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Review

Mast cells and inflammation ☆

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ABSTRACT

Mast cells are well known for their role in allergic and anaphylactic reactions, as well as their involvement in acquired and innate immunity. Increasing evidence now implicates mast cells in inflammatory diseases where they are activated by non-allergic triggers, such as neuropeptides and cytokines, often exerting synergistic effects as in the case of IL-33 and neurotensin. Mast cells can also release pro-inflammatory mediators selectively without degranulation. In particular, IL-1 induces selective release of IL-6, while corticotropin-releasing hormone secreted under stress induces the release of vascular endothelial growth factor. Many inflammatory diseases involve mast cells in cross-talk with T cells, such as atopic dermatitis, psoriasis and multiple sclerosis, which all worsen by stress. How mast cell differential responses are regulated is still unresolved. Preliminary evidence suggests that mitochondrial function and dynamics control mast cell degranulation, but not selective release. Recent findings also indicate that mast cells have immunomodulatory properties. Understanding selective release of mediators could explain how mast cells participate in numerous diverse biologic processes, and how they exert both immunostimulatory and immunosuppressive actions. Unraveling selective mast cell secretion could also help develop unique mast cell inhibitors with novel therapeutic applications. This article is part of a Special Issue entitled: Mast cells in inflammation.

1. Introduction

Mast cells derive from distinct precursors in the bone marrow or other hematopoietic tissues [1,2]. They mature under the influence of local tissue microenvironmental conditions, through various cytokines such as stem cell factor (SCF) [2,3]. SCF enhances mast cell degranulation and cytokine production through cross-linking of their high affinity surface receptors for IgE (FcεRI), even though it does not induce degranulation on its own [4–7]. Other molecules that promote mast cell maturation include nerve growth factor (NGF) [8], which acts via tyrosine kinase receptors (TrkA, B, C), different from the c-kit activated by SCF [9]. Neurotrophin-3 was also shown to promote maturation of both fetal mouse skin mast cells [10] and human intestinal mast cells [11]. Moreover, human mast cells express mRNA

Abbreviations: AD, atopic dermatitis; BBB, blood–brain barrier; Bcl10–Malt1, B cell lymphoma 10–Mucosal-associated lymphoid tissue 1; BDNF, brain-derived neurotrophic factor; CRH, corticotropin-releasing hormone; CRHR, corticotropin-releasing hormone receptor; Drp1, dynamin related protein 1; EAE, experimental allergic encephalomyelitis; FcεRI, high affinity surface receptors for IgE; GM-CSF, granulocyte-macrophage colony-stimulating factor; hCBMCs, human umbilical cord-derived mast cells; HPA, hypothalamic–pituitary–adrenal; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; LT, leukotriene; MBP, myelin basic protein; MCP-1, monocyte chemoattractant protein-1; MS, multiple sclerosis; MMP, matrix metalloproteinase; NGF, nerve-growth factor; NK, neurokinin; NT, neurotensin; PACAP, pituitary adenylate cyclase activating polypeptide; PAF, platelet activating factor; PAR, protease activated receptors; PI3-K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homologue; RANTES, regulated upon activation, normal T cell expressed and secreted; RBL, rat basophil leukemia; SCF, stem cell factor; SF-1α, stromal cell-derived factor-1 alpha; SLPI, secretory leukocyte protease inhibitor; SP, substance P; TGFβ, transforming growth factor β; TLR, toll-like receptor; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin; Ucn, urocortin; UCP2, uncoupling protein 2; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal peptide

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and protein for the Trk ligands NGF, brain-derived neurotrophic factor (BDNF) and neurotrophin-3 [9], suggesting autocrine actions. However, unlike NGF, which stimulates mast cell degranulation [12], neurotrophins do not. Mast cell chemoattractants include SCF, monocyte chemoattractant protein-1 (MCP-1) and the "regulated upon activation, normal T cell expressed and secreted" (RANTES) [13]. SP is also a potent chemoattractant for human basophils [14]. Depending on their location, stage of maturation or species [15], mast cells express different types and levels of surface antigens and receptors, some of which are involved in activation and others in cell recognition (Table 1) [16].

In addition to IgE and antigen [5], immunoglobulin free light chains [17,18], anaphylatoxins, hormones and neuropeptides [19,20] can trigger mast cell secretion [21–23] (Table 2). The latter include substance (SP) [24], hemokinin [25], neurotensin (NT) [26], NGF [12,27] which is released under stress [28], and pituitary adenylate cyclase activating polypeptide (PACAP) [29,30]. Skin mast cells are located close to sensory nerve endings and can be triggered by neuropeptides [21,31], such as NT [26], NGF [12], SP [32], and PACAP [30] (Fig. 1), which can be released from dermal neurons. In fact, skin mast cells contain SP [33], while cultured mouse and human mast cells contain and secrete NGF [34]. Thymic stromal lymphopoietin (TSLP), released in response to inflammation, pathogens and trauma [35], also activates mast cells, but only in the presence of interleukin-1 (IL-1) and tumor necrosis factor (TNF) [35,36]. A number of additional

Table 1
Mast cell receptors and their agonists.[a]

Adenosine receptors A2A, A2B, A3	Adenosine
β_2-Adrenoreceptor	Adrenaline
C3α receptor	C3α
C5α receptor	C5α
Cannabinoid CB_2 receptor	2-Arachidonoyl-glycerol, anandamide
CD47 (=integrin-associated protein, IAP)	Integrins
CD200 receptor	CD200 (0X2)
$Cd300_\alpha$ receptor	Eosinophil granule proteins
Chemokine receptors	Chemokines
CXCR1–4, CX3 CR1, CCR1, 3–5	
CRHR-1, CRHR-2	Corticotropin releasing hormone
Estrogen receptors (A, B)	Estrogens
FcαR (CD89)	IgA
FcεRI	IgE
FcγRI	IgG
FcγRIIA	IgG
FcγRIIB	IgG
FcγRIII	IgG
GPR34	Lysophosphatidylserine
GPR92	Lysophosphatidic acid
Histamine receptors H_1, H_2, H_3, H_4	Histamine
$5\text{-}HT_{1A}$	Serotonin
Kit receptor tyrosine kinase (CD17)	Stem cell factor
LPA_1, LPA_3	Lysophosphatidic acid
Leptin receptor	Leptin
Leukotriene receptors 1 and 2	Leukotrienes
MRGX2	Mastoparan, somatostatin, SP
Myeloid-associated Ig-like receptor 1	?
Neurokinin receptors	CGRP, Hemokinin-A, SP, VIP
NK1R, NK2R, NK3R, VPAC2	
Neurotensin receptor	Neurotensin
Neurotrophin receptors	
TrkA	NGF
TrkB	BDNF
TrkC	Neurotrophin 3
Nicotinic acetylcholine receptor	Acetylcholine
0X40	0X40-ligand
Protease activated receptors 1–4	Serine proteases (e.g. trypsin, tryptase)
Peripheral benzodiazepine receptor	?
Progesterone receptor	Progesterone
Prostaglandin E receptors	Prostaglandin E
EP_2, EP_3, EP_4	
Purinoreceptors	
$P2Y_1$, $P2Y_{12}$, $P2Y_{13}$	ADP
$P2Y_2$	ATP, UTP
$P2Y_{11}$	ATP
Sphingosine-1-phosphate	S1P
$S1P_1$, $S1P_2$, $S1P_5$	
Toll-like receptors 1–9	Bacterial and viral products
Urokinase receptor	Urokinase
Vitamin D receptor	Vitamin D

[a] There are differences in the expression of cell surface receptors between human and rodent mast cells.

Table 2
Mast cell mediators.[a]

Mediators	Main pathophysiologic effects
Prestored	
Biogenic amines	
Histamine	Vasodilation, angiogenesis, mitogenesis, pain
5-Hydroxytryptamine (5-HT, serotonin)	Vasoconstriction, pain
Chemokines	
IL-8 (CXCL8), MCP-1 (CCL2), MCP-3 (CCL7), MCP-4, RANTES (CCL5), eotaxin (CCL11)	Chemoattraction and tissue infiltration of leukocytes
Enzymes	
Arylsulfatases	Lipid/proteoglycan hydrolysis
Carboxypeptidase A	Peptide processing
Chymase	Tissue damage, pain, angiotensin II synthesis
Kinogenases	Synthesis of vasodilatory kinins, pain
Phospholipases	Arachidonic acid generation
Tryptase	Tissue damage, activation of PAR, inflammation, pain
Matrix metalloproteinases	Tissue damage, modification of cytokines/chemokines
Peptides	
Angiogenin	Neovascularization
Corticotropin-releasing hormone	Inflammation, vasodilation
Endorphins	Analgesia
Endothelin	Sepsis
Kinins (bradykinin)	Inflammation, pain, vasodilation
Leptin	Food intake regulator
Renin	Angiotensin synthesis
Somatostatin	Anti-inflammatory (?)
Substance P	Inflammation, pain
Urocortin	Inflammation, vasodilation
VEGF	Neovascularization, vasodilation
Vasoactive intestinal peptide	Vasodilation, mast cell activation
Proteoglycans	
Chondroitin sulfate	Cartilage synthesis, anti-inflammatory
Heparin	Angiogenesis, nerve growth factor stabilization
Hyaluronic acid	Connective tissue, nerve growth factor stabilization
De novo synthesized	
Cytokines	
Interleukins (IL)-1, 2, 3, 4, 5, 6, 8, 9, 10, 13, 16, 18	Inflammation, leukocyte migration, pain
IFN-α, IFN-β, IFN-γ; MIF; TGFβ; TNF-α, MIP-1α, MCP-1	Inflammation, leukocyte proliferation/activation
Growth factors	
SCF, GM-CSF, β-FGF, neurotrophin 3, NGF, PDGF, TGFβ, VEGF	Growth of a variety of cells
Nitric oxide	Vasodilation
Phospholipid metabolites	
Leukotriene B_4	Leukocyte chemotaxis
Leukotriene C_4	Vasoconstriction, pain
Platelet activating factor	Platelet activation, vasodilation
Prostaglandin D_2	Bronchonstriction, pain

β-FGF, β-fibroblast growth factor; GM-CSF, granulocyte monocyte-colony stimulating factor; IFNγ, interferon-γ; MCP, monocyte chemoattractant protein; MIF, macrophage inhibitory factor; MIP, macrophage inflammatory protein; NGF, nerve growth factor; PDGF, platelet-derived growth factor; SCF, stem cell factor; TGFβ, transforming growth factor β; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor.

[a] There are differences in the expression of mediators between human and rodent mast cells.

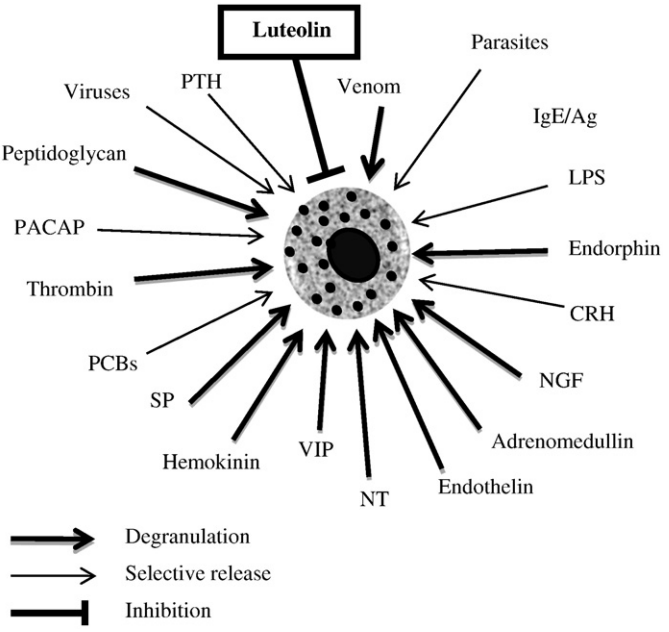

Fig. 1. Schematic representation of physiological and environmental mast cell triggers, and the inhibitory effect of certain flavonoids, such as luteolin. Many of these triggers stimulate selective release of mediators such as IL-6, TNF or VEGF without degranulation. CRH, corticotropin releasing hormone; LPS, lipopolysaccharide; NT, neurotensin; PACAP, pituitary adenylate cyclase activating polypeptide; PCBs, polychlorinated biphenols; PTH, parathyroid hormone; SP, substance P; VIP, vasoactive intestinal peptide.

immune and infectious triggers (e.g. stimulants of Toll-like receptors, TLR) can lead to *selective* release of mast cell mediators (see under "Selective release" below).

Once activated, mast cells secrete numerous vasoactive and pro-inflammatory mediators [37–42]. These include pre-formed molecules such as histamine, serotonin, TNF, kinins and proteases stored in secretory granules. Leukotrienes (LT), prostaglandins and platelet activated factor (PAF) are synthesized during mast cell activation from arachidonic acid liberated by the action of phospholipases. In addition, a number of cytokines (e.g. IL-1, 2, 5, 6, 8, 9, 13, and TNF) and vascular endothelial growth factor (VEGF) [43] are synthesized *de novo* and released several hours after stimulation (Table 2). VEGF is also released from normal human cultured mast cells selectively in response to corticotropin-releasing hormone (CRH) [44].

CRH is secreted from the hypothalamus under stress and regulates the hypothalamic–pituitary–adrenal (HPA) axis [45] through specific receptors [46]. These include CRHR-1 [47] and CRHR-2 [48], the latter being subdivided into CRHR-2α and CRHR-2β [49]. All CRHR are activated by urocortin (Ucn), a peptide with about 50% structural similarity to CRH [50]. Ucn II [51] and Ucn III [52] are potent selective CRHR-2 agonists. CRH can also be secreted from immune cells [53] and mast cells [54]. CRH and related peptides released locally under stress may regulate mast cell function [55], and the brain–skin connection [56]. It was recently reported that CRH stimulates generation of mast cells from human hair follicle precursors [57].

Mature mast cells vary considerably in their cytokine [58] and proteolytic enzyme content, but their phenotypic expression is not fixed [59,60]. Mast cells in the presence of SCF produce predominantly pro-inflammatory cytokines, whereas when used together with SCF and IL-4, they produce mostly Th2 cytokines [61]. For instance, human umbilical cord-derived mast cells (hCBMCs) primed with IL-4 or IL-5 before stimulation with IgE released more TNF, IL-5, and granulocyte-macrophage colony-stimulating factor (GM-CSF), compared to hCBMCs maintained in SCF alone. In contrast, IL-4 enhanced SCF-dependent mast cell proliferation and shifted IgE-stimulated response to Th2 cytokines such as IL-3, IL-5 and IL-13, but not IL-6 [62].

Mast cells play an important role in innate or acquired immunity [63], bacterial infections [64–66], as well as in autoimmunity [67]. Mast cells are also important for maturation of Th17 cells and are recognized as key cells in autoimmune disorders [68]. For instance, mast cells in the presence of IL-6 and transforming growth factor β (TGFβ) are necessary for the production of Th17 cells [69], while TNF and vasoactive intestinal peptide (VIP) drive IL-6-independent Th17 cell maturation [69–71]. A number of immune molecules also contribute to mast cell activation. Addition of complement fragment 3a (C3a) led to increased degranulation of human mast cells stimulated by aggregated IgG [72]. Immunoglobulin-free light chains elicited immediate hypersensitivity-like reactions [18,73], with subsequent T cell-mediated immune responses. The antibacterial peptides, human B-defensins, can activate mast cells and induce degranulation [74]. In fact, mast cells interact with T cells [75,76] and superactivate them through TNF, as shown with mouse [77,78] and human [79,80] mast cells. It was recently shown that T cells release "microparticles" that stimulate human mast cell degranulation and IL-8 release [81]. Mast cells, in turn, secrete heparin "microparticles" that contain and deliver TNF to lymph nodes [82].

