Ο Ρόλος των Μαστοκυττάρων στην Φλεγμονή

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Adjunct Professor, Department of Immunology
Tufts University School Medicine, Boston, MA, USA

Clinical Pharmacologist, Massachusetts
Drug Formulary Commission

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1

All Inflammation Is Not the Same

Inflammation=A defense mechanism of the body involving the immune system to a real or perceived danger, that could become destructive if it is not controlled.

- Systemic-cytokine storms=Sepsis
- Systemic-IL-1β=Cryopyrin diseases
- Localized IL-4=Asthma
- Localized IL-28=Psoriasis
- Localized-IL-31=Chronic urticaria
- Generalized in the brain=Encephalomyelitis
- Localized to the brain lining=Meningitis
- Localized to the nerve insulation=Multiple sclerosis
- Localized to the amygdala of the brain=Autism

Blood

Pro-inflammatory

- IL-1β, IL-6, IL-8, IL-17, IL-33, TNF
- Granzyme, lysozyme
- Metalloproteinases (MMP-9)
- Calprotectin (S100A8A)

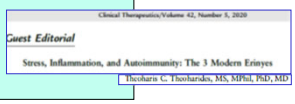
Anti-inflammatory

- Alpha$_1$-antitrypsin
- Alpha$_2$-macroglobulin
- C1-esterase inhibitor
- IgA, IgG, IgM
- IL-10, IL-37, IL-38
- IL-1sr, IL-33sr

2

Inflammatory Conditions Involving Mast Cells And Affected by Stress

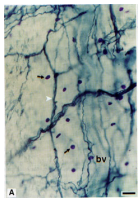
- Atopic dermatitis (AD)
- Autism spectrum disorder (ASD)
- Chronic inflammatory response syndrome (CIRS)
- Electromagnetic hypersensitivity
- Fibromyalgia syndrome (FMS)
- Inflammatory response syndrome (IRS)
- Interstitial cystitis/bladder pain syndrome (IC/BPS)
- Long-COVID syndrome
- Mast cell activation syndrome (MCAS)
- Multiple chemical sensitivity syndrome (MCSS)
- Multisystem inflammatory syndrome (MIS)
- Myalgic encephalomyelitis/Chronic fatigue syndrome (ME/CFS)
- Neurofibromatosis
- Pediatric acute neuropsychiatric syndrome (PAN)
- Post-Lyme syndrome (PLS)
- Psoriasis
- Rheumatoid arthritis (RA)
- Sick building syndrome (SBS)
- Toxic mold syndrome
- Vitiligo

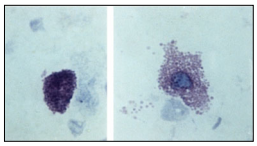


3

Typical Skin Mast Cell Metachromasia as First Noted by Dr. Paul Ehrlich in 1887

- Derives from distinct hemopoietic precursors
- Is Myeloid, Mononuclear CD34+
- PHENOTYPE: CD117+ (c-kit Receptor, SCF ligand)
- Expresses CD23+ CD25+, CD2+
- Expresses FcεR1 (surface receptor for IgE)
- Contains 500-1000 secretory granules
- Is distinct from Basophils
- Is present in all tissue
- Is located around blood vessels and nerves

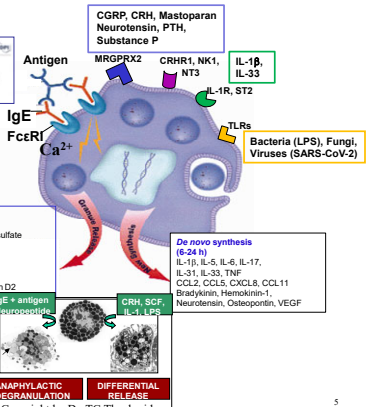


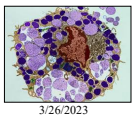


4

Activation of Mast Cells

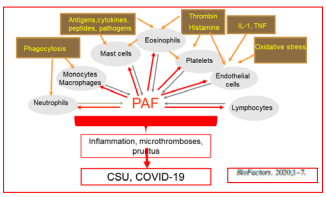
Int J Mol Sci 2021, 22, 3968
Cytokines Stimulated by IL-33 in Human Skin Mast Cells: Involvement of NF-κB and p38 at Distinct Levels and Potent Co-Operation with FcεRI and MRGPRX2

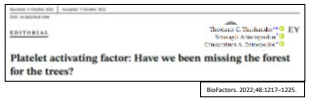




5

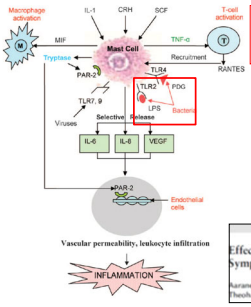
Biological Actions of Platelet Activating Factor (PAF)




EDITORIAL
Theoharis C. Theoharides, Smaragdi Antoniopoulou, Constantinos A. Demopoulos
Platelet activating factor: Have we been missing the forest for the trees?
BioFactors. 2022;48:1217–1225.

6

Mast Cells Communicate With Other Immune Cells and Pathogens



Borrelia burgdorferi Spirochetes Induce Mast Cell Activation and Cytokine Release

JEFFREY TALKINGTON AND STEVEN P. NICKELL[1]

ISHAM

Short Communication

***Sporothrix schenckii* yeasts induce ERK pathway activation and secretion of IL-6 and TNF-α in rat mast cells, but no degranulation**

Clinical Therapeutics/Volume 8, Number 8, 2018

Effects of Mycotoxins on Neuropsychiatric Symptoms and Immune Processes

Karane M. Ratnaseelan, MBS[1]; Irene Tuliani, PhD[2]; and Theoharis C. Theoharides, MS, MPhil, PhD, MD[1,2,3,4,5]

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Diagnosis of Atopic Diseases

Blood

- IgE, IgG_1, IgG_4
- Anti-IgE receptor antibody
- Food Intolerance Panel
- Immune IgE (RAST for alpha-gal, casein,
- gluten, dust mites, fungi, grass, pollen)
- Anti-IgE receptor antibody
- IL-4, IL-6, IL-31, TNF
- PGD_2
- Tryptase

