Review

Are mast cells important in diabetes?

Duraisamy Kempuraj[1], Alessandro Caraffa[2], Gianpaolo Ronconi[3], Gianfranco Lessiani[4], Pio Conti[5]

[1]Department of Neurology, Carver College of Medicine, University of Iowa, Iowa, USA
[2]Department of Pharmacology, University of Perugia, Perugia, Italy
[3]Policlinico Gemelli, Rome, Italy
[4]Villa Serena Hospital, Città Sant'Angelo, Italy
[5]Postgraduate Medical School, Università G. d'Annunzio, Chieti, Italy

Diabetes is a metabolic disorder characterized by hyperglycemia and associated with microvascular and macrovascular syndromes mediated by mast cells. Mast cells are activated through cross-linking of their surface high affinity receptors for IgE (FcεRI) or other antigens, leading to degranulation and release of stored inflammatory mediators, and cytokines/chemokines without degranulation. Mast cells are implicated in innate and acquired immunity, inflammation and metabolic disorders such as diabetes. Histamine and tryptase genes in mast cells are overexpressed in pancreatic tissue of type 2 diabetes mellitus (T2DM) patients. Histamine is a classic inflammatory mediator generated by activated receptors of mast cells from the histamine-forming enzyme histidine decarboxylase (HDC), which can be activated by two inflammatory chemokines, RANTES and MPC1, when injected intramuscularly or intradermally in mice. This activation is inhibited in genetically mast cell-deficient W/W^v mice, which show higher insulin sensitivity and glucose tolerance. This study contributes to understanding the mechanism by which mast cells profoundly affect diabetes, and their manipulation could represent a new therapeutic strategy. However, further studies are needed to clarify the role of mast cells in inflammation and metabolic disorders such as diabetes.

Key words: type 1 diabetes, type 2 diabetes, mast cells, autoimmunity, immune modulation, peripheral vascular disease.

Introduction

This article reviews the literature and our experience accumulated over the past twenty years on the pathophysiology of mast cells (MCs).

Autoimmune disease occurs when the body tissues are attacked by its own immune system [1], and it is generally accepted that type 1 diabetes mellitus (T1DM) is an autoimmune disease triggered in susceptible individuals by an unknown agent(s) [2]. Often autoimmune diseases are caused by delayed-type hypersensitivity (DTH) reactions induced by auto-reactive T lymphocytes which cross-talk with MCs and provoke tissue injury by triggering a DTH reaction [3]. Mast cells release considerable amounts of interleukin (IL)-4 upon stimulation, and participate in the induction of T-cell differentiation [4]. Apart from MCs, also basophils, Th2 cells, NK1.1$^+$ cells, γδ$^+$T cells, and eosinophils have been found to produce IL-4 [5].

After activation, T cells, macrophages, endothelial cells and MCs participate in DTH by generating and releasing a sequential cascade of inflammatory products such as reactive oxygen intermediates, nitric

oxide, hydrolytic enzymes, and inflammatory cytokines, including IL-1β, tumor necrosis factor (TNF), IL-18, IL-32 and IL-33 [6].

Type 1 diabetes mellitus is an autoimmune disorder which affects about 0.2% of the population in western countries, mostly boys aged 11 to 12 years [7].

Type 1 diabetes mellitus was previously called insulin-dependent diabetes mellitus (IDDM) and is a complex metabolic disease with impaired insulin production. It is a progressive and persistent autoimmune disease without resolution [8].

Diabetes is a metabolic disease characterized by hyperglycemia and associated with microvascular and macrovascular syndromes [9].

Type 1 diabetes mellitus can occur for genetic and environmental reasons, and presents with destruction of pancreatic β cells due to the infiltration of immune and inflammatory cells, including MCs, in the pancreas (an effect called insulitis) [10]. Therefore, inhibition of activated MCs and their degranulation and/or inflammatory cytokine/chemokine generation might act to protect pancreatic β cells in T1DM [11].