Mast cells, specifically a subset highly expressing both FcεRI and MHC II [83], can function as antigen presenting cells [84–86]. Basophils can also act as Th2-inducing antigen-presenting cells [87,88]. Basophils promote Th2 responses [89,90] and co-operate with dendritic cells for optimal Th2 responses [91]. Moreover, basophil activation by "autoreactive IgE" induces their "homing" to lymph nodes, where they promote Th2 cell differentiation and production of auto-reactive antibodies that contribute to lupus nephritis [92]. Interestingly, mast cells can act both as positive and negative modulators of immunity [93]. In addition, mast cells can coordinate the adaptive immune response by directing migration of dendritic and T cells to lymph nodes and secreting T cell-polarizing cytokines [94]. Such regulatory activities of mast cells may stem from *selective* release of immunomodulatory molecules that could have both autocrine and paracrine actions (Fig. 2).

Mast cells also have the unusual ability to be triggered by certain molecules and then either activate them or degrade them. For instance, mast cells can act on precursor protein molecules and generate active peptides [95], such as histamine-releasing peptides [96] and NT, [97] from plasma. However, mast cells can also degrade NT [98] and limit its biologic effects [99]. Mast cells can also synthesize

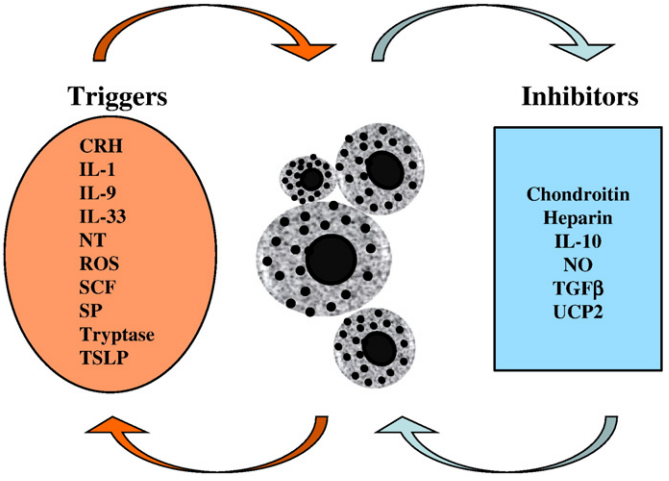

Fig. 2. Schematic representation of mast cell autocrine triggers and modulators. Numerous molecules secreted by mast cells can have autocrine actions, either activating or inhibiting mast cells. CRH, corticotropin-releasing hormone; IL, interleukin; NT, neurotensin; NO, nitric oxide; ROS, reactive oxygen species; SCF, stem cell factor; SP, substance P; TGFβ, transforming growth factor β; TSLP, thymic stromal lymphopoietin; UCP2, uncoupling protein 2.

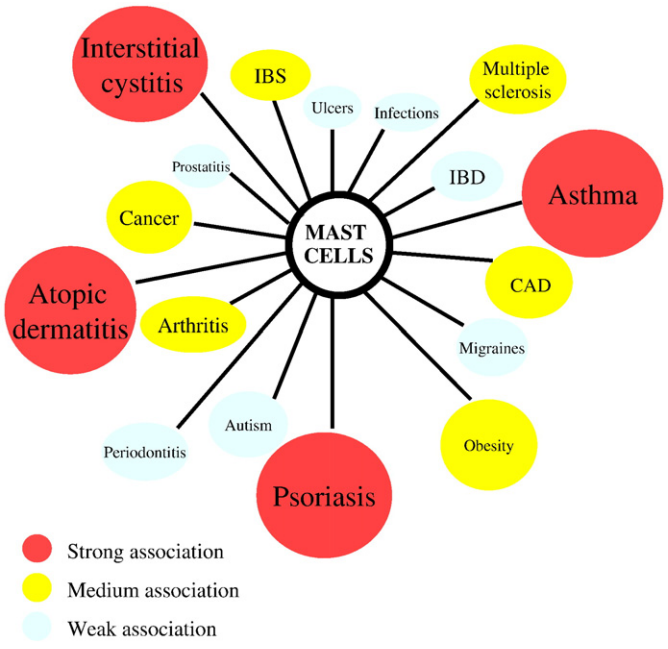

Fig. 3. Mast cell involvement in inflammatory diseases. Increasing evidence indicates that mast cells are involved in many diseases. Colors indicate the strength of the association (red = strongest, white = weakest). CAD, coronary artery disease; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome.

endothelin [100], but also release proteases that degrade endothelin [64]. Finally, mast cells can be activated by snake toxins [101,102], but also degrade them [103]. Whether these actions will be proven useful or detrimental obviously depends on the ability of mast cells to secrete specific mediators selectively in a well-regulated fashion.

2. Inflammatory processes and the role of selective release

Increasing evidence indicates that mast cells are critical for the pathogenesis of inflammatory diseases [19,20], such as arthritis [104], atopic dermatitis, psoriasis [105,106], and multiple sclerosis [107] (Fig. 3). Gene array analysis of human mast cells activated by IgE showed overexpression of numerous, mostly inflammation-related genes [108]. Proteases released from mast cells could act on plasma albumin to generate histamine-releasing peptides [96,109] that would further propagate mast cell activation and inflammation. Proteases could also stimulate protease-activated receptors (PAR) inducing microleakage and widespread inflammation [110,111]. However, unlike allergic reactions, mast cells are rarely seen to degranulate during inflammatory processes. The only way to explain mast cell involvement in non-allergic processes would be through "*differential*" or "*selective*" secretion of mediators without degranulation [112].

This ability could occur through different mechanisms: (A) mast cells can secrete the content of individual granules [113]; (B) mast cells can secrete some granular contents through a process associated with ultrastructural alterations of their electron dense granular core indicative of secretion, but without evidence of degranulation [114], a process that has been termed "activation" [115], "intragranular activation" [116] or "piecemeal" degranulation [117] (Table 3, Fig. 4); (C) mast cells can undergo selective release of specific mediators such as serotonin without histamine [118]. Selective release of serotonin occurred through sequestration from secretory granules inside vesicles containing high affinity serotonin-binding proteins from which it was released [119]. A somewhat similar process was reported for eosinophils where it was shown that eotaxin stimulation induced movement of preformed IL-4 from granules into secretory vesicles from which it was released [120]. Human mast cells stimulated by IL-1 selectively released IL-6 without degranulation through vesicles (40–80 nm) much smaller than the secretory granules (800–1000 nm) [121]. Selective release of eicosanoids has also been shown [122–124].

Table 3
Selective release of mast cell mediators.

Stimuli	MC type	Mediators released	Mediators NOT released	Pathophysiological importance	References
Endogenous					
CD8 ligands	RPMC	TNF, NO	H	T cell interaction	[279]
CRH	hCBMC	VEGF	H, tryptase, IL-8	Inflammation	[25]
Endothelin-1 and -3	RMMC	TNF, IL-12↑	IL-4, IL-10, IL-13↓	Th1 immunity	[280]
IL-1	hCBMC	IL-6, IL-8, TNF	H, tryptase	Inflammation	[92]
IL-1β	RPMC	NO	PAF, H	Inflammation	[281]
IL-12	P815	IL-13		Host defence against bacteria	[282]
IL-12	RPMC	IFN-γ	H	Th1 immunity	[283]
LTC_4/LTD_4	IL-4-primed hCBMC	TNF, MIP-1α, IL-5	H	Non-IgE mediated inflammation	[284]
Monomeric IgE	BMMC	IL-6	H, LTC_4	Mast cell survival	[285]
PGE_2	RPMC	IL-6	H, TNF	Cytoprotection	[286]
SCF	BMMC	IL-6	H, LTC_4, TNF	Mast cell development	[83]
SDF	hCBMC	IL-8	H, GM-CSF, IFN-γ, IL-1β	Endothelial transmigration	[88]
Thrombin	BMMC	IL-6	Serotonin, TNF	Anticlotting	[287]
Urocortin	hCBMC	IL-6	H, tryptase, IL-8, VEGF	Inflammation	[288]
Exogenous/pharmacological					
Amitriptyline	RPMC	Serotonin	HA	Headaches	[73]
Cholera Toxin	RPMC	IL-6	HA, TNF	Inflammation	[289]
Clostridium difficile Toxin A	RPMC	TNF	HA	GI tract inflammation	[290]
CpG DNA	BMMC	TNF, IL-6	HA, IL-4, IL-12, GM-CSF, IFN	Host response to bacteria	[291]
H. pylori VacA Toxin	BMMC	IL-6, IL-8, TNF	HA	Gastric injury	[102]
LPS (TLR-4)	RPMC	IL-6	HA	Bacterial infection	[81]
PMA	BMMC	VPF/VEGF	5HT	Angiogenesis	[292]
S.a.peptidoglycan (TLR-2)	hCBMC	HA, IL-1β, RANTES, LTC_4	IL-6	Exacerbation of asthma by bact. infection	[98]
Suboptimal FcεRI stimulation	BMMC	MCP-1, HA low	IL-10, HA	Chemokines≫cytokines/HA	[120]
Viruses (TLR-3, 5, 9)	FSMC	TNF, IL-6	HA	Recruitment of other immune cells	[103]

BMMC, bone marrow mast cells; CRH, corticotropin-releasing hormone; FSMC, fetal skin-derived cultured mast cells; GM-CSF, granulocyte monocyte-colony stimulating factor; H, histamine; HA, hexosaminidase; hCBMC, human cord blood-derived mast cells; IFN, interferon; LT, leukotriene; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; NO, nitric oxide; PAF, platelet activating factor; PMA, phorbol myristate acetate; PG, prostaglandin; RMMC, rat mucosal mast cells; RPMC, rat peritoneal mast cells; S.a, Staphylococcus aureus; SCF, stem cell factor; SDF, stromal cell-derived factor; TLR, toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

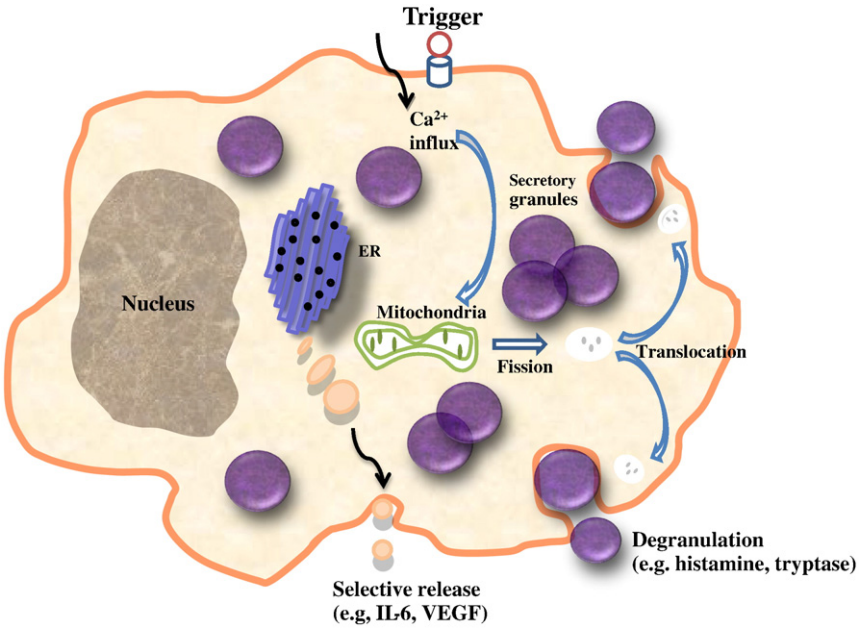

Fig. 4. Schematic representation showing mast cell degranulation as compared to selective mediator release. During selective release, vesicles much smaller than secretory granules transport mediators to the cell surface for exocytosis. ER, endoplasmic reticulum; VEGF, vascular endothelial growth factor.

Selective release of IL-6 was reported in response to bacterial lipopolysaccharide (LPS), in the presence of the phosphatidylinositol 3-kinase (PI3-K) inhibitor wortmannin, or triggered by SCF [125–127]. CRH induced selective VEGF release [128], and PGE_2 also induced release of VEGF [129] and MCP-1 without degranulation [130]. Yet, PGE_2 *inhibited* FcεRI-induced histamine release from human lung mast cells [131]. Stromal cell-derived factor-1 alpha (SF-1α) selectively produced IL-8 from human mast cells without degranulation as well [132]. Activation of human cultured mast cells by CD30 ligands led to release of the chemokines IL-8 and MCP-1 without histamine and without degranulation [133]. IL-33 induced IL-13 release independent of IgE stimulation [134].

TLR are critical in innate and acquired immunity [135,136]. TLR activation on mast cells leads to release of different cytokines [137]. For instance, rodent mast cell TLR-4 activation by LPS induces TNF release without degranulation. TLR-4 is also activated by extra domain A of fibronectin to release several cytokines, including TNF, in the same way as LPS [138]. Furthermore, LPS induces secretion of IL-5, IL-10 and IL-13, but not GM-CSF, IL-1 or LTC_4. [139,140]. In contrast, staphylococcal peptidoglycan induces degranulation and histamine release through TLR-2 [139,141]. TLR-2 and TLR-4 activation has a synergistic action with antigen in enhancing cytokine production from rodent mast cells [142]. Elsewhere, it was shown that TLR-2 activation produces IL-4, IL-6 and IL-13, but not IL-1, while LPS produces TNF, IL-1, IL-6 and IL-13, but not IL-4 or IL-5, again without degranulation [143].

TLR 3, 7 and 9 activation by poly-oligodeoxynucleotide and C-phosphate-G (CpG) induces release of TNF and IL-6 without degranulation from fetal rat skin-derived mast cells [144]. Human mast cells produce IL-6 through viral TLR-9 activation [145], while they produce interferon (IFN) following TLR-3 activation by double-stranded RNA [146].

3. Regulation of mast cell activation

FcεRI-induced mast cell degranulation involves calcium-dependent exocytosis, and SNAP-23 phosphorylation [147], but granule translocation to the surface is calcium-independent [148]. Mast cell activation by different triggers apparently engages different downstream pathways. FcεRI aggregation induces PI3K, ERK, JNK, NF-κB and PKC activation, although the PKCε isozyme may be redundant [149,150]. Phosphatase and tensin homologue (PTEN) knockdown induces constitutive cytokine production, without degranulation, that involves phosphorylation of AKT, p38/MAPK and JNK [151]. Secretion in response to compound 48/80 requires PLC, tyrosine kinase, p38/MAPK and PKC [152]. In contrast, IL-1 stimulation of selective IL-6 release is extracellular calcium-independent and involves p38/MAPK, but only PKCθ isozyme activation [153]. CRH-induced selective VEGF release from mast cells is also extracellular calcium-independent, and involves only PKA and p38/MAPK activation [128].

Degranulation in response to FcεRI-aggregation was severely impaired in IL-2-inducible T cell kinase (IKT) −/− mice [154]. FcεRI-induced mast cell activation in rat basophil leukemia (RBL) cells was inhibited by the Syk-tyrosine kinase inhibitor Piceatannol [155]. Suboptimal antigen challenge of human mast cells led to FcεRI-unresponsiveness that correlated with reduced Syk levels [156], apparently through actin assembly that blocked degranulation [157]. However, low antigen still permitted MCP-1 release, suggesting yet another mechanism of differential release [158].

The Src family kinase Lyn is a negative regulator of allergic mast cell activation, but Lyn−/− mice had increased FcεRI expression, circulating histamine and eosinophilia [159]. Fyn deficient mast cells could not generate IL-6, TNF or MCP-1 during FcεRI aggregation, but IL-13 production was intact, suggesting divergent regulatory pathways [160].

Adaptor complexes such as B cell lymphoma 10–mucosal-associated lymphoid tissue 1 (Bcl10–Malt1) permit FcεRI-dependent IL-6 and TNF release without degranulation [161]. Mice deficient in either Bcl10 or MALT1 proteins did not produce TNF or IL-6 upon FcεRI signaling: yet, degranulation and LT secretion was normal [162]. Neutralization of the inhibitory receptor IRp60 (CD300a) in human cord blood mast cells in mice led to increased mediator release [163]. In contrast, engagement of the myeloid cell inhibitory receptor CD200 in human mast cells inhibited FcεRI-induced activation [164]. Mast cells also express the inhibitory receptors CD300 and Siglec-8, as well as the death receptor TRAIL [165]. Two peptides derived from the complement components C3a, C3a+ and C3a9 inhibited FcεRI-induced degranulation and TNF release [166].

