NESA 10/2022

Mast Cell Activation Syndrome (MCAS): Controversies and Differential Diagnosis

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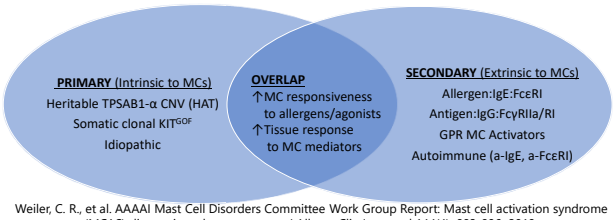
Mast Cell Activation Syndrome (1° MC disorder)

1. Clinical presentation of episodic anaphylaxis
2. Elevated acute MC biomarker(s): tryptase; metabolites of histamine, PGD_2, LTC_4
3. Response to anti-MC mediator/activation therapies

? Inherited/Acquired genetic trait



Weiler, C. R., et al. AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management. J Allergy Clin Immunol 144(4): 883-896, 2019.

Primary MCA/ANA Disorders

1. Clonal MCs with *c-KIT*^{GOF} (D816V): spontaneous or allergic insect sting ANA, ±mastocytosis criteria; ~40% lifetime prevalence of ANA
2. HaT (5-6% European, *TPSAB1*$^{\alpha}$CNV): 17% idiopathic; 10% insect sting ANA
3. HaT (12-18% of SM) : ↑↑prevalence (~90%) of ANA/MCAS
4. Idiopathic ANA cases not a/w TPSAB1$^{\alpha}$CNV or *c-KIT*^{GOF} - perhaps awaiting identification of genetic or clonal traits in other genes a/w MCA

MCAS is NOT an Epidemic, more likely an Epiphenomenon

1. **Symptom Creep**: Fatigue, Fibromyalgia-like Pain, Dermographism, Tired Appearance, Chronically Ill Appearance, Edema, GERD, HBP, Drug Reactions, Abdominal Pain

2. **Unvalidated tests**
   chromogranin A: not produced by mast cells (*Hanjra P et al. JACI Pract 6:687-9, 2018), elevated with blockers of gastric acid production*

   Heparin: plasma pre<post venous occlusion min; no convincing evidence this stimulates MC activation or discriminates MCAS from either mastocytosis or healthy controls

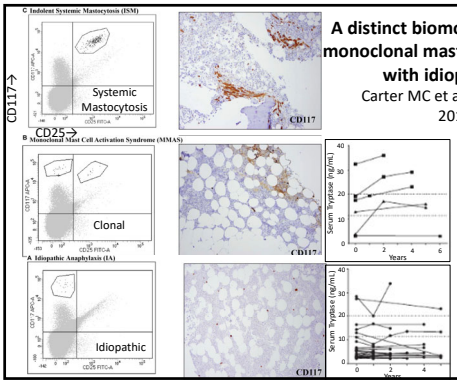
Weiler, C. R., et al. AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management. J Allergy Clin Immunol **144**(4): 883-896, 2019.

Demonstration of aberrant clonal MC population with *KIT*^{GOF} in a subset of patients with "idiopathic" anaphylaxis

~no allergen trigger identified

Akin C et al. Blood 110:2331-3, 2007

Characteristic	Mastocytosis (cutaneous or systemic) ± SA	Clonal MC (± UP or mastocytosis) ± SA	Idiopathic SA ± clonal MCs
n=	12	5	7
UP or BM MC aggregates	+	-	-
Kit^{GOF}, CD25^{+}, or spindled MCs	+	+	-
Tryptase >20	+	<50%	<50%



A distinct biomolecular profile identifies monoclonal mast cell disorders in patients with idiopathic anaphylaxis

Carter MC et al. J Allergy Clin Immunol. 2018;141:180–8

Clonal *KIT*^{GOF} MCs or heritable TPSAB1-α CNVs predispose one to severe insect sting-triggered anaphylaxis

Bonadonna P et al. J Allergy Clin Immunol. 123:680-6, 2009
Clonal mast cell disorders in patients with systemic reactions to Hymenoptera stings and increased serum tryptase levels

Zanotti R et al. J Allergy Clin Immunol. 136:135-9, 2015
Clonal mast cell disorders in patients with severe Hymenoptera venom allergy and normal serum tryptase levels

Lyons et al: J Allergy Clin Immunol. 147:622, 2020
Heritable risk for severe anaphylaxis associated with increased α-tryptase-encoding germline copy number at TPSAB1 (HAT)

Treatment of MCAS (outpatient)

