Mast Cell Disorders

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Osteopathic Recognition Allergy and Immunology Fellowship
University Hospitals Cleveland Medical Center

Cleveland Academy of Osteopathic Medicine
Allergy and Immunology Section

Outline

- Brief History of Mast Cells
- Development of Mast Cells
- Histology of Mast Cells
- Natural Role and Pathophysiology of the Mast Cell
- Disorders of the Mast Cell
- Summary

Brief History of Mast Cells

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- 500 Millions years ago: Mast cells are theorized to have joined with simple eukaryotic organisms[1]

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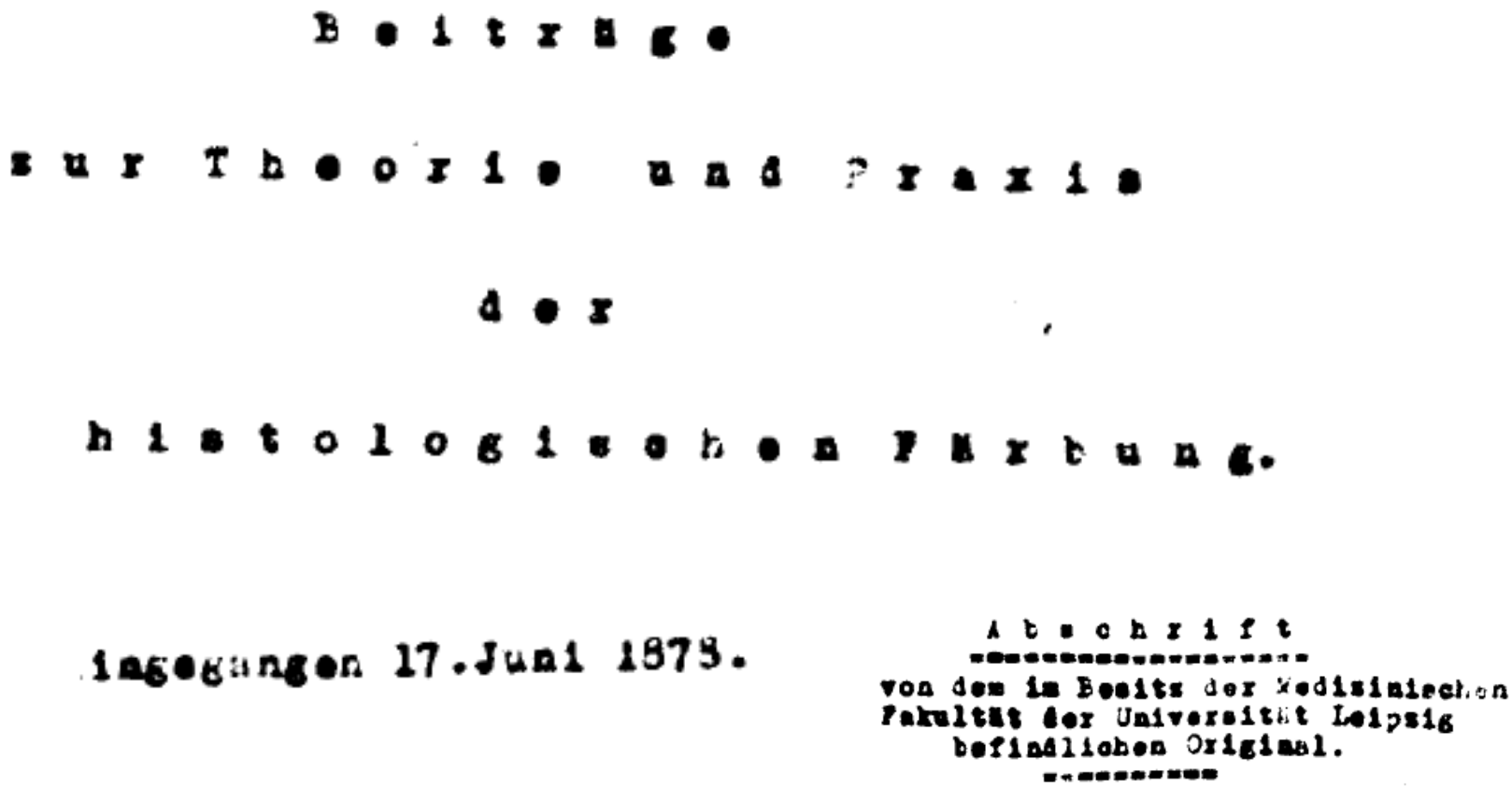
- 500 Millions years ago: Mast cells are theorized to have joined with simple eukaryotic organisms[1]
- 1878: First described by Paul Ehrlich in his doctoral thesis on the basis of their unique staining characteristics and large granules[2]
- Originally, believed that the granules existed to nourish the surrounding tissue, and he named them "*Mastzellen*" (from the German: *Mast*, "fattening" as of animals).

1) Crivellato, Enrico, and Domenico Ribatti. "The mast cell: an evolutionary perspective." *Biological Reviews* 85.2 (2010): 347-360.
2) Metcalfe, Dean D., Dana Baram, and Yoseph A. Mekori. "Mast cells." *Physiological reviews* 77.4 (1997): 1033-1079.

Actual Thesis June 17, 1878



B e i t r ä g e

z u r T h e o r i e u n d P r a x i s

d e r

h i s t o l o g i s c h e n F ä r b u n g.

