The Spectrum of Mast Cell Disease

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Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.

- Takeda Advisory Board Participant (2021)
- Leo Pharma Advisory Board Participant (2021)
- Sanofi Advisory Board Participant and Speaker (2021-present)
- Nectar Allergy Advisory Board Participant (2021-present)
- Nectar Allergy Medical Consultant (2021-present)
- Cogent Advisory Board Participant (2023)
- Discussing off-label use of several medications (antihistamines, biologics)

Objectives

- List the types of mast cell disease seen in the clinical setting
- Describe the management considerations for patients with various types of mast cell disease

Clinical Case #1

- DS is a 25 yo female presents to your clinic
  - Symptoms: Flushing, pruritus, nausea/vomiting, syncopal events, tachycardia, and fatigue
  - Triggers: Stress, NSAIDs, idiopathic
  - Significantly affects QoL due to fear of anaphylactic events

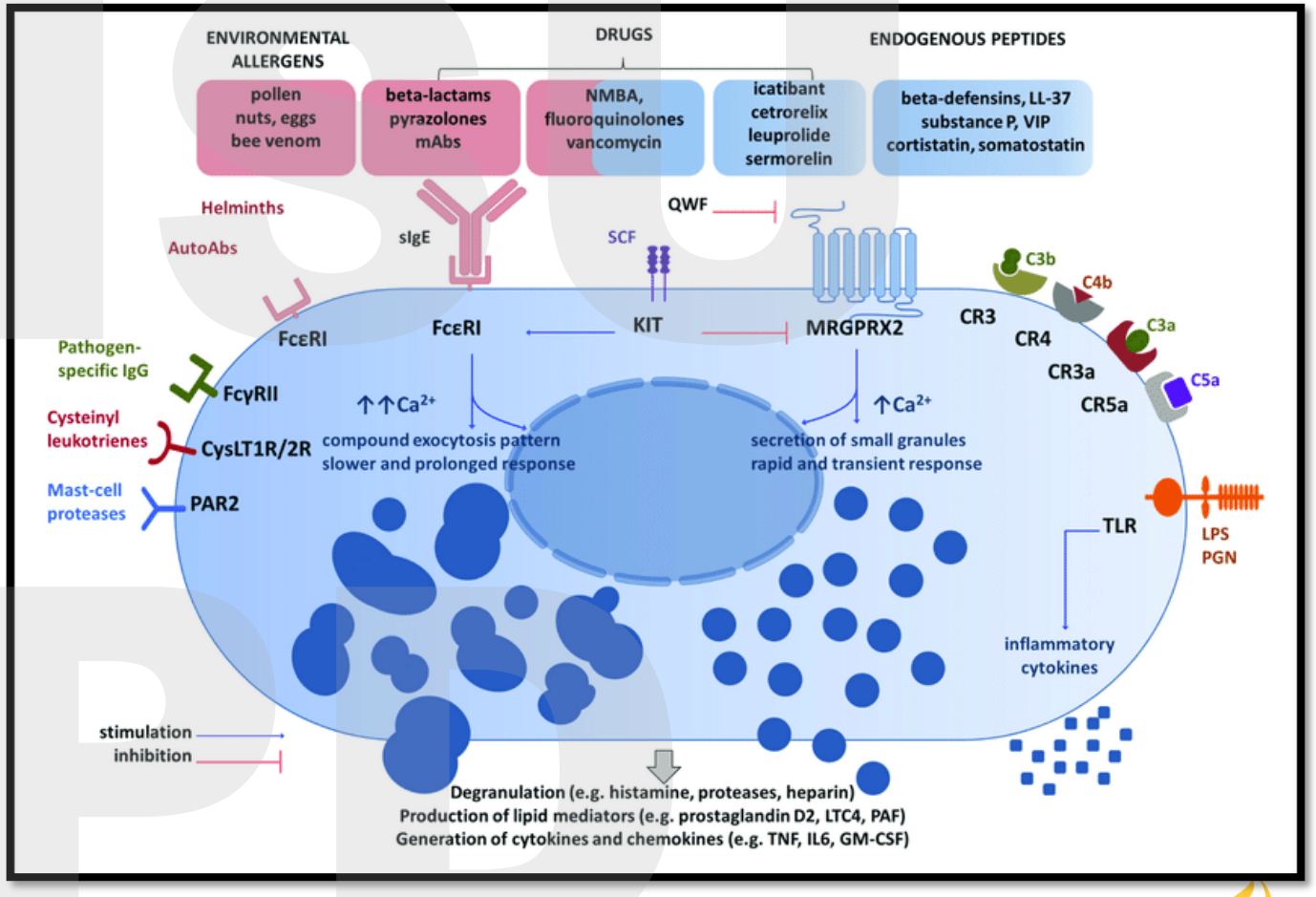
  - Current medication regimen: Cetirizine 10mg daily, epinephrine autoinjector

