Mast Cells are Beautiful.

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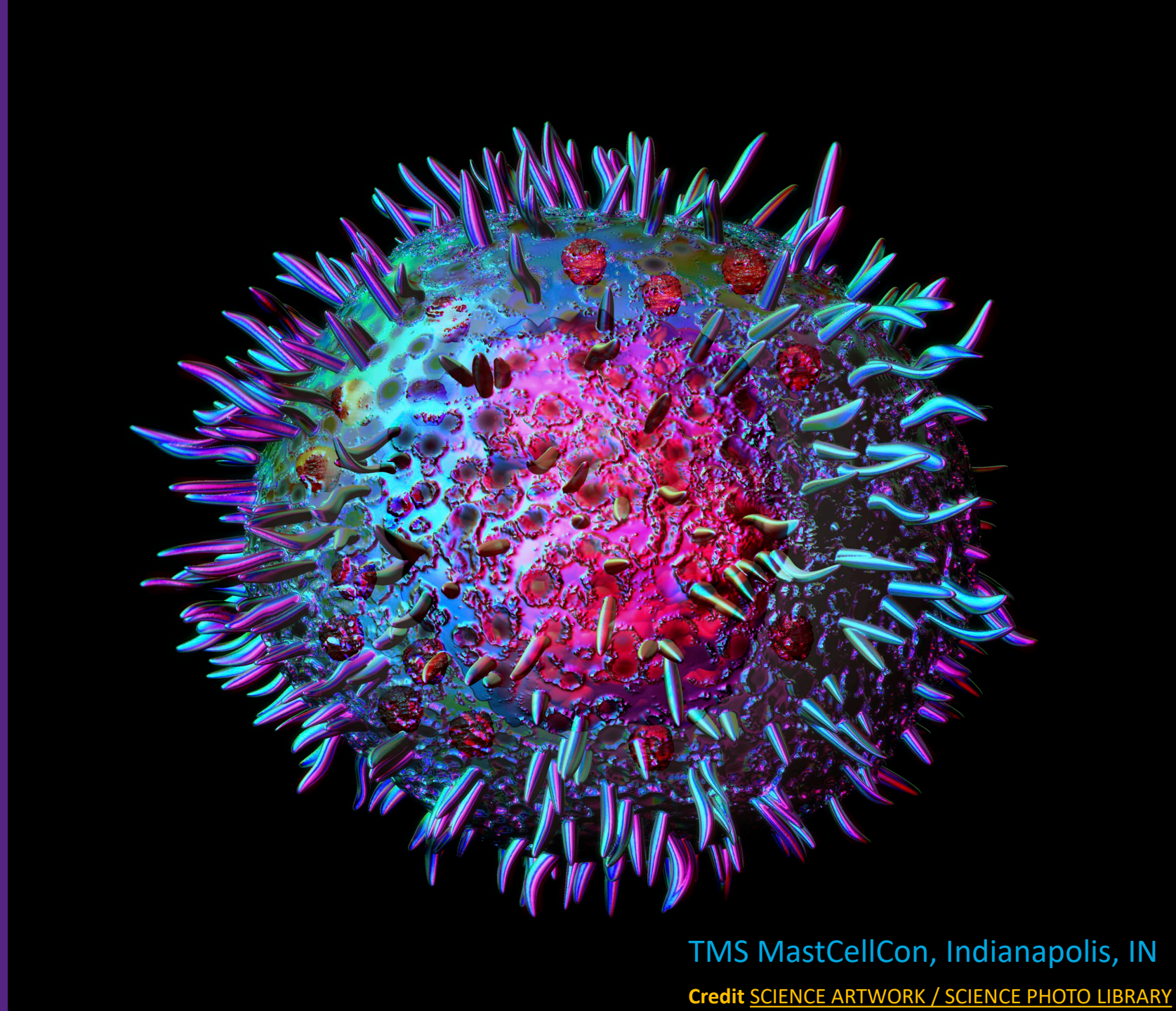