Cytokines/chemokines are low-molecular-weight soluble polypeptides released by immune cells as well as other cell types. They are produced in response to microbes and other antigens, regulate immune and inflammatory responses, and act in paracrine and autocrine manners [12]. Cytokines/chemokines play an important role in the pathogenesis of several infectious and non-infectious diseases including autoimmune disorders [13, 14]. An increase in pro-inflammatory cytokines/chemokines has been associated with tissue lesions and clinical dysfunction in patients with autoimmune diseases [15]. The stimulation of multiple cytokines/chemokines probably reflects the complex pathology of autoimmune disorders [16].

Autoimmunity, including T1DM, is associated with apoptosis and the generation and up-regulation of several pro-inflammatory cytokines such as interferon γ (IFN-γ), interleukin 1 (IL-1) family members, extracellular matrix, integrins expressed by immune cells, and tumor necrosis factor (TNF) [17]. Therefore, innate immunity and inflammatory mediators might play a crucial role in inducing and amplifying the immune attack against the β cells of the pancreas. In addition, the arrival of inflammatory immune cells, recruited by chemokines, induces immunity against infection by microorganisms and self-tissue [18].

The over-expression of MHC class-1 antigens leads to the production of several chemokines including RANTES and MCP-1 that attract MCs and other immune cells, which can be deleterious for the pancreatic β cells [19]. We previously reported that RANTES and MCP-1, which are part of the chemokine supergene family (8- to 10-kD proteins) inducible in a number of pathophysiologic processes, intradermally injected (10 ng/50 μl subcutaneously in the abdominal skin of rat) produce a strong inflammatory reaction, due to the recruitment of mast cells, showing that these chemokines are potent pro-inflammatory proteins with specific chemoattraction on inflammatory MCs [20]. When genetically mast cell-deficient W/W^v mice were used, neither RANTES nor MCP-1 provoked any appreciable inflammatory reaction or MC extravasation, demonstrating that MCs are important for the inflammatory responses [20].

Mast cells are multifunctional immune cells implicated in the pathogenesis of allergy [21], autoimmunity [22], and neurodegenerative disorders [23]. Mast cells are the first line of defense and are located preferentially in intraepithelial locations, in connective tissue, and around blood vessels, performing important beneficial roles in host defense [24]. A number of immune molecules and a variety of pathogens contribute to triggerring mast cells, which, after activation, play a crucial role in immunity and the inflammatory process [25].

Mast cells participate in innate, acquired immunity, inflammation, autoimmunity, allergy, infectious diseases and metabolic disorders [26]. Antigen stimulates B lymphocytes to produce IgE, and MCs can provide the necessary signals for IgE production such as IL-4, IL-13, and CD40L [27]. The induction of IgE synthesis is completely abrogated by neutralizing IL-4 and IL-13 (which are differentially controlled by IL-3 and protein kinase C [PKC]) with monoclonal antibodies or CD40L with soluble CD40 *in vitro* [28].

Mast cells are activated through cross-linking of their surface high affinity receptors for IgE (FcεRI), leading in seconds to degranulation and release of stored mediators such as histamine, heparin, tryptase, chymase, kinogenases, carboxypeptidase A3 and TNF. Mast cells synthesize *de novo* inflammatory compounds, such as growth factors, leukotrienes, prostaglandins, NO, and cytokines/chemokines, which are selectively released later, since the proinflammatory action of the mast cells can occur through non-histamine and non-IgE-mediated routes [29] (Table I). Therefore, MCs are activated not only by IgE and specific antigens, but can also be triggered via innate mechanisms, such as *K*it-ligand, stem cell factors (SCF), IL-33, IL-1, complement C3a, C5a, LPS, pathogen-associated molecular patterns (PAMPs), endothelin-1 (ET-1), and venom components [30]. Activation of MCs by cross-linking of FcεRI molecules or other antigens, such as neuropeptides, leads to the generation of PI3K, ERK, JNK, NF-κB and PKC, resulting in release of potent inflammatory mediators and to differential release of distinct mediators without degranulation [31] (Table II). PKCs, which induce signaling events, mediate diverse and important cellular functions, and their mutation and dysregulation contribute to the pathogenesis of many human diseases, including diabetes and its vascular