Clinical Case #2

- LR is a 38 yo female with a history of mast cell activation syndrome
  - Symptoms: Hot flashes, throat tightening sensation with shortness of breath, nausea, bloating, palpitations, and “brain fog”
  - Triggers: Multiple foods/drugs, smoke exposure, strong odors
  - Significantly affects QoL due to limited diet and medication restrictions
  - Current medication regimen: Cetirizine 10mg 2XD, cromolyn nasal spray PRN, oral cromolyn 4XD

Pathophysiology

- Mast cell activation
  - FcεR1 (IgE)
  - Toll-like receptors, NOD-like receptors
  - Fcγ receptors (IgG)
  - G-protein-coupled receptor X2 (MRGPRX2)
  - KIT receptors
  - Siglec-8



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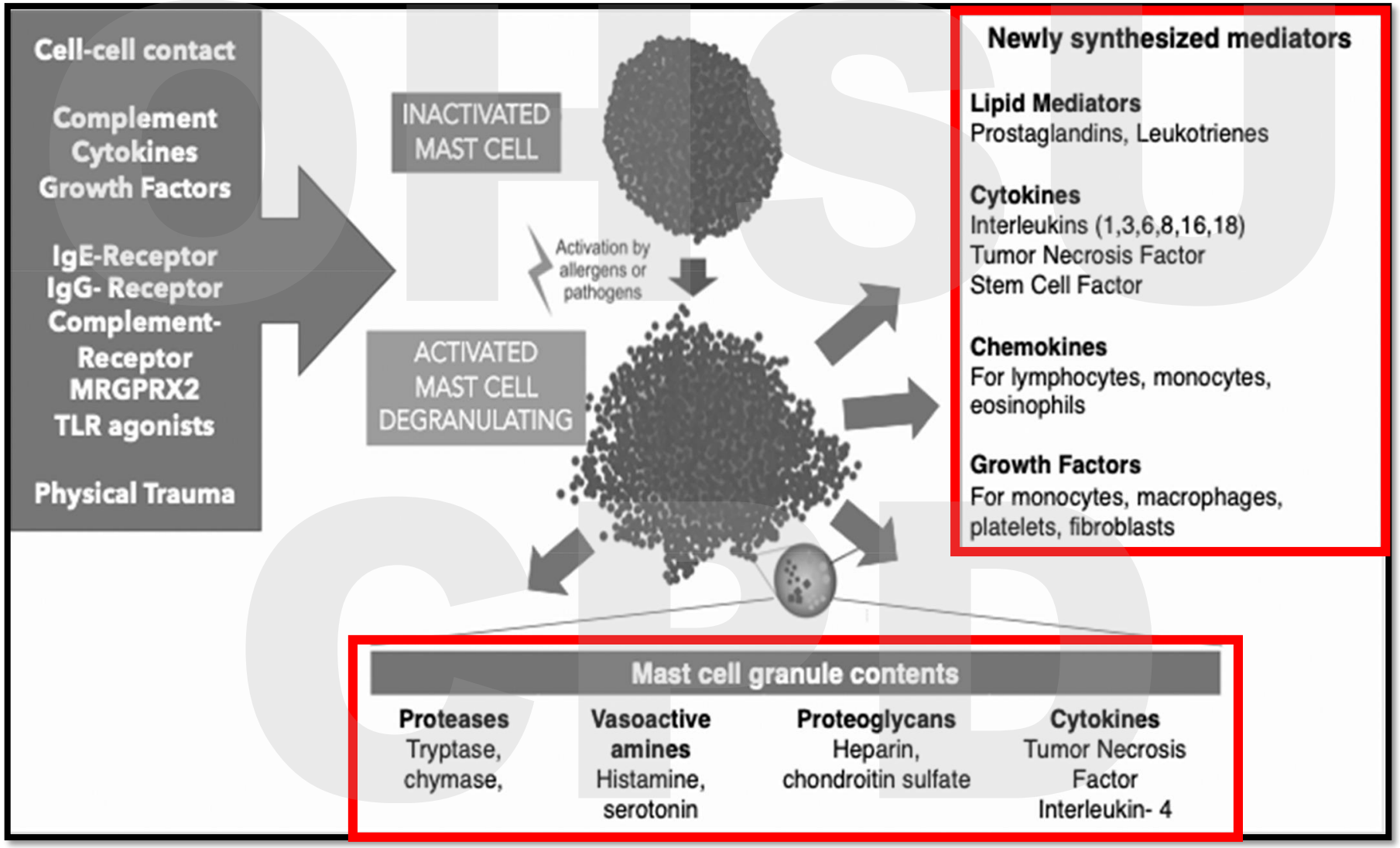
Mast Cell Degranulation



