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Fine-tuning Mast Cells is Essential for the Maintenance and Regulation of the Systemic and Immune Homeostasis

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ABSTRACT

During the past decades, populous expansion in mast cell scientific literature came forth with more than forty-four thousand PubMed publications available to date. Such surge is due to the appreciation of the momentous role of mast cells in the evolution of species, in the development and maintenance of vital physiological functions, such as reproduction, homeostasis, and fluids, diverse immunological roles, and the potential of far-reaching effects despite minute numbers. While the emerging knowledge of the importance of mast cells in equilibrium comes of age when looking at the matter from an evolutionary perspective, the recognition of mast cells beyond detrimental performance in allergies and asthma, during protection against parasites, falters. Beyond well-known classical functions, mast cells can process and present antigens, can serve as a viral reservoir, can respond to hormones and xenobiotics, initiate antiviral and antibacterial responses, phagocytosis, apoptosis, and participate in important developmental cornerstones. During evolution, upon the development of a sophisticated niche of innate and adaptive cell populations, certain mast cell functions became partially transmutable, yet the potency of mast cells remained considerable. Reviewing mast cells enables us to reflect on the certitude, that our sophisticated, complex physiology is rooted deeply in evolution, which we carry ancient remnants of, ones that may have decisive roles in our functioning. This communication sets out the goal of characterizing mast cells, particularly the aspects less in limelight yet of immense significance, without the aspiration exhaust it all.

1. Introduction

Reflection on mast cells allows us to understand that the human and natural environment is subject to constant adaptation and there is a fine-tuned balance established with careful selection of the fittest throughout evolution. The message from looking at mast cells must trigger a warning signal in judging our choices, because harefooted, rough disturbances to the delicate balance of homeostatic organization may have far-reaching, irreversible consequences. Due to the genuine qualities of mast cells, therapeutic interventions may not always be feasible, it appears to be prudent to concentrate our efforts at preventing harsh perturbations into our balance, because during quick-fired changes, time for adaptation is not allowed, and selection of the fittest may be outweighed by shifting the phenotype towards disease and degeneration.

This review is a recollection to emphasize how

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pathophysiological happenings are interconnected, how external influences are widespread, and how obsolete it is to analyze and conclude from a narrow-angle. The second major objective is to direct the attention of healthcare professionals towards unsettling matters of contention, the process of understanding from a research perspective. There is an increasing price for the comforts of modern lifestyle, which is often driven by a material growth-oriented attitude, inconsiderate demand, producing excess waste, spreading all over the world.

### Overall features

Phylogenetically at the beginning of the emergence of vertebrates, mast cells (MCs) were the primordial immune cells, carrying out the majority of self-defensive functions \(^1\). Their appearance reaches back to invertebrates chordae, two hundred million years before the emergence of immunoglobulins, when mast cells served wide housekeeping functions, beyond immunological ones. MCs are pleiotropic and plastic, even today in highly sophisticated and specialized organisms. MCs are well fed as their name implies, filled with preformed forcible mediators with the proficiency of very early release upon stimulation, powerful, multifarious, and long-reaching effects. The diverse nature of granule content reflects their primordial origin. It is heparin, histamine, proteases, (such as tryptase, carboxypeptidase, and chymase), TNFα, prostaglandins, leukotrienes, and many more. MCs are customarily categorized based on their granule content tryptase and chymase, their strategical location on interfaces between host and environment, tissue and vessels to mucosal and connective tissue mast cells \(^2\). Despite their rarity, the effector potency can be immense, best demonstrated by the abrupt, profound, life-threatening anaphylactic reactions, elicited by disproportionally small stimuli in susceptible individuals. Intensivists, who appreciate the crucial notion of early effective interventions in facing forceful noxious stimuli severely compromising organ functions, may turn their eyes towards the early and persuasively reacting mast cells.

### 2. Origin, Ligands, Signaling Pathways

The fundamental cradle of immature mast cells is the bone marrow. They are derived from pluripotent hematopoietic progenitors. The main driver of mast development is SCF (stem cell factor), eliciting its effect upon binding to the ckit receptor (CD117) \(^3\). SCF is a growth factor produced by endothelial cells and fibroblasts, present in membrane-bound and soluble forms, leading to proliferation and differentiation of hematopoietic cells, melanocytes, and germ cells, inhibiting their apoptosis. Mast cells are derived from the bone marrow CD13+, CD34+, CD117+ progenitors, upon egress circulate in the blood as immature progenitors. When homed, complete their development in a cytokine environment of the target tissue to achieve mature phenotype. Mast cells are abundant in tissues with proximity to the external environment. SCF is upregulated by hypoxia-inducible factor1-alpha (HIF-1α), epidermal growth factor, ultraviolet B light, for example.

SCF binds to ckit (CD117), a type III tyrosine kinase receptor, which is present on early hematopoietic cells, later ckit expression is lost, except mainly on mast cells, which express high levels and depend on ckit for their survival, proliferation, homing, and function, such as degranulation and cytokine production. Upon ckit dimerization or oligomerization, the downstream PI3K-Akt prosurvival pathway is activated. CD117 is also present on melanocytes, germs cells, interstitial cells of Cajal, eosinophils, NK cells. Dendritic cell (DC) ckit expression is upregulated by Th2/Th17 inducing stimuli and ckit induced PI3K-Akt pathway mounts IL-6 production \(^4\). Mice devoid of SCF or CD117 are deficient in mast cells (W, S1) and have further abnormalities. If completely devoid of ckit receptor, mice die within 10 days after birth for severe macrocytic anemia, ckit hence is indispensable for survival and development, it is a prerequisite for the development of myeloid cells. In utero transplantation of wild type, fetal liver rescues mice and enables research application. To overcome the lack of exclusivity, diphtheria toxin-, and cre-inducible, more mast cell-specific ablation techniques were developed \(^5\).