Urine 24 hours (must be kept and sent cold)

- Methylhistamine (30% of histamine)
- **MIA**=methyl imidazole acetic acid (60% of histamine
- 23BPG=2,3-Dinor-11β-$PGF_{2\alpha}$

Dark under-eye circles "allergic shiners"

Dermatographia

8

The NEW ENGLAND JOURNAL of MEDICINE

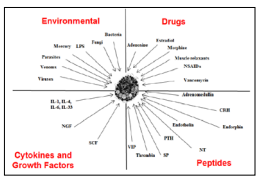
REVIEW ARTICLE

Julie R. Ingelfinger, M.D., Editor

N ENGL J MED 373;2 NEJM.ORG JULY 9, 2015

Mast Cells, Mastocytosis, and Related Disorders

Theoharis C. Theoharides, Ph.D., M.D., Peter Valent, M.D., and Cem Akin, M.D., Ph.D.



Primary
- Mastocytosis
- Monoclonal mast cell activation disorder (MMAS)

Secondary
- Allergies
- Mast cell activation in inflammation or cancer
- Physical urticarias
- Chronic autoimmune urticaria

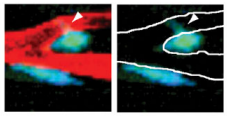
Idiopathic
- Anaphylaxis
- Angioedema
- Urticaria
- Mast cell activation syndrome (MCAS)

Adopted from (Akin et al. JACI 126:1099-104, 2010)

Perivascular Mast Cells Dynamically Probe Cutaneous Blood Vessels to Capture Immunoglobulin E

Laurence E. Cheng,[1] Karin Hartmann,[4] Axel Roers,[2] Matthew F. Krummel,[1] and Richard M. Locksley[1,*]

Immunity 38, 166–175, January 24, 2013



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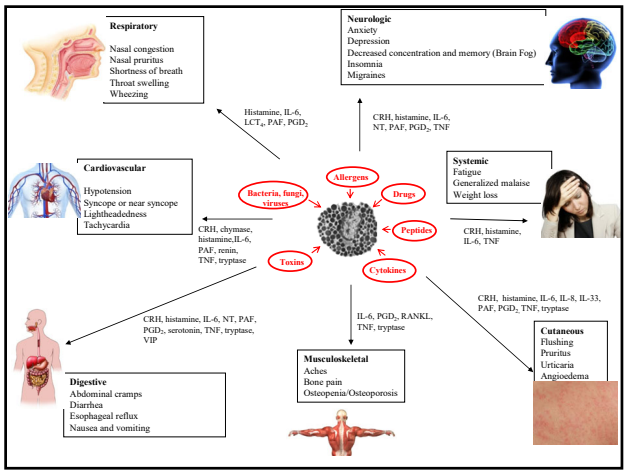
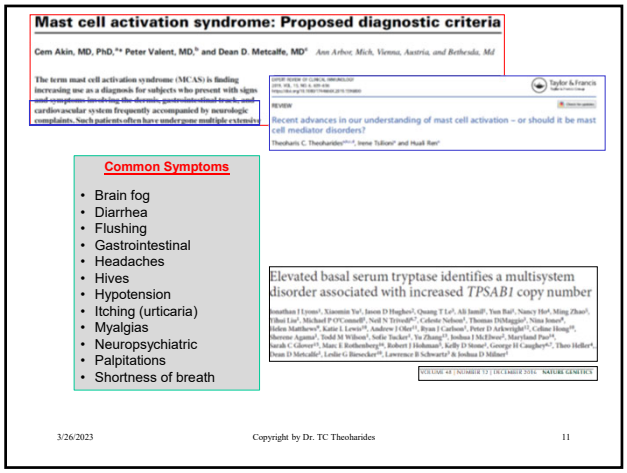

Respiratory
Nasal congestion
Nasal pruritus
Shortness of breath
Throat swelling
Wheezing
Neurologic
Anxiety
Depression
Decreased concentration and memory (Brain Fog)
Insomnia
Migraines
Histamine, IL-6, LCT4, PAF, PGD2
CRH, histamine, IL-6, NT, PAF, PGD2, TNF
Cardiovascular
Hypotension
Syncope or near syncope
Lightheadedness
Tachycardia
Systemic
Fatigue
Generalized malaise
Weight loss
Allergens
Bacteria, fungi, viruses
Drugs
Peptides
Toxins
Cytokines
CRH, chymase, histamine, IL-6, PAF, renin, TNF, tryptase
CRH, histamine, IL-6, TNF
CRH, histamine, IL-6, NT, PAF, PGD2, serotonin, TNF, tryptase, VIP
IL-6, PGD2, RANKL, TNF, tryptase
CRH, histamine, IL-6, IL-8, IL-33, PAF, PGD2, TNF, tryptase
Cutaneous
Flushing
Pruritus
Urticaria
Angioedema
Digestive
Abdominal cramps
Diarrhea
Esophageal reflux
Nausea and vomiting
Musculoskeletal
Aches
Bone pain
Osteopenia/Osteoporosis