Eingegangen 17. Juni 1878.

A b s c h r i f t

von dem im Besitz der Medizinischen Fakultät der Universität Leipzig befindlichen Original.

Paul Ehrlich, “Beiträge zur Theorie und Praxis der Histologischen Färbung”, Doctoral Thesis, University of Leipzig June 17, 1878
(“Contributions to the theory and practice of the histological coloring”)

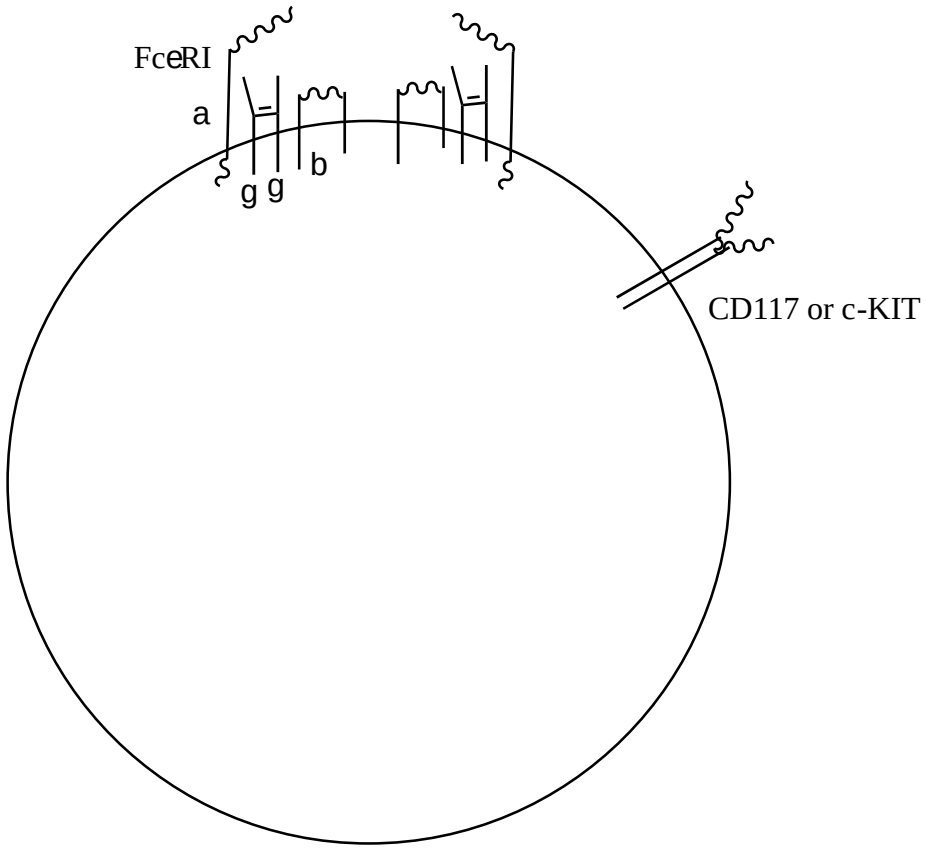
Development of Mast Cells

- Mast cells are traditionally difficult to capture and culture in humans.
  - This is secondary to their low numbers in the blood and contamination with other cells in the marrow.
- Mast cells are thought to originate from bone marrow precursors expressing the CD34 molecule.[2,3]
- Mast cell circulates in an immature form, only maturing once in a tissue site.
- The site an immature mast cell settles in probably determines its precise characteristics.

2) Metcalfe, Dean D., Dana Baram, and Yoseph A. Mekori. "Mast cells." *Physiological reviews* 77.4 (1997): 1033-1079.

3) Kirshenbaum, Arnold S., et al. "Demonstration of the origin of human mast cells from CD34+ bone marrow progenitor cells." *The Journal of immunology* 146.5 (1991): 1410-1415.

Mast Cell FcεRI and c-KIT



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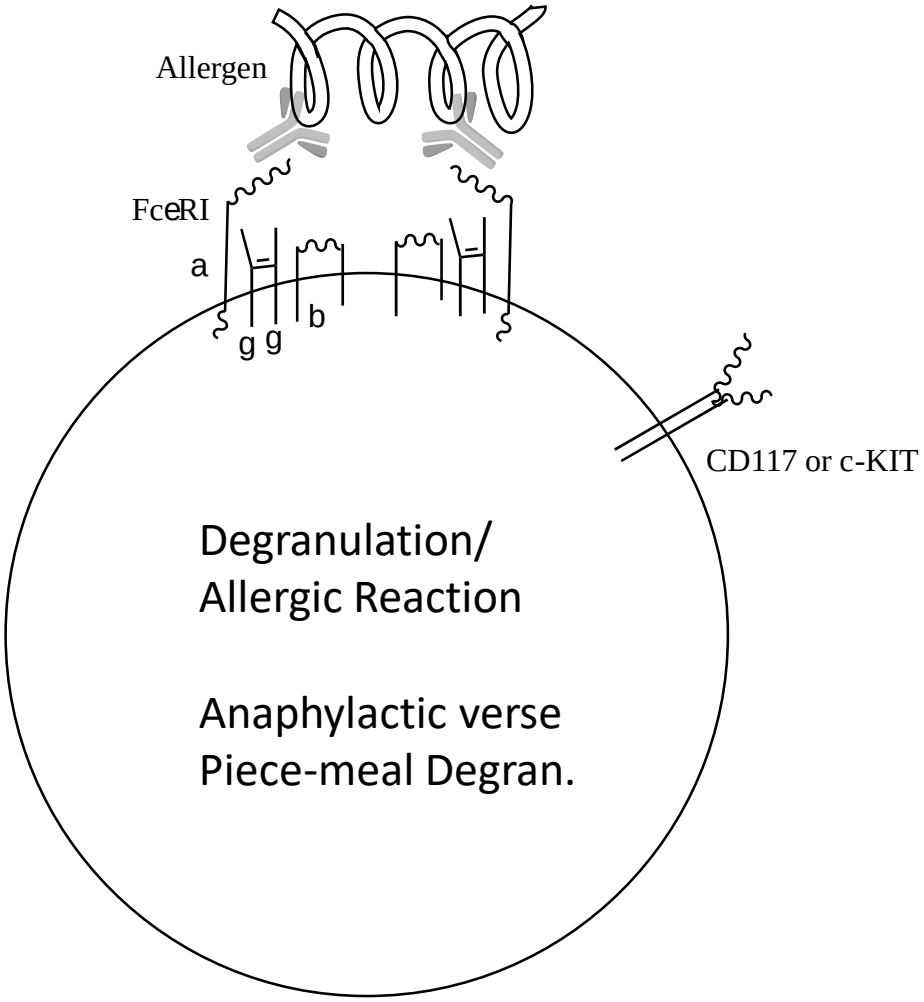