A multitude of mutations exists within the ckit gene, often leading to enhanced or aberrant activation and behavior of mast cells. These mutations are clinically difficult to pinpoint, there is only one mutation clinically screenable, the remaining fifty or so already described mutations are only possible to identify in research settings. Mast cell activation syndrome is a recognized entity, due to the usually concomitant presence of several ckit gene mutations in the same individual. The diagnosis of the syndrome is cumbersome for the transient nature and vast variability in the clinical and laboratory presentations \(^6\). Mutations in stem cell factor may lead to leukemia, small cell lung cancer, gastrointestinal- and germline tumors.

As mice and humans age, mast cells increase in numbers, beyond that strain specificity is present, BALB/c mice are more abundant in mast cells than C57BL6/J mice, females have more mast cells than males, and chronic allergic conditions are associated with increased
mast cell numbers.

Recently, white adipose tissue (WAT) is becoming appreciated as an important source of mast cells and precursors, that are committed to the mast cell lineage, home to peripheral tissues. Adipose tissue-derived colony-forming cells when cultured with IL-3 and SCF, gradually acquire mast cell phenotype, and more than 40% express tryptase, can differentiate into both mast cells types and very efficiently colonize the periphery, but they do not home to hematopoietic tissues \(^\text{(7)}\). In the WAT of lean subjects without inflammatory activity, mast cells represent a minute proportion, but their numbers and tryptase activity \(^\text{(8)}\) increase in metabolic syndrome and obesity, characterized by low-level inflammation \(^\text{(9)}\). Mast cells regulate adipocyte adaptation to cold in the white adipose tissue \(^\text{(10)}\).

There is an abundance of signaling receptors present on mast cells \(^\text{(11)}\): FcεRI, FcεRII/low affinity (CD23), Fcγ receptors, pattern recognition receptors (PRRs, TLRs), complement receptors C3aR, C5aR \(^\text{(12)}\), purinergic P2X4, prostanoid PR3 \(^\text{(13)}\), etc, hormone receptors. MC activation upon IgE crosslinking is the prototypic MC response to allergens, but MCs are multifaced cells with a multitude of immune functions. The variety of recognition receptors enables mast cells to react to environmental, exogenous, and endogenous triggers, as primary effectors or adjuvants, aggravating immune response, deriving towards a Th1, Th17, or Th2 phenotype, presenting processed antigens in an inflammatory environment, unfolding cryptic epitopes, enhancing inflammatory cell death, serving as viral reservoirs, modulating cytokines, and impelling the extent of the immune response.

While a significant redundancy may be present in receptor utilization and immune functions in innate microbial defense, MCs may become prevalent in an aberrant immune environment, such as irradiation for example into which mast cells in comparison to other immune cell types are relatively more resistant \(^\text{(14)}\). Mast cells respond to various types of stimuli with differential degranulations, or chemokine, cytokine production. Anti-IgE or IgG cross-linking produces a slower, progressive, and sustained degranulatory response, while activation of MCs via substance P (SP), C3a, C5a, produces a fast, explosive response. Differences exist also in intracellular degranulatory signaling pathways in the context of stimulus \(^\text{(15)}\). The direction and extent of the immune response are based on the complexion of the exogenous or endogenous danger signals, the engaged recognition receptors with their signaling pathways, and the underlying cytokine milieu. TLRs, particularly TLR4 function in this manner proximally, including mast cells, setting the stage for an overall immune response \(^\text{(16)}\). Mast cells can be activated by cytokines. IL-33, released from barrier cells: keratinocytes, endothelial and epithelial cells, fibroblasts in response to damage and inflammation, is a potent mast cell activator. IL-4, the major Th2 and allergy-related cytokine serves as a selective modifier of mast cell action deriving towards Th2 related cytokine response (IL-4,5,13) and downregulation of proinflammatory IL-6 and TNFα production in response to IgE mediated reactions and gram-negative bacterial activation. Follicular T cell-produced IL-4 is required to generate and sustain IgE production \(^\text{(17)}\).

3. MC Secretory Products

The variety of mast cell secretory products is overwhelming, a few examples are highlighted here. As opposed to pancreatic proteases, MC proteases are released from the cell in active form. Proteases are constitutive and distinct components of mast cells, with low levels present in basophils and macrophages, too. MC subpopulation signature chymase, a peptidolytic serine protease has a wide assortment of targets: fibronectin, procollagenase, high mobility group box 1 (HMGB1), tight junction proteins, thrombin, angiotensin I, substance P, IL-1β, IL-6, IL-13, TNFα, etc. Human MC chymase can degrade alarmins (HMGB1), degrade the virulence factor of Trichinella spiralis, cleave influenza hemagglutinin to increase virulence \(^\text{(19,20)}\). A male predominance is known in acute coronary events and dilated cardiomyopathy, and interestingly estrogen can inhibit MC chymase release and prevent pressure overload-induced adverse cardiac remodeling \(^\text{(21)}\). The chymase effect can be thereupon detrimental or beneficial, depending on the context.