10


Mast cell activation syndrome: Proposed diagnostic criteria
Cem Akin, MD, PhD, Peter Valent, MD, and Dean D. Metcalfe, MD
Ann Arbor, Mich, Vienna, Austria, and Bethesda, Md
The term mast cell activation syndrome (MCAS) is finding increasing use as a diagnosis for subjects who present with signs and symptoms involving the dermis, gastrointestinal tract, and cardiovascular system frequently accompanied by neurologic complaints. Such patients often have undergone multiple extensive
Recent advances in our understanding of mast cell activation – or should it be mast cell mediator disorders?
Common Symptoms
Brain fog
Diarrhea
Flushing
Gastrointestinal
Headaches
Hives
Hypotension
Itching (urticaria)
Myalgias
Neuropsychiatric
Palpitations
Shortness of breath
Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number
3/26/2023
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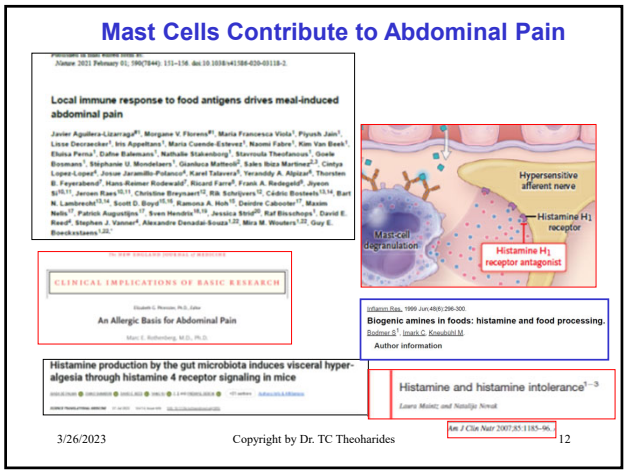
Mast Cells Contribute to Abdominal Pain
Local immune response to food antigens drives meal-induced abdominal pain
Hypersensitive afferent nerve
Histamine H1 receptor
Mast cell degranulation
Histamine H1 receptor antagonist
CLINICAL IMPLICATIONS OF BASIC RESEARCH
An Allergic Basis for Abdominal Pain
Biogenic amines in foods: histamine and food processing.
Histamine production by the gut microbiota induces visceral hyperalgesia through histamine 4 receptor signaling in mice
Histamine and histamine intolerance
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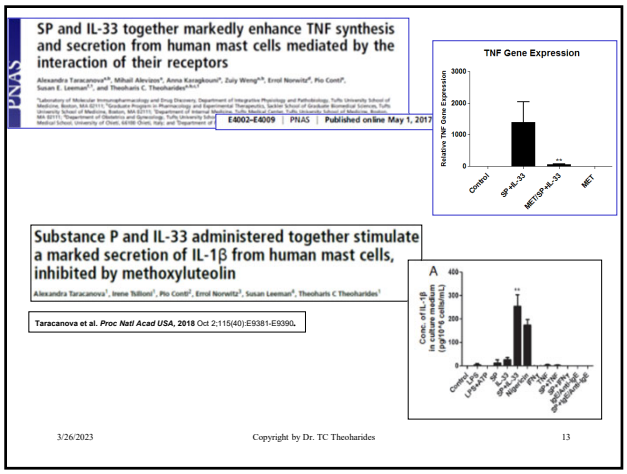
SP and IL-33 together markedly enhance TNF synthesis and secretion from human mast cells mediated by the interaction of their receptors
E4002–E4009 | PNAS | Published online May 1, 2017
TNF Gene Expression
Relative TNF Gene Expression
Control
SP+IL-33
MET/SP+IL-33
MET
Substance P and IL-33 administered together stimulate a marked secretion of IL-1β from human mast cells, inhibited by methoxyluteolin
Alexandra Taracanova, Irene Tollioni, Pio Conti, Errol Norwitz, Susan Leeman, Theoharis C Theoharides
Taracanova et al. Proc Natl Acad USA, 2018 Oct 2:115(40):E9381-E9390.
Conc. of IL-1β in culture medium (pg/10^6 cells/mL)
3/26/2023
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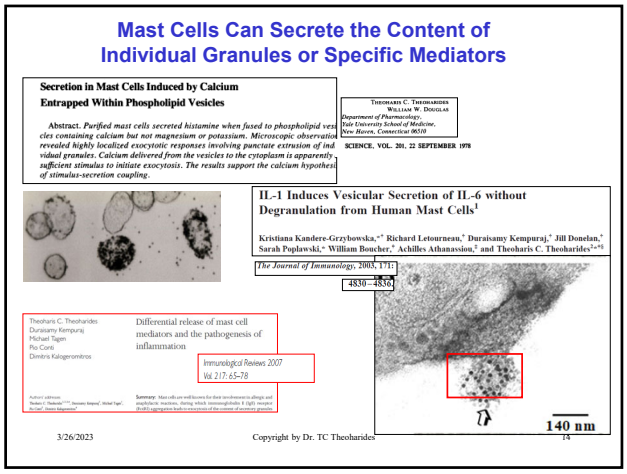
Mast Cells Can Secrete the Content of Individual Granules or Specific Mediators
Secretion in Mast Cells Induced by Calcium Entrapped Within Phospholipid Vesicles
Theoharis C. Theoharides
William W. Douglas
Department of Pharmacology, Yale University School of Medicine, New Haven, Connecticut 06510
SCIENCE, VOL. 201, 22 SEPTEMBER 1978
IL-1 Induces Vesicular Secretion of IL-6 without Degranulation from Human Mast Cells
Kristiana Kandere-Grzybowska, Richard Letourneau, Duraisamy Kempuraj, Jill Donelan, Sarah Poplawski, William Boucher, Achilles Athanassiou, and Theoharis C. Theoharides
The Journal of Immunology, 2003, 171: 4830–4836
Differential release of mast cell mediators and the pathogenesis of inflammation
Immunological Reviews 2007 Vol. 217: 65–78
140 nm
3/26/2023
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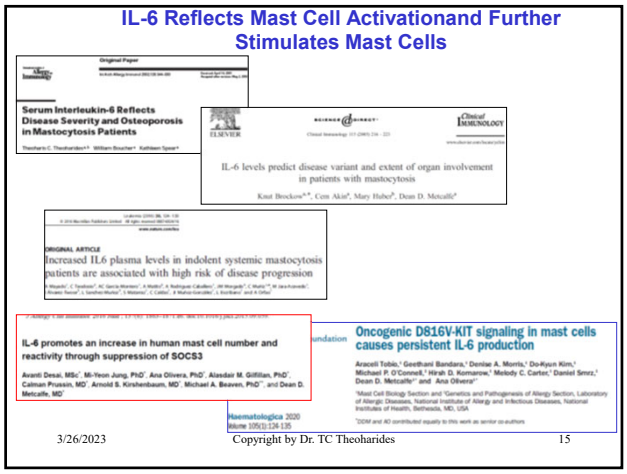
IL-6 Reflects Mast Cell Activationand Further Stimulates Mast Cells
Serum Interleukin-6 Reflects Disease Severity and Osteoporosis in Mastocytosis Patients
IL-6 levels predict disease variant and extent of organ involvement in patients with mastocytosis
Increased IL6 plasma levels in indolent systemic mastocytosis patients are associated with high risk of disease progression
IL-6 promotes an increase in human mast cell number and reactivity through suppression of SOCS3
Oncogenic D816V-KIT signaling in mast cells causes persistent IL-6 production
3/26/2023
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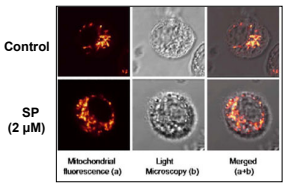
Mast Cells Can Release Mitochondrial DNA that Triggers Autoinflammatory Responses