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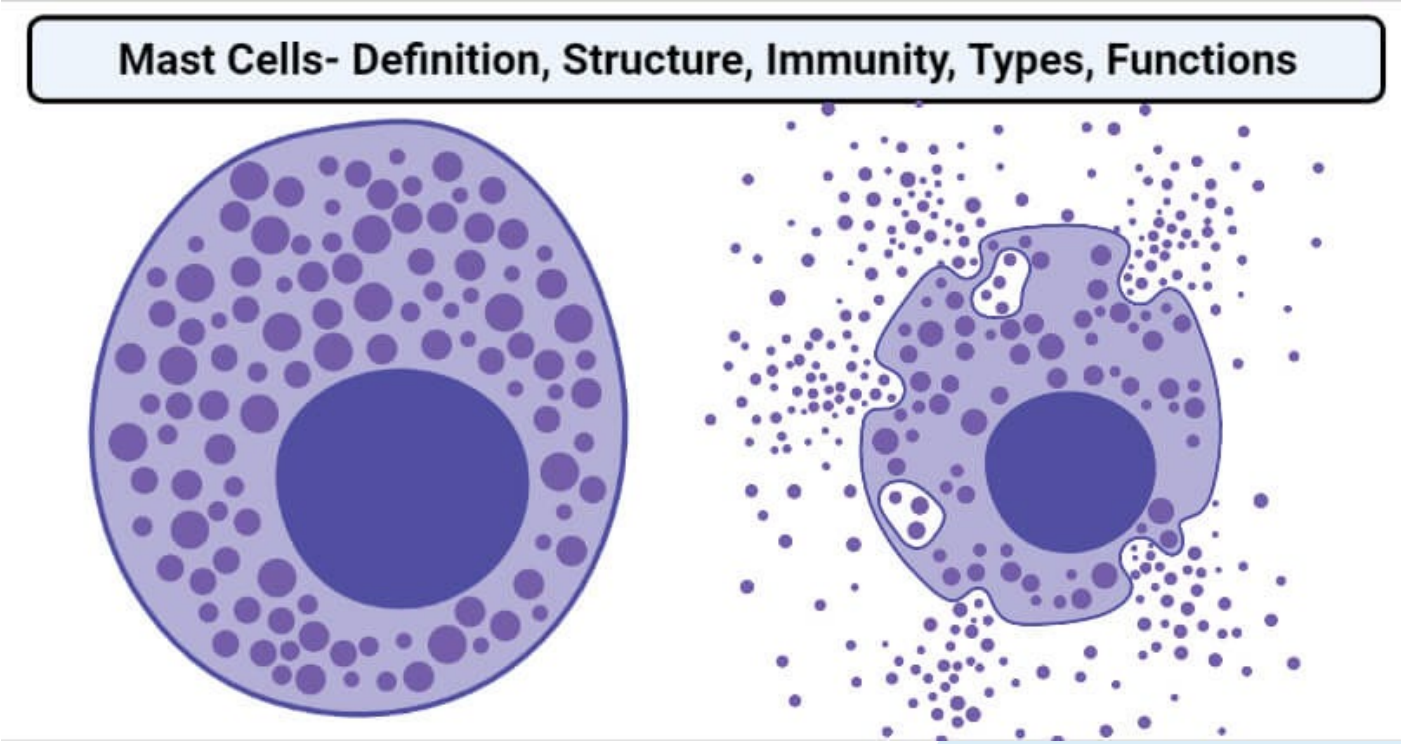
Objectives



- Discuss basic biology of mast cells and mediators

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Credit Mast Cells- Definition, Structure, Immunity, Types, Functions (microbenotes.com)

Key Terms to Know

Term	Definition
Mast Cell	Mast cells are immune system cells (white blood cells) that live in the bone marrow and in body tissues, internal and external, such as the gastrointestinal tract, the lining of the airway and the skin.
Hematopoietic	They are made where blood is made- primarily bone marrow.
Immune response	The body's ability to stay safe by providing protection against harmful agents.
KIT	A gene that helps build protein receptors, tyrosine kinases.
Hereditary alpha tryptasemia (HαT)	A genetic trait (condition) that causes elevated serum tryptase (a high level of protein, alpha tryptase, in the blood). Can be associated with increased frequency / severity of anaphylactic events for some.
Mediator	A chemical released by a mast cell.
Tryptase	A specific enzyme released from a mast cell when activated.

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Key Terms to Know

Term	Definition
Antihistamine	A type of medication that blocks the action of histamine, a chemical released by the immune system in response to a stimuli or allergen (aka, trigger).
Degranulate	When a cell releases molecules or other substances from secretory vessels called granules.
Receptor	A protein molecule found on the surface of cells that receive signals or binds to specific molecules.
Clonal	A group of identical cells that share the same ancestry; they are derived from the same cell.
Non-clonal	Cells that do not originate from one cell.
Monoclonal	A group of cells or cell products that originate from a single cell; they have the same genetic makeup.
Proliferation	The process by which a cell reproduces to create more cells.
Activation	The process of making a cell more effective at carrying out a specific function; they become more reactive, active, or excited.