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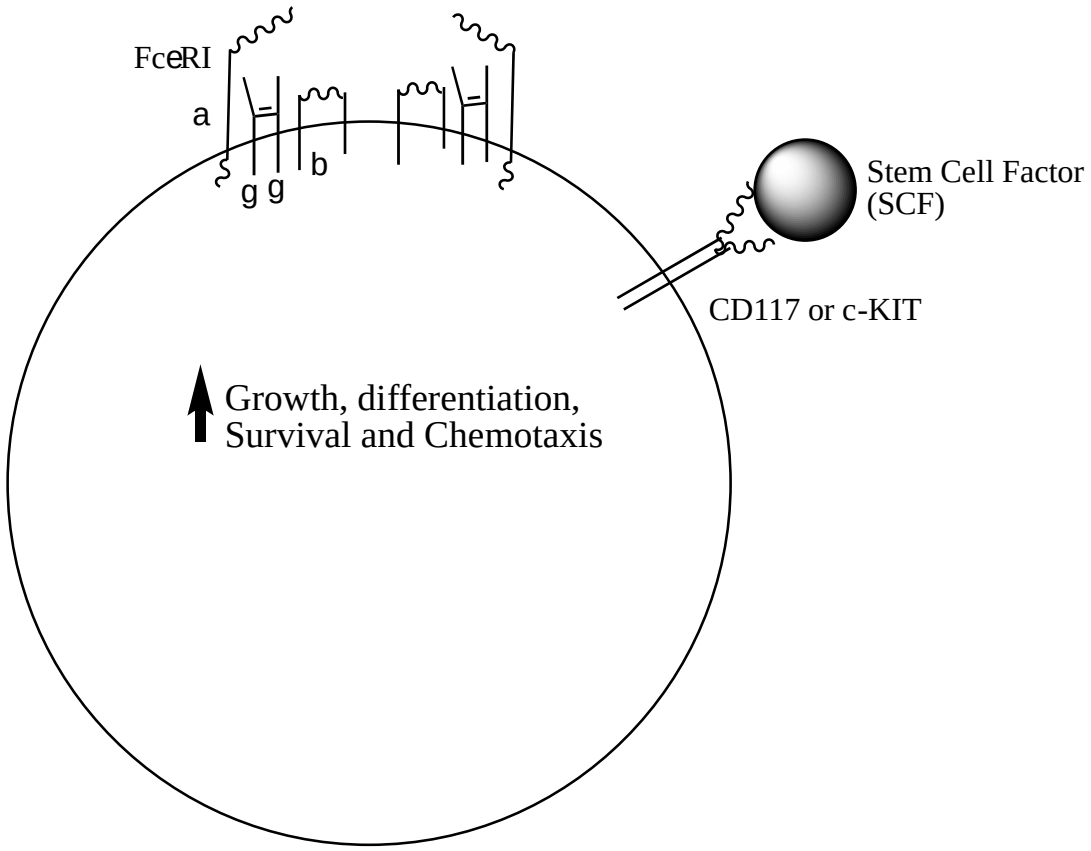

Histology of Mast Cells

microplicae

Electron microsopy of a
Human Skin Mast Cell

Electron microsopy of Granules
Left (B): Scrolls
Middle (C): Grates
Right (D): Lattices

4) Adkinson Jr, N. Franklin, et al. *Middleton's Allergy E-Book: Principles and Practice*. Elsevier Health Sciences, 2013.p232

Mast cell types

- One type contains the neutral proteases, tryptase and chymotryptic proteinase, and is termed the TC mast cell or MC_{TC}.
- The second type contains only tryptase and is termed the T mast cell or MC_{T}.