There appear to be some innate inhibitors of mast cell secretion (Fig. 2). Chondroitin sulfate and heparin, the major constituents of

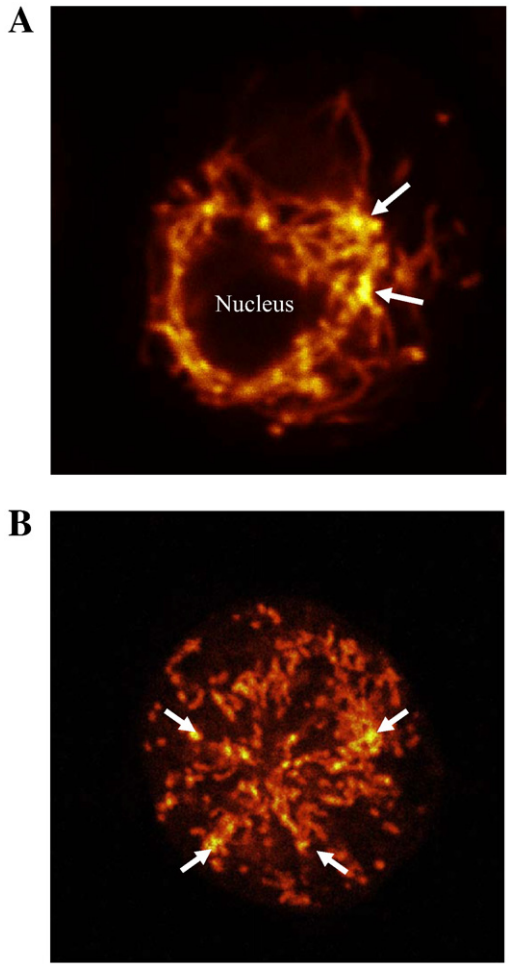

Fig. 5. Two human cultured LAD2 mast cells, showing distribution of mitochondria stained with MitoTracker and photographed using confocal microscopy; (A) control in which mitochondria form a "net" around the nucleus and (B) after stimulation with SP (2 μM for 30 min at 37 °C) in which mitochondria are distributed throughout the cell. (Magnification: ×1000). Arrows point to the areas with the highest concentration of MitoTracker (yellow color), thus the highest aggregation of mitochondria.

mast cell granules, inhibit human mast cell secretion [167]. Nitric oxide (NO) blocks FcεRI-induced cytokine secretion through inhibition of Jun [168]. In contrast IL-10 appears to have divergent effects depending on the mast cell type and stimulus [169]. The natural chymase inhibitors alpha 1-antitrypsin and secretory leukocyte protease inhibitor (SLPI) inhibit histamine release from human cells [170].

Recent evidence indicates that mitochondria are involved in the regulation of mast cell degranulation (Fig. 4). Mitochondrial uncoupling protein 2 (UCP2) inhibits mast cell activation [171]. Moreover, our recent results indicate that mast cell degranulation requires mitochondrial translocation to the cell surface [172] (Fig. 5). Inhibition or downregulation of Dynamin Related Protein 1 (Drp1), a cytoplasmic protein responsible for mitochondrial fission and translocation, blocks mast cell degranulation [173]. The involvement of mitochondria in mast cell regulation may also explain the ability of certain flavonoids [174] to inhibit mast cell degranulation [175], since quercetin was shown to accumulate in mitochondria [176].

4. Atopic dermatitis and psoriasis

Skin mast cells may have important functions as "sensors" of environmental and emotional stress [56], possibly due to direct activation by CRH secreted under stress, and related peptides [55]. Mast cell-related atopic dermatitis (AD) and psoriasis, are triggered or exacerbated by stress through mast cell activation [177,178]. Mast cell activation in AD may also be induced by cytokines, such as TSLP. We recently reported increased serum levels and skin gene expression of TSLP in AD patients as compared to controls [179], in agreement with previous studies [180,181].

Computer-induced stress enhanced allergen specific responses with concomitant increase in plasma SP levels in patients with AD [182]. Similar findings with increased plasma levels of SP, VIP and NGF, along with a switch to a Th2 cytokine pattern, were reported in patients with AD playing video games [183]. Skin has its own equivalent of the HPA axis [184,185]. CRH and CRHR mRNA is expressed in human and rodent skin [186,187] and CRH can be secreted from dorsal root ganglia and from sympathetic ganglia [188,189]. CRH administration in humans causes peripheral vasodilation and flushing reminiscent of mast cell activation [190]. Moreover, intradermal administration of CRH and Ucn activates skin mast cells and increases vascular permeability in rodents [191] and humans [192,193], through activation of CRHR-1 [56]. CRHR-1 expression was increased in chronic urticaria [194]. Acute stress released CRH in the skin and increased local vascular permeability [195]. Acute stress also exacerbated skin delayed hypersensitivity reactions [196], and chronic contact dermatitis in rats, an effect that involved significantly increased mast cells in the dermis, and was dependent on CRHR-1 [197]. Acute restraint stress induced rat skin vascular permeability [198], which was inhibited by a CRH receptor antagonist, and was absent in mast cell deficient mice [191,199].

Psoriasis is also triggered or exacerbated by acute stress [105,200–202]. We showed that psoriasis is associated with increased serum CRH and decreased lesional skin CRHR-1 gene expression possibly due to downregulation [203]. Psoriasis is characterized by keratinocyte proliferation and inflammation, as well as mast cell accumulation and activation [106,204]. Mast cells are increased in lesional psoriatic skin [105,106]. Neuropeptides [205], especially SP [206], are involved in the pathogenesis of psoriasis. In particular, SP reactive fibers are localized close to mast cells [105,207]. SP can stimulate mast cells [208,209] and contributes to inflammation [210,211]. SP-positive nerve fibers are denser in psoriatic lesions and have an increased number of mast cell contacts compared to normal skin [207,212,213]. SP-positive nerve fibers and mast cell contacts are also increased by acute stress in mice [214], leading to dermal mast cell degranulation [201,208,215]. Keratinocytes also express neurokinin (NK) 2 receptors and can be stimulated by SP [216], to release IL-1 [217]. Keratinocyte proliferation is accelerated by PAF, which can be secreted from mast cells [218], and stimulates human mast cells [219].

Psoriasis is associated with chronic inflammation and it often coexists with inflammatory arthritis [220], in which IL-33 was recently implicated [221]. IL-33 is one of the newest members of the IL-1 family of inflammatory cytokines [222], and can mediate IgE-induced anaphylaxis in mice [223]. IL-33 also induces release of IL-6 from mouse bone marrow-derived cultured mast cells [224], and IL-8 from hCBMCs [225]. We showed that IL-33 augments SP-stimulated VEGF release from human mast cells and IL-33 gene expression is increased in lesional skin from patients with psoriasis [226]. Mast cells may, therefore, be involved in the pathogenesis of psoriasis and other inflammatory skin diseases.

5. Multiple sclerosis

Functional mast cell–neuron interactions occur in the brain [227,228] and could mediate neuroinflammation [20]. In the brain, mast cells are found in the leptomeninges [228,229], the choroid plexus, thalamus and hypothalamus, especially the median eminence [230,231], where most of histamine derives from mast cells [232–235]. We had proposed that mast cells can act as "*the immune gate to the brain*" [107], and we later showed that mast cells regulate BBB permeability [236,237]. BBB breakdown [238] precedes any

pathological or clinical signs of MS [239–241], as shown by MRI-gadolinium studies and trans-BBB leakage of albumin [242]. Mast cells have been implicated in multiple sclerosis (MS), a demyelinating condition involving brain and MS plaque infiltration [243] by lymphocytes and activated mast cells [244,245]. Gene array analysis of MS plaques showed overexpression of genes for FcεRI, the histamine-1 (H_1) receptor and tryptase, all of which are associated with mast cells [246,247]. A recent paper reported that experimental autoimmune encephalomyelitis (EAE) development depends on H_1 receptor activation [248]. Mast cells are located close to the cerebral microvasculature and do not express FcεRI protein under normal conditions [249]. This is not surprising as the brain is not known to develop allergic reactions since IgE does not cross the blood–brain-barrier (BBB). Brain mast cells also do not normally express their surface growth factor (c-kit) receptor [250], but do so during EAE [251]. We first showed that mast cells migrate into the brain from the meninges, and it was later shown that they can also enter the CNS from blood [252]. Mast cell-derived products can enter neurons, a process termed "transgranulation", indicating a novel form of brain–immune system communication [253]. We further hypothesized that perivascular brain mast cells could come in contact with circulating T cells and not only allow them to enter the BBB, but also activate them [80]. TNF can be released from rat brain mast cells [254], and is involved in both brain inflammation [255,256] and increased vascular permeability [257]. Mast cell tryptase is elevated in the CSF of MS patients [258] and can activate peripheral mononuclear cells to secrete TNF and IL-6 [259], as well as stimulate PAR that can lead to microvascular leakage and widespread inflammation [260]. It was recently reported that meningeal mast cells promote T cell infiltration in the CNS by disrupting BBB integrity through TNF [261]. However, this paper did not include any of earlier publications discussed above and did not consider the possibility that lack of TNF may eventually worsen EAE [262]. The above findings imply that mast cells may be able to secrete both prestored and *de novo* synthesized TNF [263,264] with different biological actions.

The role of $CD4^+$ T cells is well-documented in MS, but this CD4-Th1 model has recently been questioned [265], because increasing evidence also implicates Th2 processes typically associated with allergic reactions [266,267]. Some studies reported the inability of mast cell deficient mice to fully develop EAE, but suggested that reduced T cell activation may also be involved [268,269]. Mast cell contact with activated T cells leads to secretion of matrix metalloproteinase (MMP)-9 and IL-6 from human mast cells [270]. Moreover, mast cells can promote IgE-dependent and T cell-independent proliferation and activation through TNF release [77,78]. We showed that mast cells superstimulate activated T cells, an action which is further increased when mast cells are activated by myelin basic protein (MBP) and is partially dependent on TNF [79,80]. MBP could induce homogeneic mast cell activation and brain demyelination [271]. Moreover, virally-induced encephalomyelitis could not develop in W/W^v mast cell deficient mice, and EAE was attenuated and delayed in these mice [272].

Mast cell-derived mediators can increase BBB permeability [273]. Selective release of IL-6 could have profound effects on brain function [274] and could activate the HPA axis [275]. Selective release of VEGF, an isoform of which is particularly vasodilatory [43,276], could lead to BBB disruption [277]. Mast cells are localized close to CRH-positive neurons in the median eminence [278] and express functional CRH receptors [44]. Activation of hypothalamic mast cells can stimulate the HPA axis [279–281], through histamine, which regulates the hypothalamus, and can also increase hypothalamic CRH mRNA expression [282]. Moreover, human mast cells can synthesize and secrete large amounts of CRH [283], as well as IL-1 and IL-6 which are independent activators of the HPA axis [284].

The effect of stress and CRH on mast cell activation and BBB permeability may help explain some of the clinical findings in MS patients. Acute stress worsens the symptoms of MS, and the appearance of new MRI lesions has been repeatedly shown to be precipitated by psychological stress [285–288]. In one study in Denmark, parents who had unexpectedly lost a young child had a significantly increased risk of MS, compared to other bereaved parents [289]. Meta-analysis of 14 prospective studies showed a significantly increased risk of MS exacerbations after stressful events [290]. A review of the effect of stress on MS proposed that it may be due to glucocorticoid-insensitive immune cells [291]. Another study argued that stress could not affect MS because the function of peripheral blood leukocytes in MS patients was apparently unaffected by stress [292]. However, such findings may not be relevant as stress may predominantly affect mast cells and T cells, but not peripheral leukocytes. Release of CRH and cytokines outside the brain may be more relevant instead. For instance, examination-stress dramatically increased serum TNF levels in medical student volunteers [293], and restraint stress induced mast cell-dependent increase in mouse serum IL-6 [294]. Rat brain mast cells were activated by acute stress, and led to CSF elevation of rat mast cell protease I [278], the equivalent of tryptase in humans. These effects were abolished by polyclonal antiserum to CRH and by the CRHR-1 antagonist Antalarmin [228,278]. A short period of restraint [295] or maternal deprivation stress [296] increased the severity of EAE. Acute restraint stress also shortened the time required for the development of EAE in mice [295]. Moreover, EAE was characterized by decreased clinical disability and brain infiltration by immune cells in CRH−/− mice as compared to normal controls [297]. Restraint stress was also reported to increase mortality rates and lead to higher CNS viral load during Theiler's virus infection [298]. Stressed mice had increased inflammatory spinal cord lesions and developed autoimmune antibodies to MBP [299]. Mast cell activation was shown to occur in response to isolation stress [300], restraint stress [278], subordination stress [301], and during courtship following isolation of male doves [302].

Mast cells could, therefore, participate in the pathogenesis of MS in many different ways: they could (A) be stimulated to release cytokines/chemokines selectively inducing T cell/macrophage recruitment and activation; (B) present myelin antigens to T cells; (C) disrupt the BBB and permit entry of active T cells that are sensitized to MBP; (D) damage myelin and release fragments that could stimulate secretion of tryptase, which may in turn enhance demyelination and induce further inflammation through stimulation of PAR. As a result, mast cells were considered as a possible therapeutic target for MS [303]. It is of interest that flavonoids [174] known to inhibit mast cell secretion [175] have also been shown to inhibit macrophage myelin phagocytosis [304], and EAE [305,306]. The flavone luteolin, which is structurally related to quercetin, was also a strong inhibitor of human autoimmune T cells [307]. Quercetin and luteolin also inhibit IL-6 release from microglia [308] and induce an anti-inflammatory phenotype [309]. Luteolin is neuroprotective [309] and is closely related to 7,8-dihydroxyflavone recently shown to mimic the action of BDNF [310]. We showed that luteolin can inhibit mast cell activation and mast cell-dependent superstimulation of activated T cells with or without stimulation by MBP [80]. Luteolin can also inhibit activation of peripheral lymphocytes from MS patients [311], and it was, therefore, proposed as adjuvant therapy for MS [312].

6. Conclusion

Mast cells clearly participate in the induction and/or propagation of certain inflammatory diseases, through selective release of mediators. The pharmacologic inhibition of this process would, therefore, have clear therapeutic potential. Luteolin formulations, alone or together with drugs that can selectively inhibit the release of pro-inflammatory mediators hold promise for the treatment of skin and brain inflammatory diseases.

Disclosures

TCT is the inventor of US patents 6,635,625; 6,641,806; 6,645,482; 6,689,748; 6,984,667 and EPO 1365777 covering the role of mast cells in inflammatory diseases, US 6,020,305 covering stress-induced skin diseases, as well as US patent application 11/214,831 and 12/861,152 covering the treatment of multiple sclerosis and brain inflammation.