Table I. Mast cell release mediators after activation

Mast cell compounds synthesized *de novo* and preformed in granules	
	Synthesized *de novo*
Cytokines	IL-1, IL-1R antagonist, IL-3, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-18, TNF-α, TNF-β, INF-α, basic FGF, VEGF, NGF, NT-3, LIF, LT-β, GM-CSF, M-CSF, MIF, SCF, EGF, PDGFs
Eicosanoids	PGD2, LTB4, LTC4, LTD4, PAF
Chemokines	CCL1, CCL2 (MCP-1), CCL3 (MIP-1α), CCL3L1, CCL4 (MIP-1β), CCL5, CCL7, CCL8, CCL11, CCL13, CCL16, CCL17, CCL20, CCL22, CXCL1, CXCL2, CXCL3, CXCL10, XCL1
Preformed in granules	heparin, chondroitin sulfates, tryptases (α, β, γ), chymase, carboxypeptidase-A, cathepsin, major basic protein, histamine

Table II. Mast cell antigen activation generates cytokines/chemokines without degranulation (schematic representation)

Cytokine generation by mast cell
ANTIGEN → IgE → FcεRI → TYROSINE KINASES (LyN, Syk) → activation → PI 3-KINASES ERK, MAP KINASES (Vav, Ras) and PLC
PI 3-KINASES → target → P38 MAP KINASES, Rac/Rho GTPase → CYTOKINE generation
PI 3-KINASES → Rac/Rho, Calcitonin, p38 → NFAT → cFos → ELK-1 → cJun → IL-4 and IL-13

complications [32]. Several lines of evidence suggest that MCs are implicated in diabetes, and it is likely that histamine and tryptase genes are over-expressed in pancreatic tissue of T2DM patients [33]. Type 1 diabetes mellitus is a chronic disease, which may lead to ischemic necrosis of organs, microvascular obstruction of the retina, renal glomeruli, peripheral nerve diseases, and atherosclerosis [34]. The vascular damage is caused by abnormal glucose metabolism with a still unclear mechanism. In some patients the presence of autoantibody against the islet cells without the disease may predict the development of T1DM [35].

In T1DM, MCs present pancreatic antigens to T cells, permitting pro-inflammatory cytokines/chemokines to enter and aggravate and damage the functionality and survival of the pancreatic β cells [36].

Tumor necrosis factor, which participates in T1DM, is a pro-inflammatory cytokine [37] involved in the acute phase reaction, in increased vascular permeability and can be generated and released by degranulated and non-degranulated activated mast cells [38].

Lymphocyte infiltration around the pancreatic tissue consists in both $CD4^+$ and $CD8^+$ [39]. Macrophages $CD11c^+$ and $CD11c^-$ and $CD4^+$ Th1 cells play an important role in T1DM since they are infiltrated around the islets of Langerhans in the pancreas, provoking the destruction of insulin-producing β cells in the islets with a consequence of deficiency in insulin production [40]. This phenomenon can be reproduced by transferring the T cell autoimmunity involved from one affected animal to another (healthy animal) [41]. Cytolytic T lymphocytes (CTLs), reacting with antigen of islet cells, mediate the lysis along with the generation of inflammatory cytokines that damage the islet cells, and autoantibody which contribute to their injury [42].

It has been reported that MCs are also determinant for the maturation of Th17 cells, which are recognized as key cells in autoimmune disorders including T1DM [43]. In this disease, which is a T-cell-dependent process, MCs participate in the activation of T cells by producing inflammatory TNF [44]. It has been reported that diabetic mice had decreased numbers of T regulatory (Treg) cells and a reduction in IL-10, TGF-β, and IL-6 expression in the pancreatic tissue [45]. These deficiencies make the mice more susceptible to contracting T1DM. Many genes are involved in T1DM, including *HLA-DR3* and *DR4* genes, which are present in the white population in about 93% [46]. In an experimental animal model, it is interesting that IL-2 (a T cell growth factor) knockout mice readily develop autoimmune diseases, including T1DM, through an unknown mechanism [47].

Experiments are ongoing in our laboratory to verify whether W/W^v mast cell deficient mice [48] are insulin resistant compared with healthy mice, and this could explain some of the clinical findings in patients affected by T1DM.