Mast Cell Type and Distribution

Characteristics of Human Mast Cell Subsets		
Characteristic	MC(T)	MC(TC)
Neutral Protease	Tryptase	Tryptase Chymase Carboxypeptidase Cathepsin G
Granule Structure	Scrolls	Lattice/grating
T Cell Dependence	Yes	No
Inhibited by NaCromoglycate	Yes	No
Distribution %		
Skin	Less Than 1	99+
Alveolar Tissue	93	7
Nasal Mucosa	66	34
Tonsils	40	60
Small Intestine		
Mucosa	81	19
submucosa	23	77

2) Metcalfe, Dean D., Dana Baram, and Yoseph A. Mekori. "Mast cells." *Physiological reviews* 77.4 (1997): 1033-1079.

Mast Cell Type and Function

Characteristics of Human Mast Cell Subsets		
Characteristic	MC(T)	MC(TC)
Activated by Antigen	Yes	Yes
Activated by Substance P	No	Yes
Responds to C5a	No	Yes
Responds to PAF	Yes	No
Responds to Opiods	No	Yes
Inhibited by NaCromoglycate	Yes	No

4) Adkinson Jr, N. Franklin, et al. *Middleton's Allergy E-Book: Principles and Practice*. Elsevier Health Sciences, 2013.p231

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Clinical signs and symptoms of mast cell stimulation

Constitutional:

- Fatigue, malaise

Dermatological:

- Urticaria pigmentosa, pruritus, flushing

Ophthalmologic:

- Irritation, conjunctivitis, dry eyes

Otologic, oropharyngeal:

- Ear/nose/throat inflammation, distorted taste, ulcers, sores, rhinitis, and sinusitis

Cardiopulmonary:

- Hyper/Hypotension, chest discomfort, faintness, syncope, dyspnea (low grade – often), wheezing, URI, bronchitis, pneumonia, and anaphylaxis (with or without shock)

Gastrointestinal:

- Abdominal discomfort, nausea/vomiting/diarrhea, malabsorption, ulcers, GERD, IBS, Food and drug intolerance, organomegly (spleen, liver)

Musculoskeletal:

- Bone and muscle pain, osteopenia/osteoporosis/osteosclerosis, joint laxity/mobility, fibromyalgia in past medical history

Neurologic:

- Headache, peripheral neuropathy

Immunologic:

- Type I (II-IV) hypersensitivity reactions, impaired wound healing, increased risk of: infections/ malignancy/autoimmune

5) Afrin, Lawrence B., et al. "Often seen, rarely recognized: mast cell activation disease–a guide to diagnosis and therapeutic options." *Annals of medicine* 48.3 (2016): 190-201.

List of Mast Cell Disorders[6]

Cutaneous Mastocytosis

- Urticaria Pigmentosa (UP)/Maculopapular Cutaneous mastocytosis (MPCM)
- Telangiectasia macularis eruption perstans(TMEP)
- Diffuse cutaneous mastocytosis
- Solitary mastocytoma of skin

Extracutanenous Mastocytoma

Systemic Mastocytosis (SM)

- Indolent, systemic, aggressive systemic
- Mast Cell Leukemia
- Mast Cell Sarcoma

Mast Cell Activation syndrome[5]

Vibratory Urticaria[7]

5) Afrin, Lawrence B., et al. "Often seen, rarely recognized: mast cell activation disease–a guide to diagnosis and therapeutic options." *Annals of medicine* 48.3 (2016): 190-201.
6) Pardanani, Animesh. "Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management." *American journal of hematology* 91.11 (2016): 1146-1159.
7) Boyden, Steven E., et al. "Vibratory urticaria associated with a missense variant in ADGRE2." *New England Journal of Medicine* 374.7 (2016): 656-663.

Urticaria Pigmentosa

- Urticaria pigmentosa occurs in both children and adults
  - Common for spontaneous remission (~50% of children by adulthood)
  - Children may have bullous eruptions with hemorrhage
  - Present in >90% of individuals with Indolent SM
  - Present in <50% of individuals with Systemic and severe or aggressive SM.
  - Mild irritation or stimulus can cause urticaria
    - (Darier's sign)
  - Diagnosis is confirmed by skin histopathology

8) Metcalfe, D. D. (2003). The mastocytosis syndrome. Freedberg IM, Eisen AZ, Wolf K, Austen KF, Lowell AG, Katz SI, Fitzpatrick TB, editors. Dermatology in general medicine.

Urticaria Pigmentosa

Left: UP in children, small and discrete
But can also have less discrete boarders and larger

Right: Close up of UP lesions

4) Adkinson Jr, N. Franklin, et al. *Middleton's Allergy E-Book: Principles and Practice*. Elsevier Health Sciences, 2013. p1228

Diffuse Cutaneous Pigmentosa

- Normally occurs before the age of 3
- May have bullous eruptions with hemorrhage
- Skin is often thickened
- Biopsy shows diffuse mast cell infiltrates in the skin

Left: Diffuse CP[10]
Right: Bullous eruptions
With hemorrhage[10]

9) Rossi, A. G., Ward, C., Dransfield, I., Haslett, C., & Adkinson, N. F. (2003). Middleton's Allergy: Principles and Practice. *Middleton's Allergy: Principles and Practice*.
10) Adkinson Jr, N. Franklin, et al. *Middleton's Allergy E-Book: Principles and Practice*. Elsevier Health Sciences, 2013. p1229

Telangiectasia macularis eruption perstans (TMEP)

- Adults
- 2-6mm red macule with tan brown background
- Seen in <1% of individuals with mastocytosis
- Pruritus and blistering not commonly associated with TMEP
  - May become edematous
  - Originally described as a blanching macule[12]
    - Diascopy test

11) Costa, D. L. M., Moura, H. H., Rodrigues, R., Pineiro-Maceira, J., & Ramos-e-Silva, M. (2011). Telangiectasia macularis eruptiva perstans: a rare form of adult mastocytosis. *The Journal of clinical and aesthetic dermatology*, *4*(10), 52.
12) Weber, F. P., & Hellenschmied, R. (1930). Telangiectasia macularis eruptiva perstans. *British Journal of Dermatology*, *42*(8-9), 374-382.