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References

[1] H.R. Rodewald, M. Dessing, A.M. Dvorak, S.J. Galli, Identification of a committed precursor for the mast cell lineage, Science 271 (1996) 818–822.
[2] C.C. Chen, M.A. Grimbaldeston, M. Tsai, I.L. Weissman, S.J. Galli, Identification of mast cell progenitors in adult mice, Proc. Natl Acad. Sci. USA 102 (2005) 11408–11413.
[3] Y. Kitamura, A. Ito, Mast cell-committed progenitors, Proc. Natl Acad. Sci. USA 102 (2005) 11129–11130.
[4] T.R. Hundley, A.M. Gilfillan, C. Tkaczyk, M.V. Andrade, D.D. Metcalfe, M.A. Beaven, Kit and FcepsilonRI mediate unique and convergent signals for release of inflammatory mediators from human mast cells, Blood 104 (2004) 2410–2417.
[5] U. Blank, J. Rivera, The ins and outs of IgE-dependent mast-cell exocytosis, Trends Immunol. 25 (2004) 266–273.
[6] R.P. Siraganian, Mast cell signal transduction from the high-affinity IgE receptor, Curr. Opin. Immunol. 15 (2003) 639–646.
[7] S. Kraft, J.P. Kinet, New developments in FcepsilonRI regulation, function and inhibition, Nat. Rev. Immunol. 7 (2007) 365–378.
[8] L. Aloe, R. Levi-Montalcini, Mast cells increase in tissues of neonatal rats injected with the nerve growth factor, Brain Res. 133 (1977) 358–366.
[9] S.Y. Tam, M. Tsai, M. Yamaguchi, K. Yano, J.H. Butterfield, S.J. Galli, Expression of functional TrkA receptor tyrosine kinase in the HMC-1 human mast cell line and in human mast cells, Blood 90 (1997) 1807–1820.
[10] M. Metz, V.A. Botchkarev, N.V. Botchkareva, P. Welker, D.J. Tobin, J. Knop, M. Maurer, R. Paus, Neurotrophin-3 regulates mast cell functions in neonatal mouse skin, Exp. Dermatol. 13 (2004) 273–281.
[11] A. Lorentz, J. Hoppe, H. Worthmann, T. Gebhardt, U. Hesse, J. Bienenstock, S.C. Bischoff, Neurotrophin-3, but not nerve growth factor, promotes survival of human intestinal mast cells, Neurogastroenterol. Motil. 19 (2007) 301–308.
[12] M. Tal, R. Liberman, Local injection of nerve growth factor (NGF) triggers degranulation of mast cells in rat paw, Neurosci. Lett. 221 (1997) 129–132.
[13] P. Conti, X. Pang, W. Boucher, R. Letourneau, M. Reale, R.C. Barbacane, J. Thibault, T.C. Theoharides, Impact of Rantes and MCP-1 chemokines on *in vivo* basophilic mast cell recruitment in rat skin injection model and their role in modifying the protein and mRNA levels for histidine decarboxylase, Blood 89 (1997) 4120–4127.
[14] K. Cima, H. Vogelsinger, C.M. Kahler, Sensory neuropeptides are potent chemoattractants for human basophils in vitro, Regul. Pept. 160 (2010) 42–48.
[15] S.C. Bischoff, Role of mast cells in allergic and non-allergic immune responses: comparison of human and murine data, Nat. Rev. Immunol. 7 (2007) 93–104.
[16] G.J. Molderings, Mast cell function in physiology and pathophysiology, BIOTREND Reviews No.5, 2010.
[17] F.A. Redegeld, F.P. Nijkamp, Immunoglobulin free light chains and mast cells: pivotal role in T-cell-mediated immune reactions? Trends Immunol. 24 (2005) 181–185.
[18] F.A. Redegeld, M.W. van der Heijden, M. Kool, B.M. Heijdra, J. Garssen, A.D. Kraneveld, H. Van Loveren, P. Roholl, T. Saito, J.S. Verbeek, J. Claassens, A.S. Koster, F.P. Nijkamp, Immunoglobulin-free light chains elicit immediate hypersensitivity-like responses, Nat. Med. 8 (2002) 694–701.
[19] T.C. Theoharides, Mast cell: a neuroimmunoendocrine master player, Int. J. Tissue React. 18 (1996) 1–21.
[20] T.C. Theoharides, D.E. Cochrane, Critical role of mast cells in inflammatory diseases and the effect of acute stress, J. Neuroimmunol. 146 (2004) 1–12.
[21] E.J. Goetzl, P.P.J. Cheng, A. Hassner, D.C. Adelman, O.L. Frick, S.P. Speedharan, Neuropeptides, mast cells and allergy: novel mechanisms and therapeutic possibilities, Clin. Exp. Allergy 20 (1990) 3–7.
[22] J.C. Foreman, Peptides and neurogenic inflammation, Brain Res. Bull. 43 (1987) 386–398.
[23] J. Janiszewski, J. Bienenstock, M.G. Blennerhassett, Picomolar doses of substance P trigger electrical responses in mast cells without degranulation, Am. J. Physiol. 267 (1994) C138–C145.
[24] H. Matsuda, K. Kawakita, Y. Kiso, T. Nakano, Y. Kitamura, Substance P induces granulocyte infiltration through degranulation of mast cells, J. Immunol. 142 (1989) 927–931.
[25] Y. Zhang, L. Lu, C. Furlonger, G.E. Wu, C.J. Paige, Hemokinin is a hematopoietic-specific tachykinin that regulates B lymphopoiesis, Nat. Immunol. 1 (2000) 392–397.
[26] R. Carraway, D.E. Cochrane, J.B. Lansman, S.E. Leeman, B.M. Paterson, H.J. Welch, Neurotensin stimulates exocytotic histamine secretion from rat mast cells and elevates plasma histamine levels, J. Physiol. 323 (1982) 403–414.
[27] J. Bienenstock, M. Tomioka, H. Matsuda, R.H. Stead, G. Quinonez, G.T. Simon, M.D. Coughlin, J.A. Denburg, The role of mast cells in inflammatory processes: evidence for nerve mast cell interactions, Int. Arch. Allergy Appl. Immunol. 82 (1987) 238–243.
[28] R. De Simone, E. Alleva, P. Tirassa, L. Aloe, Nerve growth factor released into the bloodstream following intraspecific fighting induces mast cell degranulation in adult male mice, Brain Behav. Immun. 4 (1990) 74–81.
[29] J. Seebeck, M.L. Kruse, A. Schmidt-Choudhury, W.E. Schmidt, Pituitary adenylate cyclase activating polypeptide induces degranulation of rat peritoneal mast cells via high-affinity PACAP receptor-independent activation of G proteins, Ann. NY Acad. Sci. 865 (1998) 141–146.
[30] L. Odum, L.J. Petersen, P.S. Skov, L.B. Ebskov, Pituitary adenylate cyclase activating polypeptide (PACAP) is localized in human dermal neurons and causes histamine release from skin mast cells, Inflamm. Res. 47 (1998) 488–492.
[31] E.J. Goetzl, T. Chernov, F. Renold, D.G. Payan, Neuropeptide regulation of the expression of immediate hypersensitivity, J. Immunol. 135 (1985) 802s–805s.
[32] C.M.S. Fewtrell, J.C. Foreman, C.C. Jordan, P. Oehme, H. Renner, J.M. Stewart, The effects of substance P on histamine and 5-hydroxytryptamine release in the rat, J. Physiol. 330 (1982) 393–411.
[33] M. Toyoda, T. Makino, M. Kagoura, M. Morohashi, Immunolocalization of substance P in human skin mast cells, Arch. Dermatol. Res. 292 (2000) 418–421.
[34] Z. Xiang, G. Nilsson, IgE receptor-mediated release of nerve growth factor by mast cells, Clin. Exp. Allergy 30 (2000) 1379–1386.
[35] Z. Allakhverdi, M.R. Comeau, H.K. Jessup, B.P. yoon, A. Breuer, S. Chartier, N. Paquette, S.F. Ziegler, M. Sarfati, G. Delespesse, Thymic stromal lymphopoietin is released by human epithelial cell in response to microbes, trauma, or inflammation and potently activates mast cells, J. Exp. Med. 19 (2007) 253–258.
[36] B. Bashyam, TSLP-tickled mast cells, J. Exp. Med. 204 (2007) 209.
[37] A.M. Dvorak, New aspects of mast cell biology, Int. Arch. Allergy Immunol. 114 (1997) 1–9.
[38] W.E. Serafin, K.F. Austen, Mediators of immediate hypersensitivity reactions, N. Engl. J. Med. 317 (1987) 30–34.
[39] L.B. Schwartz, Mediators of human mast cells and human mast cell subsets, Ann. Allergy 58 (1987) 226–235.
[40] S.J. Galli, New concepts about the mast cell, N. Engl. J. Med. 328 (1993) 257–265.
[41] S.T. Holgate, The role of mast cells and basophils in inflammation, Clin. Exp. Allergy 30 (2000) 28–32.
[42] S.J. Galli, J. Kalesnikoff, M.A. Grimbaldeston, A.M. Piliponsky, C.M. Williams, M. Tsai, Mast cells as "tunable" effector and immunoregulatory cells: recent advances, Annu. Rev. Immunol. 23 (2005) 749–786.
[43] A. Grutzkau, S. Kruger-Krasagakes, H. Baumeister, C. Schwarz, H. Kogel, P. Welker, U. Lippert, B.M. Henz, A. Moller, Synthesis, storage and release of vascular endothelial growth factor/vascular permeability factor (VEGF/VPF) by human mast cells: implications for the biological significance of $VEGF_{206}$, Mol. Biol. Cell 9 (1998) 875–884.
[44] J. Cao, N. Papadopoulou, D. Kempuraj, W.S. Boucher, K. Sugimoto, C.L. Cetrulo, T.C. Theoharides, Human mast cells express corticotropin-releasing hormone (CRH) receptors and CRH leads to selective secretion of vascular endothelial growth factor, J. Immunol. 174 (2005) 7665–7675.
[45] G.P. Chrousos, The hypothalamic–pituitary–adrenal axis and immune-mediated inflammation, N. Engl. J. Med. 332 (1995) 1351–1362.
[46] D.T. Chalmers, T.W. Lovenberg, D.E. Grigoriadis, D.P. Behan, E.B. DeSouza, Corticotropin-releasing factor receptors: from molecular biology to drug design, Trends Pharmacol. Sci. 17 (1996) 166–172.
[47] R. Chen, K.A. Lewis, M.H. Perrin, W.W. Vale, Expression cloning of a human corticotropin-releasing factor receptor, Proc. Natl Acad. Sci. USA 90 (1993) 8967–8971.
[48] T.W. Lovenberg, C.W. Liaw, D.E. Grigoriadis, W. Clevenger, D.T. Charmers, E.B. DeSouza, T. Oltersdorf, Cloning and characterization of a functionally distinct corticotropin-releasing factor receptor subtype from rat brain, Proc. Natl Acad. Sci. USA 92 (1995) 836–840.
[49] T.W. Lovenberg, D.T. Chalmers, C. Liu, E.B. DeSouza, $CRF_{2\alpha}$ and $CRF_{2\beta}$ receptor mRNAs are differentially distributed between the rat central nervous system and peripheral tissues, Endocrinology 136 (1995) 4139–4142.
[50] J. Vaughan, C. Donaldson, J. Bittencourt, M.H. Perrin, K. Lewis, S. Sutton, R. Chan, A.V. Turnbull, D. Lovejoy, C. Rivier, J. Rivier, P.E. Sawchenko, W. Vale, Urocortin, a mammalian neuropeptide related to fish urotensin I and to corticotropin-releasing factor, Nature 378 (1995) 287–292.
[51] M. Million, C. Maillot, P. Saunders, J. Rivier, W. Vale, Y. Taché, Human urocortin II, a new CRF related peptide, displays selective CRF2-mediated action on gastric transit in rats, Am. J. Physiol. Gastrointest. Liver Physiol. 282 (2002) G34–G40.
[52] K. Lewis, C. Li, M.H. Perrin, A. Blount, K. Kunitake, C. Donaldson, J. Vaughan, T.M. Reyes, J. Gulyas, W. Fischer, L. Bilezikjian, J. Rivier, P.E. Sawchenko, W.W. Vale, Identification of urocortin III, an additional member of the corticotropin-releasing factor (CRF) family with high affinity for the CRF 2 receptor, Proc. Natl Acad. Sci. USA 98 (2001) 7570–7575.