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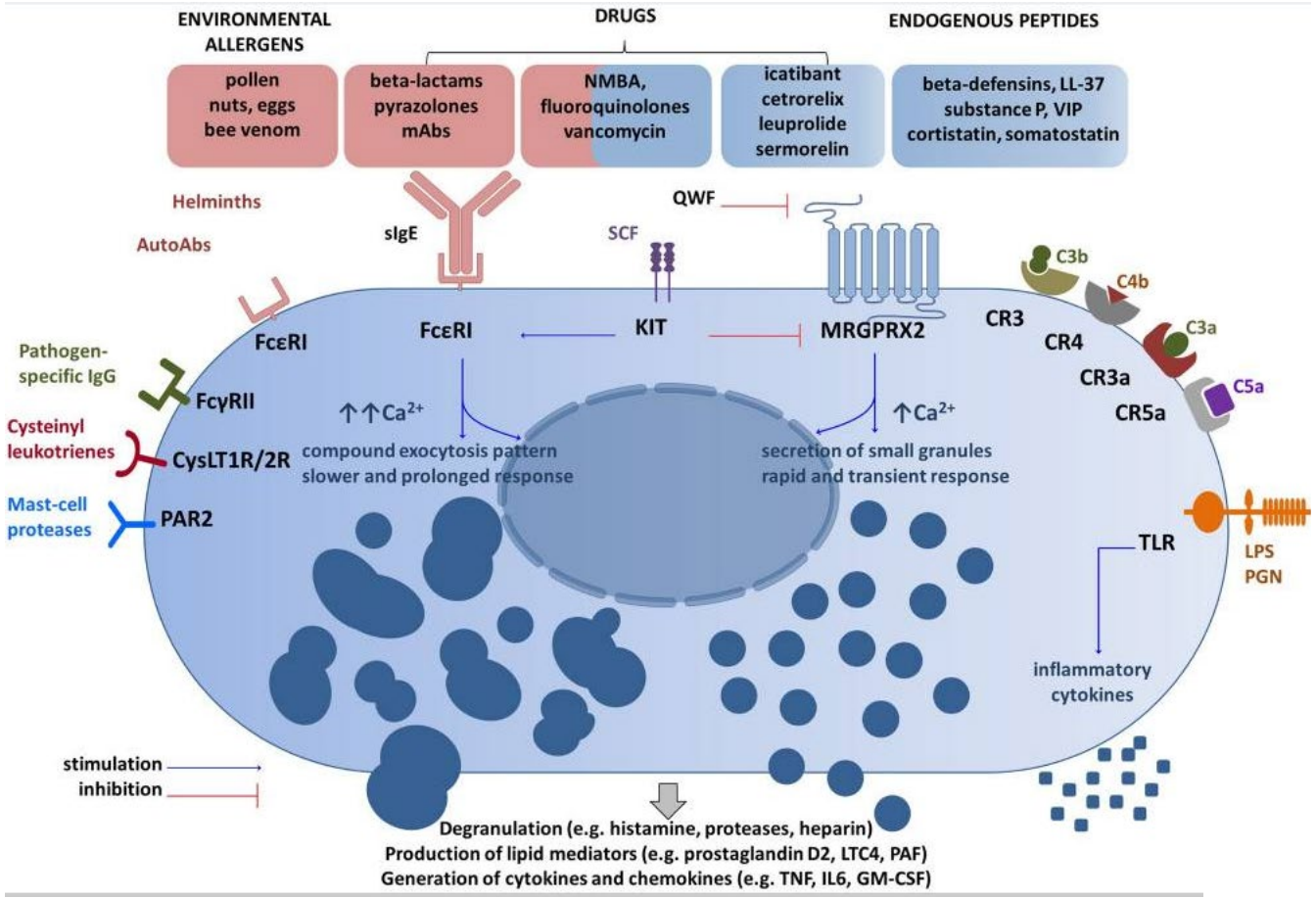
Mast Cell Structure



Legend

- Allergens, drugs, peptides: examples of items that can trigger mast cell degranulation
- MRGPRX2- receptor activated by specific drugs
- FCERI: high-affinity IgE receptor
- IgE: antibody class that regulates allergic reactions
- IgG: antibody class that regulates allergic reactions
- KIT (D816V)- mutation in KIT
- Complement C3a, C5a, C3b, CR4: small peptides that induce tissue inflammation by binding to specific receptors (CR3, CR4, CR3a, CR5a)
- TLR: toll-like receptor: activated by bacterial products (LPS, PGN)
- FCγRII: receptor for IgG
- CysLT1R/2R: Cysteinyl leukotriene receptor
- PAR2: Proteinase Activated Receptor 2: activated by tryptase
- Ca2+: calcium

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Figure from: Porebski, Kwiecien, Pawica, Kwitniewski. Front Immunol 2018; 9: 3027.