Atopic dermatitis and skin disease

Human mast cell degranulation and preformed TNF secretion require mitochondrial translocation to exocytosis sites: Relevance to atopic dermatitis

Bodi Zhang, MD, MPH, PhD,[1,2] Konstantinos-Dionysios Alysandratos, MD,[1,*] Asimenia Angelidou, MD,[1,*] Shahrzad Asadi, Pharm.D.,[1] Nikolaos Sismanopoulos, MD,[1] Doron-Anastasia Delivanis, MD,[1] Zuyi Wang, MD,[1] Alexandra Miniati, MD,[1,*] Magdalini Vasilaki, BS,[1,*] Alexandra Katsarou-Katsari, MD, PhD,[1] Denchun Miao, PhD,[1] Susan E. Leeman, PhD,[1] Dimitrios Kalogeromitros, MD, PhD,[1] and Theoharis C. Theoharides, MS, PhD, MD[1,2,3,4]
Boston, Mass, and Athens, Greece

J Allergy Clin Immunol 2011;127:1522-31

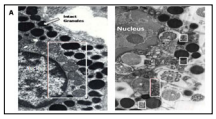


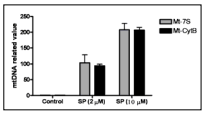
OPEN ACCESS Freely available online PLOS

Stimulated Human Mast Cells Secrete Mitochondrial Components That Have Autocrine and Paracrine Inflammatory Actions

Bodi Zhang[1,2], Shahrzad Asadi[1,*], Zuyi Wang[1,*], Nikolaos Sismanopoulos[1], Theoharis C. Theoharides[1,2,3,4,5]

December 2012 | Volume 7 | Issue 12 | e49767





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Free Mitochondrial DNA Indicates COVID-19 Severity

Circulating Mitochondrial DNA is an Early Indicator of Severe Illness and Mortality from COVID-19

bioRxiv

Davide Scozzi, Marlene Cano, Lina Ma, Dequan Zhou, Ji Hong Zhu, Jane A O'Halloran, Charles Goss, Adriana M. Rauseo, Zhiyi Liu, Valentina Peritore, Monica Rocco, Alberto Ricci, Rachele Amodeo, Laura Aimati, Mohsen Ibrahim, Ramsey Hachem, Daniel Kreisel, Philip A. Mudd, Hrishikesh S. Kulkarni, Andrew E. Gelman
doi: https://doi.org/10.1101/2020.07.30.227553

Am J Physiol Cell Physiol 319: C258–C267, 2020.
First published June 8, 2020; doi:10.1152/ajpcell.00224.2020.

PERSPECTIVES | *Virus-Host Cell Interactions and the Viral Life Cycle: Basic Science to Therapeutics*

Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis

Keshav K. Singh,[1,*] Gyaneshwer Chaubey,[2,*] Jake Y. Chen,[3] and Prashanth Suravajhala[4]

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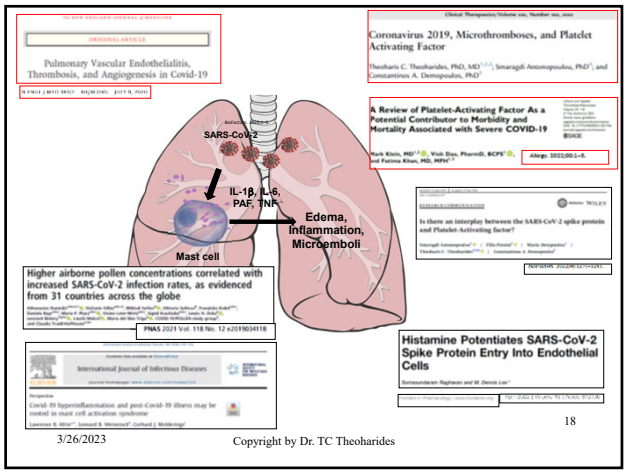

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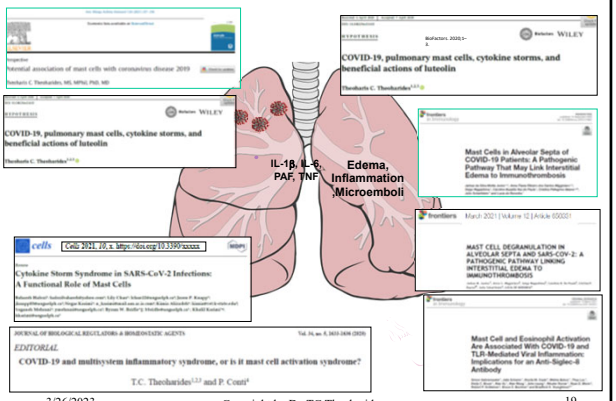
Additional Evidence of Mast Cell Involvement in COVID-19