MC tryptase, another serine protease has the potential to induce extracellular matrix proliferation, by stimulating fibroblast migration factor release \(^\text{(22)}\). MC tryptase contributes to the pervasive macrophage population of chronic obstructive pulmonary disease (COPD) lungs and dynamizes their pro-inflammatory cytokine expression (IL-1β, TNFα) \(^\text{(23)}\). During chronically ongoing inflammation, in COPD for example, mast cells contribute to the development of fibrosis via TgFβ induction. An important excretory product of mast cells is granzyme D (GD), a serine protease produced by NK and CD8 cells, likewise. GD released upon stimuli from gram-positive or gram-negative bacteria, or IgE cross-linking enters target cells via perforins and induces apoptosis per caspase-dependent and independent pathways, activation of reactive oxygen species (ROS) production. GD expression is decreased in TLR2 KO mice, pointing towards TLR signaling pathway involvement at GD production \(^\text{(24)}\).
Histamine generated and released from mast cell granules serves physiological roles by regulating the sleep and wakefulness cycle, inducing vasodilation, vasopermeability, smooth muscle contraction, and mucus production. Histamine has a profound effect on monocyte and T lymphocyte phenotypes. Myeloid-derived suppressor cells (MDSCs), harboring the histamine (HR1-3) receptors are conditioned by mast cells, in their presence both granulocytic and monocytic monocytes increase in numbers and histamine promotes their survival and proliferation in culture, and coculture of monocytes and histamine enhances IL-10 and decreases Th1 related IL-12 production. Allergic patients have higher MDSCs in comparison to healthy control. MDSCs, mast cells, and regulatory T cells assemble in an immune-suppressive network, that promotes tumor growth. Mast cells histamine can upregulate TLR2 and TLR4 expression.

4. Mast Cells and Endocrine Disruptors

Behavioral neuroscience is deeply engaged in understanding the regulation of social and sexual behavior. The important function of mast cells, sexual/gonadal development during intrauterine and postnatal life comes to scrutiny when realizing how deeply they can be affected via minute dysbalances in hormonal levels, and how decisive an impact the environment may have on human health and reproduction.

In many aspects of immunity, sexual hormones have important functions and the reversed question, how immunity affects sexuality, has been asked less frequently. Brain mast cells are strategic mediators of brain sexual differentiation. Male mice have more mast cells and dendritic cell synapses in the preoptic area (POA), the main center of sexual behavior. When newborn female mice were exposed to either testosterone or its active metabolite estradiol, phenotypic switching took place by mast cell proliferation and engagement. Dendritic cell spine proliferation in POA was increased via the estradiol-mast cell-histamine-microglial axis.

Epigenetic modification has been suggested to have the capability to modify sexual orientation. According to Lenz et al, for example, prenatal exposure to allergens may contribute to adulthood social and sexual behavioral changes via disrupting sexual differentiation. Adult female mice, exposed to an allergen during prenatal development demonstrated male patterns of mounting behavior, while male mice had increased copulatory behavior and decreased olfactory preference towards females. Prenatal indirect exposure of mice to microbial TLR ligands via maternal infection, has led to behavioral "difficulties" and it appears that mast cells may be responsible for the effect of sex hormones on the developing brain.

Mast cells harbor on their surface the estrogen receptors (ER), progesterone receptors (PR), and testosterone receptors. Beyond the influence on sexual differentiation, EDCs can interfere with prostaglandin (PG) synthesis in Sertoli cells and mast cells. PG is inhibited via EDC binding to the active site of the cyclooxygenase (COX) enzyme. Sertoli cells fulfill important functions during spermatogenesis. The PG pathway is important in the masculinization of the male reproductive tract during prenatal development.

Endocrine disruptors (EDCs) are environmental chemicals that interrupt or modify various natural hormonal pathways, they modulate biotransforming enzyme activities, ion channels, occupy plasma protein transporters, induce mast cell degranulation, etc. EDCs are a diverse entity of chemicals used in food processing, cosmetics, toys, drinking containers, plastic containers, water pipes, laundry detergents, herbicides, pesticides, etc. Among important disruptors are phthalates, benzophenones, parabens, estradiol, bisphenols, dioxins, etc. EDCs interface with many hormonal receptors, such as estrogen receptors, progesterone receptors, aryl hydrocarbon receptors (AhR), adrenal, and thyroid receptors. EDCs influence signaling pathways through the engagement of the above receptors variably, in a competitive manner. Their dose-effect may be proliferative, suppressive, mutagenic, they can inhibit, activate, modulate enzymatic activities, they can have binary dose effect, delayed effect, epigenetic effect through DNA, and histone methylation, importantly their effect is often cumulative. EDCs may be soluble in water or in fats, may have metabolically active and toxic degradations products, and due to often long half-lives their amount may sump up in the adipose tissue or organs, and with a depo effect, they may continuously assault the human body to the point beyond repair. The brain is a lipid-rich tissue and prenatal to toddler exposure may be relatively higher than in adults. Around 62000 different chemicals are in use currently, in which the Environmental Protection Agency could not produce evidence in their separate, singular toxicity to the environment or humans. There are many attempts to regulate the use of EDCs. To be considered EDC, the producing company or scientific literature must present data regarding adverse health effects. Certain chemicals have proven harmful to humans and animals. But while many chemicals introduced into the environment, particularly with the speedy technical, biochemical, and agricultural development of the past 20th century comply individually with the "safety dose limits", the potential cumulative effect on the limited number of...
human and animal hormonal receptors represents a real, underrated danger. The disputes over the potential toxicity of already prefaced chemicals are lengthy, the causative relationship between the environmental chemical and disease development providing long term low dose exposure is hard to prove, and during the period of legal debate and often beyond, contamination is proceeding.