Type 2 diabetes mellitus and mast cells

Type 2 diabetes is the most common type of diabetes and is a major health problem in the 21st century [49].

Mast cells are inflammatory cells which perform pleiotropic roles in autoimmunity and atherosclerosis

as well as other inflammatory diseases and metabolic disorders including diabetes [50]. A limited number of mast cells are located in healthy human organs, but in patients with metabolic diseases the number is high, with increased activity.

Mast cell mediators, such as chemokines, cytokines, growth factors, heparin, histamine, proteases, chymase and tryptase, are biomarkers of metabolic diseases including T2DM and contribute to their pathogenesis [50]. Tryptase is the major mast cell enzyme which promotes fibroblast proliferation and collagen synthesis involved in vascular disorders associated with diabetes, while chymase is a serine protease which converts TGF-β from inactive to active form [51]. The chymase is stored in mast cells and, when released, degrades HDL components (apolipoprotein E, apoA-I and apoA-IV) in atherosclerotic lesions present in diabetic disease [52].

Histamine is a classical inflammatory mediator generated by activated receptors of mast cells from the histamine-forming enzyme histidine decarboxylase (HDC), the sole enzyme responsible for the production of histamine from histidine, and is induced in a variety of tissues in response to various stimuli including bacterial components, cytokines/chemokines, and other biochemical compounds [53]. Data are accumulating to support the idea that diabetes is under the control of numerous cytokines and hormones, and mast cell products [54]. Histamine is a biogenic amine inflammatory mediator stored in the granules of mast cells which binds to specific receptors in various tissues and causes an increase of vascular permeability and contraction of smooth muscle, and is involved in the regulation of diabetes mellitus [53]. Histamine participates in the pathophysiological actions of mast cells, immune responses, inflammation and a variety of diseases, including diabetes and its complications [55]. Therefore, HDC may mediate the inflammatory processes in T2DM [56]. Moreover, histamine and VEGF induce microvascular hyperpermeability with an angiogenic effect and chemotactic recruitment of lymphocytes, macrophages and mast cells that are able to contribute to the angiogenesis-modulating molecules and inflammation [57]. Recently, the anti-histamine anti-H3R antagonists have been studied in early-phase clinical trials for possible application in T2DM and obesity, a major risk factor for insulin resistance.

An *in vitro* experimental model using diabetes mellitus leukocytes activated with lipopolysaccharide (LPS) presented low superoxide generation, reduction of prostaglandin E_2 in macrophages, TNF, IL-1β, and inhibition of granulocytes in the generation of inflammatory arachidonic acid products [58]. Therefore, in diabetes mellitus there is compromised immunity with consequent risk of infections and cardio-circulatory diseases.

Furthermore, MCs are rich sources of proinflammatory cytokines which cause insulin resistance in adipocytes [59]. Cytokines, such as IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-16, IL-33, IFN-α, and TNF, mediate the biological effects of mast cells, including the recruitment of other inflammatory cells, and are important in diabetes mellitus infections [60]. Mast cells may store the TNF which increases the expression of E-selectin in the endothelium during bacterial infection and enhances the recruitment of dendritic cells [61].

Tumor necrosis factor (like other cytokines) is generated with the transcript and translation protein method, and it is stored in the granules of MCs for rapid and immediate release after activation. Tumor necrosis factor is also expressed in adipocytes, constituting a link between inflammation, obesity, and diabetes. Tumor necrosis factor and/or TNF receptors impair insulin sensitivity, and mice lacking TNF had improved insulin sensitivity in healthy and genetic (ob/ob) models of obesity [62].

Insulin resistance is an important sign of T2DM and has been associated with a state of low-grade inflammation. Blocking or inhibiting TNF and its receptor p55, TNF leads to an improvement of glucose homeostasis and insulin sensitivity, with a significant reduction of blood insulin level and the ratio of insulin and glucose, suggesting that this inflammatory response is relevant for the regulation of insulin [62].