[53] K. Karalis, J.M. Louis, D. Bae, H. Hilderbrand, J.A. Majzoub, CRH and the immune system, J. Neuroimmunol. 72 (1997) 131–136.
[54] D. Kempuraj, N.G. Papadopoulou, M. Lytinas, M. Huang, K. Kandere-Grzybowska, B. Madhappan, W. Boucher, S. Christodoulou, A. Athanassiou, T.C. Theoharides, Corticotropin-releasing hormone and its structurally related urocortin are synthesized and secreted by human mast cells, Endocrinology 145 (2004) 43–48.
[55] T.C. Theoharides, J.M. Donelan, N. Papadopoulou, J. Cao, D. Kempuraj, P. Conti, Mast cells as targets of corticotropin-releasing factor and related peptides, Trends Pharmacol. Sci. 25 (2004) 563–568.
[56] R. Paus, T.C. Theoharides, P.C. Arck, Neuroimmunoendocrine circuitry of the 'brain–skin connection', Trends Immunol. 27 (2006) 32–39.
[57] N. Ito, K. Sugawara, E. Bodo, M. Takigawa, N. van Beek, T. Ito, R. Paus, Corticotropin-releasing hormone stimulates the in situ generation of mast cells from precursors in the human hair follicle mesenchyme, J. Invest. Dermatol. 130 (2010) 995–1004.
[58] P. Bradding, Y. Okayama, P.H. Howarth, M.K. Church, S.T. Holgate, Heterogeneity of human mast cells based on cytokine content, J. Immunol. 155 (1995) 297–307.
[59] F. Levi-Schaffer, K.F. Austen, P.M. Gravallese, R.L. Stevens, Co-culture of interleukin 3-dependent mouse mast cells with fibroblasts results in a phenotypic change of the mast cells, Proc. Natl Acad. Sci. USA 83 (1986) 6485–6488.
[60] S.C. Bischoff, G. Sellge, A. Lorentz, W. Sebald, R. Raab, M.P. Manns, IL-4 enhances proliferation and mediator release in mature human mast cells, Proc. Natl Acad. Sci. USA 96 (1999) 8080–8085.
[61] S.C. Bischoff, G. Sellge, M.P. Manns, A. Lorentz, Interleukin-4 induces a switch of human intestinal mast cells from proinflammatory cells to Th2-type cells, Int. Arch. Allergy Immunol. 124 (2001) 151–154.
[62] H. Ochi, N.H. DeJesus, F.H. Hsieh, K.F. Austen, J.A. Boyce, IL-4 and -5 prime human mast cells for different profiles of IgE-dependent cytokine production, Proc. Natl Acad. Sci. USA 97 (2000) 10509–10513.
[63] S.J. Galli, S. Nakae, M. Tsai, Mast cells in the development of adaptive immune responses, Nat. Immunol. 6 (2005) 135–142.
[64] M. Maurer, J. Wedemeyer, M. Metz, A.M. Piliponsky, K. Weller, D. Chatterjea, D.E. Clouthier, M.M. Yanagisawa, M. Tsai, S.J. Galli, Mast cells promote homeostasis by limiting endothelin-1-induced toxicity, Nature 432 (2004) 512–516.
[65] S.J. Galli, M. Tsai, Mast cells in allergy and infection: versatile effector and regulatory cells in innate and adaptive immunity, Eur. J. Immunol. 40 (2010) 1843–1851.
[66] S.N. Abraham, A.L. St John, Mast cell-orchestrated immunity to pathogens, Nat. Rev. Immunol. 10 (2010) 440–452.
[67] M. Rottem, Y.A. Mekori, Mast cells and autoimmunity, Autoimmun. Rev. 4 (2005) 21–27.
[68] W. O'Connor Jr., L.A. Zenewicz, R.A. Flavell, The dual nature of T(H)17 cells: shifting the focus to function, Nat. Immunol. 11 (2010) 471–476.
[69] S. Piconese, G. Gri, C. Tripodo, S. Musio, A. Gorzanelli, B. Frossi, R. Pedotti, C.E. Pucillo, M.P. Colombo, Mast cells counteract regulatory T-cell suppression through interleukin-6 and OX40/OX40L axis toward Th17-cell differentiation, Blood 114 (2009) 2639–2648.
[70] S. Nakae, H. Suto, G.J. Berry, S.J. Galli, Mast cell-derived TNF can promote Th17 cell-dependent neutrophil recruitment in ovalbumin-challenged OTII mice, Blood 109 (2007) 3640–3648.
[71] M. Yadav, E.J. Goetzl, Vasoactive intestinal peptide-mediated Th17 differentiation: an expanding spectrum of vasoactive intestinal peptide effects in immunity and autoimmunity, Ann. N.Y. Acad. Sci. 1144 (2008) 83–89.
[72] M.R. Woolhiser, K. Brockow, D.D. Metcalfe, Activation of human mast cells by aggregated IgG through FcγRI: additive effects of C3a, Clin. Immunol. 110 (2004) 172–180.
[73] A.D. Kraneveld, M. Kool, A.H. van Houwelingen, P. Roholl, A. Solomon, D.S. Postma, F.P. Nijkamp, F.A. Redegeld, Elicitation of allergic asthma by immunoglobulin free light chains, Proc. Natl Acad. Sci. USA 102 (2005) 1578–1583.
[74] X. Chen, F. Niyonsaba, H. Ushio, M. Hara, H. Yokoi, K. Matsumoto, H. Saito, I. Nagaoka, S. Ikeda, K. Okumura, H. Ogawa, Antimicrobial peptides human beta-defensin (hBD)-3 and hBD-4 activate mast cells and increase skin vascular permeability, Eur. J. Immunol. 37 (2007) 434–444.
[75] I. Bachelet, F. Levi-Schaffer, Mast cells as effector cells: a co-stimulating question, Trends Immunol. 28 (2007) 360–365.
[76] Y.A. Mekori, D.D. Metcalfe, Mast cell–T cell interactions, J. Allergy Clin. Immunol. 104 (1999) 517–523.
[77] S. Nakae, H. Suto, M. Iikura, M. Kakurai, J.D. Sedgwick, M. Tsai, S.J. Galli, Mast cells enhance T cell activation: importance of mast cell costimulatory molecules and secreted TNF, J. Immunol. 176 (2006) 2238–2248.
[78] S. Nakae, H. Suto, M. Kakurai, J.D. Sedgwick, M. Tsai, S.J. Galli, Mast cells enhance T cell activation: importance of mast cell-derived TNF, Proc. Natl Acad. Sci. USA 102 (2005) 6467–6472.
[79] T.C. Theoharides, D. Kempuraj, B.P. Iliopoulou, Mast cells, T cells, and inhibition by luteolin: implications for the pathogenesis and treatment of multiple sclerosis, Adv. Exp. Med. Biol. 601 (2007) 423–430.
[80] D. Kempuraj, M. Tagen, B.P. Iliopoulou, A. Clemons, M. Vasiadi, W. Boucher, M. House, A. Wolferg, T.C. Theoharides, Luteolin inhibits myelin basic protein-induced human mast cell activation and mast cell dependent stimulation of Jurkat T cells, Br. J. Pharmacol. 155 (2008) 1076–1084.
[81] I. Shefler, P. Salamon, T. Reshef, A. Mor, Y.A. Mekori, T cell-induced mast cell activation: a role for microparticles released from activated T cells, J. Immunol. 185 (2010) 4206–4212.
[82] C.A. Kunder, A.L. St John, G. Li, K.W. Leong, B. Berwin, H.F. Staats, S.N. Abraham, Mast cell-derived particles deliver peripheral signals to remote lymph nodes, J. Exp. Med. 206 (2009) 2455–2467.
[83] J. Gong, N.S. Yang, M. Croft, I.C. Weng, L. Sun, F.T. Liu, S.S. Chen, The antigen presentation function of bone marrow-derived mast cells is spatiotemporally restricted to a subset expressing high levels of cell surface FcepsilonRI and MHC II, BMC Immunol. 11 (2010) 34.
[84] N. Novak, T. Bieber, S. Kraft, Immunoglobulin E-bearing antigen-presenting cells in atopic dermatitis, Curr. Allergy Asthma Rep. 4 (2004) 263–269.
[85] P. Poncet, M. Arock, B. David, MHC class II-dependent activation of CD4+ T cell hybridomas by human mast cells through superantigen presentation, J. Leukoc. Biol. 66 (1999) 105–112.
[86] E. Stelekati, R. Bahri, O. D'Orlando, Z. Orinska, H.W. Mittrucker, R. Langenhaun, M. Glatzel, A. Bollinger, R. Paus, S. Bulfone-Paus, Mast cell-mediated antigen presentation regulates CD8+ T cell effector functions, Immunity 31 (2009) 665–676.
[87] T. Yoshimoto, K. Yasuda, H. Tanaka, M. Nakahira, Y. Imai, Y. Fujimori, K. Nakanishi, Basophils contribute to T(H)2-IgE responses in vivo via IL-4 production and presentation of peptide–MHC class II complexes to CD4+ T cells, Nat. Immunol. 10 (2009) 706–712.
[88] C.L. Sokol, N.Q. Chu, S. Yu, S.A. Nish, T.M. Laufer, R. Medzhitov, Basophils function as antigen-presenting cells for an allergen-induced T helper type 2 response, Nat. Immunol. 10 (2009) 713–720.
[89] C.L. Sokol, R. Medzhitov, Role of basophils in the initiation of Th2 responses, Curr. Opin. Immunol. 22 (2010) 73–77.
[90] T. Yoshimoto, Basophils as T(h)2-inducing antigen-presenting cells, Int. Immunol. 22 (2010) 543–550.
[91] H. Tang, W. Cao, S.P. Kasturi, R. Ravindran, H.I. Nakaya, K. Kundu, N. Murthy, T.B. Kepler, B. Malissen, B. Pulendran, The T helper type 2 response to cysteine proteases requires dendritic cell–basophil cooperation via ROS-mediated signaling, Nat. Immunol. 11 (2010) 608–617.
[92] N. Charles, D. Hardwick, E. Daugas, G.G. Illei, J. Rivera, Basophils and the T helper 2 environment can promote the development of lupus nephritis, Nat. Med. 16 (2010) 701–707.
[93] S.J. Galli, M. Grimbaldeston, M. Tsai, Immunomodulatory mast cells: negative, as well as positive, regulators of immunity, Nat. Rev. Immunol. 8 (2008) 478–486.
[94] B. Frossi, G. Gri, C. Tripodo, C. Pucillo, Exploring a regulatory role for mast cells: 'MCregs'? Trends Immunol. 31 (2010) 97–102.
[95] T.C. Theoharides, Mast cells and precursor protein molecules, Perspect. Biol. Med. 24 (1981) 499–502.
[96] D.E. Cochrane, R.E. Carraway, R.S. Feldberg, W. Boucher, J.M. Gelfand, Stimulated rat mast cells generate histamine-releasing peptide from albumin, Peptides 14 (1993) 117–123.
[97] R.E. Carraway, S.P. Mitra, C.F. Ferris, Pepsin treatment of mammalian plasma generates immunoreactive and biologically active neurotensin-related peptides in micromolar concentrations, Endocrinology 119 (1986) 1519–1526.
[98] D.E. Cochrane, R.E. Carraway, W. Boucher, R.S. Feldberg, Rapid degradation of neutotensin by stimulated rat mast cells, Peptides 12 (1991) 1187–1194.
[99] A.M. Piliponsky, C.C. Chen, T. Nishimura, M. Metz, E.J. Rios, P.R. Dobner, E. Wada, K. Wada, S. Zacharias, U.M. Mohanasundaram, J.D. Faix, M. Abrink, G. Pejler, R.G. Pearl, M. Tsai, S.J. Galli, Neurotensin increases mortality and mast cells reduce neurotensin levels in a mouse model of sepsis, Nat. Med. 14 (2008) 392–398.
[100] L. Hultner, H. Ehrenreich, Mast cells and endothelin-1: a life-saving biological liaison? Trends Immunol. 26 (2005) 235–238.
[101] B. Damerau, L. Lege, H.D. Oldigs, W. Vogt, Histamine release, formation of prostaglandin-like activity (SRS-C) and mast cell degranulation by the direct lytic factor (DLF) and phospholipase A of cobra venom, Naunyn-Schmiedeberg's Arch. Pharmacol. 287 (1975) 141–156.
[102] C.S. Liu, J.M. Chen, C.H. Chang, S.W. Chen, C.M. Teng, I.H. Tsai, The amino acid sequence and properties of an edema-inducing Lys-49 phospholipase A2 homolog from the venom of *Trimeresurus mucrosquamatus*, Biochim. Biophys. Acta 1077 (1991) 362–370.
[103] M. Metz, A.M. Piliponsky, C.C. Chen, V. Lammel, M. Abrink, G. Pejler, M. Tsai, S.J. Galli, Mast cells can enhance resistance to snake and honeybee venoms, Science 313 (2006) 526–530.
[104] D.E. Woolley, The mast cell in inflammatory arthritis, N. Engl. J. Med. 348 (2003) 1709–1711.
[105] I.T. Harvima, H. Viinamäki, A. Naukkarinen, K. Paukkonen, H. Neittaanmäki, M. Horsmanheimo, Association of cutaneous mast cells and sensory nerves with psychic stress in psoriasis, Psychother. Psychosom. 60 (1993) 168–176.
[106] S.O. Özdamar, D. Seckin, B. Kandemir, A.Y. Turanlt, Mast cells in psoriasis, Dermatology 192 (1996) 190.
[107] T.C. Theoharides, Mast cells: the immune gate to the brain, Life Sci. 46 (1990) 607–617.
[108] M. Jayapal, H.K. Tay, R. Reghunathan, L. Zhi, K.K. Chow, M. Rauff, A.J. Melendez, Genome-wide gene expression profiling of human mast cells stimulated by IgE or FcepsilonRI-aggregation reveals a complex network of genes involved in inflammatory responses, BMC Genomics 7 (2006) 210.
[109] R.E. Carraway, D.E. Cochrane, W. Boucher, S.P. Mitra, Structures of histamine-releasing peptides formed by the action of acid proteases on mammalian albumin(s), J. Immunol. 143 (1989) 1680–1684.
[110] F. Schmidlin, N.W. Bunnett, Protease-activated receptors: how proteases signal to cells, Curr. Opin. Pharmacol. 1 (2001) 575–582.
[111] M. Molino, E.S. Barnathan, R. Numerof, J. Clark, M. Dreyer, A. Cumashi, J.A. Hoxie, N. Schechter, M. Woolkalis, L.F. Brass, Interactions of mast cell tryptase with thrombin receptors and PAR-2, J. Biol. Chem. 272 (1997) 4043–4049.
[112] T.C. Theoharides, D. Kempuraj, M. Tagen, P. Conti, D. Kalogeromitros, Differential release of mast cell mediators and the pathogenesis of inflammation, Immunol. Rev. 217 (2007) 65–78.