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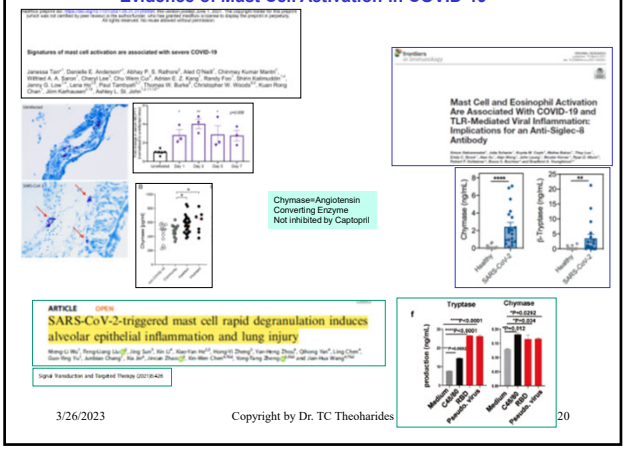
Evidence of Mast Cell Activation in COVID-19



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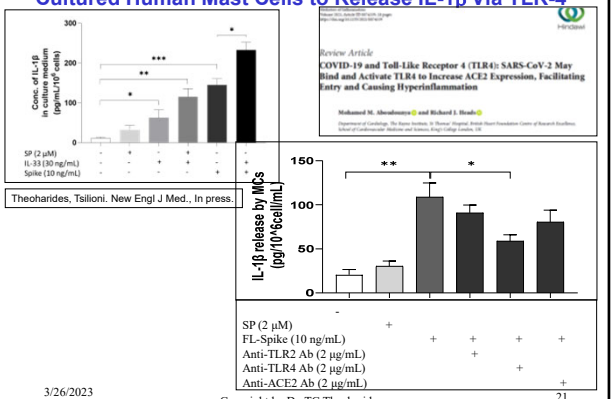
Recombinant SARS-CoV-2 Spike Protein Stimulates Cultured Human Mast Cells to Release IL-1β Via TLR-4



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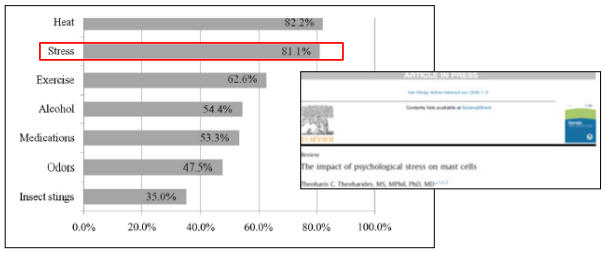
Original Article

The Mastocytosis Society Survey on Mast Cell Disorders: Patient Experiences and Perceptions☆

J ALLERGY CLIN IMMUNOL PRACT
JANUARY/FEBRUARY 2014

Susan Jennings, PhD*, Nancy Russell, DrPH*, Blair Jennings, BS*, Valerie Siva, RN, BSN*, Lisa Sterling, BS*, Mariana Castells, MD, PhD, FAAAAI*, Peter Valent, MD*, and Cem Akin, MD, PhD, FAAAAI* *Hastings, Neb; Boston, Mass; and Vienna, Austria*



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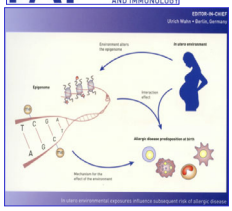
Science

Fetal mast cells mediate postnatal allergic responses dependent on maternal IgE

Kasha Moallem*, Josef Balla*, Abhay P. S. Rathore†, Hansen Karol†, Benoit Mallevre‡, Wilfried A. A. Saron‡, Jhaoyuan Liu†, Jing Wen Hang†, Charles Antoine Dutertre†, Anis Larbi†, Jerry K. Y. Chan†§¶, Ashley L. St. John†§¶, Florent Ginhoux†§¶

PAI Volume 24 • Number 5 • August 2015
PEDIATRIC ALLERGY AND IMMUNOLOGY



Allergy

ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy

J. L. Peters[1], S. Cohen[2], J. Staudenmayer[3], J. Hosen[4,5], T. A. E. Platts-Mills[6] & R. J. Wright[5,7]

[1]Department of Environmental Health, Boston University School of Public Health, Boston, MA, USA, [2]Department of Psychology, Carnegie Mellon University, Pittsburgh, PA, USA, [3]Department of Mathematics and Statistics, University of Massachusetts, Amherst, MA, USA, [4]Division of Allergy and Clinical Immunology, University of Virginia, Charlottesville, VA, USA, [5]Department of Entomology, University of Maryland, College Park, MD, USA, [6]Department of Environmental Health, Harvard School of Public Health, Boston, MA, USA, [7]The Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

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Prenatal Stress Contributes to Allergy and Inflammation

Allergy

REVIEW ARTICLE

Prenatal maternal stress and atopic diseases in the child: a systematic review of observational human studies

N. W. Andersson[1,2,3,*], M. V. Hansen[3,*], A. D. Larsen[4], K. S. Hougaard[4], H. A. Kolstad[5] & V. Schlünssen[4,5,6]

Allergy 71 (2016) 15–26 © 2015

Pediatric Allergy and Immunology

ORIGINAL ARTICLE Eye & skin

Maternal psychologic problems increased the risk of childhood atopic dermatitis

I. J. Wang[1,2,3,*], H. J. Wen[4], T. L. Chiang[5], S. J. Lin[6] & Y. L. Guo[7,8,*]

Pediatric Allergy and Immunology 27 (2016) 169–176 © 2015

Association Between Maternal Perceived Stress in All Trimesters of Pregnancy and Infant Atopic Dermatitis: A Prospective Birth Cohort Study

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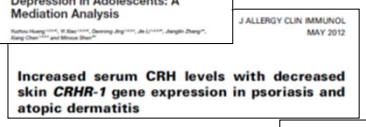
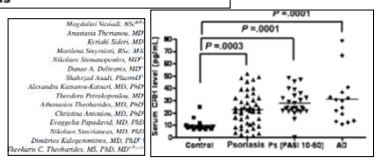
Stress Worsens CSU and AD Via CRH Acting on Mast Cells





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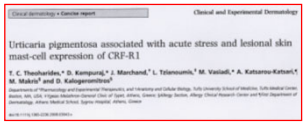
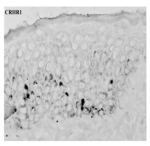
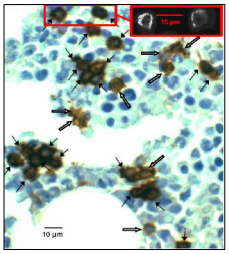




High serum CRH and bone marrow mast cell CRH receptor expression in a mastocytosis patient

Theoharis C. Theoharides, MS, PhD, MD[1,2], Anastasia I. Petra, MD[1], Julia M. Stewart, RN[1], Irene Tsiliomi, PhD[1], Cem Akin, MD, PhD[1]

J Allergy Clin Immunol.
2014 Jun 27.