Mast cells and their secretion are important for the innate immune response to bacterial infections, which are very common in diabetes, due to damage of immunity [63, 64]. Mast cells participate in the high susceptibility to and severity of infections in diabetes mellitus [65]. They are abundant in mucosal tissues, which are portals of entry for common infectious agents, in addition to allergens, and are relevant cells for the clearance of several types of bacteria [66].

Mast cell deficiency or receptor inhibition restrains generation of chemical compound mediators or cytokines/chemokines, an effect that ameliorates glucose regulation, reduces body weight gain in obesity and improves survival in diabetic experimental animals [67].

During bacterial infections in diabetes, the most reactive compounds are PGD2 (an MC product from arachidonic acid cascade), histamine, IL-6, IL-1, IL-18, TNF and IL-33, which is an alarmin cytokine repeatedly identified as predisposing to inflammation risk and allergy [68, 69]. They are all mediators of MC activity. It is generally believed that MCs are detrimental to bacteria and with their mediators help macrophages, dendritic cells, and neutrophils to clear them from tissues and circulation [70]. Bacteria may bind CD48 on MCs and induce MC activation and degranulation. In addition, MCs can be found in bacteria inflammatory tissue in response to specific C-C chemokines, such as RANTES and MCP-1, since we

previously demonstrated that injection of these two chemokines into the skin tissue, *in vivo* in a rat animal model, has a significant effect on MC recruitment and histidine decarboxylase (HDC) mRNA production [20]. Mast cell-deficient C57BL/6J-W^v/+ mice are more vulnerable to bacterial infections, but they have fewer inflammatory diseases. When the inflammatory chemokine RANTES or MCP-1 is injected intramuscularly or intradermally in genetically mast cell-deficient W/W^v mice, the inflammatory effect is almost absent [48], and they have higher insulin sensitivity and glucose tolerance [33].

It is likely that some bacteria and Toll like receptors (TLRs) can interfere with the cell surface of MCs, reducing the expression of the FcεRI receptor, influencing the generation of chemical mediators and cytokine/chemokine production, including TNF [71]. Toll like receptors play an important role in innate immunity where bacterial infections in diabetes are involved and are present in immune cells, including MCs. Receptors TLR1, 2, 4, 5, 6, 10, and 11 are expressed in cell membrane, while TLR3, 7, 8, and 9 are expressed intracellularly [72]. Toll like receptor microbial ligands and inflammatory cytokines stimulate and induce VCAM-1 expression by stimulation of TLRs [73]. Mast cells express TLRs, including TLR-9 and TLR-3, which stimulate and have a positive influence in VCAM-1 expression in diabetic patients [73]. They can be activated by several compounds, including bacteria, an effect that leads to the release of several cytokines and chemokines. These studies suggest that infections that occur in diabetes may modify the course of inflammation orchestrated by MC activity.

According to the recently published international consensus, data are accumulating to support the view that MCs are involved in insulin resistance and type 2 diabetes and participate in diabetes and other metabolic diseases where immunity is compromised [33].

It has been reported in *in vitro* studies that activated MCs may contribute to the uptake of low-density lipoproteins (LDL) to cultured macrophages, increasing the generation of foam cells which exert a series of potentially detrimental effects on many cell types, as well as atherogenic actions and diabetogenic functions on the β cells of the endocrine pancreas [74]. Leptin is also involved in T2DM and obesity, which, in some cases, is linked to asthma in children [75], and it acts through histamine produced in the brain [76]. The treatment of diabetic patients with histamine-2 receptor blockers (H2RBs) could reduce the risk of cancer diseases [76].

Increasing numbers of drugs to lower and control blood glucose are used in patients affected by T2DM. These numerous glucose-lowering compounds act with different mechanisms, and one must take into account the relationship between the beneficial effect and their side effects [49].

Targeting and blocking TNF and/or *c*-kit stem cell factor or their receptors on activated MCs, which regulates the recruitment and maturation of these cells, could be an effective therapeutic treatment for reducing the inflammatory phenomena which occur in T2DM [77].

Therapies targeting MCs may prove beneficial for treatment of inflammatory and autoimmune diseases (Table III). Therefore, anti-inflammatory therapy targeting MC degranulated mediators and cytokines/chemokines generated by these cells may improve insulin resistance and glycemic control.