Among the important endocrine disruptors (EDCs) is atrazine, the herbicide used in eliminating broadleaf weeds in crops, particularly corn. The triazine type chemical, soluble in water, has a long half-life, including metabolites. When 14C isotope of atrazine was administered to the soil for three consecutive years, follow-up studies demonstrated the presence of the radioactive substance in 83% of original levels 9 years later, and 25% still present 22 years later [32]. Due to the slow biodegradation, atrazine currently represents one of the major water pollutants despite the fact, that in 2004 it has already been officially banned in the European Union. Atrazine introduction to the environment from the 1950s has had faster dynamics than its biodegradation, creating a cumulative effect on its own. In several animal species, atrazine has been shown to interfere with gonadal development and thyroid function, slow porcine oocyte maturation, disrupt DNA integrity, and cause the death of oocytes [33]. Atrazine's influence is complex, it decreases sperm count, delays puberty and has obesogenic effect [34]. Atrazine in vitro induces degranulation of rat thyroid mast cells and in the RBL2H3 basophil cell line [35].

Alkylphenols, used as surfactants in washing detergents, are poorly water-soluble, may cumulate in adipose tissue, bind to ER receptors, and stimulate mast cell degranulation in a FcεR dependent and independent way, they also promote Th2 polarization [36].

Aryl hydrocarbon receptor (AhR) is one of the most important environmental gatekeepers in the human body. AhR is an intracellular transcription factor, that in communication with multiple signaling pathways influences proliferation, apoptosis, energy metabolism, and cholesterol synthesis, immune cell development, and function, serves constitutively in an antiinflammatory position, cell migration, hormonal pathways, and stimulates the xenobiotic detoxifying CYP genes [37,38]. The receptor is ancient in its origin, dates more than five hundred million years back, and is essential for existence, as AhR deficient mice die a few weeks after birth. AhR has several exogenous and endogenous ligands, such as dioxin, polycyclic aromatic hydrocarbons (PAH), and from endogenous ligands tryptophan metabolites, like kynurenic acid and tryptophan metabolic products of microflora activate AhR. The exogenous ligands come from tobacco smoke, diesel exhaust, indoor heating, electronics, construction material, plastics, inner coating of water pipes, and food containers. AhR is present in many cell types in the body including mast cells, epithelial cells, etc, highly expressed in the liver, lungs, etc. Because AhR possesses important biological homeostatic functions, the inappropriate and overt engagement, disabling the physiological function of the receptor, overwhelming biotransformation capacity, may lead to organ and immune dysfunction. There is variability in the character of AhR response to different ligands depending on the dose or timing, they may promote Th17 or Treg phenotype [39].

Dioxin undergoes slow degradation of seven to ten years, impersonating a particular danger skewing the immune response towards overt proinflammatory or immunosuppressed phenotype. Accidentally, the effect of xenobiotics may become protective, in the case of estrogen-dependent breast cancer AhR decreases estrogen receptor activity, or coal tar in skin psoriasis improves skin barrier function, occupationally may however cause skin cancer [40]. Polycyclic aromatic hydrocarbons (PAH) represent environmentally frequent AhR ligands, some with cancerogenic potential, upon binding to AhR and via alternative routes. They are present in the ambient air, arising upon combustion, unburned hydrocarbons in automobile exhaust, resuspended road dust, coal burning, metal manufacturing, tobacco smoke, etc. AhR enhanced CYP1B1 activity is correlated with poor outcomes in glioblastoma patients. The adverse effects may be related to overt reactive oxygen species (ROS) production and DNA damage, proliferation, loss of differentiation [41]. AhR is abundantly expressed in mast cells, colocalizes with tryptase, and is upregulated in endometriosis patients on lesion-specific mast cells [42]. Mouse bone marrow-derived MCs(BMMCs) constitutively express the AhR receptor and upon stimulation with FICZ (endogenous tryptophan ligand) show CYP1A1 and CYP1B1 activation and enhanced ROS production [43]. Bisphenol A and estradiol stimulated BMMCs in vitro showed enhanced histamine release. Perinatal Bisphenol A exposure induced decreased DNA methylation in adult mice [44]. Mast cells and AhR are antiquated motifs, essential bricks in living organisms from very early and primitive forms, to highly complex mammals. Toxic exogenous insults therefore may have far-reaching consequences for many lifeforms on Earth.

5. MC Hormonal Interactions

Mast cells contribute in alliance with stress hormones to acute and chronic stress responses. Genetic mapping demonstrated over eight thousand genes differentially expressed among
female and male mouse mast cells in response to immunological and psychological stress. IgE-mediated allergic response induced a more aggravated and speedy response in female mast cells, in terms of tryptase, histamine serum levels and BMMCs from female mice had increased TNFa, histamine, β-hexosaminidase, and tryptase release. Among the upregulated genes, differential expressions were observed in TNFa, mast cell protease 1,2,4,8, tryptase, cathepsins, and several genes involved in granule biogenesis and maturation underscoring the relevance of sex differences in mast cell-mediated immune responses.

Acute stressors, by the means of corticotropin-releasing hormone (CRH), excreted from the paraventricular nucleus of the hypothalamus, activate the hypothalamic-pituitary-adrenal axis of the flight or fight reaction. CRH receptors are present on the surface of mast cells, CRH itself is secreted by mast cells, inducing an inflammatory response, degranulation exocytosis with a massive 5-hydroxytryptamine release. Perceived stress is a major trigger for CRH release in the periphery, for example, skin sensory neurons and mast cells, nasal mucosa, react with CRH-R1 mediated mast cell degranulation. Stress-induced increase in serum CRH levels, for example, if ignited by acute restraint, leads to brain, skin, lung MC degranulation and worsens blood-brain barrier tightness, neuroinflammation, and acute asthma attacks. Patients with psoriasis and atopic dermatitis too, have increased serum CRH levels and their symptoms can be aggravated by psychological stress. CRH is implicated in gut hypersensitivity in irritable bowel syndrome (IBS) and inflammatory bowel disease.