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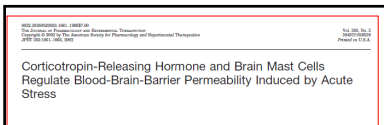
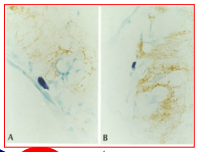
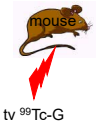
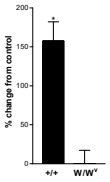




30 minutes restraint stress



tv ^{99}Tc-G



C57BL +/+ normal
W/Wv mast cell-deficient

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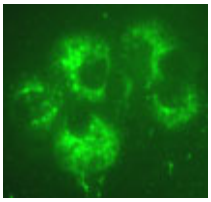
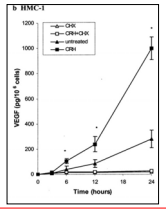
Human Mast Cells Express Corticotropin-Releasing Hormone (CRH) Receptors and CRH Leads to Selective Secretion of Vascular Endothelial Growth Factor[1]

J Immunol 2005;174:7665-7675

Jing Cao,*† Nikoletta Papadopoulou,† Duraisamy Kempuraj,† William S. Boucher,† Koreaki Sugimoto,‡1 Curtis L. Cetrulo,‡ and Theoharis C. Theoharides2*†§





Substance P (SP) Induces Expression of Functional Corticotropin-Releasing Hormone Receptor-1 (CRHR-1) in Human Mast Cells

Shahrzad Asadi[1,2], Konstantinos-Dionysios Alysandratos[1,3,7], Asimenia Angelidou[1,3,8], Alexandra Miniati[1], Nikolaos Sismanopoulos[1,3], Magdalini Vasiadi[1,3,4], Bodi Zhang[1,4,5], Dimitrios Kalogeromitros[3,9] and Theoharis C. Theoharides[1,3,4,5,6]

3/26/2023

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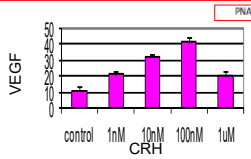
Corticotropin-releasing hormone induces skin vascular permeability through a neurotensin-dependent process

Jill Donelan*, William Boucher*, Nikoletta Papadopoulou*, Michael Lytinas*, Dean Papaliodis*, Paul Dobner†, and Theoharis C. Theoharides*‡§¶

Departments of *Pharmacology and Experimental Therapeutics, †Biochemistry, and ‡Internal Medicine, Tufts University School of Medicine, Tufts–New England Medical Center, 136 Harrison Avenue, Boston, MA 02111; and §Department of Molecular Genetics and Microbiology, University of Massachusetts Medical School, Worcester, MA 01655

PNAS | May 16, 2006 | vol. 103 | no. 20 | 7759–7764



November 2012 | Volume 7 | Issue 11 | e48934

OPEN ACCESS Freely available online PLOS ONE

Neurotensin and CRH Interactions Augment Human Mast Cell Activation

Konstantinos–Dionysios Alysandratos[1,2,4Yia], Shahrzad Asadi[1,3¶], Asimenia Angelidou[1,2,4ib], Bodi Zhang[1,4,5], Nikolaos Sismanopoulos[1,2ite], Hailing Yang[1], Agatha Critchfield[5], Theoharis C. Theoharides[1,2,4,6,7,8u]

November 2012 | Volume 7 | Issue 11 | e48934

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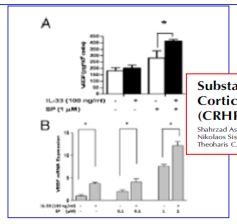
IL-33 augments substance P–induced VEGF secretion from human mast cells and is increased in psoriatic skin

4448–4453 | PNAS | March 2, 2010 | vol. 107 | no. 9

Theoharis C. Theoharides[5,b,c,d,1], Bodi Zhang[a,b,2], Duraisamy Kempuraj[a,2], Michael Tagen[a,2,3], Magdalini Vasiadi[a,2], Asimenia Angelidou[a], Konstantinos-Dionysios Alysandratos[a], Dimitris Kalogeromitros[e], Shahrzad Asadi[a], Nikolaos Stavrianeas[a], Erika Peterson[f], Susan Leeman[g,1], and Pio Conti[h]



Substance P (SP) Induces Expression of Functional Corticotropin-Releasing Hormone Receptor-1 (CRHR-1) in Human Mast Cells

Shahrzad Asadi[1,2], Konstantinos-Dionysios Alysandratos[1,3,7], Asimenia Angelidou[1,3,8], Alexandra Miniati[1], Nikolaos Sismanopoulos[1,3], Magdalini Vasiadi[1,3,4], Bodi Zhang[1,4,5], Dimitrios Kalogeromitros[3,9] and Theoharis C. Theoharides[1,3,4,5,6]

J Immunol 2005;174:7665-7675

ALLERGY CLIN IMMUNOL APRIL 2010

Autocrine hemokinin-1 functions as an endogenous adjuvant for IgE-mediated mast cell inflammatory responses

Tina L. Sumpter, PhD,[a] Chin H. Ho, MD,[a] Anna R. Pleet, BS,[a] Olga A. Tkacheva, BS,[a] William J. Shufesky, BS,[c,d] Darling M. Rojas-Canales, PhD,[c,d] Adrian E. Morelli, MD, PhD,[b,c,d] and Adriana T. Larregina, MD, PhD[a,b,c] *Pittsburgh, Pa*

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Mast Cells Increase Blood-Brain-Barrier Permeability, Which Permits Focal Inflammation of the Brain

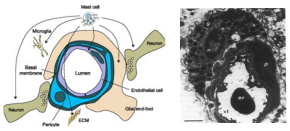
MINIREVIEW

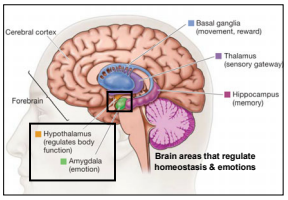
MAST CELLS: THE IMMUNE GATE TO THE BRAIN

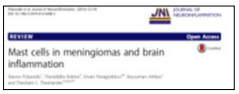
T.C. Theoharides, Ph.D., M.D.

