– 33. doi:10.1111/all.15090