Ex vivo exposure of porcine intestinal cells to CRF showed increased mast cell degranulation, tryptase, and TNFα release, and gut permeability due to disruption of tight junctions, these effects were prevented with Cromolyn pretreatment. Mice exposed to 60 or 120 minutes of restraint stress produced high levels of serum IL-6, increased vascular permeability measured by 99Tc extravasation, and skin CRH content. These changes were remarkably diminished in MC deficient mice.

The interaction of mast cells with the hormonal milieu shapes the immune response. Mast cells have been shown to interact with virtually all hormonal systems, the sex, stress hormones, the thyroid, adrenal gland. The predominant hydroxyreductase in mast cells is 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1). The function of this enzyme is to convert cortisone in target cells to cortisol, produced mostly, but not exclusively in the liver, contributing to obesity, diabetes. 11βHSD1 is upregulated in the sites of inflammation, in mast cells, in macrophages, etc. In mast cells, they lead to decreased degranulation.

The interaction of mast cells and aldosterone was demonstrated using mast cell knockout mice. Aldosterone, one of the main regulators of fluid, sodium, and potassium homeostasis is produced by the cells of zona glomerulosa of the adrenal cortex in response to low potassium levels, in order to stimulate by the renin-angiotensin system. Subcapsularly located adrenal mast cells via serotonin production stimulate aldosterone synthesis and release from the adrenal gland. Low sodium levels triggered mast cell tryptase synthesis and aldosterone production in aged female BALB/c mice. While deficiency of mast cells is rare, the question remains how inadvertent adrenal mast cell activation, for example during sepsis, influences electrolyte and fluid balance.

Thyroid hormones and metabolites are present in mast cells, and the thyroid receptors are present on their surface, consequently the MC – thyroid interaction is bidirectional. Antithyroid peroxidase (TPO) antibodies present in autoimmune thyroiditis can directly activate and degranulate mast cells, while during Graves ophthalmopathy mast cells in elevated numbers contribute to orbital fibroproliferation. The number and the distribution of mast cells are influenced by thyroid hormones in many organs. Mast cells interact with chondrocytes and osteoblasts and contribute to T3 actions on bone remodeling and chondrocyte growth. Non-thyroidal illness (NTI) or euthyroid sick syndrome is characterized by low T3 and or T4 without increased feedback thyroid-stimulating hormone (TSH) levels. Among clinical intensivists, the role of peripheral thyroid silence is debated, whether it is a maladaptive change rather than recuperation of resources during bacterial infection and sepsis. NTI is a rather frequent finding during prolonged sepsis and low T3 levels represent an independent negative predictor for sepsis mortality. The notion, that bacterial lipopolysaccharide (LPS) causes peripheral suppression of thyroid hormones via MyD88 signaling and mast cells skews the dialogue towards the maladaptive hypothesis. Mice deficient in MyD88 did not develop a hypothyroid response. The thyroid dysfunction in inflammation is also due to LPS induced hypothalamic dysfunction and can be reversed with thryrotropin-releasing hormone (TRH) administration. There is no consensus as per thyroid substitution in sepsis, and there are experimental indications that intravenous T3 administration may have beneficial relevance.

6. MC in Viral and Bacterial Infections

MCs contribute to immune response fronting primarily helminth, but also viral and bacterial infections. Mast cells are a reservoir for HIV. FccR crosslinking on the surface of mast cells leads to enhancement of CXCR4 homing.
receptor expression and increased HIV viral tropism [57]. During hepatitis B and C infection, the Fv sialoprotein is produced in large amounts from the liver, binds to the heavy chain of the main immunoglobulin subfamilies, including IgE and leads to mast cell and basophil degranulation, histamine, and tryptase release from lung and skin mast cells [58].

Mast cells have been shown to participate and degranulate upon bovine respiratory syncytial virus (RSV) infection. Involvement of virus-specific IgE and RSV infection predisposes to the future development of asthma and allergy. RSV upon nasal inoculation to guinea pigs persisted for up to 60 days [59].

MC enhances the virolytic ability of CD8 virus-specific cells in lymphocytic choriomeningitis virus (LCMV) infection, thus controlling the infection, but their function in asthmatic and COPD patients may become ambivalent due to a concomitant increase in airway reactivity [60]. Postmortem analysis of alveolar mast cells of COVID-19 patients shows increased density, enhanced IL-4 production by alveolar macrophages and type II pneumocytes in comparison to control or H1N1 infected lungs [61]. Significantly elevated serum levels of chymase, tryptase, CPA3 (mast cell carboxypeptidase A) were found in COVID-19 patients when compared to healthy volunteers. Another study showed significantly elevated CPA3 serum levels in severe COVID disease [62]. Mast cells may have a protective role in microbial clearance, and detrimental function in aggravating airway hyperresponsiveness and fibrosis.