Systemic Mastocytosis

- Slight Female:male ratio (1:1 to 3:1)
- Prevalence is estimated at 20,000-30,000 (in US)
- All ethnic background susceptible, but higher in Caucasians.
- Indolent SM is the most common

10) Adkinson Jr, N. Franklin, et al. *Middleton's Allergy E-Book: Principles and Practice*. Elsevier Health Sciences, 2013. p1229

Diagnostic Criteria for Systemic Mastocytosis (SM)

If at least 1 major and 1 one minor, or at least 3 minor criteria, are met, the diagnosis of Systemic Mastocytosis (SM) can be established.

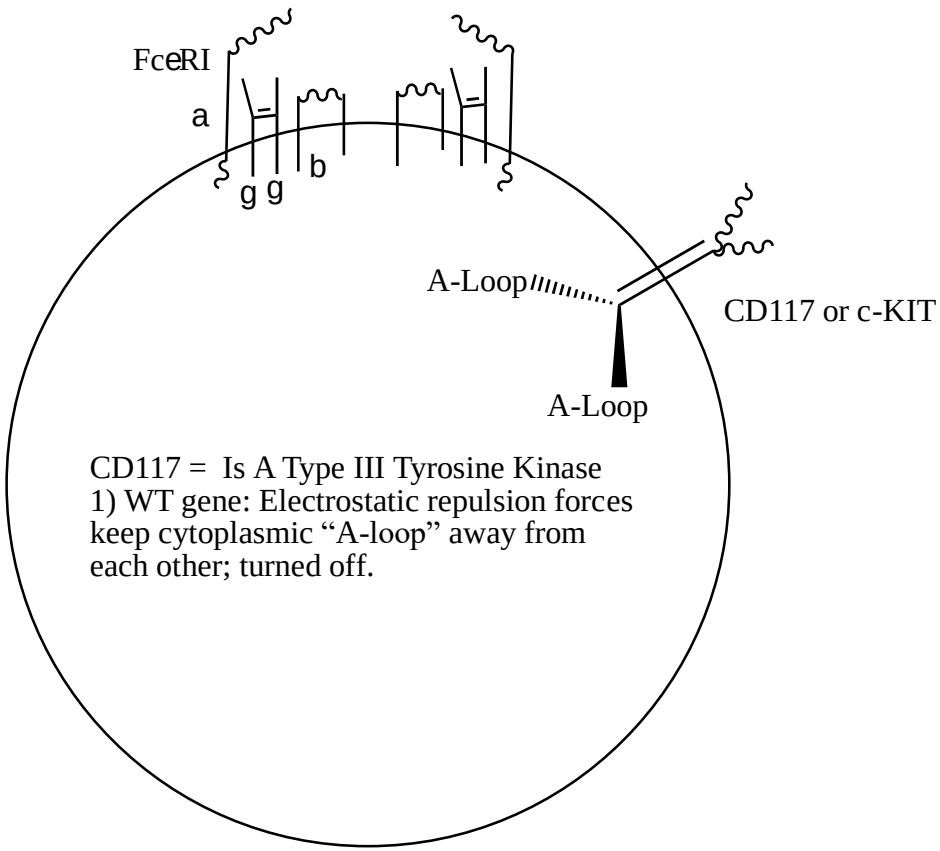
Major Criteria: Multifocal, dense infiltrates (>15 mast cells in aggregate) of mast cells in bone marrow and/or other extracutaneous organ(s) and confirmed by tryptase or other special stains.

Minor Criteria:

- a) Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (> 25%)
- b) C-kit mutation at codon 816 in extracutaneous organ(s). (Activating mutations at codon 816; in most cases, c-kit D816V)
- c) Mast cells in bone marrow express CD117with CD2 and/or CD25
- d) Serum total tryptase > 20 ng/mL (does not count in patients who have associated hematologic clonal non-mast cell lineage disease-type disease)

6) Pardanani, Animesh. "Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management. " *American journal of hematology* 91.11 (2016): 1146-1159.