Department of Pharmacology, Tufts University School of Medicine
136 Harrison Avenue, Boston, MA 02111

Theoharides TC. Life sciences 46 (1990)







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Long-COVID Syndrome

VIEWPOINT: COVID-19

Nervous system consequences of COVID-19

Neurological symptoms highlight the need to understand pathophysiologic mechanisms

By Serena Spudich and Avindra Nath

Science, 375 (6578), • DOI: 10.1126/science.abm2052

Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection

PLOS ONE | https://doi.org/10.1371/journal.pone.0240784 November 9, 2020

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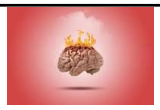
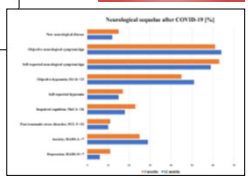
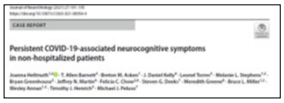
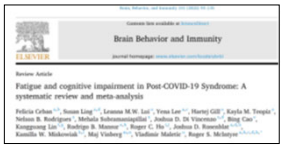
Neurological outcomes 1 year after COVID-19 diagnosis: A prospective longitudinal cohort study

Eur J Neurol. 2022;00:1–12.









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Long-COVID Syndrome Is Associated With Brain Perivascular Inflammation and Thrombosis

Microvascular Injury in the Brains of Patients with Covid-19

Myoung-Hwa Lee, Ph.D.
National Institute of Neurological Disorders and Stroke
Bethesda, MD

N ENGL J MED 384;9 NEJM.ORG FEBRUARY 4, 2021

Extensive Cerebral Venous Thrombosis as an Isolated Presentation in a COVID-19-Positive Young Adult

2022 Farzin et al. Cureus 14(9): e29561. DOI 10.7759/cureus.29561

RESEARCH LETTER

SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE 2

Circulation Research. 2021;128:1323–1326.

Increased levels of inflammatory molecules in blood of Long COVID patients point to thrombotic endothelitis

34

Long-COVID Syndrome Is Associated With Activation of Microglia

RESEARCH ARTICLE

COVID-19-related neuropathology and microglial activation in elderly with and without dementia

Brain Pathology. 2021;00:e12997. https://doi.org/10.1111/bpa.12997

Neuropathobiology of COVID-19: The Role for Glia

Brain, Behavior, & Immunity - Health

SARS-CoV-2 Spike Glycoprotein S1 Induces Neuroinflammation in BV-2 Microglia

35

Cross-talk Between Mast Cells and Microglia Leading to Inflammation of the Brain

The role of mast cells in neuroinflammation

Microglia and mast cells: two tracks on the road to neuroinflammation

Mast cell

Neurotensin, mtDNA, Tryptase

IL-6, TNF

Microglia

Pro-inflammatory mediators

IL-1β, IL-6, TNF & CCL2, CCL5, CXCL8

Induction of Microglial Activation by Mediators Released from Mast Cells

Mast Cell Tryptase Induces Microglia Activation via Protease-activated Receptor 2 Signaling

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Mast Cells and Microglia in Neuro-COVID

Could SARS-CoV-2 Spike Protein Be Responsible for Long-COVID Syndrome?

Role of SARS-CoV-2 Spike-Protein-Induced Activation of Microglia and Mast Cells in the Pathogenesis of Neuro-COVID

Theoharis C. Theoharides and Duraisamy Kempuraj

Cells 2023, 12, 688.

The S1 protein of SARS-CoV-2 crosses the blood-brain barrier in mice

37

The Effects of Plant Flavonoids on Mammalian Cells: Implications for Inflammation, Heart Disease, and Cancer

ELLIOTT MIDDLETON, JR.,* CHITHAN KANDASWAMI, AND THEOHARIS C. THEOHARIDES*

Chebogue Island Institute of Natural Product Research, Chebogue Island, Maryland (E.M., C.K.) and Department of Pharmacology/Experimental Therapeutics, Tufts University School of Medicine, Boston, Massachusetts (T.C.T.)

This paper is available online at http://www.pharmrev.org

Luteolin
(3',4',5,7-tetrahydroxyflavone)

Unique Properties of Luteolin

- Reduces oxidative stress
- Inhibits inflammation
- Inhibits mast cell activation
- Inhibits microglia activation
- Inhibits neurotoxicity
- Is weak metal chelator
- Increases memory

Anti-Oxidant, Anti-Inflammatory and Anti-Allergic Activities of Luteolin

Planta Med 2008; 74: 1667–1677

Brain Inflammation, Neuropsychiatric Disorders, and Immunoendocrine Effects of Luteolin

Theoharis C. Theoharides, BA, MS, MPhil, MD, PhD,*†‡§ Pio Conti, DSc,|| and Marina Economu, MD, DSc¶

Journal of Clinical Psychopharmacology • Volume 34, Number 2, April 2014

Long-COVID syndrome-associated brain fog and chemofog: Luteolin to the rescue

BioFactors. 2021;47:232–241.

Theoharis C. Theoharides | Christos Cholevas | Konstantinos Polyzoidis | Antonios Politis

38

Successful Treatment of a COVID-19 Patient on Lung Transplant List

This 49-year-old Caucasian female tested positive for COVID-19 on 11/30/2020 and complained of dyspnea and fatigue. The patient was admitted to the hospital on 12/20/2020 severely hypoxic with a Diagnosis of acute respiratory failure. CRP and D-Dimer were elevated. O2 sat=52%.