[113] T.C. Theoharides, W.W. Douglas, Secretion in mast cells induced by calcium entrapped within phospholipid vesicles, Science 201 (1978) 1143–1145.
[114] H. Van Loveren, S.K. Kops, P.W. Askenase, Different mechanisms of release of vasoactive amines by mast cells occur in T cell-dependent compared to IgE-dependent cutaneous hypersensitivity responses, Eur. J. Immunol. 14 (1984) 40–47.
[115] V. Dimitriadou, M.G. Buzzi, M.A. Moskowitz, T.C. Theoharides, Trigeminal sensory fiber stimulation induces morphologic changes reflecting secretion in rat dura mast cells, Neuroscience 44 (1991) 97–112.
[116] R. Letourneau, X. Pang, G.R. Sant, T.C. Theoharides, Intragranular activation of bladder mast cells and their association with nerve processes in interstitial cystitis, Br. J. Urol. 77 (1996) 41–54.
[117] A.M. Dvorak, R.S. McLeod, A. Onderdonk, R.A. Monahan-Earley, J.B. Cullen, D.A. Antonioli, E. Morgan, J.E. Blair, P. Estrella, R.L. Cisneros, W. Silen, Z. Cohen, Ultrastructural evidence for piecemeal and anaphylactic degranulation of human gut mucosal mast cells *in vivo*, Int. Arch. Allergy Immunol. 99 (1992) 74–83.
[118] T.C. Theoharides, P.K. Bondy, N.D. Tsakalos, P.W. Askenase, Differential release of serotonin and histamine from mast cells, Nature 297 (1982) 229–231.
[119] H. Tamir, T.C. Theoharides, M.D. Gershon, P.W. Askenase, Serotonin storage pools in basophil leukemia and mast cells: characterization of two types of serotonin binding protein and radioautographic analysis of the intracellular distribution of [^{3}H] serotonin, J. Cell Biol. 93 (1982) 638–647.
[120] L.A. Spencer, R.C. Melo, S.A. Perez, S.P. Bafford, A.M. Dvorak, P.F. Weller, Cytokine receptor-mediated trafficking of preformed IL-4 in eosinophils identifies an innate immune mechanism of cytokine secretion, Proc. Natl Acad. Sci. USA 103 (2006) 3333–3338.
[121] K. Kandere-Grzybowska, R. Letourneau, D. Kempuraj, J. Donelan, S. Poplawski, W. Boucher, A. Athanassiou, T.C. Theoharides, IL-1 induces vesicular secretion of IL-6 without degranulation from human mast cells, J. Immunol. 171 (2003) 4830–4836.
[122] R. Benyon, C. Robinson, M.K. Church, Differential release of histamine and eicosanoids from human skin mast cells activated by IgE-dependent and non-immunological stimuli, Br. J. Pharmacol. 97 (1989) 898–904.
[123] F. Levi-Schaffer, M. Shalit, Differential release of histamine and prostaglandin D_2 in rat peritoneal mast cells activated with peptides, Int. Arch. Allergy Appl. Immunol. 90 (1989) 352–357.
[124] C.M. van Haaster, W. Engels, P.J.M.R. Lemmens, G. Hornstra, G.J. van der Vusse, J.W.M. Heemskerk, Differential release of histamine and prostaglandin D_2 in rat peritoneal mast cells; roles of cytosolic calcium and protein tyrosine kinases, Biochim. Biophys. Acta 1265 (1995) 79–88.
[125] I. Leal-Berumen, P. Conlon, J.S. Marshall, IL-6 production by rat peritoneal mast cells is not necessarily preceded by histamine release and can be induced by bacterial lipopolysaccharide, J. Immunol. 152 (1994) 5468–5476.
[126] D.L. Marquardt, J.L. Alongi, L.L. Walker, The phosphatidylinositol 3-kinase inhibitor wortmannin blocks mast cell exocytosis but not IL-6 production, J. Immunol. 156 (1996) 1942–1945.
[127] E. Gagari, M. Tsai, C.S. Lantz, L.G. Fox, S.J. Galli, Differential release of mast cell interleukin-6 via c-kit, Blood 89 (1997) 2654–2663.
[128] J. Cao, C.L. Curtis, T.C. Theoharides, Corticotropin-releasing hormone induces vascular endothelial growth factor release from human mast cells via the cAMP/protein kinase A/p38 mitogen-activated protein kinase pathway, Mol. Pharmacol. 69 (2006) 998–1006.
[129] R.M. Abdel-Majid, J.S. Marshall, Prostaglandin E2 induces degranulation-independent production of vascular endothelial growth factor by human mast cells, J. Immunol. 172 (2004) 1227–1236.
[130] T. Nakayama, N. Mutsuga, L. Yao, G. Tosato, Prostaglandin E2 promotes degranulation-independent release of MCP-1 from mast cells, J. Leukoc. Biol. 79 (2006) 95–104.
[131] L.J. Kay, W.W. Yeo, P.T. Peachell, Prostaglandin E2 activates EP2 receptors to inhibit human lung mast cell degranulation, Br. J. Pharmacol. 147 (2006) 707–713.
[132] T.J. Lin, T.B. Issekutz, J.S. Marshall, Human mast cells transmigrate through human umbilical vein endothelial monolayers and selectively produce IL-8 in response to stromal cell-derived factor-1 alpha, J. Immunol. 165 (2000) 211–220.
[133] M. Fischer, I.T. Harvima, R.F. Carvalho, C. Moller, A. Naukkarinen, G. Enblad, G. Nilsson, Mast cell CD30 ligand is upregulated in cutaneous inflammation and mediates degranulation-independent chemokine secretion, J. Clin. Invest. 116 (2006) 2748–2756.
[134] L.H. Ho, T. Ohno, K. Oboki, N. Kajiwara, H. Suto, M. Iikura, Y. Okayama, S. Akira, H. Saito, S.J. Galli, S. Nakae, IL-33 induces IL-13 production by mouse mast cells independently of IgE-FcepsilonRI signals, J. Leukoc. Biol. 82 (2007) 1481–1490.
[135] S. Akira, K. Takeda, T. Kaisho, Toll-like receptors: critical proteins linking innate and acquired immunity, Nat. Immunol. 2 (2001) 675–680.
[136] A. Aderem, R.J. Ulevitch, Toll-like receptors in the induction of the innate immune response, Nature 406 (2000) 782–787.
[137] Y. Okayama, Mast cell-derived cytokine expression induced via Fc receptors and Toll-like receptors, Chem. Immunol. Allergy 87 (2005) 101–110.
[138] S.P. Gondokaryono, H. Ushio, F. Niyonsaba, M. Hara, H. Takenaka, S.T. Jayawardana, S. Ikeda, K. Okumura, H. Ogawa, The extra domain A of fibronectin stimulates murine mast cells via toll-like receptor 4, J. Leukoc. Biol. 82 (2007) 657–665.
[139] J.D. McCurdy, T.J. Olynych, L.H. Maher, J.S. Marshall, Cutting edge: distinct Toll-like receptor 2 activators selectively induce different classes of mediator production from human mast cells, J. Immunol. 170 (2003) 1625–1629.
[140] A. Masuda, Y. Yoshikai, K. Aiba, T. Matsuguchi, Th2 cytokine production from mast cells is directly induced by lipopolysaccharide and distinctly regulated by c-Jun N-terminal kinase and p38 pathways, J. Immunol. 169 (2002) 3801–3810.
[141] S. Varadaradjalou, F. Feger, N. Thieblemont, N.B. Hamouda, J.M. Pleau, M. Dy, M. Arock, Toll-like receptor 2 (TLR2) and TLR4 differentially activate human mast cells, Eur. J. Immunol. 33 (2003) 899–906.
[142] H. Qiao, M.V. Andrade, F.A. Lisboa, K. Morgan, M.A. Beaven, FcepsilonR1 and toll-like receptors mediate synergistic signals to markedly augment production of inflammatory cytokines in murine mast cells, Blood 107 (2006) 610–618.
[143] V. Supajatura, H. Ushio, A. Nakao, S. Akira, K. Okumura, C. Ra, H. Ogawa, Differential responses of mast cell Toll-like receptors 2 and 4 in allergy and innate immunity, J. Clin. Invest. 109 (2002) 1351–1359.
[144] H. Matsushima, N. Yamada, H. Matsue, S. Shimada, TLR3-, TLR7-, and TLR9-mediated production of proinflammatory cytokines and chemokines from murine connective tissue type skin-derived mast cells but not from bone marrow-derived mast cells, J. Immunol. 173 (2004) 531–541.
[145] R.K. Ikeda, M. Miller, J. Nayar, L. Walker, J.Y. Cho, K. McElwain, S. McElwain, E. Raz, D.H. Broide, Accumulation of peribronchial mast cells in a mouse model of ovalbumin allergen induced chronic airway inflammation: modulation by immunostimulatory DNA sequences, J. Immunol. 171 (2003) 4860–4867.
[146] M. Kulka, L. Alexopoulou, R.A. Flavell, D.D. Metcalfe, Activation of mast cells by double-stranded RNA: evidence for activation through Toll-like receptor 3, J. Allergy Clin. Immunol. 114 (2004) 174–182.
[147] R. Hepp, N. Puri, A.C. Hohenstein, G.L. Crawford, S.W. Whiteheart, P.A. Roche, Phosphorylation of SNAP-23 regulates exocytosis from mast cells, J. Biol. Chem. 280 (2005) 6610–6620.
[148] K. Nishida, S. Yamasaki, Y. Ito, K. Kabu, K. Hattori, T. Tezuka, H. Nishizumi, D. Kitamura, R. Goitsuka, R.S. Geha, T. Yamamoto, T. Yagi, T. Hirano, Fc{epsilon}RI-mediated mast cell degranulation requires calcium-independent microtubule-dependent translocation of granules to the plasma membrane, J. Cell Biol. 170 (2005) 115–126.
[149] E. Lessmann, M. Leitges, M. Huber, A redundant role for PKC-epsilon in mast cell signaling and effector function, Int. Immunol. 18 (2006) 767–773.
[150] J. Rivera, A.M. Gilfillan, Molecular regulation of mast cell activation, J. Allergy Clin. Immunol. 117 (2006) 1214–1225.
[151] Y. Furumoto, S. Brooks, A. Olivera, Y. Takagi, M. Miyagishi, K. Taira, R. Casellas, M.A. Beaven, A.M. Gilfillan, J. Rivera, Cutting edge: lentiviral short hairpin RNA silencing of PTEN in human mast cells reveals constitutive signals that promote cytokine secretion and cell survival, J. Immunol. 176 (2006) 5167–5171.
[152] M. Stempelj, I. Ferjan, Signaling pathway in nerve growth factor induced histamine release from rat mast cells, Inflamm. Res. 54 (2005) 344–349.
[153] K. Kandere-Grzybowska, D. Kempuraj, J. Cao, C.L. Cetrulo, T.C. Theoharides, Regulation of IL-1-induced selective IL-6 release from human mast cells and inhibition by quercetin, Br. J. Pharmacol. 148 (2006) 208–215.
[154] J. Forssell, P. Sideras, C. Eriksson, M. Malm-Erjefalt, K. Rydell-Tormanen, P.O. Ericsson, J.S. Erjefalt, Interleukin-2-inducible T cell kinase regulates mast cell degranulation and acute allergic responses, Am. J. Respir. Cell Mol. Biol. 32 (2005) 511–520.
[155] C.J. Seow, S.C. Chue, W.S. Wong, Piceatannol, a Syk-selective tyrosine kinase inhibitor, attenuated antigen challenge of guinea pig airways in vitro, Eur. J. Pharmacol. 443 (2002) 189–196.
[156] C.L. Kepley, Antigen-induced reduction in mast cell and basophil functional responses due to reduced Syk protein levels, Int. Arch. Allergy Immunol. 138 (2005) 29–39.
[157] T. Oka, M. Hori, A. Tanaka, H. Matsuda, H. Karaki, H. Ozaki, IgE alone-induced actin assembly modifies calcium signaling and degranulation in RBL-2H3 mast cells, Am. J. Physiol. Cell Physiol. 286 (2004) C256–C263.
[158] C. Gonzalez-Espinosa, S. Odom, A. Olivera, J.P. Hobson, M.E. Martinez, A. Oliveira-Dos-Santos, L. Barra, S. Spiegel, J.M. Penninger, J. Rivera, Preferential signaling and induction of allergy-promoting lymphokines upon weak stimulation of the high affinity IgE receptor on mast cells, J. Exp. Med. 197 (2003) 1453–1465.
[159] S. Odom, G. Gomez, M. Kovarova, Y. Furumoto, J.J. Ryan, H.V. Wright, C. Gonzalez-Espinosa, M.L. Hibbs, K.W. Harder, J. Rivera, Negative regulation of immunoglobulin E-dependent allergic responses by Lyn kinase, J. Exp. Med. 199 (2004) 1491–1502.
[160] G. Gomez, C. Gonzalez-Espinosa, S. Odom, G. Baez, M.E. Cid, J.J. Ryan, J. Rivera, Impaired FcepsilonRI-dependent gene expression and defective eicosanoid and cytokine production as a consequence of Fyn deficiency in mast cells1, J. Immunol. 175 (2005) 7602–7610.
[161] J. Rivera, Adaptors discriminate mast-cell cytokine production from eicosanoid production and degranulation, Trends Immunol. 27 (2006) 251–253.
[162] S. Klemm, J. Gutermuth, L. Hultner, T. Sparwasser, H. Behrendt, C. Peschel, T.W. Mak, T. Jakob, J. Ruland, The Bcl10–Malt1 complex segregates Fc epsilon RI-mediated nuclear factor kappa B activation and cytokine production from mast cell degranulation, J. Exp. Med. 203 (2006) 337–347.
[163] I. Bachelet, A. Munitz, A. Moretta, L. Moretta, F. Levi-Schaffer, The inhibitory receptor IRp60 (CD300a) is expressed and functional on human mast cells, J. Immunol. 175 (2005) 7989–7995.
[164] H.M. Cherwinski, C.A. Murphy, B.L. Joyce, M.E. Bigler, Y.S. Song, S.M. Zurawski, M.M. Moshrefi, D.M. Gorman, K.L. Miller, S. Zhang, J.D. Sedgwick, J.H. Phillips, The CD200 receptor is a novel and potent regulator of murine and human mast cell function, J. Immunol. 174 (2005) 1348–1356.
[165] L. Karra, B. Berent-Maoz, M. Ben-Zimra, F. Levi-Schaffer, Are we ready to downregulate mast cells? Curr. Opin. Immunol. 21 (2009) 708–714.
[166] M. Andrasfalvy, H. Peterfy, G. Toth, J. Matko, J. Abramson, K. Kerekes, G. Vamosi, I. Pecht, A. Erdei, The beta subunit of the type I Fcepsilon receptor is a target for peptides inhibiting IgE-mediated secretory response of mast cells, J. Immunol. 175 (2005) 2801–2806.

[167] T.C. Theoharides, P. Patra, W. Boucher, R. Letourneau, D. Kempuraj, G. Chiang, S. Jeudy, L. Hesse, A. Athanasiou, Chondroitin sulfate inhibits connective tissue mast cells, Br. J. Pharmacol. 131 (2000) 1039–1049.
[168] B.J. Davis, B.F. Flanagan, A.M. Gilfillan, D.D. Metcalfe, J.W. Coleman, Nitric oxide inhibits IgE-dependent cytokine production and Fos and Jun activation in mast cells, J. Immunol. 173 (2004) 6914–6920.
[169] P. Conti, D. Kempuraj, K. Kandere, M.D. Gioacchino, R.C. Barbacane, M.L. Castellani, M. Felaco, W. Boucher, R. Letourneau, T.C. Theoharides, IL-10, an inflammatory/inhibitory cytokine, but not always, Immunol. Lett. 86 (2003) 123–129.
[170] S.H. He, H. Xie, X.J. Zhang, X.J. Wang, Inhibition of histamine release from human mast cells by natural chymase inhibitors, Acta Pharmacol. Sin. 25 (2004) 822–826.
[171] M. Tagen, A. Elorza, W. Boucher, C.L. Kepley, O. Shirihai, T.C. Theoharides, Mitochondrial uncoupling protein 2 (UCP2) inhibits mast cell activation and reduces histamine content, J. Immunol. 183 (2009) 6313–6319.
[172] B. Zhang, K.D. Alysandratos, A. Angelidou, D. Kempuraj, M. Tagen, M. Vasiadi, S. Asadi, T.C. Theoharides, TNF secretion from human mast cells is regulated by mitochondrial dynamics and mitochondrial uncoupling protein 2 (UCP2), J. Immunol. 184 (2010) 11.
[173] B. Zhang, K.D. Alysandratos, A. Angelidou, A. Asadi, S. Sismanopoulos, N. Delivanis, M. Vasiadi, Alexandra Katsarou-Katsari, B. Miao, Z. Weng, A. Miniati, S.E. Leeman, D. Kalogeromitros, T.C. Theoharides, Human mast cell degranulation and granule-stored TNF secretion require mitochondrial translocation to exocytosis sites—relevance to atopic dermatitis, J Allergy Clin Immunol. 127 (2011) 1522–1531.
[174] E. Middleton Jr., C. Kandaswami, T.C. Theoharides, The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer, Pharmacol. Rev. 52 (2000) 673–751.
[175] D. Kempuraj, B. Madhappan, S. Christodoulou, W. Boucher, J. Cao, N. Papadopoulou, C.L. Cetrulo, T.C. Theoharides, Flavonols inhibit proinflammatory mediator release, intracellular calcium ion levels and protein kinase C theta phosphorylation in human mast cells, Br. J. Pharmacol. 145 (2005) 934–944.
[176] M. Fiorani, A. Guidarelli, M. Blasa, C. Azzolini, M. Candiracci, E. Piatti, O. Cantoni, Mitochondria accumulate large amounts of quercetin: prevention of mitochondrial damage and release upon oxidation of the extramitochondrial fraction of the flavonoid, J. Nutr. Biochem. 21 (2010) 397–404.
[177] A. Katsarou-Katsari, A. Filippou, T.C. Theoharides, Effect of stress and other psychological factors on the pathophysiology and treatment of dermatoses, Int. J. Immunopathol. Pharmacol. 12 (1999) 7–11.
[178] M.K. Church, G.F. Clough, Human skin mast cells: in vitro and in vivo studies, Ann. Allergy Asthma Immunol. 83 (1999) 471–475.
[179] K.D. Alysandratos, A. Angelidou, M. Vasiadi, B. Zhang, D. Kalogeromitros, A. Katsarou-Katsari, T.C. Theoharides, Increased affected skin gene expression and serum levels of thymic stromal lymphopoietin in atopic dermatitis, Ann. Allergy Asthma Immunol. 105 (2010) 403–404.
[180] V. Soumelis, P.A. Reche, H. Kanzler, W. Yuan, G. Edward, B. Homey, M. Gilliet, S. Ho, S. Antonenko, A. Lauerma, K. Smith, D. Gorman, S. Zurawski, J. Abrams, S. Menon, T. McClanahan, Rd.R. de Waal-Malefyt, F. Bazan, R.A. Kastelein, Y.J. Liu, Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP, Nat. Immunol. 3 (2002) 673–680.
[181] E.B. Lee, K.W. Kim, J.Y. Hong, H.M. Jee, M.H. Sohn, K.E. Kim, Increased serum thymic stromal lymphopoietin in children with atopic dermatitis, Pediatr. Allergy Immunol. 21 (2010) e457–e460.
[182] H. Kimata, Enhancement of allergic skin wheal responses and in vitro allergen-specific IgE production by computer-induced stress in patients with atopic dermatitis, Brain Behav. Immun. 17 (2003) 134–138.
[183] H. Kimata, Enhancement of allergic skin wheal responses in patients with atopic eczema/dermatitis syndrome by playing video games or by a frequently ringing mobile phone, Eur. J. Clin. Investig. 33 (2003) 513–517.
[184] A. Slominski, J. Wortsman, Neuroendocrinology of the skin, Endocr. Rev. 21 (2000) 457–487.
[185] A. Slominski, J. Wortsman, T. Luger, R. Paus, S. Solomon, Corticotropin releasing hormone and proopiomelanocortin involvement in the cutaneous response to stress, Physiol. Rev. 80 (2000) 979–1020.
[186] A. Slominski, G. Ermak, J. Hwang, A. Chakraborty, J.E. Mazurkiewicz, M. Mihm, Proopiomelanocortin, corticotropin releasing hormone and corticotropin releasing hormone receptor genes are expressed in human skin, FEBS Lett. 374 (1995) 113–116.
[187] A. Slominski, J. Wortsman, A. Pisarchik, B. Zbytek, E.A. Linton, J.E. Mazurkiewicz, E.T. Wei, Cutaneous expression of corticotropin-releasing hormone (CRH), urocortin, and CRH receptors, FASEB J. 15 (2001) 1678–1693.
[188] G. Skofitsch, N. Zamir, C.J. Helke, J.M. Savitt, D.M. Jacobowitz, Corticotropin-releasing factor-like immunoreactivity in sensory ganglia and capsaicin sensitive neurons of the rat central nervous system: colocalization with other neuropeptides, Peptides 6 (1985) 307–318.
[189] I. Merchenthaler, M.A. Hynes, S. Vingh, A.V. Schally, P. Petrusz, Immunocytochemical localization of corticotropin-releasing factor (CRF) in the rat spinal cord, Brain Res. 275 (1983) 373–377.
[190] A. Kubler, G. Rothacher, V.A. Knappertz, G. Kramer, M. Nink, J. Beyer, H. Lehnert, Intra and extracerebral blood flow changes and flushing after intravenous injection of human corticotropin-releasing hormone, Clin. Investig. 72 (1994) 331–336.
[191] T.C. Theoharides, L.K. Singh, W. Boucher, X. Pang, R. Letourneau, E. Webster, G. Chrousos, Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its pro-inflammatory effects, Endocrinology 139 (1998) 403–413.
[192] R. Crompton, V.L. Clifton, A.T. Bisits, M.A. Read, R. Smith, I.M. Wright, Corticotropin-releasing hormone causes vasodilation in human skin via mast cell-dependent pathways, J. Clin. Endocrinol. Metab. 88 (2003) 5427–5432.
[193] V.L. Clifton, R. Crompton, R. Smith, I.M. Wright, Microvascular effects of CRH in human skin vary in relation to gender, J. Clin. Endocrinol. Metab. 87 (2002) 267–270.
[194] N. Papadopoulou, D. Kalogeromitros, N.G. Staurianeas, D. Tiblalexi, T.C. Theoharides, Corticotropin-releasing hormone receptor-1 and histidine decarboxylase expression in chronic urticaria, J. Invest. Dermatol. 125 (2005) 952–955.
[195] M. Lytinas, D. Kempuraj, M. Huang, W. Boucher, P. Esposito, T.C. Theoharides, Acute stress results in skin corticotropin-releasing hormone secretion, mast cell activation and vascular permeability, an effect mimicked by intradermal corticotropin-releasing hormone and inhibited by histamine-1 receptor antagonists, Int. Arch. Allergy Immunol. 130 (2003) 224–231.
[196] F.S. Dhabhar, B.S. McEwen, Enhancing versus suppressive effects of stress hormones on skin immune function, Proc. Natl Acad. Sci. USA 96 (1999) 1059–1064.
[197] K. Kaneko, S. Kawana, K. Arai, T. Shibasaki, Corticotropin-releasing factor receptor type 1 is involved in the stress-induced exacerbation of chronic contact dermatitis in rats, Exp. Dermatol. 12 (2003) 47–52.
[198] L.K. Singh, X. Pang, N. Alexacos, R. Letourneau, T.C. Theoharides, Acute immobilization stress triggers skin mast cell degranulation via corticotropin-releasing hormone, neurotensin and substance P: a link to neurogenic skin disorders, Brain Behav. Immun. 13 (1999) 225–239.
[199] L.K. Singh, W. Boucher, X. Pang, R. Letourneau, D. Seretakis, M. Green, T.C. Theoharides, Potent mast cell degranulation and vascular permeability triggered by urocortin through activation of CRH receptors, J. Pharmacol. Exp. Ther. 288 (1999) 1349–1356.
[200] A. Katsarou-Katsari, A. Filippou, T.C. Theoharides, Stress and inflammatory dermatoses, Int. J. Immunopathol. Pharmacol. 12 (1999) 7–11.
[201] D.G. Fortune, H.L. Richards, C.E. Griffiths, Psychologic factors in psoriasis: consequences, mechanisms, and interventions, Dermatol. Clin. 23 (2005) 681–694.
[202] R.J. Harvima, H. Viinamäki, I.T. Harvima, A. Naukkarinen, L. Savolainen, M.-L. Aalto, M. Horsmanheimo, Association of psychic stress with clinical severity and symptoms of psoriatic patients, Acta Derm.-Venereol. (Stockh.) 76 (1996) 467–471.
[203] M. Tagen, L. Stiles, D. Kalogeromitros, S. Gregoriou, D. Kempuraj, M. Makris, J. Donelan, M. Vasiadi, N.G. Staurianeas, T.C. Theoharides, Skin corticotropin-releasing hormone receptor expression in psoriasis, J. Invest. Dermatol. 127 (2007) 1789–1791.
[204] I.T. Harvima, G. Nilsson, M.M. Suttle, A. Naukkarinen, Is there a role for mast cells in psoriasis? Arch. Dermatol. Res. 300 (2008) 461–476.
[205] R. Saraceno, C.E. Kleyn, G. Terenghi, C.E. Griffiths, The role of neuropeptides in psoriasis, Br. J. Dermatol. 155 (2006) 876–882.
[206] C. Remröd, S. Lonne-Rahm, K. Nordliond, Study of substance P and its receptor neurokinin-1 in psoriasis and their relation to chronic stress and pruritus, Arch. Dermatol. Res. 299 (2007) 85–91.
[207] A. Naukkarinen, A. Jarvikallio, J. Lakkakorpi, I.T. Harvima, R.J. Harvima, M. Horsmanheimo, Quantitative histochemical analysis of mast cells and sensory nerves in psoriatic skin, J. Pathol. 180 (1996) 200–205.
[208] S. Kawana, Z. Liang, M. Nagano, H. Suzuki, Role of substance P in stress-derived degranulation of dermal mast cells in mice, J. Dermatol. Sci. 42 (2006) 47–54.
[209] K. Kandere-Grzybowska, D. Gheorghe, J. Priller, P. Esposito, M. Huang, N. Gerard, T.C. Theoharides, Stress-induced dura vascular permeability does not develop in mast cell-deficient and neurokinin-1 receptor knockout mice, Brain Res. 980 (2003) 213–220.
[210] S.E. Leeman, S.L. Ferguson, Substance P: an historical perspective, Neuropeptides 34 (2000) 249–254.
[211] T.M. O'Connor, J. O'Connell, D.I. O'Brien, T. Goode, C.P. Bredin, F. Shanahan, The role of substance P in inflammatory disease, J. Cell. Physiol. 201 (2004) 167–180.
[212] J. Chan, B.R. Smoller, S.P. Raychauduri, W.Y. Jiang, E.M. Farber, Intraepidermal nerve fiber expression of calcitonin gene-related peptide, vasoactive intestinal peptide and substance P in psoriasis, Arch. Dermatol. Res. 289 (1997) 611–616.
[213] M.S. Al'Abadie, H.J. Senior, S.S. Bleehen, D.J. Gawkrodger, Neuropeptides and general neuronal marker in psoriasis—an immunohistochemical study, Clin. Exp. Dermatol. 20 (1995) 384–389.
[214] E.M. Peters, A. Kuhlmei, D.J. Tobin, S. Muller-Rover, B.F. Klapp, P.C. Arck, Stress exposure modulates peptidergic innervation and degranulates mast cells in murine skin, Brain Behav. Immun. 19 (2005) 252–262.
[215] R. Paus, T. Heinzelmann, S. Robicsek, B.M. Czarnetzki, M. Maurer, Substance P stimulates murine epidermal keratinocyte proliferation and dermal mast cell degranulation in situ, Arch. Dermatol. Res. 287 (1995) 500–502.
[216] J.Y. Liu, J.H. Hu, Q.G. Zhu, F.Q. Li, H.J. Sun, Substance P receptor expression in human skin keratinocytes and fibroblasts, Br. J. Dermatol. 155 (2006) 657–662.
[217] I.S. Song, N.W. Bunnett, J.E. Olerud, B. Harten, M. Steinhoff, J.R. Brown, K.J. Sung, C.A. Armstrong, J.C. Ansel, Substance P induction of murine keratinocyte PAM 212 interleukin 1 production is mediated by the neurokinin 2 receptor (NK-2R), Exp. Dermatol. 9 (2000) 42–52.
[218] S. Sato, K. Kume, C. Ito, S. Ishii, T. Shimizu, Accelerated proliferation of epidermal keratinocytes by the transgenic expression of the platelet-activating factor receptor, Arch. Dermatol. Res. 291 (1999) 614–621.
[219] N. Kajiwara, T. Sasaki, P. Bradding, G. Cruse, H. Sagara, K. Ohmori, H. Saito, C. Ra, Y. Okayama, Activation of human mast cells through the platelet-activating factor receptor, J. Allergy Clin. Immunol. 125 (2010) 1137–1145.
[220] F.O. Nestle, D.H. Kaplan, J. Barker, Psoriasis, N. Engl. J. Med. 361 (2009) 496–509.