Gain of Function Mutation of D816V



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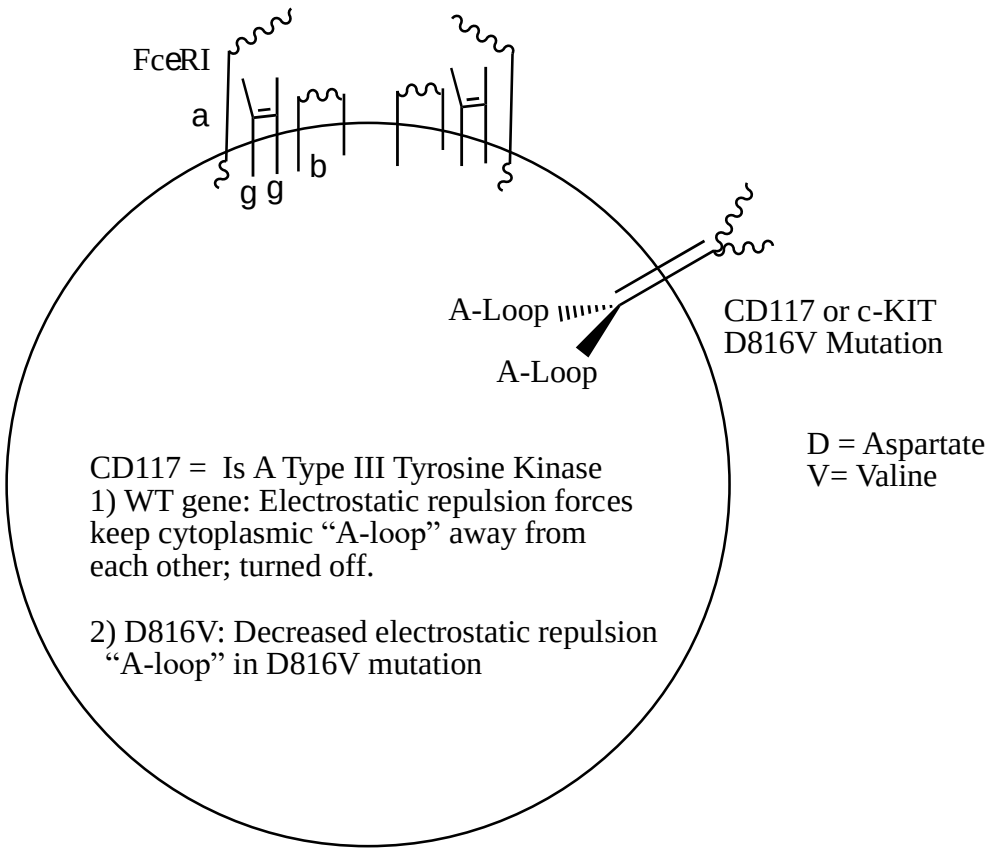


13) Laine, E., de BeauchLaine, E., de Beauchêne, I. C., Perahia, D., Auclair, C., & Tchertanov, L. (2011). Mutation D816V alters the internal structure and dynamics of c-KIT receptor cytoplasmic region: implications for dimerization and activation mechanisms. *PLoS computational biology*, *7*(6), e1002068.

Indolent, Systemic (AHNMD), and Aggressive SM

Diagnosis of SM
If at least 1 major and 1 one minor, or at least 3 minor criteria, are met, the diagnosis of Systemic Mastocytosis (SM) can be established.
Major Criteria:
Multifocal, dense infiltrates (>15 mast cells in aggregate) of mast cells in bone marrow and/or other extracutaneous organ(s) and confirmed by tryptase or other special stains.
Minor Criteria:
a) Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (> 25%) b) C-kit mutation at codon 816 in extracutaneous organ(s) c) Mast cells in bone marrow express CD117with CD2 and/or CD25 d) Serum total tryptase > 20 ng/mL (does not count in patients who have associated hematologic clonal non-mast cell lineage disease-type disease)

Each must meet all the criteria for SM in general (Left)

B Findings
1) Bone Marrow biopsy >30% inflitration by mast cells and/or Serum total tyrptase >200ng/mL 2) Signs of non-mast cell dysplasia or myeloproliferation (must not meet neoplasm criteria) 3) Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy
C Findings
1) No mast cell malignancy with bone marrow dysfunction seen as cytopenias 2) Palpable hepatomegaly with impairment of liver function, ascites, and/or portal hypertension 3) Skeletal involvement with large osteolytic lesions and/or pathologic fractures 4) Palpable splenomegaly with hypersplenisms (overactive spleen) 5) Malabsorption with weight loss caused by gastrointestinal mast cell infiltrates

