# The MCAS and Covid-19 Theory:

## A Multidimensional Epigenetic Phenomenon

Volume One, 2nd Edition

**Chapter Three: MCAS**

by, Diane M. Kane

**talkMCAS.com** is an independent science platform dedicated to
mast cell research, education and advocacy for the betterment of global health.
Email Diane M. Kane at: info@talkMCAS.com

This book is dedicated to all those who have suffered from mast cell disease unaided, to all those who have lost their lives or had their lives impaired by disease processes yet to be understood by medical science, and to the healthcare practitioners who have assisted these patients without turning them away.

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This current draft of *The Early Chapters* is a work-in-progress, with publishing and editorial notes below:

**Publishing notes**: *The MCAS and Covid-19 Theory* will eventually be published in four separate volumes, each containing extensive research excerpts from relevant medical journal publications. Volume One, which will serve as a Synopsis version with greater accessibility for the lay reader, may also serve as an introductory overview for scientists. Due to the current global health crisis, the author will work in an open-book format sharing Research Editions which will be made available in PDF form to all healthcare stakeholders who inquire via **info@talkmcas.com**, with the agreement that all copies printed in paper-form or shared online will be used for research purposes and not for financial gain. It is hoped that this document will be shared far and wide.

All scientists are encouraged to extrapolate from this body of work and publish independently on these findings for the purpose of helping the sick. Highlights, summaries and updates of *The MCAS and Covid-19 Theory* will be posted on the MCAS research hub: **www.talkMCAS.com**, providing direct access to all who seek to expand their knowledge, advance medical science and improve global health.

Please submit any new publications to be considered for entry into the final draft of the work to the above-mentioned email address. For all of those who authored publications contained in this catalog of investigational research, please note that the publisher of *The MCAS and Covid-19 Theory* will respect all appropriate copyright agreements and will seek all necessary reprint permissions prior to publication. This current iteration of the document is intended to assist the medical community in meeting the challenges that are upon us with Covid-19.

**Editorial notes**: The author is presenting this work from a layperson's perspective, seeking a platform for the patient's voice within global healthcare. Support for the patient community from the authors of the work contained herein is respectfully sought. The research excerpts contained in this book have been extracted from a wide variety of peer-reviewed publications from credentialled scientific journals, as well as several valuable magazine and book entries.

For the sake of continuity, the bibliographic footnotes contained within the original publications have been removed and the formatting structures have been unified and abbreviated for the benefit of consolidating the research into a single work. It is hoped that the authors of the individual publications will appreciate the need to present these complex findings as accessibly and effectively as possible.

**About the Author:** Diane M. Kane, an American born in 1964, was diagnosed with MCAS in 2017 at Cedars-Sinai Medical Center in Los Angeles after a lifelong struggle with an unidentified chronic illness. As a recovering MCAS patient and a suspected SARS sufferer from a 2003 trip to Vietnam, Diane is advocating for appropriate care for other MCAS patients and for all global citizens who may be impacted by Covid-19, MCAS or both.

As a researcher, writer and MCAS patient-advocate, Diane is sharing her knowledge of MCAS and its complex epigenetic relationship to infectious disease from both a scientific perspective and a place of hard-earned personal experience. After travelling throughout the United States, Europe and Asia for several decades in search of a greater understanding of her complex health challenges, the author reveals through this work that previously elusive explanations now appear to be within grasp for the many doctors and patients who are struggling with these perplexing and often debilitating illnesses.

It is hoped that the hypothesis of interrelated co-morbidity presented in this book will encourage all who read it, especially medical scientists worldwide, to seek a more comprehensive and translational understanding of the epigenetic etiologies of Mast Cell Activation Syndrome and Covid-19, as well as MCAS and many other acute and chronic illnesses. Although this book may ultimately pose more questions than answers, the stimulation of a robust dialogue regarding mast cell disease and pathogenic infections will, in itself, be a major victory on the road to global wellness. Together, we can walk forward in hopeful expectation that the answers to these questions will soon bring great healing to many and better protections to all.

**The MCAS and Covid-19 Theory, Complete Four Volume Table of Contents:**

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Characterization of Mast Cell Activation Syndrome

## Chapter Three: Mast Cell Activation Syndrome (MCAS)

MCAS is a subcategorization of an umbrella classification of hematological mast cell diseases known by the similar acronym MCAD, which is short for Mast Cell Activation Diseases. With MCADs having a genomically-proven prevalence in an estimated 17% of the global population[i], and MCAS being the most commonly presenting MCAD by a substantial margin, it is important to note that MCAS is also the mast cell disease most recently discovered, least known and least researched.

From a research paper previously referenced in *Chapter One, The Host Factor*, the following excerpt provides a fundamental description of MCAS along with a statement estimating its wide global prevalence based on a German population study, as published in *Naunyn-Schmiedeberg's Archives of Pharmacology* journal in July of 2016 from the Institute of Human Genetics, University Hospital of Bonn, Bonn; German Center for Neurodegenerative Diseases (DZNE), Bonn; Kreiskrankenhaus Waldbröl, Waldbröl; Gemeinschaftskrankenhaus, Bonn; and, RWTH Aachen University, Aachen- all in Germany; and the Mayo Clinic, Rochester and the University of Minnesota, Minneapolis- both in the Minnesota, USA:

**Pharmacological Treatment Options for Mast Cell Activation Disease**, (Gerhard J. Molderings, Britta Haenisch, Stefan Brettner, Jürgen Homann, Markus Menzen, Franz Ludwig Dumoulin, Jens Panse, Joseph Butterfield, Lawrence B. Afrin): Mast cells (MCs) are immune cells of hematopoietic origin found in all human tissues, especially at the environmental interfaces. They act as both effector and regulatory cells and play a central role in adaptive and innate immunity. Their important role in immunological as well as non-immunological processes is reflected by the large number of mediators (>200) including pre-stored ones such as histamine and tryptase as well as numerous mediators synthesized de novo in response to allergic or non-immune triggers such as chemokines and cytokines, by which MCs may influence other cells. Their evolved arrays of sensory and response mechanisms engender diverse havoc when MC dysfunction emerges…Pathogenetically, MCAD denotes a group of polygenic MC disorders characterized by aberrant release of variable subsets of MC mediators and also an accumulation of either morphologically altered and immunohistochemically identifiable mutated MCs due to MC proliferation (SM and MCL) or morphologically ordinary MCs due to decreased apoptosis (MCAS). According to recent molecular genetic findings, the subclasses and clinical subtypes of MCAD do not represent distinct disease entities but should be more accurately regarded as variable presentations of a common generic state of MC dysfunction. Due to both the widespread distribution of MCs and the great heterogeneity of aberrant mediator expression patterns, symptoms can occur in virtually all organs and tissues; hence, the clinical presentation of MCAD is very diverse, sometimes to the even-further-confounding point of presenting opposite abnormalities in different patients (or even in the same patient at different times, or in different sites in the same patient at the same time). While the prevalence of SM in Europeans ranges between 0.3 and 13 per 100,000, the prevalence of MCAS may be as high as 17 % (in Germany).[ii]
https://link.springer.com/content/pdf/10.1007%2Fs00210-016-1247-1.pdf

The following excerpt, published over ten years ago by several of the world's leading MCAS experts, states emphatically that mast cell diseases deserve a vastly increased level of attention in current healthcare. Although there remains much for scientists to determine regarding the exact contribution of aberrantly behaving mast cells to the pathophysiology of many human diseases, it is clear that there are many mast cell therapeutics capable of ameliorating suffering and preventing disease progression, as published in the *Journal of Hematology-Oncology* in March of 2011 from the Institute of Human Genetics, University of Bonn and Evangelische Kliniken Bonn, Bonn, Germany; Kreiskrankenhaus Waldbröl, Waldbröl, Germany; and, Medical University of South Carolina, Charleston, South Carolina, USA:

> **Mast Cell Activation Disease: A Concise Practical Guide for Diagnostic Workup and Therapeutic Options**, (Gerhard J Molderings, Stefan Brettner, Jürgen Homann, Lawrence B Afrin): Mast cell activation disease comprises disorders characterized by accumulation of genetically altered mast cells and/or abnormal release of these cells' mediators, affecting functions in potentially every organ system, often without causing abnormalities in routine laboratory or radiologic testing. In most cases of mast cell activation disease, diagnosis is possible by relatively non-invasive investigation. Effective therapy often consists simply of antihistamines and mast cell membrane-stabilizing compounds supplemented with medications targeted at specific symptoms and complications. Mast cell activation disease is now appreciated to likely be considerably prevalent and thus should be considered routinely in the differential diagnosis of patients with chronic multisystem polymorbidity or patients in whom a definitively diagnosed major illness does not well account for the entirety of the patient's presentation.[iii]
> https://jhoonline.biomedcentral.com/track/pdf/10.1186/1756-8722-4-10

In simple language, MCAS is a chronic allergic and immunological response syndrome whereby the allergy and immune cells in our bodies that are called mast cells will mutate in response to certain toxic and overbearing substances and stressors. Through the mutagenic process vulnerable mast cells become hypersensitive due to both an increased permeability in their cellular wall and the development of distorted signaling patterns; they then more readily leak their contents into our bodies at destabilizing and disease-causing levels while also exchanging dysfunctional signaling patterns with other cells. It is important to note that mast cells, a type of myeloid cell known as leukocytes which constitute a portion of our white blood cells, begin their formation in the bloodstream and can be present in almost every tissue, every organ and every system of the human body; and medical science has, historically and to date, grossly underestimated the conceivable range of mast cell phenotypes, behaviors and multi-cellular influences.