However, several authors have reported that in diabetes, during the inflammatory response, there is re-

Table III. Mast cell mediator release participates in innate acquired immunity, inflammation, autoimmunity and metabolic disorders, including diabetes

Mast cells and diabetes cross-talk
Contribute to autoimmune diabetes by releasing interleukin-6
Mediate autoimmune diseases
Exert an anti-inflammatory action and protect mice from obesity and diabetes
Infiltrate pancreatic islets in human type 1 diabetes
Participate in cardio-metabolic diseases and diabetes
Control insulitis and increase Treg cells to confer protection
Have an impact on cardiovascular diseases in diabetes
Have a role in wound healing in induced diabetic mice
Their reduction improves vascular functions
Are involved in adipose tissue fibrosis
Histamine H_2 receptor signaling participates in the pathogenesis of sepsis in diabetes
Participate in myocardial remodeling in diabetes
Proteases are potential risk factors of impaired fasting glucose and glucose tolerance
Affect wound healing in a diabetic rat model
Chymase and tryptase as targets for metabolic diseases including diabetes
Inhibition of phospholipase A2 in mast cells modulates adipocyte signaling and diabetes
Mast cells and NK T-cells are activated in T2DM patients
Proteases are potential risk factors of human pre-diabetes and diabetes mellitus
Anti-FcεRI antibody activates mast cells and delays T1DM

duced MC degranulation and production of reactive oxygen species, a decrease of microvascular response to MC mediators, including histamine, and reduced release of cytokines and arachidonic acid products [78]. All these effects can be ameliorated by insulin therapy. MCs have also emerged as modulators and down regulators of allergic inflammation. MCs may exert promotion or protection of wound healing, angiogenesis, cardiovascular diseases, obesity, diabetes and other disorders [67].

In addition, in some studies, it has been reported that mast cells may prevent obesity and diabetes in experimental animal models [79]. Moreover, diabetes mellitus may present inhibition of mast cell activation, a decrease of leukocyte-endothelial cell interactions, reduced numbers of leukocytes in inflammatory sites, a decrease of microvascular responses to inflammatory compounds, including histamine, a reduction in protein loss, and a decrease of acute inflammatory reactions [80].

We previously reported that MCs appear to be able to promote tumor development through the generation of certain inflammatory mediators and are therefore beneficial to the tumor, while producing other products may be detrimental to the tumor by participating in its rejection [81]. Regarding the involvement of the MCs in diabetes, it might be in the same situation. Indeed, MCs may be detrimental in diabetic patients by producing inflammatory mediators, PGD2 and cytokine/chemokine generation, but may also be protective, since their proteases may reduce the damage of pancreatic tissue by inducing Tregs generating IL-10 and TGF-β, as well as $CD4^+$ $CD25^+$ $FoxP3^+$ T cells [82]. Furthermore, they activate the newly discovered siglec-8 receptor, which acts as an inhibitor of mast cell-mediated inflammation [28]. In addition, the induction of IgE synthesis is completely abrogated by neutralizing IL-4 and IL-13 with monoclonal antibodies, or CD40L with soluble CD40 [28, 83].

Mast cells and their mediators could represent an important therapeutic target for diabetes and its complications [77].

Therefore, cytokines produced by MCs in pancreatic cells are important mediators, demonstrating an association between inflammatory cytokines and diabetes exacerbation, but the evidence is not conclusive. However, the role of cytokines/chemokines in diabetes is still unclear.

These studies contribute to the understanding of the mechanisms by which MCs profoundly affect T1DM and T2DM, and generate immune-inflammatory responses, suggesting that the antagonist(s) against MC inflammatory mediators and cytokines/chemokines released may have inhibitory biological effects on diabetes. Moreover, manipulation of MCs could represent a new additional therapeutic strategy in diabetes and other metabolic disorders. However, the mechanism by which MCs and their products mediate metabolic diseases is still unclear.

More studies are needed to confirm the direct involvement of mast cell-derived inflammatory mediators in diabetic pathogenesis and other metabolic syndromes.

The authors declare no conflict of interest.