Brock I, et al. Am J Med Genet C Semin Med Genet. 2021 Dec;187(4):473-481.

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Spectrum of Mast Cell Disease

Idiopathic
MCAS

Less-Aggressive Mastocytosis
- Cutaneous mastocytosis
- Indolent systemic mastocytosis
- Smoldering systemic mastocytosis

Hereditary Alpha-Tryptasemia

Nonclonal Mast Cell Activation
- Allergic (IgE) Conditions
- Chronic Urticaria
- MCA due to neoplasm

Idiopathic Anaphylaxis
Exercise-induced
Anaphylaxis

Systemic Mastocytosis
- Aggressive SM
- SM with hematologic neoplasm
- Mast cell leukemia/sarcoma

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Mast Cell Activation Disorders

Definition: MCAS is a condition in which the patient experiences repeated episodes of the symptoms of anaphylaxis – allergic symptoms such as hives, swelling, low blood pressure, difficulty breathing and severe diarrhea. High levels of mast cell mediators are released during those episodes.

- AAAAI Practice Parameters

MCAS Symptoms

- Cardiac:
  - Tachycardia, hypotension, and syncope
- Cutaneous:
  - Pruritus, urticaria, angioedema, and flushing
- Pulmonary:
  - Wheezing, shortness of breath and stridor that occurs with throat swelling
- Gastrointestinal:
  - Diarrhea, nausea with vomiting and crampy abdominal pain

Diagnostic Clues for Mast Cell Disease

- Unexplained anaphylaxis
  - Particularly if syncope/hypotension is involved
- Anaphylaxis/hypotension due to venom stings
- Osteoporosis in young patients
- Episodic flushing with moderate to severe pruritus

- MCD is unlikely if the following are presenting symptoms:
  - Chronic fatigue, intolerances to various environmental factors, food and medication, memory loss or headache

Diagnostic Criteria

Proposed criteria for the diagnosis of mast cell activation syndrome

1. Episodic symptoms consistent with mast cell mediator release affecting two or more organ systems
2. A decrease in the frequency or severity; or resolution of symptoms with anti-mediator therapy: H1 and H2 histamine receptor antagonists, anti-leukotriene medications, or mast cell stabilizers (cromolyn sodium)
3. Evidence of an elevation in a validated urinary or serum marker of mast cell activation: Documentation of elevation of the marker above the patient's baseline during a symptomatic period on at least two occasions; Total serum tryptase is recommended as the markers of choice.