Demonstrating the broad range of potential triggers of mast cell activation in people with MCAD, the following known MCAS triggers are listed on The Mast Cell Society's website www.TMSforacure.org:

**Figure 1. Some Potential Mast Cell Triggers**

Heat, cold or sudden temperature changes
Stress: emotional, physical, including pain, or environmental (i.e., weather changes, pollution, pollen, pet dander, etc.)
Exercise
Fatigue
Food or beverages, including alcohol
Drugs (opioids, NSAIDs, antibiotics and some local anesthetics) and contrast dyes
Natural odors, chemical odors, perfumes and scents
Venoms (bee, wasp, mixed vespids, spiders, fire ants, jelly fish, snakes, biting insects, such as flies, mosquitos and fleas, etc.)
Infections (viral, bacterial or fungal)
Mechanical irritation, friction, vibration
Sun/sunlight[iv]
https://tmsforacure.org/symptoms/symptoms-and-triggers-of-mast-cell-activation/

The Mast Cell Society emphasizes that triggers can change over time and a person can become reactive to something which they could previously tolerate. TMSforacure.org also lists specific medications that are known to cause difficulties for MCAD patients. The pharmacological issues pertaining specifically to MCAS are complex and will require a substantial increase in mast cell research as well as more stringent protections prohibiting the use of potentially harmful excipient ingredients such as certain binders, fillers, preservatives and dyes used in current drug manufacturing.

With regard to one group of ecotoxic factors that appear to be triggering MCAS, and exacerbating MCAS symptoms after initial mutations have occurred, the world-at-large and medical science in-particular are underinformed regarding the resounding long-term molecular changes instigated within the host by pathogenic invaders. In addition, there exists a broken belief system amongst the human population regarding the alleged safety of much of what is being consumed and the risks inherent in toxic environmental exposures which are chronically impacting society at the levels of both individual and community health. While the current evidence points strongly towards pathogenic infections being causal in a substantial portion of mast cell mutations, it is also possible that other ecotoxic exposures may cause novel mast cell mutations and/or the exacerbation of existing mutations. Unfortunately, and to the great detriment of human health, the overriding reality is that we have mainstreamed mutagenic substances and stressors into our lives and these ecotoxic insults then wreak a multisystemic havoc in and through molecularly-modified and structurally fragile mast cells.

MCAS has long-existed in humans but has only been identified by medical science since 2010; and, in spite of a growing body of knowledge about MCAS, this vital science remains largely ignored or suppressed within the highest echelons of the U.S. and European medical communities. Prior to knowing of MCAS, many of MCAS' downstream subset disease states have been identified, named and treatments have been developed. These diseases still exist in their

own right and they will still require identification and treatment, but once understood within the context of MCAS then more appropriate treatments could vastly improve outcomes. Getting doctors and patients alike to re-orientate their understanding of these illnesses in light of MCAS, both on an individual and collective basis, requires a massive shift in perceptions and there currently exist many barriers to such progress.

People who have MCAS are largely unaware for many years that they have it, although over time many patients present with a progression of MCAS-related conditions. Decades of misdiagnoses, along with healthcare's siloed focus on subset diagnoses without identifying disease etiology, leads to a continual downward spiral for the patients. Even once MCAS has been correctly diagnosed, the MCAS-knowledgeable doctors and patients are still being required to work from incomplete mast cell science in an attempt to establish safe and effective treatment plans. With an increasing population of mast cell patients burdening the healthcare system, these attempts to apply insufficient knowledge through experimental science is causing great strife.

While trying to explain it as accessibly as possible, it is important to note that MCAS is complex in various ways: it is a polyfactorial multisystemic polymorbidity. Firstly, MCAS has multiple causes. And then, a variety of illnesses develop in a variety of organs systems with the greatest impacts being dermatological, respiratory, cardiovascular, gastrointestinal, and neurological. Making the overall situation even harder to navigate for the patients and their doctors can be the neurological impacts of MCAS which in some people may include issues of brain fog, somatic anxiety and depression, as well as more profound deficits in memory and recurrent lapses in cognitive brain function as the condition advances.

There is a waxing and waning quality to MCAS, with highly destabilizing hyperinflammatory episodes that can calm down enough over time for a person to then continue on with life. It can present more overtly for a period of time in one area of the body or another and then it can recede, eventually popping up somewhere else while leaving behind a compounding set of problems wherever it has taken root. And it appears that more mast cell mutations will occur in a person over time depending on the individual's mutagenic exposures explaining, at least in part, the progression of the disease. MCAS is a major driver of illness and disease and its many diverse variances explain how it has existed somewhat covertly in up to 17% of the population. Yet, with the catastrophic levels of chronic illness in our world, once people learn about MCAS it becomes clear to see that it has been hiding in plain sight all along.

Within the mast cell research community, disagreement exists regarding the prevalence statistics for MCAS with two contradictory views presenting markedly different diagnostic criteria for the disease. The discord is attributable to a relatively small group of widely-published doctors who appear committed to resisting the new science. This denial of the genomic facts, albeit a temporary barrier of convenience for over-burdened doctors, has greatly impeded a more vigorous effort to advance mast cell research while also severely limiting access to appropriate clinical care for a struggling mast cell patient population. In MCAS patient circles, this self-titled "Consensus Group" committed a particularly divisive offense by publishing a 2019 paper entitled "*Doctor, I Think I Am Suffering from MCAS: Differential Diagnosis and Separating Facts from Fiction*"[v]. In this highly-contested paper, when referencing the proposed diagnostic algorithms

which are considered grossly insufficient and diminishing by many, it is started that, "…These criteria and assays may be useful in daily practice and help avoid unnecessary referrals and unjustified fears in patients." With civility and respect, it must be emphasized that chronically ill patients who cannot find a doctor to help them with their suspected mast cell disorder are not unjustifiably fearful and this MCAS-minimizing approach does not help them; rather, it hurts them. There is a grassroots patient movement with a change.org platform petitioning to have the *Journal of Allergy and Clinical Immunology* remove this article from its medical research catalogue due to its unsupported scientific claims and condescending anti-patient bias.

In a recent paper authored by the "Consensus-2" group of MCAS specialists, these diagnostic and prevalence discrepancy issues are explained in great detail. To gain an extensive insight into how MCAS can behave symptomatically, and to access the most accurate MCAD and MCAS diagnostic criteria currently available, a review of the following publication in its entirety is encouraged. This work will be revisited again several times throughout this work; for now, a summary overview is presented, as published in the *De Gruyter* journal on January 5, 2020 and authored by clinical researchers from a wide diversity of medical specialties who are focused on MCAS as a distinct disease entity, from: the AIM Center for Personalized Medicine, Purchase, New York; My Passion 4 Health, Tucson, AZ; Medical College of Wisconsin, Wausau, WI; Plaza Infectious Disease, Kansas City, MO; Alaska Internal Medicine and Pediatrics, Anchorage, AK; Peachtree Allergy and Asthma, Atlanta, GA; Beaver Medical Group, Banning, CA; University of Kentucky, Lexington, KY; Complex Cares, Shoreview, MN; Allergy and Asthma Specialists of Cadillac, Cadillac, MI; Oregon Health and Science University, Portland, OR; Healing Dragon, Portland, OR; Center for Complex Diseases, Mountain View, CA; CHI Health St. Elizabeth, Lincoln, NE; Healthwell Physical Therapy Group, San Francisco, CA; Heart of the Valley Pediatric Cardiology, Pleasanton, CA; The Spring Center, Costa Mesa, CA; Integrative Cancer Consulting, Aptos, CA; Helfgott Research Institute, National College of Natural Medicine, Portland, OR; University of Utah, Salt Lake City, UT; Elevate Health, Portland, OR; Restoration Healthcare, Irvine, CA; Haven Medical, Chapel Hill, NC; Royal College of General Practitioners, London, UK; University of California San Francisco, San Francisco, CA; University of Colorado, Denver, CO; Johns Hopkins University, Baltimore, MD; Center for Healing Neurology, Seattle, WA; Center for Complex Neurology, EDS and POTS, Phoenix, AZ; Patient Navigator, Reston, VA; University of Colorado School of Medicine, Aurora, CO; University of Colorado, Denver, CO; Washington University, St. Louis, MO; Keck School of Medicine, University of Southern California, Los Angeles, CA- all in the USA; Hoffman Centre for Integrative and Functional Medicine, Calgary, Alberta, Canada; University Hospital Lübeck, Lübeck, Germany; Westaway Medical, Brisbane, Queensland, Australia; and, the Institute of Human Genetics, University Hospital of Bonn, Bonn, Germany:

**Diagnosis of Mast Cell Activation Syndrome: A Global "Consensus-2**", (Lawrence B. Afrin, Mary B. Ackerley, Linda S. Bluestein, Joseph H. Brewer, Jill B. Brook, Ariana D. Buchanan, Jill R. Cuni, William P. Davey, Tania T. Dempsey, Shanda R. Dorff, Martin S. Dubravec, Alena G. Guggenheim, Kimberly J. Hindman, Bruce Hoffman, David L. Kaufman, Stephanie J. Kratzer,