Indolent: No C-findings

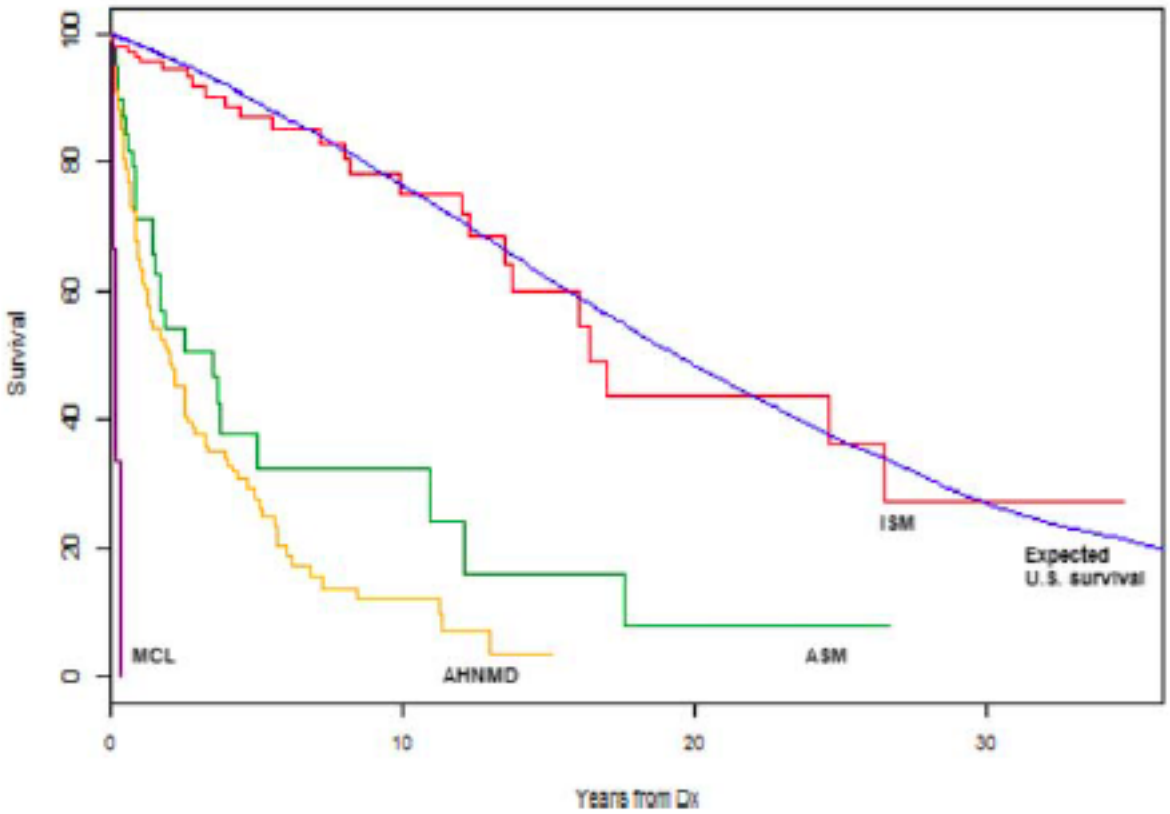
Smoldering: 2 or more B Findings

SM-AHNMD(AHN): SM with MDS, MPS, AML, plasma cell myeloma, etc.

Aggressive: one or more C Findings

6) Pardanani, Animesh. "Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management." *American journal of hematology* 91.11 (2016): 1146-1159.

Survival Rates for SM



Expect US survival: Blue line; Observed survival rate for: Indolent (Red), AHNMD (Yellow), Aggressive (Green), Mast Cell Leukemia (~6 months, Purple)

6) Pardanani, Animesh. "Systemic mastocytosis in adults: 2017 update on diagnosis, risk stratification and management. " *American journal of hematology* 91.11 (2016): 1146-1159.

Treatment for Symptom Control

Pharmacologic Therapies for Symptom Control		
System	Treatment	Drug Class
Cutaneous	1st line	H1-antagonist
	2nd line	Leukotriene antagonist
	3rd line	NSAIDs
		Psolaren plus ultraviolet A (PUVA) Photchemicaltherapy
Adominal	1st line	H2-antagonist
	2nd line	Proton Pump Inhibtors
	3rd line	Sodium Cromolyn
	4th Line	Corticosteroid[1]
Headache	1st line	H1 and H2 antagonist
	2nd line	Sodium Cromolyn
Recurrent Hypotension	1st line	Epinephrine
	2nd line	H1 and H2 antagonist
	3rd line	Corticosteroid[1]
	4th Line	Cytoreductive Therapy
Osteoporosis	1st line	Bisphosphonate
	2nd line	Cytokine/Immunodulatory
	3rd line	Purine nucleoside analogue

1) Prednisone 0.5-1mg/kg/d; taper as feasible based on response/tolerance

Mast Cell Activation Syndrome

Proposed Diagnosis of Mast Cell Activation Syndrome
Major Criteria:
1) Multifocal, or disseminated dense infiltrates (>15 mast cells in aggregate) of mast cells in bone marrow and/or other extracutaneous organ(s) and confirmed by tryptase or other special stains.
2) Clinical Sysmtoms of increased Mast Cell activity
Minor Criteria:
a) Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (> 25%)
b) C-kit mutation at codon 816 in extracutaneous organ(s)
c) Mast cells in bone marrow express CD117with CD2 and/or CD25
d) evidence of above-normal levels of MC Mediators
e) Clinical Response to treatement of MC activation/mediators

Basic difference:

1) MCAS is unable to meet the full Criteria for SM (ISM)

2) Tryptase <20 ng/mL

**Clinical symptoms with clinical response is the most significant addition

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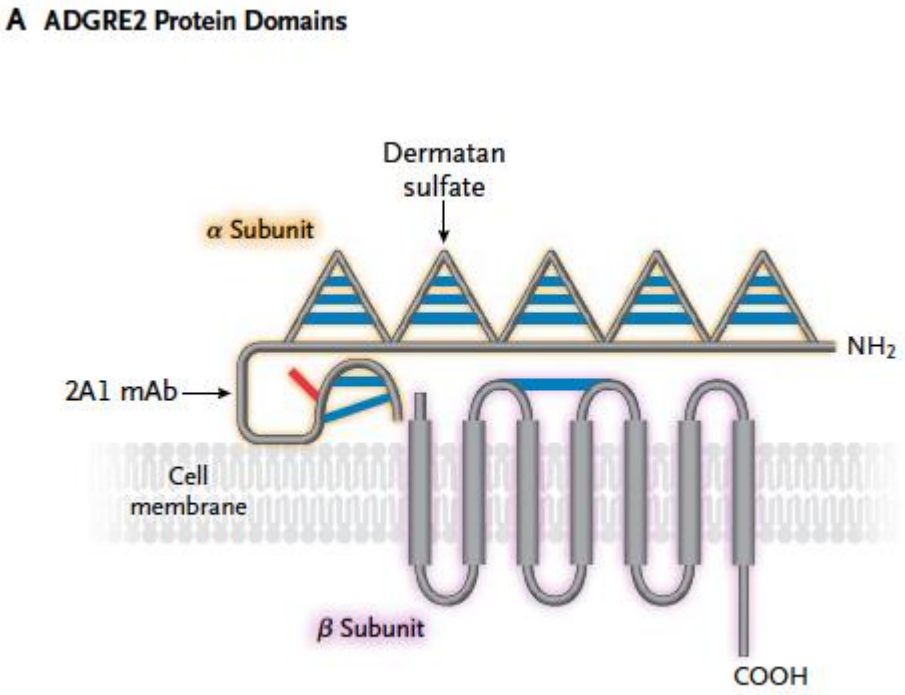
5) Afrin, Lawrence B., et al. "Often seen, rarely recognized: mast cell activation disease–a guide to diagnosis and therapeutic options." *Annals of medicine* 48.3 (2016): 190-201.