[221] D. Xu, H. Jiang, P. Kewin, Y. Li, R. Mu, A.R. Fraser, N. Pitman, M. Kurowska-Stolarska, A.N.J. McKenzie, I.B. Mclinnes, F.Y. Liew, IL-33 exacerbates antigen-induced arthritis by activating mast cells, Proc. Natl. Acad. Sci. 105 (2008) 10913–10918.
[222] M.L. Castellani, D.J. Kempuraj, V. Salini, J. Vecchiet, S. Tete, C. Ciampoli, F. Conti, G. Cerulli, A. Caraffa, P. Antinolfi, T.C. Theoharides, D. De Amicis, A. Perrella, C. Cuccurullo, P. Boscolo, Y. Shaik, The latest interleukin: IL-33 the novel IL-1-family member is a potent mast cell activator, J. Biol. Regul. Homeost. Agents 23 (2009) 11–14.
[223] P.N. Pushparaj, H.K. Tay, S.C. H'ng, N. Pitman, D. Xu, A. McKenzie, F.Y. Liew, A.J. Melendez, The cytokine interleukin-33 mediates anaphylactic shock, Proc. Natl Acad. Sci. USA 106 (2009) 9773–9778.
[224] D. Moulin, O. Donze, D. Talabot-Ayer, F. Mezin, G. Palmer, C. Gabay, Interleukin (IL)-33 induces the release of pro-inflammatory mediators by mast cells, Cytokine 40 (2007) 216–225.
[225] M. Iikura, H. Suto, N. Kajiwara, K. Oboki, T. Ohno, Y. Okayama, H. Saito, S.J. Galli, S. Nakae, IL-33 can promote survival, adhesion and cytokine production in human mast cells, Lab. Invest. 87 (2007) 971–978.
[226] T.C. Theoharides, B. Zhang, D. Kempuraj, M. Tagen, M. Vasiadi, A. Angelidou, K.D. Alysandratos, D. Kalogeromitros, S. Asadi, N. Stavrianeas, E. Peterson, S. Leeman, P. Conti, IL-33 augments substance P-induced VEGFsecretion from human mast cells and is increased in psoriatic skin, Proc. Natl Acad. Sci. USA 107 (2010) 4448–4453.
[227] V. Dimitriadou, A. Rouleau, M.D. Trung Tuong, G.J.F. Newlands, H.R.P. Miller, G. Luffau, J.-C. Schwartz, M. Garbarg, Functional relationships between sensory nerve fibers and mast cells of dura mater in normal and inflammatory conditions, Neuroscience 77 (1997) 829–839.
[228] J.J. Rozniecki, V. Dimitriadou, M. Lambracht-Hall, X. Pang, T.C. Theoharides, Morphological and functional demonstration of rat dura mast cell–neuron interactions *in vitro* and *in vivo*, Brain Res. 849 (1999) 1–15.
[229] V. Dimitriadou, P. Aubineau, J. Taxi, J. Seylaz, Ultrastructural evidence for a functional unit between nerve fibers and type II cerebral mast cells in the cerebral vascular wall, Neuroscience 22 (1987) 621–630.
[230] L. Edvinsson, C. Owman, N.O. Sjöberg, Autonomic nerves, mast cells and amine receptors in human brain vessels. A histochemical and pharmacological study, Brain Res. 115 (1976) 377–393.
[231] M.Z. Ibrahim, The mast cells of the mammalian central nervous system. Part I. Morphology, distribution and histochemistry, J. Neurol. Sci. 21 (1974) 431–478.
[232] H. Pollard, S. Bischoff, C. Llorens-Cortes, J.C. Schwartz, Histidine decarboxylase and histamine in discrete nuclei of rat hypothalamus and the evidence for mast cells in the median eminence, Brain Res. 118 (1976) 509–513.
[233] R.C. Goldschmidt, L.B. Hough, S.D. Glick, Rat brain mast cells: contribution to brain histamine levels, J. Neurochem. 44 (1985) 1943–1947.
[234] M. Lambracht-Hall, V. Dimitriadou, T.C. Theoharides, Migration of mast cells in the developing rat brain, Dev. Brain Res. 56 (1990) 151–159.
[235] M. von During, M. Bauersachs, B. Bohmer, R.W. Veh, K.H. Andres, Neuropeptide Y- and substance P-like immunoreactive nerve fibers in the rat dura mater encephali, Anat. Embryol. (Berl.) 182 (1990) 363–373.
[236] P. Esposito, N. Chandler, K. Kandere-Grzybowska, S. Basu, S. Jacobson, R. Connolly, D. Tutor, T.C. Theoharides, Corticotropin-releasing hormone (CRH) and brain mast cells regulate blood–brain-barrier permeability induced by acute stress, J. Pharmacol. Exp. Ther. 303 (2002) 1061–1066.
[237] P. Esposito, D. Gheorghe, K. Kandere, X. Pang, R. Conally, S. Jacobson, T.C. Theoharides, Acute stress increases permeability of the blood–brain-barrier through activation of brain mast cells, Brain Res. 888 (2001) 117–127.
[238] H.E. De Vreis, J. Kuiper, A.G. de Boer, T.J.C. Van Berkel, D.D. Breimer, The blood–brain barrier in neuroinflammatory diseases, Pharmacol. Rev. 49 (1997) 143–155.
[239] A.G. Kermode, A.J. Thompson, P. Tofts, D.G. MacManus, B.E. Kendall, D.P.E. Kingsley, I.F. Moseley, P. Rudge, W.I. McDonald, Breakdown of the blood–brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis, Brain 113 (1990) 1477–1489.
[240] A.C.E. Moor, H.E. de Vries, A.G. de Boer, D.D. Breimer, The blood–brain barrier and multiple sclerosis, Biochem. Pharmacol. 47 (1994) 1717–1724.
[241] E.E. Kwon, J.W. Prineas, Blood–brain barrier abnormalities in longstanding multiple sclerosis lesions. An immunohistochemical study, J. Neuropathol. Exp. Neurol. 53 (1994) 625–636.
[242] K. Syndulko, W.W. Tourtellotte, A.J. Conrad, G. Izuierdo, Multiple Sclerosis Study Group, Alpha Interferon Study Group, Trans-blood–brain-barrier albumin leakage and comparisons of intrathecal IgG synthesis calculations in multiple sclerosis patients, J. Neuroimmunol. 46 (1993) 185–192.
[243] D.C. Mohr, D.E. Goodkin, P. Bacchetti, A.C. Boudewyn, L. Huang, P. Marrietta, W. Cheuk, B. Dee, Psychological stress and the subsequent appearances of new brain MRI lesions in MS, Neurology 55 (2000) 55–61.
[244] Y. Olsson, Mast cells in plaques of multiple sclerosis, Acta Neurol. Scand. 50 (1974) 611–618.
[245] P.G. Krüger, L. Bo, K.M. Myhr, A.E. Karlsen, A. Taule, H.I. Nyland, S. Mork, Mast cells and multiple sclerosis: a light and electron microscopic study of mast cells in multiple sclerosis emphasizing staining procedures, Acta Neurol. Scand. 81 (1990) 31–36.
[246] C. Lock, G. Hermans, R. Pedotti, A. Brendolan, E. Schadt, H. Garren, A. Langer-Gould, S. Strober, B. Cannella, J. Allard, P. Klonowski, A. Austin, N. Lad, N. Kaminski, S.J. Galli, J.R. Oksenberg, C.S. Raine, R. Heller, L. Steinman, Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis, Nat. Med. 8 (2002) 500–508.
[247] R. Bomprezzi, M. Ringner, S. Kim, M.L. Bittner, J. Khan, Y. Chen, A. Elkahloun, A. Yu, B. Bielekova, P.S. Meltzer, R. Martin, H.F. McFarland, J.M. Trent, Gene expression profile in multiple sclerosis patients and healthy controls: identifying pathways relevant to disease, Hum. Mol. Genet. 12 (2003) 2191–2199.
[248] C. Lu, S.A. Diehl, R. Noubade, J. Ledoux, M.T. Nelson, K. Spach, J.F. Zachary, E.P. Blankenhorn, C. Teuscher, Endothelial histamine H1 receptor signaling reduces blood–brain barrier permeability and susceptibility to autoimmune encephalomyelitis, Proc. Natl Acad. Sci. USA 107 (2010) 18967–18972.
[249] X. Pang, R. Letourneau, J.J. Rozniecki, L. Wang, T.C. Theoharides, Definitive characterization of rat hypothalamic mast cells, Neuroscience 73 (1996) 889–902.
[250] U. Shanas, R. Bhasin, A.K. Sutherland, A.-J. Silverman, R. Silver, Brain mast cells lack the c-kit receptor: immunocytochemical evidence, J. Neuroimmunol. 90 (1998) 207–211.
[251] R. Letourneau, J.J. Rozniecki, V. Dimitriadou, T.C. Theoharides, Ultrastructural evidence of brain mast cell activation without degranulation in monkey experimental allergic encephalomyelitis, J. Neuroimmunol. 145 (2003) 18–26.
[252] R. Silver, A.-J. Silverman, L. Vitkovic, I.I. Lederhendler, Mast cells in the brain: evidence and functional significance, Trends Neurosci. 19 (1996) 25–31.
[253] M. Wilhelm, R. Silver, A.J. Silverman, Central nervous system neurons acquire mast cell products via transgranulation, Eur. J. Neurosci. 22 (2005) 2238–2248.
[254] R. Cocchiara, A. Bongiovanni, G. Albeggiani, A. Azzolina, D. Geraci, Evidence that brain mast cells can modulate neuroinflammatory responses by tumor necrosis factor-α production, NeuroReport 9 (1998) 95–98.
[255] L. Probert, K. Akassoglou, G. Kassiotis, M. Pasparakis, L. Alexopoulou, G. Kollias, TNF-α transgenic and knockout models of CNS inflammation and degeneration, J. Neuroimmunol. 72 (1997) 137–141.
[256] W.E.F. Klinkert, K. Kojima, W. Lesslauer, W. Rinner, H. Lassmann, H. Wekerle, TNF-α receptor fusion protein prevents experimental auto-immune encephalomyelitis and demyelination in Lewis rats: an overview, J. Neuroimmunol. 72 (1997) 163–168.
[257] K.S. Kim, C.A. Wass, A.S. Cross, S.M. Opal, Modulation of blood–brain barrier permeability by tumor necrosis factor and antibody to tumor necrosis factor in the rat, Lymphokine Cytokine Res. 11 (1992) 293–298.
[258] J.J. Rozniecki, S.L. Hauser, M. Stein, R. Lincoln, T.C. Theoharides, Elevated mast cell tryptase in cerebrospinal fluid of multiple sclerosis patients, Ann. Neurol. 37 (1995) 63–66.
[259] V. Malamud, A. Vaaknin, O. Abramsky, M. Mor, L.E. Burgess, A. Ben-Yehudah, H. Lorberboum-Galski, Tryptase activates peripheral blood mononuclear cells causing the synthesis and release of TNF-alpha, IL-6 and IL-1 beta: possible relevance to multiple sclerosis, J. Neuroimmunol. 138 (2003) 115–122.
[260] N.W. Bunnett, Protease-activated receptors: how proteases signal to cells to cause inflammation and pain, Semin. Thromb. Hemost. 32 (Suppl 1) (2006) 39–48.
[261] B.A. Sayed, A.L. Christy, M.E. Walker, M.A. Brown, Meningeal mast cells affect early T cell central nervous system infiltration and blood–brain barrier integrity through TNF: a role for neutrophil recruitment? J. Immunol. 184 (2010) 6891–6900.
[262] G. Kassiotis, G. Kollias, Uncoupling the proinflammatory from the immunosuppressive properties of tumor necrosis factor (TNF) at the p55 TNF receptor level: implications for pathogenesis and therapy of autoimmune demyelination, J. Exp. Med. 193 (2001) 427–434.
[263] J.R. Gordon, S.J. Galli, Mast cells as a source of both preformed and immunologically inducible TNF-α/cachectin, Nature 346 (1990) 274–276.
[264] B.F. Gibbs, J. Wierecky, P. Welker, B.M. Henz, H.H. Wolff, J. Grabbe, Human skin mast cell rapidly release preformed and newly generated TNF-alpha and IL-8 following stimulation with anti-IgE and other secretagogues, Exp. Dermatol. 10 (2001) 312–320.
[265] H. Lassmann, R.M. Ransohoff, The CD4-Th1 model for multiple sclerosis: a crucial re-appraisal, Trends Immunol. 25 (2004) 132–137.
[266] M. Robbie-Ryan, M.B. Tanzola, V.H. Secor, M.A. Brown, Cutting edge: both activating and inhibitory Fc receptors expressed on mast cells regulate experimental allergic encephalomyelitis disease severity, J. Immunol. 170 (2003) 1630–1634.
[267] R. Pedotti, J.J. De Voss, L. Steinman, S.J. Galli, Involvement of both 'allergic' and 'autoimmune' mechanisms in EAE, MS and other autoimmune diseases, Trends Immunol. 24 (2003) 479–484.
[268] M. Robbie-Ryan, M. Brown, The role of mast cells in allergy and autoimmunity, Curr. Opin. Immunol. 14 (2002) 728–733.
[269] M.A. Brown, M. Tanzola, M. Robbie-Ryan, Mechanisms underlying mast cell influence on EAE disease course, Mol. Immunol. 38 (2002) 1373–1378.
[270] D. Baram, G.G. Vaday, P. Salamon, I. Drucker, R. Hershkoviz, Y.A. Mekori, Human mast cells release metalloproteinase-9 on contact with activated T cells: juxtacrine regulation by TNF-alpha, J. Immunol. 167 (2001) 4008–4016.
[271] T.C. Theoharides, V. Dimitriadou, R.J. Letourneau, J.J. Rozniecki, H. Vliagoftis, W.S. Boucher, Synergistic action of estradiol and myelin basic protein on mast cell secretion and brain demyelination: changes resembling early stages of demyelination, Neuroscience 57 (1993) 861–871.
[272] D.E. Griffin, Q.P. Mendoza, Identification of the inflammatory cells present in the central nervous system of normal and mast cell-deficient mice during Sindbis virus encephalitis, Cell. Immunol. 97 (1986) 454–459.
[273] N.J. Abbott, Inflammatory mediators and modulation of blood–brain barrier permeability, Cell. Mol. Neurobiol. 20 (2000) 131–147.
[274] T.C. Theoharides, C. Weinkauf, P. Conti, Brain cytokines and neuropsychiatric disorders, J. Clin. Psychopharmacol. 24 (2004) 577–581.
[275] G. Mastorakos, G.P. Chrousos, J.S. Weber, Recombinant interleukin-6 activates the hypothalamic–pituitary–adrenal axis in humans, J. Clin. Endocrinol. Metab. 77 (1993) 1690–1694.
[276] R.J. Laham, J. Li, M. Tofukuji, M. Post, M. Simons, F.W. Sellke, Spatial heterogeneity in VEGF-induced vasodilation: VEGF dilates microvessels but not epicardial and systemic arteries and veins, Ann. Vasc. Surg. 17 (2003) 245–252.