Prevention

1. Reduce triggers (drugs, physical, insect stings)
2. Immunotherapy (insect sting)/Desensitization (drugs)
3. Anti-mediator therapy targeting histamine (H1/2Rs), PGD2 and/or LTC4
4. MCA inhibitors: omalizumab, CS-A, c-Kit inhibitor (±cytoreductive)

Acute

1. Hypotension: supine position (↓empty ventricle syndrome), epinephrine (glucagon or vasopressin if on non-selective β-blocker), IV fluids
2. Airway angioedema/bronchospasm: epinephrine, bronchodilator, O_2 … intubation/tracheotomy

Case

56 y/o stung by an insect and soon c/o dizziness, dyspnea, and chest pain; underlying HBP (HCTZ, lisinopril), . ER: hypotensive

Acute: EKG: Inferior MI
Troponin: elevated
Tryptase =15 ng/ml
} Clinically did well with MI-appropriate RX

Baseline (1 month later): Tryptase =4 (15 > 2+1.2x4=6.8)
Venom IgE skin test: positive

Systemic anaphylaxis to venom, which precipitated the MI.
Begin venom immunotherapy (↓risk of ANA after future stings >95%)
Consider underlying clonal or hereditary MC disorder

Case

25 y/o with frequent ↓BP, ↑P, lightheaded spells; POTS dx; ±(flushing or GI or dyspnea).

Baseline: Tryptase = 4 ng/ml
Acute (<3 h after onset): Tryptase = 4 & 5 ng/ml (<6.8 (2 + 1.2x4) & <6.7 (1.685*4))
Semi-acute: acute urine histamine, LTC_4 and PGD_2 metabolite levels each wnl

Autonomic dysfunction, not MCA, most likely to account for hypotensive/tachycardic spells.

Case

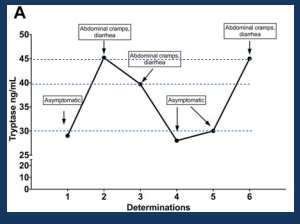
40 y/o M with ISM (sBT 10-13) & frequent syncopal episodes, some with ↑acute tryptase, began Xolair - c/o lightheaded soon after 1st shot → cold, clammy ↓BP ↓P; supine positioning.
Fellow: ?SA - IV saline 1 L, epipen – no improvement.
Attending: Vasovagal - Improved with reassurance.

Baseline (1 month earlier): Tryptase = 12 ng/ml
Acute (1 h after onset): Tryptase = 8 ng/ml (<17 (2+1.2*sBT) & <20 (1.685*sBT))

Clinical presentation favored a vasovagal reaction; supported by lack of an elevated acute tryptase level.

Case 3: Idiopathic Anaphylaxis?

Adult F: recurrent episodes diarrhea & abdominal cramps. Similar symptoms in 3|6 sibs.
GI studies & bx wnl, *KIT* D816V negatve.
Acute tryptase levels 40-45 > baseline levels 28-30.



↑sBT and autosomal dominant inheritance
~Hereditary α-Tryptasemia
(*TPSAB1* α-tryptase quintuplication)

MCA?
40-45 > 2 + 1.2x(28-30) = 36-38
not > 1.685*(28-30) = 47-51
± > 1.374*(28-30) = 38-41
? ~ clinically-significant MC activation

Sabato et al. JACI 134:1448, 2014; → J Clin Immunol 38:457, 2018
Idiopathic Anaphylaxis → HaT

How does α-tryptase overexpression relate to HaT?

Quang Le, PhD

homotetramers

α α
α α Inactive=α

β β
β β Active=β

heterotetramer

α β
β α Active=α/β

$$\frac{\alpha/\beta}{\alpha/\beta+\beta}\text{active tryptase ratio}\sim\frac{\alpha}{\alpha+\beta}\ gene\ ratio$$

TPSB2 *TPSAB1*
Always β β or α

Normal Tryptase Genotypes
Maternal:Paternal

B2 AB1:B2 AB1		*α/α+β*
ββ:ββ→	β4	0.0
ββ:βα→	α1β3	0.25
βα:ββ→	α1β3	0.25
βα:βα→	α2β2	0.5

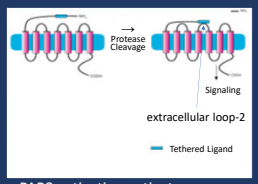
Le et al J Exp Med 216:2348, 2019; Lyons et al. JACI 147:622-32, 2021

Is tryptase a mediator?

HaT ~ ↑formation of α/β-tryptase

1. Vibratory urticaria
2. Severe anaphylaxis

Protease-Activated Receptor (PAR)-2 Activation ~ ANA Severity?