Theodore M. Lee, Mindy S. Marantz, Andrew J. Maxwell, Kelly K. McCann, Dwight L. McKee, Laurie Menk Otto, Laura A. Pace, Dahra D. Perkins, Laurie Radovsky, Mary S. Raleigh, Sonia A. Rapaport, Emma J. Reinhold, Mark L. Renneker, William A. Robinson, Aaron M. Roland, E. Scott Rosenbloom, Peter C. Rowe, Ilene S. Ruhoy, David S. Saperstein, David A. Schlosser, Jill R. Schofield, Janet E. Settle, Leonard B. Weinstock, Martina Wengenroth, Mark Westaway, Shijun Cindy Xi and Gerhard J. Molderings): Abstract: The concept that disease rooted principally in chronic aberrant constitutive and reactive activation of mast cells (MCs), without the gross MC neoplasia in mastocytosis, first emerged in the 1980s, but only in the last decade has recognition of “mast cell activation syndrome” (MCAS) grown significantly. Two principal proposals for diagnostic criteria have emerged. One, originally published in 2012, is labeled by its authors as a “consensus” (re-termed here as “consensus-1”). Another sizable contingent of investigators and practitioners favor a different approach (originally published in 2011, newly termed here as “consensus-2”), resembling “consensus-1” in some respects but differing in others, leading to substantial differences between these proposals in the numbers of patients qualifying for diagnosis (and thus treatment). Overdiagnosis by “consensus-2” criteria has potential to be problematic, but underdiagnosis by “consensus-1” criteria seems the far larger problem given (1) increasing appreciation that MCAS is prevalent (up to 17% of the general population), and (2) most MCAS patients, regardless of illness duration prior to diagnosis, can eventually identify treatment yielding sustained improvement. We analyze these proposals (and others) and suggest that, until careful research provides more definitive answers, diagnosis by either proposal is valid, reasonable, and helpful. Introduction: The concept that a class of diseases rooted principally just in chronic aberrant constitutive and/or reactive activation of mast cells (MCs; and with only modest increases in MC numbers due to reduced apoptosis rather than the marked MC neoplasia defining the rare disorder of mastocytosis) ought to exist was first published in 1984–1991. The heterogeneity of the full range of such patients’ clinical presentations is extreme, but symptoms/findings (typically waxing/waning and migratory) often include flushing, allergic-type issues, fatigue, dermatographism, cognitive dysfunction, irritated eyes/nose/mouth/throat, adenitis, dyspnea, palpitations, nausea, reflux, abdominal pain, diarrhea (often alternating with constipation), interstitial cystitis, vulvovaginitis, menorrhagia, dysmenorrhea, fibromyalgia-type pain, joint hypermobility, benign growth anomalies (e.g. cysts, fibrosis, vascular anomalies, poor healing), headache, sensory neuropathy, dysautonomias (e.g. orthostatic hypotension, blood pressure and heart rate lability, thermal dysregulation), anxiety and mood disorders, and an assortment of metabolic/endocrinologic (e.g. thyroid) aberrancies. In 2007, the first case reports were published, followed shortly by a limited proposal for diagnostic criteria in cases where MC clonality could be identified. Subsequent literature regarding this newly recognized (but of course not truly new) “mast cell activation syndrome” (MCAS) included case reports as well as formal studies (mostly relatively small scale), reviews, and various proposals for formal diagnostic criteria. Two principal such proposals emerged – the first published initially in late 2010 and the second published initially in early 2011. The former proposal was adjusted by its authors and others and re-published in 2012], labeled by them at that time as a “consensus.”

However, followers of MCAS literature know there is another sizable world-wide contingent of investigators and practitioners – and patients – who feel there are significant problems with the "consensus" approach and who thus favor the alternative approach advocated by the authors of the 2011 paper, which resembles the "consensus" approach in some respects but differs in a number of other respects. An important difference between these proposals is the number of patients who would qualify for an MCAS diagnosis. Underdiagnosis by inappropriately restrictive criteria is dangerous given (1) increasing evidence of substantial prevalence of MCAS (various publications, based on varying amounts of data, have provided estimates ranging from "rare" to as high as 17% of the general population, the latter perhaps unsurprising given the increasingly recognized great prevalence of a wide range of allergic and inflammatory disorders which may be rooted at least partly in MCAS), and (2) experience to date suggesting that most MCAS patients, regardless of the (typically decades long) duration of their complex multisystem unwellness prior to diagnosis, eventually identify some regimen which helps them gain significant, largely sustainable improvement. Overdiagnosis, however, also could be problematic…Given that the original proposals for both of the principal schools of MCAS diagnostic thought were first published nearly a decade ago and that multiple updates of each have been published since, we feel that review, and a frank discussion of the pros and cons, of the two proposals, as well as how HAT (Hereditary Alpha Tryptasemia) now "fits in" to diagnostic considerations of MCAS, would be helpful. We follow this analysis with our recommendations for steps forward in research and in practice. Before diving into this analysis, though, a brief overview of what MCAS is – or at least what it is thought by most to be – may be helpful. The different "schools of thought" proposing different diagnostic criteria have different senses of what the entity of MCAS encompasses, and these different senses drive the differences in diagnostic criteria. However, there is much about MCAS which is uncontested. It is helpful to understand these areas first. Prior to the introduction of the term "mast cell activation disease" (MCAD), "mast cell disease" was the moniker usually used to refer to the full spectrum of diseases of the MC, which consisted principally of assorted forms of the rare disease of mastocytosis and assorted allergic diseases of varying prevalence ranging from rare (e.g., certain urticarias) to common (e.g., environmental and food allergies). That the allergic illnesses very commonly reflect aberrant MC activation (MCA) was a background biological fact largely lost from conscious consideration in everyday practice. Also often lost was the consideration as to what manifestations of MCA other than "allergic-type" phenomena might also be present in allergy patients. These patients often experience "non-allergic" problems (commonly inflammatory, sometimes even dystrophic) potentially rooted in chronic aberrant MCA but which are left to be addressed by non-allergists even less likely to recognize those problems as rooted in MCA. Thus, the only "MC disease" recognized by most health professionals until recently was the range of (prevalent) overtly allergic-type phenomena and (rare) mastocytosis… Table 1; Potential manifestations of MCAD: (Constitutional) Fatigue, subjective or objective hyperthermia and/or hypothermia, sweats, flushing, plethora or pallor, increased or decreased appetite, weight gain or loss, migratory pruritus, chemical/physical sensitivities (often "odd"), poor healing;

(Dermatologic/integument) Dermatographism, rashes/lesions of many sorts (migratory patchy macular erythema, telangiectasias, angiomata, xerosis, striae, warts, tags, folliculitis, ulcers, dyshydrotic eczema), angioedema, alopecia, onychodystrophy (e.g. brittle and/or longitudinally ridged nails); (Ophthalmologic) Irritated (often "dry") eyes, episodic difficulty focusing, lid tremor/tic (blepharospasm); (Otologic/osmic) Infectious or sterile otitis externa and/or media, hearing loss and/or tinnitus, dysosmia, coryza, post-nasal drip, congestion, epistaxis; (Oral/oropharyngeal) Pain or irritation (sometimes "burning"), leukoplakia, ulcers, angioedema, dysgeusia, dental and/or periodontal inflammation/decay despite good personal and professional attention to dental hygiene; (Lymphatic) Adenopathy (usually sub-pathologic and spontaneously waxing/waning in size, often migratory), adenitis, splenitis (typically only modest); (Pulmonary) Airway inflammation at any or all levels, cough, dyspnea (usually mild, episodic, "just can't catch a deep breath" despite normal pulmonary function tests), wheezing (usually quite mild), obstructive sleep apnea regardless of weight; (Cardiovascular) Presyncope [co-diagnosis of postural orthostatic tachycardia syndrome (POTS) is common; full syncope is relatively rare], hypertension, blood pressure lability, palpitations (usually not correlating with electrocardiographic events), migratory edema, chest pain (usually non-anginal), atherosclerosis, odd heart failure (e.g. takotsubo), allergic angina (Kounis syndrome), vascular anomalies; (Gastrointestinal) Dyspepsia, gastroesophageal reflux, nausea, vomiting (sometimes cyclical), diarrhea and/or constipation (often alternating), gastroparesis, angioedema, dysphagia (usually proximal), bloating/gas (usually post-prandial, often acute/subacute, sometimes to the appearance of full pregnancy), migratory abdominal pain from luminal or solid organ inflammation or distention, malabsorption; cholecystectomy is common, though often yielding normal pathology; ascites is rare; (Genitourinary) Migratory luminal and solid organ inflammation ("urinary tract infection," often culture-negative, is commonly misdiagnosed instead of interstitial cystitis), chronic kidney disease, endometriosis, chronic back/flank/abdominal pain, infertility, decreased libido, vulvodynia, vaginitis (often misdiagnosed as infectious), painful and/or irregular dysmenorrhea, menorrhagia; miscarriages are common and occasionally signal an anti-phospholipid antibody syndrome possibly rooted in MCAS; (Musculoskeletal/connective tissue) Migratory bone/joint/muscle pain (co-diagnosis of fibromyalgia is common), joint laxity/hypermobility [co-diagnosis of hypermobile Ehlers-Danlos syndrome (hEDS) is common], osteopenia/osteoporosis (osteosclerosis is seen but is rare), and other tissue growth/development anomalies (i.e. dystrophisms, usually benign) such as cysts, fibrosis, vascular anomalies such as hemorrhoids, aneurysms, and arteriovenous malformations, occasionally even liquid or solid malignancies; (Neurologic) Headache, sensory neuropathies (most commonly episode/migratory paresthesias in the distal extremities), episodic weakness (though proven motor neuropathy is rare), dysautonomias, seizure disorders, "pseudoseizures" (likely dysautonomic events), cognitive dysfunction (most commonly memory, concentration, and/or word-finding difficulties), dyssomnias (insomnia, frequent waking, hypersomnolence, non-restorative sleep, restless legs; less commonly or rarely: sleep apnea, sleepwalking, sleep talking, sleep paralysis, night terrors); (Psychiatric) Mood disturbances (e.g. depression, anger/irritability,