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Diagnostic Studies

Serum tryptase

~~Serum histamine~~

Urinary N-methylhistamine

~~Urinary PGD2~~

~~Urinary LTE4~~

Urinary PGF2-alpha

~~Chromogranin A~~

~~Serotonin~~

~~Heparin~~

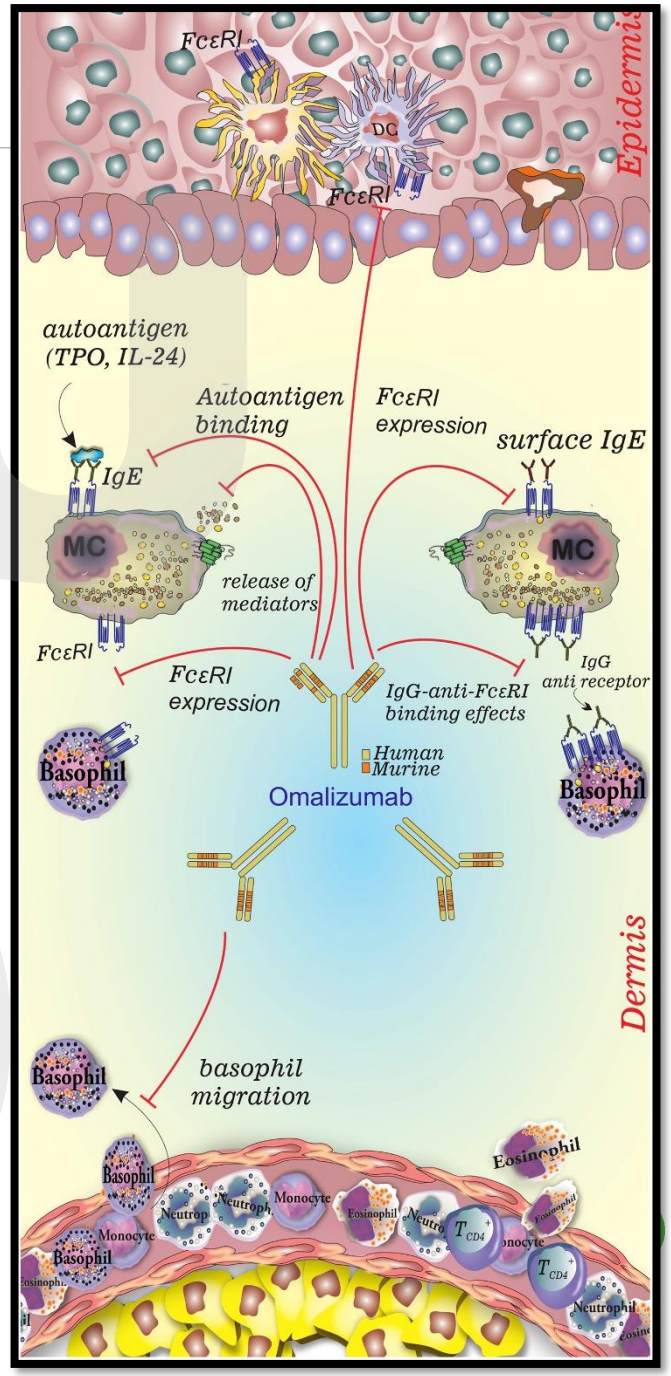
~~Diamino-oxidase (DAO)~~

Therapy

- Symptomatic management of specific organ systems
  - H1 Antihistamines (cetirizine, levocetirizine, fexofenadine)
  - H2 Antihistamines (famotidine)
  - Leukotriene modifying agents (montelukast, zileuton)
  - Mast cell stabilizing agents (cromolyn, ketotifen)
  - Anti-IgE monoclonal antibodies (omalizumab)

Omalizumab: Proposed Mechanisms

1. Rapid reduction in free IgE autoantibodies
2. Decreasing FcεRI expression and surface bound IgE (reducing cross-linking)
   - Thereby lowering effects of IgG-anti-FcεRI, IgG-anti-IgE, autoantigen binding, and IgE-autoantibodies
3. Decreased reactivity and degranulation of mast cells systemically



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Take Home Points

1. Patients often receive the presumed diagnosis of mast cell activation syndrome without meeting diagnostic criteria
2. MCAS can produce significant and debilitating symptoms. Clinicians must have a high degree of suspicion.
3. Combination of antihistamines, leukotriene modifying agents, and mast cell stabilizers are often adequate to manage symptoms.

Thank you!!

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