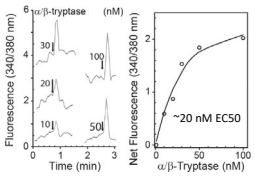
PAR2 activation activates:
Endothelium: vasopermeability
Smooth muscle: bronchospasm, abdominal cramping
Neurons: pruritus, hyperalgesia
Epithelium: inflammation

Is PAR2 a target for mast cell tryptase?
Discrepancies in literature with different tryptase preparations.

No PAR2 activation with α- or β- rhu-tryptases;
No PAR2 activation with tissue-derived tryptase (ββ:ββ tryptase genotype)
(*Le et al J Exp Med 216:2348, 2019)*

Hypothesis
α/β but not β tryptase activates PAR2

α/β-Tryptase Heterotetramers activate Protease-Activated Receptor-2 on Jurkat cells

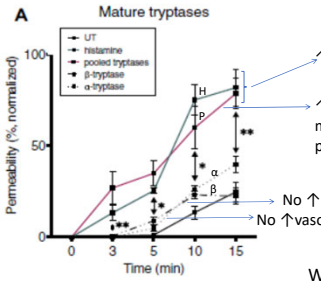


Calcium signal prevented by:
1. Anti-tryptase B12 mAb inhibitor
2. PAR-2 peptide inhibitor

Le et al J Exp Med 216:2348, 2019

Pooled mature lung-derived tryptases increase PAR-2–dependent vascular endothelial permeability, but neither α- nor β- tryptase homotetramers do so

Lyons et al. JACI 147:622-32, 2021



↑Permeability to Histamine and Pooled lung tryptase

↑Permeability blocked by anti-tryptase mAb inhibitor or by a PAR2-specific peptide inhibitor.

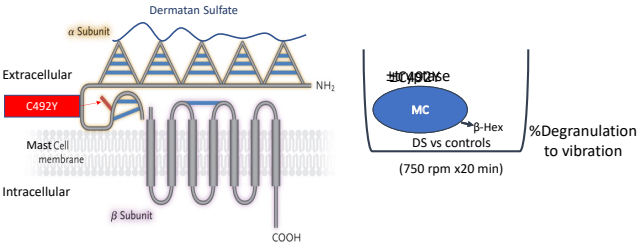
No ↑vasopermeability to α-tryptase

No ↑vasopermeability to β-tryptase

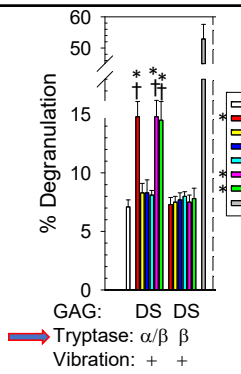
Will this translate to *in vivo*?

Severe Hereditary Vibratory Urticaria ~ C492Y in Adhesion GPCR (*ADGR-E2*; CD312, EMR2)

Boyden SE et al. New Engl J Med 374:656-663, 2016



%Degranulation to vibration



α/β-Tryptase but not β-tryptase makes skin MCs degranulate to vibration

- Buffer Control
- Tryptase High
- Tryptase Lo
- B12+Tryptase Hi
- B12+Tryptase Lo
- SBTI+Tryptase Hi
- B2+Tryptase Hi
- Anti-FcεRI mAb

Degranulation does not occur if:
1. MCs are not vibrated
2. MCs are attached to chondroitin sulfate A

Physiologic MCA *in vivo*?

1.Skin: ?vibration/rubbing/dermographism

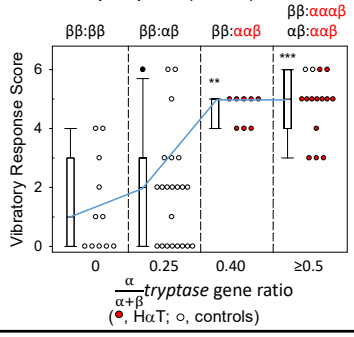
2. Pulmonary/GI/Blood Vessels: ?stretch

Le et al J Exp Med 216:2348, 2019

$\frac{\alpha}{\alpha+\beta}$ *Tryptase* Gene Ratio ~ Cutaneous Vibratory Response (*in vivo*)

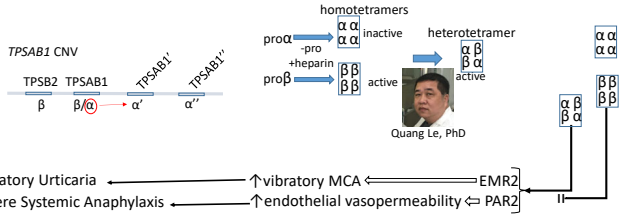
3000 rpm
x3 min

Clinical Manifestation	Score
Erythema	1
Induration	1
Pruritus/Tingling/Pain	1
Warmth	1
Expansion beyond vortex margin or systemic symptoms	2



Quang Le et al. J Exp Med 216:2348 (2019)

How does α-tryptase overexpression relate to clinical features in HaT?