mood lability), anxiety disorders (anxiety, panic, obsession-compulsion), attention deficit/hyperactivity; frank psychosis is rare; (Endocrinologic/metabolic) Abnormal electrolytes and liver function tests, hypo- or hyperthyroidism (often just sheer (but modest) lability of thyroid function), dyslipidemia, impaired glucose control (hyperglycemia, hypoglycemia, glycemic lability), hypo- or hyper-ferritinemia; nutritional deficiencies are often suspected but are relatively rare, (more commonly micronutrient than general protein/calorie), delayed puberty; adrenal dysfunction is often suspected but rarely proven; (Hematologic/coagulopathic) Polycythemia or anemia [typically just mild, most commonly normocytic but sometimes macrocytic or microcytic; other causes (e.g. iron deficiency), whether consequent to MCAS or not, must be ruled out and addressed; note that "normal" erythropoietic parameters (a relative polycythemia?) may seem odd given the extent of chronic multisystem inflammation], leukocytosis or leukopenia (typically mild), monocytosis or eosinophilia or basophilia (typically modest, occasionally moderate or even robust), thrombocytosis or thrombocytopenia (typically mild), arterial and/or venous thromboembolic disease, otherwise inexplicable "easy" bruising/bleeding (co-diagnosis of mild type 1 von Willebrand disease is common, too); there usually is no histologic or molecular evidence of MC aberrancy in the marrow in MCAS, but sometimes a modest hypocellularity or mild myeloproliferative or myelodysplastic appearance is seen, insufficient for diagnosis of a myeloproliferative neoplasm or myelodysplastic syndrome, and genetic and flow cytometric analyses almost always are normal; (Immunologic) Hypersensitivity reactions, increased risk for malignancy and autoimmunity, impaired healing, increased susceptibility to infection, increased or decreased levels of immunoglobulin of any isotype; monoclonal gammopathy of undetermined significance (MGUS) is occasionally seen. *Few patients display all of these symptoms; most display subsets, and the heterogeneity of full clinical profiles among MCAD patients is extreme. Most symptoms are chronic and low-grade; some are persistent, but many are either episodic or waxing/waning…In the last 10–15 years, though, it has become apparent that most of the clinical problems in patients with any form of "MC disease" – even mastocytosis – are rooted in the aberrant activation of the abnormal MCs (i.e. aberrant MC mediator production/release), thus leading to the designation of the new term of MCAD to describe the full spectrum of MC diseases, constantly reminding all clinicians of the critical issue of aberrant MC activation in these patients. Because it also became apparent that some MCAD patients did not have either mastocytosis or merely the various defined allergic-type phenomena but in fact a wide range of clinical consequences of MCA, the term "mast cell activation syndrome" was coined to refer broadly to this entity. Table 1 lists symptoms/problems which various MCAS patients commonly exhibit consequent (directly or indirectly) to chronic aberrant MC mediator expression. Other elements, too, though, are needed to make a clear diagnosis of MCAS, and disputes have arisen regarding these elements. For one, laboratory evidence of MCA is highly desirable. However, even if one sets aside arguments about which laboratory criteria should be deemed supportive of an MCAS diagnosis, mere acquisition of laboratory evidence is problematic for much of the world's population without access to these tests. As such, consideration needs to be given to methods

of diagnosing MCAS in situations where testing is unobtainable, but disputes have led to differences in diagnostic criteria proposals, thus challenging diagnosticians. Other areas of dispute were therapeutic in nature, namely, the validity of, and approach to, (1) treating patients who have not yet acquired laboratory evidence and (2) incorporating treatment results into diagnostic criteria. Given that impact potentially extends to millions of patients (if the higher estimates of prevalence are closer to the truth), we feel these differences warrant detailed analysis and open discussion. We focus this paper on (1) rare patients with primary (i.e. clonal) MCAS proven by the presently very limited range of laboratory testing routinely available for proving such [KIT-D816X mutational analysis, and flow cytometry seeking co-expression on the surfaces of MCs of CD117 (the extracellular domain of transmembrane tyrosine kinase KIT, the dominant MC regulatory element) together with CD25 (the alpha chain of the interleukin-2 receptor, dominantly expressed by T-cells) and/or CD2 (ordinarily a surface adhesion molecule restricted to T/NK-lymphocytes)], and (2) far more common patients with "idiopathic" MCAS, which preliminary research strongly suggests is almost always driven by one (largely MC-restricted, largely somatic) mutational profile or another among a very large menagerie of such profiles in KIT and other MC regulatory elements. Unfortunately, such somatic mutational profiling in MCs is not presently available in clinical laboratories, relegating such patients to an "idiopathic" diagnosis. We acknowledge a diagnostic category of "secondary MCAS," but its diagnosis and treatment pales in importance compared to "primary" and "idiopathic" MCAS given that in secondary MCAS, it is expected that treatment of the underlying disorder, which presumably is driving normal activation of the patient's exclusively normal MCs, will result in improvement of the MCAS. As such, all mentions of "MCAS" subsequently in this paper should be taken to refer to primary and idiopathic MCAS. Also, the behavior of cutaneous mastocytosis (CM, grossly limited to cutaneous presentation of mastocytosis, though recent research now suggests all cases of CM, at least in adults, can be found to have circulating, thus systemic, clonal mast cells) shares far more of the behaviors of systemic mastocytosis (SM) than of MCAS. Therefore, all subsequent mentions of "SM" should be taken to refer to SM and CM…Discussion: …MCA disorders (largely as allergic-type diseases and more complex presentations now termed "MCAS") are prevalent, judging merely by the known 10–50% global prevalence of allergy. This figure unsurprisingly is congruent with not only some of the higher estimates of prevalence for MCAS, but also (given that chronic multisystem inflammation is, more than any other clinical feature, the sine qua non of MCAS) estimates for prevalence of the spectrum of chronic inflammatory diseases. Mastocytosis, on the other hand, is a rare disease. As such, the global impact of accuracy in diagnosing MCAS likely is much greater than in diagnosing SM…The extent of unnecessary suffering from underdiagnosis of MCAS is amplified by present estimates of prognosis in MCAS of a normal lifespan in most. Delay in access to effective treatment for MCAS may stretch decades and likely was present lifelong before MCAS became recognized. (Indeed, an MCAS patient's history often will date back to a childhood of excessive "colic," "allergies," "food intolerances," dysmenorrhea/menorrhagia soon after menarche, and other inflammatory or allergic-type problems either incorrectly diagnosed as normal or

dismissed as of unknown cause and insignificant.) The adverse consequences on both personal and societal scales seem incalculable. In our collective experience, most patients diagnosed with MCAS using the consensus-2 criteria experience meaningful improvement – sometimes quite astounding improvement – with MC-directed therapies no matter the years to decades they have suffered with previously unexplained multisystem issues not infrequently leading to partial or full disability…[vi]

https://www.degruyter.com/document/doi/10.1515/dx-2020-0005/html

It is with a scientific olive branch that the mast cell research presented within this hypothesis is being proffered to all of the mast cell experts who are debating these critically important issues. To date, it appears that the overall mast cell activation disease science and MCAS prevalence interpretations have been based on tissue studies of mast cells procured solely from bone-marrow-derived Hematopoietic Stem Cells and it is now suggested that there is an alternative hematopoietic pathway which generates mast cells from Embryonic Stem Cells (ECSs) and that these ESC-derived mast cells (and macrophages) are instrumental in driving the production of an inflammatory myeloid tissue that is critical to the initiation and progression of MCAS, and perhaps other MCADs.[vii]

It seems equally important to factor the emerging lipid raft science into our epigenomic understanding of mast cell disease, as it is the lipid-structured membrane walls of the hyperreactive mast cells in question which become hyperpermeable when there is an acquired disordering of the mast cell's membrane-based lipid structures.[viii] Also, the emerging science regarding the maladaptive inflammatory tissue issues potentially influenced by DHCR7 gene mutations, as seen in severe Covid-19 patients[ix], portend to play a significant role in MCAS and perhaps other mast cell diseases. Cooperatively, with open and inquiring minds, we must apply the new scientific findings in order to reach a unified Global Consensus on MCAS prevalence statistics and diagnostic protocols.

Whereby the stalled-out debate regarding MCAS diagnostic criteria and the resultant belittlement of MCAS need to be overcome, and an independent corroboration of the Bonn mast cell mutational findings will help to achieve this once and for all, these discrepancies serve as an indicator of the frustrating and often acrimonious gap between doctors and chronically ill patients. Of note, it is not that scores of scientists have tried to recapitulate the Bonn findings and failed, but rather that science has not even pursued the confirmation of these findings due to the dismally anemic intentions directed towards these ever-burgeoning medical issues from the NIH in the United States, their counter-agencies globally, and from the healthcare industry as a whole. There are a great many people seeking medical assistance who are being shunned by physicians who unfortunately know little if anything about MCAS. Instead of stepping down on an already bursting-at-the-seams population of sick patients, doctors need to reach up institutionally by sounding the alarms and asking for support; and, institutional support absolutely must materialize from the highest levels.

The societal realities of mast cell disease can no longer be avoided. Without awareness and an earnest approach, this complex and potentially catastrophic medical reality will not disappear on

its own. Rather it will continue to expand exponentially as it may well be doing in the Long-Covid population, many of whom have been diagnosed with POTS and other dysautonomic conditions which are suspected co-morbidities of MCAS. The final word on MCAS prevalence will be determined by advancing our understanding of mast cell science including further elucidation of the not-fully-understood genetic and epigenetic determinants of the disease. Hopefully, more supportive doctor-patient interactions will follow providing more expedient diagnostics and more efficacious therapeutics.