7. Mast Cells, Allergies, and Asthma

Mast cells and basophils are essential components of type I immediate hypersensitivity reactions. The prototypic anaphylactic response is triggered by crosslinked IgE in previously sensitized individuals and mediated by histamine, tryptase, platelet-activating factor (PAF), etc [63]. IgE crosslinking leads to abrupt activation of signaling pathways: IgE binds to high-affinity FcεRI on the surface of mast cells. There are approximately $3 \times 10^8$ FcεRs on the surface of mast cells and a 0.3% or antigen-specific IgE receptor occupancy is needed for mast cell activation, and importantly certain mono-antigenic IgEs render polyreactivity. Several viral, bacterial, helminth superallergen proteins possess the capacity to crosslink IgE and contribute to an aggravated mast cell sensitivity [64]. Fine particular matter of the ambient air has been shown to crosslink FcεR and worsen asthma symptoms in susceptible patients. Upon IgE engagement, prestored mediators are rapidly released via degranulation (histamine, heparin, proteases, TNFα), later de novo synthesized prostaglandins, leukotrienes, cytokines follow. A predominantly Th2 immune environment enhances the allergic phenotype. Th2 associated cytokines IL-4 and IL-13 promote IgG and IgM antibody switch to IgE subtype, and pattern recognition receptor (PRR) activation may serve a synergistic function. Human DCs harbor histamine receptors and histamine modulates the cytokine profile of DCs by downregulating IL-12 and stimulating IL-10 production to skew T cells toward an IL-4 producing phenotype [65]. As to why certain individuals are susceptible to allergens, remains to be fully understood, the number of allergic and asthmatic individuals in recent decades however is growing. House dust mite (HDM) induced allergies, female sex, airway hyperresponsiveness in childhood are all independent predictors of adulthood asthma persistence. Importantly, anaphylactoid or pseudo-allergic reactions can occur without previous sensitization independent of IgE crosslinking, via activation of Mas-Related G-protein coupled receptor-X2 (MRGPRX2) on the surface of connective tissue mast cells, inducing a more transient and speedy degranulation, with dominant tryptase contribution. Drug-induced anaphylactoid reactions represent a sizeable group of potentially severe adverse medication effects, particularly in intravenously applied cationic small molecules. Among the most widely used medications are nondepolarizing nonsteroidal muscle relaxants and opioids used in general anesthesia and intensive care, fluoroquinolone antibiotics, vancomycin, antidepressants [66,67]. Endogenous mediators like substance P(SP) can lead to MC degranulation via MRGPRX2 receptor, mediating pain and itching. Further, somatostatin, defensins can act via binding to MRGPRX2. There are 30 single nucleotide polymorphisms (SNP) described in the receptor structure, rendering some individuals more, others less reactive to receptor agonists.

Protease allergens (PA) represent a particularly dangerous group of allergens because they possess multiple immunomodulatory properties and trypsin, cysteine, chymotrypsin-like protease activities. Protease allergens are particularly abundant in house dust mites, moreover, cockroaches, certain fungal allergens, and staphylococcal proteins possess protease activity [68]. HDM PAs are dispersed upon fecal contamination of fine particular matter (FPM). In susceptible individuals, PAs activate MCs employing crosslinking IgE, via SP release and MRGPRX2 engagement, and a dominant PA, Depr mimics the MD-2 molecule of the TLR signaling complex, promoting inflammation via adjuvant effect. According to studies, HDM is present in 70% of the central European households, and 50% of allergic patients are sensitized to dust mites. The effect of inhalational PA on the immune
system of the host is surprisingly manyfold. Derp1, with cysteine-like protease activity, can disrupt the tight junctions between airway epithelial cells, can destroy IL-2 receptors, required for Th1 and Treg proliferation, further skewing T cells towards Th2 phenotype. The lung-protective surfactant A can bind allergens, Depr1 however overcomes this obstacle by cleaving the surfactant protein. CD23, the low-affinity IgE receptor on the surface of B cells, negatively regulates IgE levels but is cleaved too by Derp1. A similar immunomodulatory effect has been shown experimentally for Per a 10, a major cockroach allergen [69]. Fine particular matter, defined by size below 2.5 mm associated with air pollution in urbanized areas, is of preponderant interest for its small size and ability to reach small airways, alveoli. Inhalation of the fine particular matter is associated with acute agitation of asthma symptoms, particularly in children with allergic asthma. In vitro experiments confirm reactivity of bone marrow-derived mast cells, particularly to higher doses of FPM in terms of apoptosis, enhanced IgE mediated degranulation [70], increased IL-6, TNFα, and MCP-1 secretion.

8. Mast Cells and the Heart

The human heart accommodates mast cells in vascular intima, perivascularly, and interstitially. The involvement of mast cells and immune-mediated processes is compelling in acute and permanent atrial fibrillation, heart failure, myocardial ischemia, atherosclerotic plaque development, and rupture.