Treatment Approach:
- Acetyl salicylic acid
- BrainGain (Berberine, Calcium folinate, Luteolin, Hydroxytyrosol)
- Erythropoietin
- Misoprostol (Cytotec)
- FibroProtek (Luteolin & Quercetin)
- Rupatadine (antihistamine, antiPAF, antifibrotic, mast cell inhibitor)

INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES

Fig. 1A-Before Treatment **Fig. 1B-After treatment**

A ventilation-perfusion (V/Q) scan on 3/1/2021 revealed coarse heterogenous perfusion of the lungs bilaterally, suggestive of diffuse microthromboembolic disease (Fig. 1A). Pulmonary clots were apparently fossilized and deep within the lungs rendering athromboendartectomy not a viable option. The patient was placed on the lung transplant list. A repeat V/Q perfusion scan on 8/6/2021 showed minimal heterogeneity of uptake (Fig. 1B).

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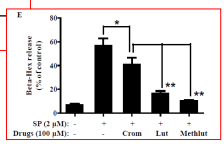
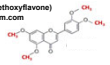
Advantages of TetramethoxyLuteolin

The novel flavone tetramethoxyluteolin is a potent inhibitor of human mast cells

Zuyi Weng, MS, PhD,[a,b] Arti B. Patel, MS,[a,c] Smaro Panagiotidou, MA,[a] and Theoharis C. Theoharides, MS, PhD, MD[a,b,c,d] *Boston, Mass*



Methoxyluteolin
(3',4',5,7-tetramethoxyflavone)
www.GentleDerm.com

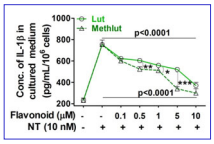


- Better absorbed
- Decreased metabolism
- Methyl donor
- No phenol intolerance

Neurotensin stimulates NTR3/sortilin and mTOR in human microglia: Potential therapeutic target in autism inhibitable by methoxyluteolin

Arti B. Patel[b,h], Irene Tsilioni[a], Susan E. Leeman[c] and Theoharis C. Theoharides[a,b,d,e,*]

E7138 | PNAS | November 8, 2016 | vol. 113 | no. 45



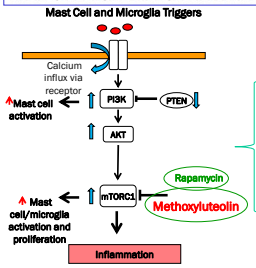
40

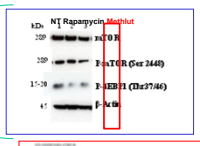
Microglia and Mast Cell Activation Involves mTOR

Neurotensin stimulates sortilin and mTOR in human microglia inhibitable by methoxyluteolin, a potential therapeutic target for autism

Arti B. Patel[a,b], Irene Tsilioni[a], Susan E. Leeman[c,1], and Theoharis C. Theoharides[a,b,d,e,1]

www.pnas.org/cgi/doi/10.1073/pnas.1604992113





41

www.GentleDerm.com

A unique antioxidant lotion containing a novel flavonoid for dry, irritated or sensitive skin

- Aloe vera extract
- Olive fruit extract
- Chamomile oil
- Oregano oil
- Honey

Plus • Methoxyluteolin (Tetramethoxyflavone)

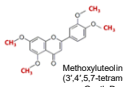
GentleDerm®

A unique antioxidant lotion containing a novel flavonoid for dry, irritated or sensitive skin

Hydrates-Nourishes-Soothes

Let Nature Calm Your Skin™

Net weight 2 oz (56.7 gm)



Methoxyluteolin
(3',4',5,7-tetramethoxyflavone)
www.GentleDerm.com

Properties of methoxyluteolin:

- Better absorbed
- Decreased metabolism
- Methyl donor
- No phenol intolerance

Tolerability and benefit of a tetramethoxyluteolin-containing skin lotion

Theoharis C Theoharides,[1,2,3] Julia M Stewart[1] and Irene Tsilioni[1]

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Summary of Clinical Implications

- Mast cells are ubiquitous in the body, including critical areas of the brain.
- Mast cells contain as many as 1,000 secretory granules/cell each storing as many as 50 preformed mediators such as bradykinin, histamine, chymase, tryptase and TNF.
- Mast cells can synthesize and release another 50 or so pro-inflammatory mediators such as PAF, chemokines, cytokines and peptides.
- Mast cells can be triggered by allergic, but also pathogenic and stress stimuli.
- Mast cells can sense the outside environment, but also the blood vessel lumen
- Mast cell can orchestrate and regulate inflammatory reactions.
- Mast cells in the lungs are involved in the pathogenesis of COVID-19 and in the brain in Long-COVID and Neuro-COVID.
- There are no effective drugs to block mast cell activation.
- Liposomal (in olive pomace oil) dietary supplements containing pure flavonoids luteolin and quercetin (e.g. NeuroProtek and FibroProtek) can inhibit mast cells.
- A new supplement ViralProtek containing oleurupein, eriodictyol, hydroxytyrosol and sulphraphane inbits multiple viral targets including ACE2, serine proteases, and TLR4.

(12) **United States Patent**
Theoharides

(10) **Patent No.: US 8,268,365 B2**
(45) **Date of Patent: *Sep. 18, 2012**

(54) **ANTI-INFLAMMATORY COMPOSITIONS FOR TREATING BRAIN INFLAMMATION**

(75) Inventor: **Theoharis C. Theoharides**, Brookline, MA (US)

(73) Assignee: **Theta Biomedical Consulting & Development Co., Inc.**, Brookline, MA (US)

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Mast cells and inflammation

Theoharis C. Theoharides, Konstantinos-Dionysios Alysandratos, Asimenia Angelidou, Danae-Anastasia Delivanis, Nikolaos Stamatopoulos, Bodi Zhang, Shahrzad Asadi, Magdalini Vasiadi, Zuyi Weng, Alexandra Miniati, Dimitrios Kalogeromitros