Although there exists a familial predisposition to MCAS and all MCADs, these are in-fact acquired somatic mutations reflecting an epigenetic process with a familial predisposition rather than in-born germline mutations, as described on the Mast Cell Activation Disease information page published on the website of The Institute for Human Genetics at the University of Bonn, Germany:

> **Mast Cell Disease: Clinical Presentation and Genetics**, (Gerhard Molderings): Systemic mast cell activation disease (MCAD) denotes a group of primary mast cell disorders characterized by aberrant release of variable subsets of mast cell mediators and/or accumulation of pathological mast cells in potentially any or all organs and tissues. The clinical presentation of MCAD is very diverse, since due to both the widespread distribution of mast cells and the great heterogeneity of aberrant mediator expression patterns, symptoms can occur in virtually all organs and tissues. According to the current classification of MCAD the traditionally recognized rare variant termed systemic mastocytosis (SM) is characterized by specific pathological somatic mutations in exon 17 of the tyrosine kinase KIT (for which KITD816V accounts for the great majority) and immunohistochemical findings (known as the World Health Organization (WHO) criteria) caused by these mutations. The other variant, only recently recognized, is termed mast cell activation syndrome (MCAS; seemingly borne of a large collection of mutations in various genes) and presents a complex clinical picture of multiple proven mast cell mediator-induced symptoms (relevant differential diagnoses excluded) and failure to meet the WHO criteria for diagnosis of SM. Recent findings suggest that MCAS is a fairly common disorder in contrast to SM. According to recent findings, the variants and clinical subtypes of MCAD do not represent distinct disease entities but should be more accurately regarded as varying compositions of a common process of mast cell dysfunction. Although almost all mutations causing MCAD were somatic rather than germline, evidence was provided for common familial occurrence of MCAD. Irrespective of systemic MCAD variant and gender, around 75% of the index patients had at least one first-degree relative with MCAD. The molecular processes which result in familial aggregation of MCAD remain speculative. The detection of differing systemic MCAD-associated somatic mutations within given families suggests that the disease arises secondary to a dysfunction of as yet unidentified operator and/or regulator genes.[x]
> https://www.humangenetics.uni-bonn.de/de/forschung/forschungsprojekte/mastzellerkrankungen

Epigenetic mutations, including mast cell mutations, are acquired throughout our lifetime as a result of mutagenic exposures and can occur anytime within our life cycle from the first cleavage of a fertilized egg to the cell divisions that occur during cell replacement in a senile individual. The genotoxic insults are a process by which properties of molecular chemical agents damage the genetic information within a cell causing phenotypically varying mutations which may lead to cancer and other diseases including mast cell activation diseases. Through identifying and eliminating MCAS triggers, it becomes apparent that there exists an optimal temperateness for all biological life forms, or at least there is an optimal range. And these epigenetic mutations result from issues of overbearance from toxic offenses upon biological systems.

Mast cell mutations occur in the somatic tissue of an organism resulting in an epigenetically mosaic individual. Somatic tissue and somatic cells include all body cells of an organism apart from the sperm and egg cells, the cells from which they arise (gametocytes) and undifferentiated stem cells. Examples of somatic cells are cells of internal organs, skin, bones, blood and connective tissue. Domiciled broadly throughout our mucosal and connective tissue, mast cells are ubiquitous and constitutionally intrinsic. Mutated and molecularly modified mast cells, both broadly located and aberrantly behaving, are not just capable of but are likely to instigate and influence multisystemic disease processes.

Another important variable is that mast cells display a phenotypic plasticity exhibiting expression patterns unique to the various microenvironments in which they reside while demonstrating a fluctuating malleability to those microenvironmental influences. As we continue to learn from both research and anecdotal experience, there is reason to believe that through non-toxic consumption and protectionary exposure practices along with advanced healing therapeutics we can influence the calming or dampening of the somatic mutations which dictate the variable microenvironmental influences. Whereby science or nature may learn how to reverse or overcome these mutations one day; for now, we can certainly lessen the detrimental impacts they wreak upon the host immune response.

The reality is that we all have genetic and epigenetic mutations, every living being has them. In terms of evolutionary biology, mutations are a matter of fact. Immunologically speaking, they are adaptive strategies and some may have no discernable effect, some may be beneficial and others may lead to disease. If we can allay our fears associated with the concept of these mutations then we can learn that therein lie the answers. We are based on genetic code and we get glitches in our code. In acquired mutations the glitches are in our RNA which is the environmentally reactive expression of our DNA. We can fear the *acquisition* of the mutations but not the *knowledge* of the mutations. Knowledge is power and our genetic profile is a valuable prognostic and diagnostic tool that is vital to disease prevention, management and in many cases bringing about the curing or remission of many confounding illnesses.

With the aim of establishing a fuller picture of the mast cell's intra- and inter-cellular repertoire of functions and influences, the following excerpt depicts mast cell capacities that are highly-correspondent to the immunological dysfunctions present in symptomatic and severe Covid-19 episodes, as published in *Frontiers in Immunology* in January of 2016 from the University of Kansas Medical Center, Kansas City, KS, USA:

**Mast Cell: A Multi-Functional Master Cell**, (Melissa Krystel-Whittemore, Kottarappat N. Dileepan and John G. Wood): Mast cells are immune cells of the myeloid lineage and are present in connective tissues throughout the body. The activation and degranulation of mast cells significantly modulates many aspects of physiological and pathological conditions in various settings. With respect to normal physiological functions, mast cells are known to regulate vasodilation, vascular homeostasis, innate and adaptive immune responses, angiogenesis, and venom detoxification. On the other hand, mast cells have also been implicated in the pathophysiology of many diseases, including allergy, asthma, anaphylaxis, gastrointestinal disorders, many types of malignancies, and cardiovascular diseases. This review summarizes the current understanding of the role of mast cells in many pathophysiological conditions. Introduction: Mast cells are important cells of the immune system and are of the hematopoietic lineage. Mast cells are originated from pluripotent progenitor cells of the bone marrow, and mature under the influence of the c-kit ligand and stem cell factor in the presence of other distinct growth factors provided by the microenvironment of the tissue where they are destined to reside. Under normal conditions, mature mast cells do not circulate in the bloodstream. However, mast cell progenitors migrate into tissues and differentiate into mast cells under the influence of stem cell factor and various cytokines. Mast cells are present throughout the body and they play important roles in the maintenance of many physiological functions as well as in the pathophysiology of diseases. Accordingly, this review is focused on the role of mast cells in a wide range of physiological functions and pathogenesis of a variety of disease states. Location of Mast Cells: Mast cells are found in mucosal and epithelial tissues throughout the body. In rodents, mast cells also reside in peritoneal and thoracic cavities. Mast cells are found in all vascularized tissues except for the central nervous system and the retina. Mast cells are located at the junction point of the host and external environment at places of entry of antigen (gastrointestinal tract, skin, respiratory epithelium). Mast cells are located in areas below the epithelium in connective tissue surrounding blood cells, smooth muscle, mucous, and hair follicles. The cytoplasm of the mast cell contains 50–200 large granules that store inflammatory mediators, including histamine, heparin, a variety of cytokines, chondroitin sulfate, and neutral proteases. In order for mast cells to migrate to their target locations, the coordinated effects of integrins, adhesion molecules, chemokines, cytokines, and growth factors are necessary…There are two phenotypes of human mast cells: mucosal mast cells that produce only tryptase and connective tissue mast cells that produce chymase, tryptase, and carboxypeptidases. Mast cell activation and mediator release have different effects in various tissues and organs. Most common sites in the body exposed to antigens are the mucosa of the respiratory tract (airborne), gastrointestinal tract (food borne), blood (wounds, absorption from respiratory tract/gastrointestinal tract), and connective tissues…Mechanism of Activation: Mast cells are known for their main mechanism of action: IgE-mediated allergic reactions through the FcεRI receptor. IgE antibodies are produced by mature B cells in response to CD4+ Th2 cells…When an antigen comes in contact with the mast cell, it crosslinks two or more FcεRI molecules and activates the release of granules from the mast cell. IgE is found in the connective tissue under epithelial layers of the skin, in the respiratory tract, and also in the gastrointestinal tract. In addition to FcεRI, mast cells also express Fc receptors for IgA and IgG, receptors for adenosine, C3a, chemokines, cytokines, and pathogen-associated molecular patterns (PAMPs), as well as

toll-like receptors (TLRs), all of which are involved in mast cell activation and immune response… Physiological Roles of Mast Cells: Mast cells are involved in the regulation of a variety of physiological functions, including vasodilation, angiogenesis, bacterial, and parasite elimination. In addition, mast cells regulate functions of many cell types, such as dendritic cells, macrophages, T cells, B cells, fibroblasts, eosinophils, endothelial cells, and epithelial cells. Since mast cells generate and release multi-potent molecules, such as histamine, proteases, prostanoids, leukotrienes, heparin, and many cytokines, chemokines, and growth factors, they have the capacity to be involved in regulating the functions of many organs and tissues. One of the mostly studied functions of the mast cell is its role in vascular and bronchial homeostasis. Mast cells also play a significant role in the regulation of bone growth, remodeling, and mineral homeostasis… Innate and Adaptive Immunity: Mast cells play an important role in innate and adaptive immunity. Mast cells recognize harmful antigens by binding to pathogens directly or associating with PAMPs on the mast cell surface. Most commonly the receptors on the mast cells are TLRs and receptors for complement. Once the antigen binds to the receptors on the mast cell, it causes the release of inflammatory mediators, which helps to eliminate the pathogen that activated it…Mast cells also contribute to antiviral responses by recruiting CD8+ T cells, which produce IFN-α and IFN-β…Mast cells are also involved in adaptive immunity. Mast cells process and present antigens via MHCI and MHCII. Mast cells activate dendritic cells that also function as antigen-presenting cells. When mast cells are stimulated through TLF-7, they release IL-1 and TNFα, which causes dendritic cells to move from their location in the skin and go to local lymph nodes and activate cytotoxic T cells. Additionally, mast cells release TNFα, which can activate cytotoxic T cells directly. Activation and Mediator Release: Mast cells upon activation release preformed and newly synthesized mediators in a phasic fashion. A variety of endogenous and exogenous agents can stimulate mast cells to release mediators immediately. Activation of mast cells occurs when an antigen crosslinks IgE molecules that are bound to FcεRI on the surface of the mast cell. FcεRI receptor for IgE has an affinity 100 times greater for the Fc of IgE than of IgG. Because of this, IgE is found bound to the FcεRI receptors on the mast cell even when there are no antigens present. As a result, this makes the response of the mast cell to an antigen very fast. FcεRI signaling uses the Lyn-dependent phosphorylation of ITAMs on the B and y subunits of the FcεRI. Protein kinase Syk is activated and autophosphorylated after being recruited to the ITAMs. Syk phosphorylates linker activation of T cells (LAT) and non-T cell activation linker (NTAL). LAT phosphorylates PLC, which produces IP3 and DAG, which activates intracellular calcium influx and PKC activation. NTAL activates PI3K, which also helps with calcium release. This results in degranulation of the mast cells, lipid mediator production, and cytokine production…Degranulation occurs a few seconds after crosslinking and results in release of the inflammatory mediators that are stored in the granules. Many of the mediators that are stored or newly synthesized by the mast cells attract leukocytes (eosinophils, basophils, Th2 lymphocytes, neutrophils) to the inflammatory site and amplify the inflammatory response. The inflammatory mediators increase the permeability of the blood vessels so that the immune cells can move from the blood stream to the affected tissue. After degranulation, mast cells resynthesize the mediators and repopulate granules. Mast cells express TLRs 1–7 and 9, NOD-like receptors (NLRs), and retinoic acid-inducible gene 1. If a TLR on the mast cell is activated, MyD88 and MAL/TIRAP are associated and promote NFκB translocation to the