Cardiomyocytes are not capable of proliferation and nonphysiological stress leads to their hypertrophy and/or degeneration. The renin-angiotensin-aldosterone system (RAS) is a driving force behind hypertensive cardiomyopathy and human mast cells are involved due to renin production and angiotensin-II generation from angiotensin-I by chymase, behaving in a convertase manner [71]. The profibrotic potential of RAS has been demonstrated, and angiotensin-converting enzyme inhibitors carry the potential of reducing cardiac remodeling. The signature profibrotic cytokine is TgFB, and mast cell degranulation leads to the activation of profibrotic signature, myofibroblast generation, and collagen deposition [72]. Pressure overload due to increased peripheral vascular resistance leads to infiltration and proliferation of cardiac mast cells, with interstitial fibrosis and increased sensibility towards ectopic atrial pacing, irregular ectopic atrial activity- atrial fibrillation by creating aberrant pathways for cardiac conduction. Both pathognomonic features are abrogated upon mast cell stabilization with cromolyn and in MC knockout (KO) mice [73]. Repeated paroxysms of atrial fibrillation may conclude in permanent atrial fibrillation, signatures of acute versus chronic inflammation and degeneration, mast cell degranulation versus fibrosis. Histamine release from cardiac mast cells may trigger coronary spasm in predisposed patients. Experimentally, injection of histamine caused spasm in cadaveric coronaries [74]. Due to the strategical location of MCs in and around coronary vessels, their contribution to atherosclerotic changes is of interest. Beyond obesity, diabetes, and dyslipidemia, acute and chronic stress represents contributors to the development of the acute coronary syndrome. When apolipoprotein E (apoE) KO mice on Western diet were subjected to 120 minutes of restraint stress, significant activation of mast cells in the heart was observed, altogether with increased corticosterone and IL-6 levels, a shift towards neutrophils, with large size intraplaque hemorrhages, these changes were abrogated in MC KO mice. Increased numbers of mast cells were observed in the areas of atherosclerotic lesions, with the highest numbers and greatest level of degranulation in the areas of ruptures, and the intimal thickness showed a correlation with chymase activity. MC chymase can promote apoptosis of smooth muscle cells by degrading fibronectin, by disrupting focal adhesion complexes and Akt dephosphorylation, events that are needed for cell survival and adhesion. Chymase blocks NF-κB mediated survival of smooth muscle cells, NF-κB’s translocation to the nucleus is abolished and Bcl2 mRNA levels are decreased, leading to mitochondrial swelling and cytochrome c release [75]. Mast cells have been shown to promote lipid accumulation and foam formation. Instances of acute myocardial ischemia associated with severe anaphylactic reactions, the Kounis syndrome, are documented in the literature [76]. These reports indicate mast cell-mediated coronary plaque rupture upon allergic reactions to known pharmacological and environmental allergens, such as myorelaxants, aspirin, acetaminophen, antibiotics, gadolinium, food. Three types of Kounis syndrome have been described, type I in non-stenotic coronaries, when inflammatory mediator release leads to coronary vasospasm and myocardial ischemia, type II in silent atheromatous coronaries when spasm may lead to ischemia or/and ultimately to coronary plaque rupture, finally type III representing stented patients with thrombosis or stent restenosis due to xenobiotic induced anaphylactic or anaphylactoid reaction. As mentioned earlier, mast cell degranulation may be prompted via complement component C5a, a potent anaphylatoxin arising upon C5 cleavage by alternative, mannose-binding lectin or classical complement pathway serine

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protease - C5 convertase activation, and binding upon CD88 receptor on the surface of mast cells, macrophages. C5a is a potent chemoattractant, causes smooth muscle contraction and increases vascular permeability, and can trigger mast cell degranulation. ApoE deficient mice, prone to severe atherosclerosis have been treated with C5a. Plaque disruptions increased from 13% to 56%, and the length of ruptured plaque was increased likewise, but cromolyn treatment could not reverse C5a effects. C5a induced apoptosis via the caspase apoptotic pathway, and while caspase-1 and TNFα expressions were unchanged, caspase-3 levels were increased and TUNEL assay revealed doubling of apoptotic cells from 2.4% to 5.9% of total cell number upon C5a treatment [77]. Mast cells are implicated in Coxsackie B3 virus-induced experimental myocarditis, where signature proximal positive and negative regulators of heart passaged virus-induced inflammation on mast cells and macrophages - TLR4 and TIM3 - set the inflammatory events to a degree and direction that is influenced by sex [78].

9. Mast Cells and the Brain

The pathophysiology of neurodegeneration is complex. Neuroinflammation, autoimmunity, and inflammatory cell death are common features of Alzheimer's disease, Parkinson's disease, and dementia. As per Parkinson's disease, a form of chronic neurodegeneration, the alpha-synuclein misfolded protein accumulates in dopaminergic neurons of the substantia nigra, Lewy bodies are formed and neurodegeneration materializes [83]. Among important environmental triggers paraquat (herbicide), and rotenone (pesticide) are emphasized. These substances interfere with the mitochondrial electron transport system, ultimately by producing reactive oxygen species leading to the death of dopaminergic neurons in substantia nigra. There is a locally disrupted blood-brain barrier and soon autoreactive activated, mostly Th17 producing T cells populate the region aggravating neuroinflammation. The herbicide paraquat shows a clear association between inhalational, dermal, or oral exposure and the development of Parkinson's disease (PD) [84]. Paraquat is an enhancer of reactive oxygen species (ROS) formation and in its pure form leads to severe acute respiratory distress syndrome (ARDS). MCs treated with MPP+(experimental neurotoxin) showed degranulation and MMCP6,7 (corresponding to human tryptase) release, moreover, co-culture of BMMCs with neurons aggravated this response. Mast cells are located adjacent to microglia, and upon stimulation, a persistent glial activation emanates. MMCP6 and 7 lead to CCL2 release from astrocytes and glial cells activation, neurodegeneration measured by neurite outgrowth [85]. In the brain lesions of Alzheimer's and, Parkinson's patients autoimmune T cells and Foxp+ regulatory T cells are present likewise. The emergence of autoimmune conditions is manyfold, and under preexisting inflammatory conditions presentation of previously unseen cryptic epitopes may occur, leading potentially to autoimmunity. Likewise, the presence of ROS further aggravates the apoptotic process, creating a multimodal self-perpetuating pathological circuit of death and autoinflammation. The involvement of antigen processing and presentation appears to be necessary for PD to develop, this has been demonstrated on major histocompatibility complex(MHC)II KO mice, in whom MPTP (a prodrug to MPP+) intoxication did not lead to cell death, nor release of pro-inflammatory cytokines. Even when α-synuclein is overexpressed, but MHCII is not present, mice are protected from microglial activation, and neuronal cell death [86].