New Mast Cell Disorder?

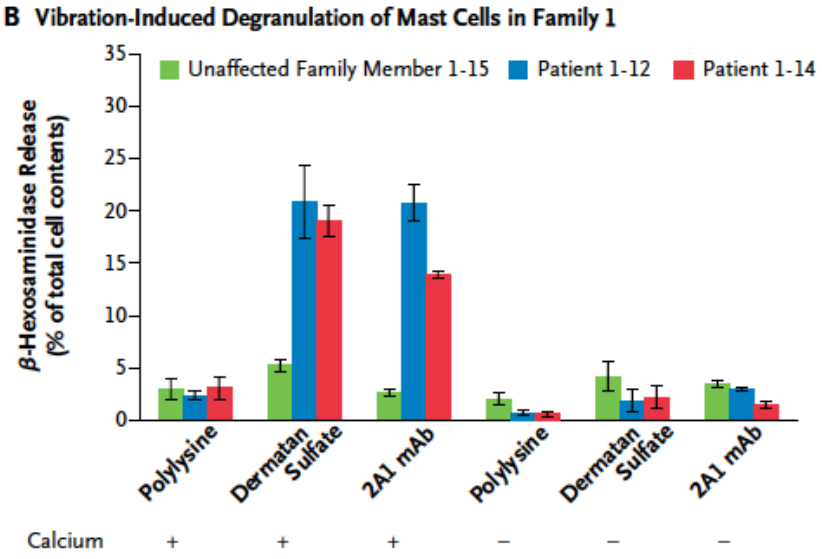
- Vibratory Urticaria
  - Defect in ADGRE2 gene discovered
    - Epidermal Growth Factor seven transmembrane (TM7) Adhesion G protein-couple receptor
    - Autosomal Dominant
    - Missense Mutation with Gain of Function
      - Thought to destabilized the the inhibitory interaction between the Alpha and Beta subunits
      - Cysteine substituted for a tyrosine at AA 492(p.C492Y)
        - » Wild Type gene: Stronger Non-covalently bond = Less Mast cell activation
        - » ADGRE2 p.C492Y: Weaker Non-covalently bond = More Mast Cell activation

Boyden, Steven E., et al. "Vibratory urticaria associated with a missense variant in ADGRE2." *New England Journal of Medicine* 374.7 (2016): 656-663.

Vibratory Urticaria Missense Variant



Left: Alpha and Beta Subunit non-covalently Associated. Blue bars are normal disulfide Bonds. Red bar is the mutation and altered Protein structure



Right: Blue and Red bars are subjects With mutations. Green = normal gene

Boyden, Steven E., et al. "Vibratory urticaria associated with a missense variant in ADGRE2."
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Review Question 1

A 56 year old female with flushing, chronic fatigue, abdominal pain and diarrhea is being tested for systemic mastocytosis. Based on her current work-up she has? Her lab results are:

- Tryptase of 21ng/mL, In range CBC with diff.
- negative ckit mutation
- negative multifocal dense mast cell aggregates in BM, no abnormal mast cells in
- Mast Cells in BM + for CD117, CD2 and CD25

A) Mast Cell Activation Syndrome
B) Systemic Mastocytosis
C) Aggressive SM
D) Mast Cell Leukemia
E) Cutaneous Mastocytosis

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Review Question 2

A 56 year old female with flushing, chronic fatigue, abdominal pain and diarrhea is being tested for systemic mastocytosis. Based on her current work-up she has? Her lab results are:

- Tryptase of 21ng/mL, ANC: 750, Platelets of 85, remainder of CBC in range
- negative ckit mutation
- negative multifocal dense mast cell aggregates in BM, no abnormal mast cells in BM
- Mast Cells in BM + for CD117, CD2 and CD25

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C) Aggressive SM

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E) Cutaneous Mastocytosis

Summary

- Cutaneous Mastocytosis in children seldom have comorbid systemic mastocytosis
- Mast Cell Disorders often present as a combination of vague clinical symptoms
- Indolent systemic Mastocytosis is the most common and least severe
- Aggressive SM and Mast Cell Leukemia are the least common and lowest life expectancy
- Although there are promising new treats in clinical trials, symptom control remains the staple management plan

Acknowledgements

- University Hospitals Cleveland Medical Center and Lake Erie Consortium of Osteopathic Medical Training
- **Fellowship Mentors:**
  - Robert W. Hostoffer, DO, LhD (Program Director)
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  - Theodore Sher, MD
  - Devi Jhevari, DO
- Colleagues in the Fellowship

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- *All of You!!!*