↑$\frac{\alpha}{\alpha}$gene ratio ⇨ ↑α/β heterotetramers ⇨ clinical phenotype biomarker?

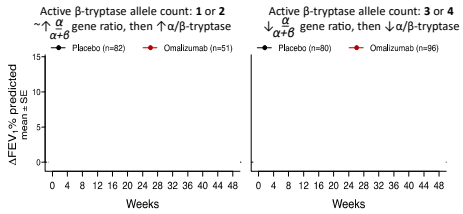
Le et al J Exp Med 216:2348, 2019

When can the $\frac{\alpha}{\beta}$ tryptase gene ratio predict a clinical phenotype?

If both β AND **α/β show the same activity** or neither **α** NOR **α/β show this activity, then trypase involvement is neither indicated or refuted.**

If either β OR **α/β*** involvement, then a dose-response relationship should emerge.

In severe persistent allergic asthmatics (*post hoc* analysis, EXTRA)
↑Response to omalizumab ~ ↑$\frac{\alpha}{\alpha+\beta}$ Tryptase Genotype



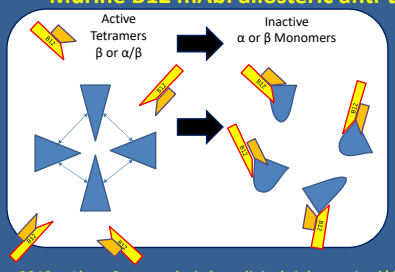
(analogous results for reduction in SABA use, and improvements in TASS & asthma QOL)

Hypothesis: α/β-Tryptase has a greater impact than β-tryptase on asthma pathogenesis, resulting in a greater clinical impact when MC/Bas degranulation is attenuated by omalizumab.

Maun et al. Cell 179:417-31, 2019

Is tryptase a pharmaceutical target?
HaT?
Asthma?
Arthritis?
Chronic urticaria?

Murine B12 mAb: allosteric anti-tryptase Inhibitor



Schwartz… J Clin Immunol 14:190, 1994

Ren… J Immunol 159:3540, 1997

Fukuoka… J Immunol 176:3165, 2006

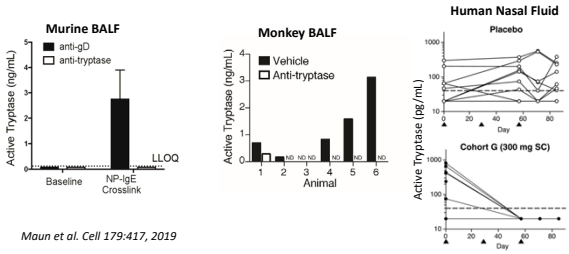
**Maun… Cell 179:417, 2019 (B12-like mAb)*

***Rymut…Clin Transl Sci 15:451, 2022 (IgG4 humanized B12 mAb)*

2012 mAb to Genentech → *preclinical → humanized/↑affinity → **Phase 1 → Phase 2a

Efficacy, Safety, & Pharmacokinetics of MTPS9579A in Patients With Moderate to Severe Asthma (NCT04092582) or Refractory Chronic Urticaria (NCT05129423)

Anti-Tryptase *in vivo*

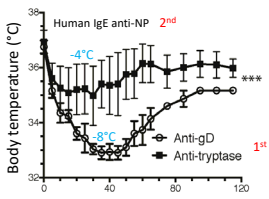


Maun et al. Cell 179:417, 2019

Rymut et al. Clin Transl Sci 15:451, 2022

Anti-tryptase antibody inhibitor attenuates huMC-mediated anaphylaxis in humanized mice

Mice reconstituted with human CD34⁺ stem cells → human MCs



3rd Time after multivalent NP-BSA injection (min)

Maun et al. Cell 179:417-31, 2019

Concluding Comments

1. MCAS, as defined with consensus guidelines, involves recurrent systemic episodes of spontaneous anaphylaxis and is uncommon.
2. The coordinated discoveries of HaT and α/β-tryptase revealed apparent involvement of this form of tryptase through activation of PAR2 and/or EMR2.
3. Using the tryptase genotype as a biomarker for differential involvement of the two types of active tryptases correlated with response of asthmatics to omalizumab with higher $\frac{\alpha}{\alpha+\beta}$ tryptase gene ratios, regardless whether the tryptase genotype was normal or contained extra copies of TPSAB1-encoded α-tryptase.
4. Whether clinical benefit occurs with tryptase inhibition remains to be determined in disorders involving MCA.

Charles Richet:

I possess every good quality, but the one that distinguishes me above all is modesty.