Concerning acute traumatic and inflammatory conditions, intracerebral bleeding, and ischemia, beyond augmenting inflammation in the central nervous system, mast cells also contribute to the increased permeability of the blood-brain barrier (BBB), enabling toxins previously precluded from entering the brain to centralize [87]. MCs are located in the pia mater, brain parenchyma, and vessels, facing the brain. Experimental stabilization with cromoglycate, similar to mast cell deficiency, led to a 50-60% decrease in brain swelling and BBB leakage. Considering our limited resources in the management of brain swelling using traditional methods, these data must be taken seriously. Histamine by its virtue increases edema formation in general, together with circulating platelet aggregating factor (PAF) from neutrophils and monocytes, upon enhancing nitric oxide (NO) production, and by VE-cadherin rearrangement in endothelium [89]. In the mouse model of focal cerebral ischemia, lack of MCs in C57BL6/J mice, similarly to intraventricular MC stabilization using cromoglycate, significantly decreased edema formation upon transient - 45 minute- middle cerebral artery occlusion [89]. The study demonstrates the contribution of mast cells to increased BBB permeability, vasogenic edema, and ischemia-reperfusion injury to disease pathology. The effect of mast cells on leukocyte infiltration, BBB permeability was present within four hours after injury, and sustained for up to 70 hours of injury, demonstrating how mast cells are immediate mediators, and later followed up by macrophages and neutrophils. The delicate response of the brain to trauma is demonstrated in experimentally induced midshaft tibial fracture under general anesthesia with sevofohrane, in C57BL6/J male mice. A significant increase in mast cell numbers was present in the hippocampus one day after surgery. While the baseline level of proinflammatory
TNFα and IL-1β was not different among experimental groups, the increased TNFα and IL-1β production were decapitated on day one upon intraventricular cromoglycate treatment in wild type mice [90]. The role of TLR4 signaling in the ischemia-reperfusion injury has been previously emphasized, the abrogation of this pathway experimentally leads to improved tissue viability and organ functionality [91].

10. MC Stabilization

Physiologically vitamin D stabilizes mast cells. Thanks to the presence of 25-hydroxyvitamin D1-alpha-hydroxylase, mast cells can convert vitamin D to its active form, which conversely has a negative regulatory role on mast cell maturation in the bone marrow. Both vitamin D and mast cell deficiencies are linked to allergic disorders, eczema, multiple sclerosis, and tumor development. Active vitamin D can induce IL-10 production in mast cells and dampen IgE mediated mast cell activation, in the presence of the functional CYP27B1 hydroxylase, that is constitutively expressed in the mast cells. In the presence of active vitamin D, percutaneous anaphylaxis is significantly blunted [79]. The clinically available mast cell stabilizers are cromolyn (disodium cromoglycate) and ketotifen [80]. Cromolyn is a preventive mast cell stablizer, approved for mastocytosis, allergic rhinitis, and asthma. It alleviates the extracellular calcium influx, preventing the degranulation of mast cells. Cromolyn has a good safety profile, but very low oral bioavailability and a short half-life [81]. Omalizumab, a humanized monoclonal antibody, binding IgE is in the introductory stages of application in severe steroid-resistant asthma and urticaria, indications carefully selected. Antihistamines, by blocking the action of histamine by binding to H1 or H2 receptors have proven to be instrumental in the management of allergy and asthma symptoms. Inhaled dexamethasone inhibits mast cell numbers within a few days of the administration, smooth muscle reactivity, and restrains IgE and IL-33 mediated mast cell reactivity [82]. Ultimately adrenaline with potent alpha- and beta-adrenergic activity counteracts the profound degranulation-induced disturbances in anaphylactic reactions.

11. Conclusions

The delicate balance in homeostasis is disrupted during illness. Understanding the pathognomic features of the illness, particularly in critical care with multiple organ dysfunctions, and treating adequately is a true challenge. This review was set to analyze and understand the less traditional mast cell aspects, it is a glimpse at mast cells in a broader context. Mast cells are inevitable or instrumental parts of the immune response and homeostasis, but when inappropriately engaged or directed, may become detrimental. Current clinical options at influencing them therapeutically further, beyond allergies and asthma, beyond well-known established ways with cromolyn, antihistamines, corticosteroids are limited, various shared receptor and pathway modulators are clinically tested. Mast cell „stabilization” from an evolutionary and inflammatory perspective may come by the virtue of indirect measures, by the considerate choice of environmental chemicals, particularly during periods of heightened developmental sensitivity. An important psychosomatic motif can be discovered in the article, that the pathological incentives are deeply embedded on a molecular level, can be ignited by stress and restraint. The epidemics of hypertension can partially be derived back to nonphysiological life choices. Mast cells as part of overall immune response optimally should clinically be monitored. In the complex niche of the immune response, that is determined by the etiology of the disease and the overall state of the patient due to comorbidities, sex, age, race, location. The disease pathology that is time sensitive, creates an immune cell and cytokine environment, that is to some degree exclusive, individual. Basic cell, mediator, survival, apoptosis, and cytokine panels, receptor levels would enable us to appreciate the governing forces driving and limiting the immediate immune response in time. Strategies to influence and direct such responses could be developed in an educated manner. Reverberations of research incentives in a complex and dynamic system, mapping, analyzing, and reacting, are extremely desirable attitudes of the future approach to immunological challenges.

References


[57] Sundstrom JB, Ellis JE, Hair GA, Kirshenbaum AS, Metcalfe DD, Yi H, Cardona AC, Lindsay MK, An-
Maccallum A, Pundir P, Meeker S, Han L, Undem BJ. DOI: https://doi.org/10.4049/jimmunol.177.6.3577.