Mast cells in our immune system

- They originate in our bone marrow.
- To mature, they need KIT activation.

This is why if you have a KIT mutation, you might have a mast cell disease.

- They leave the bone marrow and migrate into tissues, where they mature fully.
- They need stem cell factor (SCF) for growth and continued longevity.
- Mast cells can release many pro-inflammatory mediators (leukocytes and cytokines).
- The immediate response when mast cells are activated is degranulation, the process by which a mast cell releases molecules (A.K.A. mediators).
- The most important bioactive mast cell granule is histamine.
- When these mediators are released, their role is to initiate or regulate the immune response and eventually produce inflammation or tissue repair- both are part of our healthy immune system.

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What goes wrong?

Normal function

A stimuli occurs and mast cells are activated to cause inflammation or tissue repair.

This response ends and your immune system has protected you.

Malfunction

Abnormal Activation- mast cell mediators are released in an unusual amount causing a reaction (symptoms in skin or other organs, can lead to anaphylaxis)

Proliferation- mast cells grow in abundance and infiltrate organs. This causes problems specific to those affected organs in addition to increased potential for reactions including anaphylaxis.

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Mediators

*Remember:
The degranulation of mast cells lead to their release.

- Tryptase
- Heparin
- Histamine

The three most studied (but there are more).

They can play a role in:	
regulating vascular stability	acute allergic reactions, including those seen in mast cell activation syndromes, such as headache, nausea, itching, flushing, gastric hypersecretion, nasal congestion, and wheezing
the dysfunction of endothelial cells	angioedema and pulmonary edema
Edema, hypovolemia, and shock	mucus hypersecretion
gastrointestinal symptoms	fatigue
confusion	sense of impending doom
coagulation abnormalities	bleeding

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Treatment of Mediator Induced Reactions

- Focused primarily on trigger avoidance and symptom control
- Two doses of **Self-Injectable Epinephrine** (e.g., EpiPen®/EpiPen Jr®) should be carried by all patients with a mast cell disorder at all times, even if they have not previously experienced anaphylaxis. Both the patient and family members/caregivers should be trained on administering epinephrine!

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Treatment of Mediator Effects

MEDIATOR	POSSIBLE EFFECTS	Basic Medications for Symptomatic Patients with Mast Cell Diseases
Histamine	Flushing, itching, diarrhea, hypotension	H1 antihistamines: help with itching, abdominal pain, flushing, headaches, brain fog H2 antihistamines: help with gastrointestinal symptoms and overall mast cell stability (all mast cell activation symptoms) Mast cell stabilizers: help with stomach and intestinal symptoms and brain fog Leukotriene inhibitors: help with respiratory symptoms and overall mast cell stability (all mast cell activation symptoms) Aspirin therapy (under direct supervision of a physician): if tolerated and if prostaglandins are elevated, helps with flushing, brain fog and bone pain
Leukotrienes	Shortness of breath	
Prostaglandins	Flushing, bone pain, brain fog, cramping	
Tryptase	Osteoporosis, skin lesions	
Interleukins	Fatigue, weight loss, enlarged lymph nodes	
Heparin	Osteoporosis, problems with clotting/bleeding	
Tumor Necrosis Factor-α	Fatigue, headaches, body aches	

Note: *The H1 and H2 antihistamines are necessary to stabilize receptors on the mast cell. Therefore, if additional medication is required for control of gastroesophageal reflux (GERD), a proton pump inhibitor may be added to this protocol, but it cannot replace the H2 antihistamine.*

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Example Medications Used to Treat MC Mediated Symptoms

Full lists provided at link

H1 antihistamines:	H2 antihistamines:	Mast cell stabilizers:	Leukotriene inhibitors:	Targeting prostaglandins:
• diphenhydramine • loratadine • cetirizine	• famotidine • cimetidine	• cromolyn sodium • ketotifen	• montelukast • zileuton • safirlukast	• aspirin

Helpful Links

- The Mast Cell Disease Primer What Are Mast Cell Diseases? - TMS - The Mast Cell Disease Society, Inc (tmsforacure.org)
- Anaphylaxis (with video) Anaphylaxis - TMS - The Mast Cell Disease Society, Inc (tmsforacure.org)
- Testing for different MCDs Tests - TMS - The Mast Cell Disease Society, Inc (tmsforacure.org)
- Clinical Trials Clinical Trials - TMS - The Mast Cell Disease Society, Inc (tmsforacure.org)

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Thank you

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