nucleus resulting in cytokine transcription…IgE-mediated activation by FcεRI causes degranulation and synthesis of many immune mediators, such as eicosanoids and cytokines, as well as other products. When the mast cell is activated, it immediately releases prepackaged granules. Mast cell granules (MCG) can be compared to lysosomes in that there is a low pH and lysosomal enzymes, such as β-hexosaminidase and caspase-3. Tryptase, chymase, cathepsin G, and carboxypeptidase are proteases stored in prepackaged granules that activate metalloproteases in the extracellular matrix. Activation of the metalloproteases breaks down extracellular matrix proteins and remodels the connective tissue matrix. Chymase cleaves fibronectin and collagen by activation of MMPs. β-tryptase has been shown to cleave IgE once the mast cell has been activated to down regulate the allergic response. Histamine and heparin are also stored in prepackaged granules and are involved with vascular permeability and smooth muscle contraction. Histamine is the most important mediator released from the mast cell involved with an allergic response. Histamine is derived from the amino acid histidine and works through three different receptors (H1, H2, H3). Stimulation of H1 receptors by the binding of histamine induces the classic allergic reaction. H1 receptors are found on smooth muscle cells and endothelial cells. Activation of H1 receptors on endothelial cells results in increased vascular permeability and activation of smooth muscle cells resulting in contraction, constriction of airways, and mucous secretion. TNFα, also stored in the MCG, activates macrophages, endothelium, and cytokines. TNF-α binds to endothelial cells and results in increased adhesion molecule expression. Leukocytes can bind to these adhesion molecules and then are brought to the site of inflammation…Other molecules are synthesized and released after the mast cells have been activated. IL-3, IL-5, and GM-CSF are involved with eosinophil production and activation. CCL3 is a chemotactic factor for macrophages and neutrophils. Eicosanoids (prostaglandins, leukotrienes, and thromboxanes) are produced by catalytic conversion of arachidonic acid by the action of phospholipase A2 on membrane phospholipids. Mast cells express COX1 and COX2, which converts arachidonic acid into prostaglandins and thromboxanes with the action of specific isomerases. Prostaglandins increase vascular permeability and attract neutrophils. Leukotrienes are involved with smooth muscle contraction, airway constriction, and mucous secretion. Eicosanoids act at the local area of mast cell degranulation. Platelet-activating factor is released after mast cell activation that acts as a chemotactic factor for leukocytes, and activates neutrophils, eosinophils, and platelets. All of the mediators released upon activation results in increased vascular permeability, smooth muscle contraction, and airway constriction…Conclusion: In summary, mast cells play a key role in regulation of normal physiological processes as well as in many pathophysiological settings…Additional efforts to define the complex interactions of mast cells will potentially lead to novel clinical approaches for many pathological conditions.[xi]
https://www.frontiersin.org/articles/10.3389/fimmu.2015.00620/full#B8

Mast cells are hematopoietic immune cells of myeloid lineage and ancestrally they are believed to be the original immune cells of the human body. Mast cells are omnipresent in mucosal and connective tissue, simultaneously acting and reacting as modulators of many physiological aspects of human health in states of both wellness and disease. As evidenced in the previous excerpt, mast cells have maintained their role as primary immune effector cells capable of exerting dominating and directive influences over an array of other immune cell types

including but not limited to T cells, B cells, macrophages, fibroblasts, eosinophils, endothelial cells, epithelial cells, neutrophils and dendritic cells, as well as regulating the functions of vital and numerous organs and tissues. Gaining a more comprehensive understanding of the orchestrational, maestro-like capacities of the various mast cell phenotypes is essential to understanding the innate and adaptive immune response of humans infected by SARS-CoV-2 and many other pathogenic infectious diseases.

As articulated in the previous excerpt, there exist many biochemical aspects of mast cells and many of these aspects, when they become non-normative, are key to conceptualizing the MCAS and Covid-19 theory. Mast cells are the instantaneous responders to antigens and this rapid-fire response then induces mast cell degranulation, a potential disordering of endogenous and exogenous cellular lipid structures, and the production of variable lipid mediators, chemokines and cytokines. As a result, mast cells can attract other leukocytes to the site of inflammation, amplifying the inflammatory response, and this amplified inflammatory response then increases vascular permeability permitting the trafficking of immune cells out of the vascular system and into the affected tissues- a process which then serves as the basis of insult causing or exacerbating tissue injury in the disadvantaged organ system. In many disease pathologies, when aberrant mast cell impacts are chronic and progressive it can ultimately lead to a dysfunctional hemophagocytic process which can yield a vascular lymphocytic Endotheliitis which can then drive the formation of excess fibrosis, adiposity, atherosclerosis, disordered connective tissue remodeling, nerve injury and more, as will be shown over and over in the chapters ahead.

In addition, and of vital consequence in antiviral responses, mast cells can release the cytokine TNF-α through various mechanisms; and they can recruit CD8+ T cells which produce the Interferon cytokines IFN-α and IFN-β. Notably, to be demonstrated in the chapters to follow, these T-cell and cytokine pathways are mutationally disordered by SARS-CoV-2 infection in some people and yet not in others. Contributing to the innate and adaptive immune response, mast cells regulate vasodilation, vascular homeostasis, angiogenesis, venom detoxification, in addition to bacteria and parasite elimination. Through a review of this compilation of research, it will be shown that mast cells can directly influence the altered Interferon and T-cell functions while also imposing hyperinflammatory vasoactive hemodynamics within the host, all of which enjoins to produce a unique myeloid tissue through which SARS-CoV-2 infection is permitted through an Endotheliitis process in which a tissue injury and repair cycle ensues unrelentingly.

It is a scientific certainty that Covid-19 is a disease process perpetuated within the endothelium[xii], the innermost layer of blood and lymphatic vessel walls that interfaces directly with the blood and lymph fluid flowing through the respective vessels. These vessels comprise the vasculature of the human body; and, the blood and lymphatic systems are interrelated vascular components of the greater circulatory system. This vast network of blood and lymphatic vessels connect to organ systems throughout the body known as the reticulo-endothelial organs. It is within and around various reticulo-endothelial organ systems that mast cells and pathogens such as SARS-CoV-2 are trafficking excessively and causing highly variable levels of disease. Notably, , with some patients are demonstrating a broader multi-organ involvement whilst others may have a milder and/or more limited single organ system presentation.

Mast cells are implicated as being causational in many diseases whose pathophysiology relies in-part upon the dysfunction of the aforementioned regulatory functions of mast cells, and these diseases include but are not limited to: allergy; asthma; anaphylaxis; gastrointestinal and

neurological disorders; cardiovascular, liver and kidney diseases; as well as many types of malignancies. It appears that SARS-CoV-2 and many other pathogenic infectious diseases are manipulating common hyperinflammatory pathways and ought rightly to be added to this list of mast-cell-enabled diseases. When comparatively reviewed, the common cellular pathways that are active in the individual diseases start to provide a patho-epigenetic map of the MCAS and Covid-19 epigenetic co-morbidity.

The profound phenotypic plasticity displayed by mast cells means that they can have morphological tendencies allowing them to become physically and chemically altered in ways which may depend upon whether they arose from Hematopoietic Stem Cells (HSCs) or Embryonic Stem Cells (ESCs)- the latter of which produces a significantly different type of mast cell than the first. There is also a unique ESC-derived classification of macrophages which are closely related to the ESC-derived mast cells.[xiii] These unique embryogenic mast cells and macrophages, renewable throughout adulthood, are constituent cellular components of a unique myeloid tissue that appears to be active and instrumental in MCAS and Covid-19 disease pathologies. To date, the embryogenic origins of mast cell activation disease do not seem to have been investigated and yet it is likely that significant insights will be shed on a great many disease states when this science is expanded.

For all doctors and scientists who are struggling to find the appropriate biological context for the mast cell phenotypes which are active in MCAS, perhaps it would be helpful to revert back to Hematopoiesis 101 in medical school and recall the unanswered debate regarding the Deterministic and Stochastic theories of developmental hematopoiesis. It is posited herein that there are mast cell phenotypes influential in MCAS which represent a confirmation of the Stochastic Theory of Hematopoietic Blood Cell Maturation, providing evidence of morphological varieties of embryogenic-stem-cell--derived cellular phenotypes which come into existence before and beyond the hematopoietic-stem-cell-derived bone-marrow mast cells which are thought to be of pre-determined cell lineage and cell fate. In people with a predisposition to these ESC-driven disease pathways, the human body is capable of generating unique myeloid cells and unique myeloid bodily-tissues (rendered from these cells) which differ from previously identified mast cell and macrophage phenotypes and which more ably cause disease.