[277] T.C. Theoharides, A. Konstantinidou, Corticotropin-releasing hormone and the blood–brain–barrier, Front. Biosci. 12 (2007) 1615–1628.
[278] T.C. Theoharides, C.P. Spanos, X. Pang, L. Alferes, K. Ligris, R. Letourneau, J.J. Rozniecki, E. Webster, G. Chrousos, Stress-induced intracranial mast cell degranulation. A corticotropin releasing hormone-mediated effect, Endocrinology 136 (1995) 5745–5750.
[279] A.J. Bugajski, Z. Chlap, A. Gadek-Michalska, J. Borycz, J. Bugajski, Degranulation and decrease in histamine levels of thalamic mast cells coincides with corticosterone secretion induced by compound 48/80, Inflamm. Res. 44 (Supp.1) (1995) S50–S51.
[280] A. Gadek-Michalska, Z. Chlap, M. Turon, J. Bugajski, W.A. Fogel, The intracerebroventicularly administered mast cells degranulator compound 48/80 increases the pituitary-adrenocortical activity in rats, Agents Actions 32 (1991) 203–208.
[281] I. Matsumoto, Y. Inoue, T. Shimada, T. Aikawa, Brain mast cells act as an immune gate to the hypothalamic–pituitary–adrenal axis in dogs, J. Exp. Med. 194 (2001) 71–78.
[282] A. Kjaer, P.J. Larsen, U. Knigge, H. Jorgensen, J. Warberg, Neuronal histamine and expression of corticotropin-releasing hormone, vasopressin and oxytocin in the hypothalamus: relative importance of H_1 and H_2 receptors, Eur. J. Endocrinol. 139 (1998) 238–243.
[283] D. Kempuraj, N.G. Papadopoulou, M. Lytinas, M. Huang, K. Kandere-Grzybowska, Madhappan, W. Boucher, S. Christodoulou, A. Athanassiou, T.C. Theoharides, Corticotropin-releasing hormone and its structurally related urocortin are synthesized and secreted by human mast cells, Endocrinology 145 (2004) 43–48.
[284] K.E. Bethin, S.K. Vogt, L.J. Muglia, Interleukin-6 is an essential, corticotropin-releasing hormone-independent stimulator of the adrenal axis during immune system activation, Proc. Natl Acad. Sci. USA 97 (2000) 9317–9322.
[285] D.S. Goodin, G.C. Ebers, K.P. Johnson, M. Rodriguez, W.A. Sibley, J.S. Wolinsky, The relationship of MS to physical trauma and psychological stress, Neurology 52 (1999) 1737–1745.
[286] S. Warren, S. Greenhill, K.G. Warren, Emotional stress and the development of multiple sclerosis: case control evidence of a relationship, J. Chronic. Dis. 35 (1982) 821–831.
[287] K.D. Ackerman, A. Stover, R. Heyman, B.P. Anderson, P.R. Houck, E. Frank, B.S. Rabin, A. Baum, Robert Ader New Investigator award. Relationship of cardiovascular reactivity, stressful life events, and multiple sclerosis disease activity, Brain Behav. Immun. 17 (2003) 141–151.
[288] D. Buljevac, W.C. Hop, W. Reedeker, A.C. Janssens, F.G. van der Meche, P.A. van Doorn, R.Q. Hintzen, Self reported stressful life events and exacerbations in multiple sclerosis: prospective study, BMJ 327 (2003) 646.
[289] J. Li, C. Johansen, H. Bronnum-Hansen, E. Stenager, N. Koch-Henriksen, J. Olsen, The risk of multiple sclerosis in bereaved parents: a nationwide cohort study in Denmark, Neurology 62 (2004) 726–729.
[290] D.C. Mohr, S.L. Hart, L. Julian, D. Cox, D. Pelletier, Association between stressful life events and exacerbation in multiple sclerosis: a meta-analysis, BMJ 328 (2004) 731.
[291] S.M. Gold, D.C. Mohr, I. Huitinga, P. Flachenecker, E.M. Sternberg, C. Heesen, The role of stress-response systems for the pathogenesis and progression of MS, Trends Immunol. 26 (2005) 644–652.
[292] C. Heesen, H. Schulz, M. Schmidt, S. Gold, W. Tessmer, K.H. Schulz, Endocrine and cytokine responses to acute psychological stress in multiple sclerosis, Brain Behav. Immun. 16 (2002) 282–287.
[293] P.H. Lalive, P.R. Burkhard, M. Chofflon, TNF-alpha and psychologically stressful events in healthy subjects: potential relevance for multiple sclerosis relapse, Behav. Neurosci. 116 (2002) 1093–1097.
[294] M. Huang, X. Pang, K. Karalis, T.C. Theoharides, Stress-induced interleukin-6 release in mice is mast cell-dependent and more pronounced in Apolipoprotein E knockout mice, Cardiovasc. Res. 59 (2003) 241–249.
[295] N. Chandler, S. Jacobson, R. Connolly, P. Esposito, T.C. Theoharides, Acute stress shortens the time of onset of experimental allergic encephalomyelitis (EAE) in SJL/J mice, Brain Behav. Immun. 16 (2002) 757–763.
[296] M.A. Teunis, C.J. Heijnen, F. Sluyter, J.M. Bakker, A.M. Van Dam, M. Hof, A.R. Cools, A. Kavelaars, Maternal deprivation of rat pups increases clinical symptoms of experimental autoimmune encephalomyelitis at adult age, J. Neuroimmunol. 133 (2002) 30–38.
[297] C. Benou, Y. Wang, J. Imitola, L. VanVlerken, C. Chandras, K.P. Karalis, S.J. Khoury, Corticotropin-releasing hormone contributes to the peripheral inflammatory response in experimental autoimmune encephalomyelitis, J. Immunol. 174 (2005) 5407–5413.
[298] D.V. Jeyaraju, G. Cisbani, L. Pellegrini, Calcium regulation of mitochondria motility and morphology, Biochim. Biophys. Acta 1787 (2009) 1363–1373.
[299] T. Campbell, M.W. Meagher, A. Sieve, B. Scott, R. Storts, T.H. Welsh, C.J. Welsh, The effects of restraint stress on the neuropathogenesis of Theiler's virus infection: I. Acute disease, Brain Behav. Immun. 15 (2001) 235–254.
[300] A.J. Bugajski, Z. Chiap, A. Gadek-Michalska, J. Bugajski, Effect of isolation stress on brain mast cells and brain histamine levels in rats, Agents Actions 41 (1994) C75–C76.
[301] F. Cirulli, L. Pistillo, L. De Acetis, E. Alleva, L. Aloe, Mast cells increase in the central nervous system of adult male mice following chronic subordination stress, Soc. Neurosci. 23 (1997) 714.
[302] P.K. Honig, D.C. Wortham, K. Zamani, D.P. Conner, J.C. Mullin, L.R. Cantilena, Terfenadine–ketoconazole interaction: pharmacokinetic and electrocardiographic consequences, JAMA 269 (1993) 1513–1518.
[303] J.P. Zappulla, M. Arock, L.T. Mars, R.S. Liblau, Mast cells: new targets for multiple sclerosis therapy? J. Neuroimmunol. 131 (2002) 5–20.
[304] J.J. Hendriks, H.E. de Vries, S.M. van der Pol, T.K. van den Berg, E.A. van Tol, C.D. Dijkstra, Flavonoids inhibit myelin phagocytosis by macrophages; a structure–activity relationship study, Biochem. Pharmacol. 65 (2003) 877–885.
[305] O. Aktas, T. Prozorovski, A. Smorodchenko, N.E. Savaskan, R. Lauster, P.M. Kloetzel, C. Infante-Duarte, S. Brocke, F. Zipp, Green tea epigallocatechin-3-gallate mediates T cellular NF-kappa B inhibition and exerts neuroprotection in autoimmune encephalomyelitis, J. Immunol. 173 (2004) 5794–5800.
[306] J.J. Hendriks, J. Alblas, S.M. van der Pol, E.A. van Tol, C.D. Dijkstra, H.E. de Vries, Flavonoids influence monocytic GTPase activity and are protective in experimental allergic encephalitis, J. Exp. Med. 200 (2004) 1667–1672.
[307] R. Verbeek, A.C. Plomp, E.A. van Tol, J.M. van Noort, The flavones luteolin and apigenin inhibit in vitro antigen-specific proliferation and interferon-gamma production by murine and human autoimmune T cells, Biochem. Pharmacol. 68 (2004) 621–629.
[308] S. Jang, K.W. Kelley, R.W. Johnson, Luteolin reduces IL-6 production in microglia by inhibiting JNK phosphorylation and activation of AP-1, Proc. Natl Acad. Sci. USA 105 (2008) 7534–7539.
[309] K. Dirscherl, M. Karlstetter, S. Ebert, D. Kraus, J. Hlawatsch, Y. Walczak, C. Moehle, R. Fuchshofer, T. Langmann, Luteolin triggers global changes in the microglial transcriptome leading to a unique anti-inflammatory and neuroprotective phenotype, J. Neuroinflammation 7 (2010) 3.
[310] S.W. Jang, X. Liu, M. Yepes, K.R. Shepherd, G.W. Miller, Y. Liu, W.D. Wilson, G. Xiao, B. Blanchi, Y.E. Sun, K. Ye, A selective TrkB agonist with potent neurotrophic activities by 7,8-dihydroxyflavone, Proc. Natl Acad. Sci. USA 107 (2010) 2687–2692.
[311] Z. Sternberg, K. Chadha, A. Lieberman, A. Drake, D. Hojnacki, B. Weinstock-Guttman, F. Munschauer, Immunomodulatory responses of peripheral blood mononuclear cells from multiple sclerosis patients upon in vitro incubation with the flavonoid luteolin: additive effects of IFN-beta, J. Neuroinflammation 6 (2009) 28.
[312] T.C. Theoharides, Luteolin as a therapeutic option for multiple sclerosis, J. Neuroinflammation 6 (2009) 29.