The following excerpt details ground-breaking new science regarding an HSC-independent hematopoietic pathway for mast cell generation, as published in the *Journal of Molecular Cell Biology* in February 2021 from the Chinese Academy of Medical Sciences and the Peking Union Medical College, Chengdu; Institute of Medical Biotechnology, Suzhou University, Suzhou; Institute of Hematology & Blood Diseases Hospital, Tianjin- all in China; Kyoto University, Kyoto, Japan; and, the University of North Dakota, Grand Forks, North Dakota, USA:

**Early Development and Functional Properties of Tryptase/Chymase Double-Positive Mast Cells from Human Pluripotent Stem Cells**, (Guohui Bian, Yanzheng Gu, Changlu Xu, Wenyu Yang, Xu Pan, Yijin Chen, Mowen Lai, Ya Zhou, Yong Dong, Bin Mao, Qiongxiu Zhou, Bo Chen, Tatsutoshi Nakathata, Lihong Shi, Min Wu, Yonggang Zhang, Feng Ma): Abstract: Mast cells (MCs) play a pivotal role in the hypersensitivity reaction by regulating the innate and adaptive immune responses. Humans have two types of MCs. The first type, termed $MC_{TC}$, is found in the skin and other connective tissues and expresses both tryptase and chymase, while the

second, termed $MC_T$, which only expresses tryptase, is found primarily in the mucosa. MCs induced from human adult-type $CD34^+$ cells are reported to be of the $MC_T$ type, but the development of MCs during embryonic/fetal stages is largely unknown. Using an efficient coculture system, we identified that a $CD34^+$c-$kit^+$ cell population, which appeared prior to the emergence of $CD34^+CD45^+$ hematopoietic stem and progenitor cells (HSPCs), stimulated robust production of pure $Tryptase^+Chymase^+$ MCs ($MC_{TC}$s). Single-cell analysis revealed dual development directions of $CD34^+$c-$kit^+$ progenitors, with one lineage developing into erythro-myeloid progenitors (EMP) and the other lineage developing into HSPC. Interestingly, $MC_{TC}$s derived from early $CD34^+$c-$kit^+$ cells exhibited strong histamine release and immune response functions. Particularly, robust release of IL-17 suggested that these early developing tissue-type $MC_{TC}$s could play a central role in tumor immunity. These findings could help elucidate the mechanisms controlling early development of $MC_{TC}$s and have significant therapeutic implications. Introduction: Mast cells (MCs) are blood components and are classically known to originate from multipotential hematopoietic progenitor cells in the bone marrow (BM). Unlike most hematopoietic BM cells, MCs complete terminal maturation in peripheral tissues under the influence of the local microenvironment. Mature MCs can be distinguished from immature MCs by surface expression of the high-affinity IgE receptor (FcεRI) and by the presence of high c-Kit levels and characteristic secretory granules. MCs are multifunctional effector cells that play an essential role in innate immunity, host defense, host hypersensitivity, and the pathogenesis of allergic disease. MCs predominantly reside in tissues and are characterized by large cytoplasmic granules containing proteases, which are released upon activation, such as during an allergic reaction. MC activation induces a wide variety of symptoms in complex diseases that are difficult, often impossible, to diagnose. Recently, MCs have been implicated in pain and neuroinflammation in endometriosis. However, the exact physiological and pathogenic functions of MCs remain controversial due to insufficient understanding of human MC types and their development during embryonic/fetal stages. In mice, MCs are subclassified into two main subsets based on their location, staining characteristics, protease expression patterns, and histamine content. One MC subtype is connective tissue-type (CT-MCs) and the other subtype is mucosal-type (M-MCs). M-MCs are found in the normal alveolar wall and small intestinal mucosa. CT-MCs are similar to tissue-resident macrophages; are found in the skin, submucosa, and other connective tissues; and have radio-resistant and self-renewal properties. Further, M-MCs are inducible and transient with a lifespan of only 2 weeks, while CT-MCs are constitutive and long-lasting. A recent report demonstrated that MCs and macrophages exhibit similar overall development kinetics with dual hematopoietic origins, indicating diverse MCs in developmental sources, tissue distributions, and functions. In humans, three types of MCs have been classified on the basis of protease content: (i) $Tryptase^+Chymase^+$ MCs ($MC_{TC}$s), which contain tryptase, chymase, carboxypeptidase, and cathepsin G in their secretory granules, are predominantly located in normal skin and intestinal submucosa and correspond to rodent CT-MCs; (ii) $Tryptase^+Chymase^-$ MCs ($MC_T$s), which contain tryptase but lack other proteases, are the main MC type in the normal alveolar wall and small intestinal mucosa and correspond to rodent M-

MCs; and (iii) Tryptase$^-$Chymase$^+$ MCs ($MC_C$s), which are a rare MC subtype that only contain chymase and are found in endometrial tissue. In patients with T cell deficiency, a marked and selective lack of $MC_T$s in the intestinal mucosa is observed, but these patients have normal numbers of $MC_{TC}$s in the adjacent submucosa, suggesting that the development of $MC_T$s is different from that of $MC_{TC}$s in humans. Unlike the hematopoietic stem cell (HSC)-dependent hematopoiesis originating in the adult BM, early mammalian embryos generate HSC-independent hematopoietic lineage cells sharing both primitive and definitive properties. This HSC-independent wave predominately produces erythrocytes, megakaryocytes, and other myeloid lineage cells derived from erythro-myeloid progenitors (EMP) and other tissue-resident cell progenitors, such as macrophages. In humans, many reports exploring the onset of human hematopoiesis that use the *in vitro* differentiation of hPSCs (human pluripotent stem cells) accumulated data similar to what has been found in mouse ontogeny. Our group recently reported a unique pathway for early definitive erythropoiesis from hPSCs, which is phenotypically different from more mature adult hematopoietic stem and progenitor cell (HSPC)-derived definitive erythropoiesis. Moreover, in our previous study, we demonstrated that cynomolgus non-human primate embryonic stem cell (ESC)-derived MCs (ESC-MCs) have similar characteristics to $MC_{TC}$s with functional maturity in short-term cultures, suggesting a unique embryonic/fetal pathway in primates for early development of $MC_{TC}$s, which may be from a different pathway other than that of $MC_T$s. On the other hand, although human cord blood (CB) CD34$^+$ progenitors could give rise to $MC_{TC}$s in long-term cultures, generally after >10 weeks *in vitro*, these cells still cannot fully mimic the functions of $MC_{TC}$s in human skin, such as substance P-induced degranulation. At present, it is still unclear whether MCs develop via HSC-independent pathways, and the functional properties of these potential lineages remain unknown. In the present study, we applied a three-stage culture method to generate mature and functional $MC_{TC}$s from hPSCs. We found that coculture of CD34$^+$c-kit$^+$ cells for 8 days gave rise mainly to a pure MC population phenotypically and functionally similar to human $MC_{TC}$s as reported. Single-cell RNA sequencing analysis revealed two distinct pathways of MC development from CD34$^+$c-kit$^+$ cells in the coculture system. One pathway was via EMP-containing erythroids, macrophages, and MC progenitors. The other pathway was via late multilineage HSPC defined by expression of CD34 and CD45, as we previously reported. Functional comparison revealed dramatic differences between MCs generated from coculture day 8 (D8) CD34$^+$c-kit$^+$, coculture D14 CD34$^+$CD45$^+$, and CB CD34$^+$ cells, with the earlier coculture D8 CD34$^+$c-kit$^+$ cell-derived MCs (CD34$^+$c-kit$^+$-MCs) exhibiting the strongest histamine release and other innate immune responses. We established a new *in vitro* model to trace the early development of hPSC-MCs (most $MC_{TC}$s), which provides a new approach for the development of novel drugs targeting $MC_{TC}$ -mediated diseases…Discussion: Recently, several groups found that MCs have different hematopoietic origins in mouse models, similar to macrophages. The potential for differential MC origins during human development remains unclear. Because experimental manipulations cannot be conducted using human embryos, the factors and mechanisms involved in directing differentiation of immature MCs into either functional $MC_{CT}$s or $MC_T$s remain unknown. Using a sequential coculture system with unbiased

displaying for natural progression of human hematopoiesis *in vitro*, we efficiently produced scalable quantities of functionally mature $MC_{TC}$s from hPSCs even in short-term cultures. Quantitative evaluations revealed that one undifferentiated hESC could generate 258.4 ± 32.7 mature $MC_{TC}$s at 12 weeks after isolation of coculture D8 $CD34^+c\text{-}kit^+$ MC progenitors and 157.9 ± 3.3 mature $MC_{TC}$s from coculture D14 $CD34^+CD45^+$ HSPCs, much higher than what had been reported previously, i.e., ∼5.0–14.4 MCs per undifferentiated hESC. Due to the lack of a cell model for screening drugs that target human $MC_{TC}$s, the efficiency of pure $MC_{TC}$ production in our culture system provided an easy and applicable method for investigation of molecular targets and drug screening for $MC_{TC}$-related conditions on a large scale. MC progenitors have been reported to develop in a variety of hematopoietic sites and peripheral tissues in embryos and adults. Classically, human MCs are known to arise from $CD34^+c\text{-}kit^+$ progenitor cells from the BM, peripheral blood, or CB HSPCs that highly co-express CD45 and CD13, which also generate other myeloid cells such as neutrophils, eosinophils, basophils, and monocytes. Previously, the generation of functional MCs from hESCs has been reported. However, in this study, MC production was very low, and the resultant MCs held smaller granules, less heparin, and lower levels of proteolytic enzymes, similar to CB $CD34^+$ cell-MCs. Because the MC induction culture protocol used comparatively mature hESC-derived HSPCs, this approach could bypass early development pathways for hESC-MCs. A more recent report established an early rapid and robust production of MCs from mPSCs and hPSCs (1 week from mouse cultures and several weeks from human cultures) by genetic manipulation. However, hPSC-MCs in this study did not exhibit mature MC functions, and their origins were unknown. Contrastingly, in our coculture system, $CD34^+c\text{-}kit^+$ cells that differentiated as early as D8 in coculture already expressed tryptase and chymase mRNA. Particularly, the early coculture D8 $CD34^+c\text{-}kit^+$ MC precursors were $CD45^-$, exhibiting a lack of HSPCs or myeloid properties by their source. In consequential culture, $MC_{TC}$s derived from coculture D8 $CD34^+c\text{-}kit^+$ precursors exclusively exhibited $MC_{TC}$ characteristics, typically mimicking mature human skin tissue-type MCs. Phenotypically, these early $MC_{TC}$s were 100% double-positive for tryptase and chymase, small, and single-nucleated and contained scroll-shaped granules similar to human skin tissue-type MCs. Importantly, these hPSC-derived early $MC_{TC}$s already exhibited characteristics of mature MCs, including robust histamine release upon substance P stimulation, a function characteristic of human skin tissue-type $MC_{TC}$s that is seldom exhibited by CB $CD34^+$ cell-derived M-$MC_T$s. Taken together with our previous findings in non-human primate ESC-derived CT-MCs, our data point to a common embryonic/fetal pathway for early development of $MC_{TC}$s independent of HSPC-$MC_{TC}$s. The present study was suggestive of two waves of human MC development. In the first wave, a mesodermal HE precursor directly develops into a $CD34^+c\text{-}kit^+CD45^-$ MC progenitor (D6–D8 coculture-derived MC precursors in our system) that rapidly differentiated exclusively into $MC_{TC}$s with functional maturity mimicking human skin tissue-type $MC_{TC}$s. The other wave of human MC development, as widely reported, is derived from adult-type HSCs and predominately generates mature $MC_T$s functionally expressing themselves as M-MCs (CB $CD34^+$-MCs). Using a subtle cell sorting assay, we found that early coculture D8 $CD34^+c\text{-}kit^+$ MC

progenitors primarily developed from $CD34^+KDR^+$ HE precursors along with a definitive hematopoiesis pathway that could be traced back to $KDR^+CD34^-$ mesoderm cells. Further analysis by single-cell RNA sequencing confirmed the existence of two different pathways for the development of early $CD34^+$c-$kit^+$ MC progenitors. One pathway developed with EMP development, and the other pathway developed with a late multi-lineage HSPC. Although MC potential could be detected in both pathways, the MC progenitor cells in the EMP pathway highly expressed *MITF* and *STAT5B*, which are both important transcription factors for tissue-type MC development. These findings were suggestive of a unique pathway for early and rapid development of functional mature $MC_{TC}$s in a first wave independent of HSPC-MCs. The $MC_{TC}$s developed from the early wave (typically as D8 coculture-derived $MC_{TC}$s) exhibited stronger function response to release various bio-regulators of IgE stimulation. Robust IL-5 and GM-CSF (Granulocyte-Macrophage Colony-Stimulating Factor) secretion in response to these stimuli suggested a potent and pivotal role for early $MC_{TC}$s as eosinophil/basophil activators in innate immunity… Interestingly, our findings suggested that $MC_{TC}$s from the early wave exhibited the highest response to stimuli, as detected by release of various bio-regulators such as cytokines, chemokines, and pro- and anti-inflammatory factors. This finding again reflected that $MC_{TC}$s developed in this early wave could complete functional maturation along a rapid and unique pathway, rather than via myeloid development classically recognized as an HSC-dependent pathway. In conclusion, the present study describes the development of a novel method to uncover the developmental pathway of early functionally mature $MC_{TC}$s. Subsequent studies in our group will identify the molecular and cellular regulatory mechanisms underlying the early development and maturation of these unique $MC_{TC}$s, which cannot be recapitulated by animal models. In addition to the theoretical and experimental importance of our findings, this study also provides a new approach for the development of novel drugs targeting $MC_{TC}$-mediated allergic diseases and tumors.[xiv]
https://academic.oup.com/jmcb/article/13/2/104/5943881

In addition to this novel science regarding ESC-derived mast cells, and also of great significance, is the finding that the process of acquiring mast cell mutations may initiate within the mast cells during a brief ontogenetic window, as has been indicated in an investigational study of mast cell infectibility in HIV.[xv] These important factors, along with a vast body of emerging mast cell science, will be explored in greater depth in the following chapters. Hopefully, it will become apparent that diverse hematopoietic and epigenetic variables can alter a wide array of intra- and intercellular mast cell functions which can in-turn provide pathways for disease generation and progression. As such, SARS-CoV-2 is capable of acting as a highly impactful epigenetic variable.

In spite of the many yet-to-be defined nuances inherent to these mutational complexities, mast cell experts continue to emphasize the potential benefits of appropriate clinical care. It is reiterated in the excerpt below that mast cell diseases are real, they are impacting a great many people and there is often an excellent response to treatment, as published in March of 2017 in the *American Journal of Medical Science* from the University of Minnesota, Minneapolis, MN and the Medical University of South Carolina, Charleston, SC, U.S.A.:

**Characterization of Mast Cell Activation Syndrome**, (Lawrence B. Afrin, Sally Self, Jeremiah Menk, John Lazarchick): In conclusion, MCAS is a recently recognized, likely prevalent and important entity within the realm of MCAD. Its protean manifestation as a chronic multisystem polymorbidity of generally inflammatory ± allergic themes is hidden beneath a cover of extreme heterogeneity of clinical presentation (potentially due to extreme mutational heterogeneity in MC regulatory elements), contributing to significant delays in recognition, diagnosis, and treatment, and yet most MCAS patients, once diagnosed as such, can eventually find significantly helpful treatment. Appreciation by clinicians of the diversity of presentation of MCAS as described…may facilitate earlier diagnosis, all the more important given not only good prospects for identifying helpful therapy but also expected long survival in most.[xvi]
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5341697/

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For further reference, a list of some important Covid-19 and Mast-Cell-Related Papers:

**Mast Cells and COVID-19: A Case Report Implicating a Role of Mast Cell Activation in the Prevention and Treatment of Covid-19**
Isabelle Brock, Anne Maitland. Mast Cells and COVID-19: a case report implicating a role of mast cell activation in the prevention and treatment of Covid-19, 15 March 2021, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-330667/v1]
https://www.researchsquare.com/article/rs-330667/v1

**Signatures of Mast Cell Activation are Associated with Severe COVID-19**
Tan J, Anderson D, Rathore A et al. Signatures of mast cell activation are associated with severe COVID-19. 2021. doi:10.1101/2021.05.31.21255594
https://www.medrxiv.org/content/10.1101/2021.05.31.21255594v1.full.pdf

**A Scoping Review of the Pathophysiology of COVID-19**
Marik PE, Iglesias J, Varon J, Kory P. A scoping review of the pathophysiology of COVID-19. *International Journal of Immunopathology and Pharmacology*. January 2021. doi:10.1177/20587384211048026
https://journals.sagepub.com/doi/full/10.1177/20587384211048026

**Mast Cells Contribute to Coronavirus-Induced Inflammation: New Anti-Inflammatory Strategy**
Sas B. Mast cells contribute to coronavirus-induced inflammation: new anti-inflammatory strategy. - Biolife - Scientific Publisher. Biolife - Scientific Publisher. https://www.biolifesas.org/biolife/2020/02/04/mast-cells-contribute-to-coronavirus-induced-inflammation-new-anti-inflammatory-strategy/. Published 2020.
https://www.biolifesas.org/biolife/2020/02/04/mast-cells-contribute-to-coronavirus-induced-inflammation-new-anti-inflammatory-strategy/

**Covid-19 Hyperinflammation and Post-Covid-19 Illness May Be Rooted in Mast Cell Activation Syndrome**
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**Potential Association of Mast Cells with Coronavirus Disease 2019**
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https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7644430/

**The Perfect Storm Review: Immune Dysregulation in Severe COVID-19 and the Possible Role of Mast Cell-Vitamin D Interactions**

Houldsworth A (2021) The Perfect Storm: Review: Immune Dysregulation in Severe COVID-19 and the Possible Role of Mast CellVitamin D Interactions. J Emerg Dis Virol 6(1): dx.doi.org/10.16966/2473-1846.161
https://www.sciforschenonline.org/journals/virology/article-data/JEDV161/JEDV161.pdf

**Mast Cells in Alveolar Septa of COVID-19 Patients: A Pathogenic Pathway That May Link Interstitial Edema to Immunothrombosis**

Motta Junior J, Miggiolaro A, Nagashima S et al. Mast Cells in Alveolar Septa of COVID-19 Patients: A Pathogenic Pathway That May Link Interstitial Edema to Immunothrombosis. *Front Immunol*. 2020;11. doi:10.3389/fimmu.2020.574862
https://www.frontiersin.org/articles/10.3389/fimmu.2020.574862/full#B8

**What the Physicians Should Know about Mast Cells, Dendritic Cells, Urticaria, and Omalizumab during COVID-19 or Asymptomatic Infections due to SARS-CoV-2?**

Criado, PR, Pagliari, C, Criado, RFJ, Marques, GF, Belda, W. What the physicians should know about mast cells, dendritic cells, urticaria, and omalizumab during COVID-19 or asymptomatic infections due to SARS-CoV-2? *Dermatologic Therapy*. 2020; 33:e14068. https://doi.org/10.1111/dth.14068
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**COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms**

Malone RW, Tisdall P, Fremont-Smith P, et al. COVID-19: Famotidine, Histamine, Mast Cells, and Mechanisms. Preprint. *Res Sq*. 2020;rs.3.rs-30934. Published 2020 Jun 22. doi:10.21203/rs.3.rs-30934/v2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7336703/

**Mast Cell Stabilisers, Leukotriene Antagonists and Antihistamines: A Rapid Review of the Evidence for their Use in COVID-19**

Raymond M, Ching-A-Sue G, Van Hecke O. Mast cell stabilisers, leukotriene antagonists and antihistamines: A rapid review of the evidence for their use in COVID-19 - The Centre for Evidence-Based Medicine. The Centre for Evidence-Based Medicine. https://www.cebm.net/covid-19/mast-cell-stabilisers-leukotriene-antagonists-and-antihistamines-a-rapid-review-of-effectiveness-in-covid-19/. Published 2021. Accessed August 16, 2021.
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