References

1. Conti P, Youinou P, Theoharides TC. Modulation of autoimmunity by the latest interleukins (with special emphasis on IL-32). Autoimmun Rev 2007; 6: 131-137.
2. Kahaly GJ, Hansen MP. Type 1 diabetes associated autoimmunity. Autoimmun Rev 2016; 15: 644-648.
3. Kalish RS, Askenase PW. Molecular mechanisms of CD8+ T cell-mediated delayed hypersensitivity: implications for allergies, asthma, and autoimmunity. J Allergy Clin Immunol 1999; 103: 192-199.
4. Wynn TA. Type 2 cytokines: mechanisms and therapeutic strategies. Nat Rev Immunol 2015; 15: 271-282.
5. Oki S, Miyake S. Invariant natural killer T (iNKT) cells in asthma: a novel insight into the pathogenesis of asthma and the therapeutic implication of glycolipid ligands for allergic diseases. Allergol Int 2007; 56: 7-14.
6. Marcinkiewicz J. Cell-mediated immunity: role of IL-3 and IL-6 in the regulation of contact sensitivity reaction. Folia Histochem Cytobiol 1990; 28: 107-119.
7. Clardy SL, Lennon VA, Dalmau J, et al. Childhood onset of stiff-man syndrome. JAMA Neurol 2013; 70: 1531-1536.
8. Craighead JE. Current views on the etiology of insulin-dependent diabetes mellitus. N Engl J Med 1978; 299: 1439-1445.
9. Tahergorabi Z, Khazaei M. Imbalance of angiogenesis in diabetic complications: the mechanisms. Int J Prev Med 2012; 3: 827-838.
10. Di Gialleonardo V, de Vries EF, Di Girolamo M, et al. Imaging of β-cell mass and insulitis in insulin-dependent (Type 1) diabetes mellitus. Endocr Rev 2012; 33: 892-919.
11. Takai S, Jin D, Miyazaki M. Multiple mechanisms for the action of chymase inhibitors. J Pharmacol Sci 2012; 118: 311-316.
12. Gu Y, Yang DK, Spinas E, et al. Role of TNF in mast cell neuroinflammation and pain. J Biol Regul Homeost Agents 2015; 29: 787-791.
13. Venkatesha SH, Dudics S, Weingartner E, et al. Altered Th17/Treg balance and dysregulated IL-1β response influence susceptibility/resistance to experimental autoimmune arthritis. Int J Immunopathol Pharmacol 2015; 28: 318-328.
14. Zheng Z, Huang H, Yu Y, Liang J. Overexpression of FgI2 deteriorates the heart function of experimental autoimmune myocarditis rats. Eur J Inflamm 2015; 13: 66-71.
15. Sannegowda KM, Venkatesha SH, Moudgil KD. Tinospora cordifolia inhibits autoimmune arthritis by regulating key immune mediators of inflammation and bone damage. Int J Immunopathol Pharmacol 2015; 28: 521-531.
16. Theoharides TC, Petra AI, Taracanova A, Panagiotidou S, Conti P. Targeting IL-33 in autoimmunity and inflammation. J Pharmacol Exp Ther 2015; 354: 24-31.
17. Padgett LE, Broniowska KA, Hansen PA, et al. The role of reactive oxygen species and proinflammatory cytokines in type 1 diabetes pathogenesis. Ann N Y Acad Sci 2013; 1281: 16-35.
18. Hober D, Sauter P. Pathogenesis of type 1 diabetes mellitus: interplay between enterovirus and host. Nat Rev Endocrinol 2010; 6: 279-289.

19. Ahmadi Z, Arababadi MK, Hassanshahi G. CXCL10 activities, biological structure, and source along with its significant role played in pathophysiology of type I diabetes mellitus. Inflammation 2013; 36: 364-371.
20. Conti P, Pang X, Boucher W, et al. Impact of Rantes and MCP-1 chemokines on in vivo basophilic cell recruitment in rat skin injection model and their role in modifying the protein and mRNA levels for histidine decarboxylase. Blood 1997; 89: 4120-4127.
21. Licari A, De Amici M, Nigrisoli S, et al. Tryptase and histamine may support oral food challenge in the diagnosis of allergy. J Biol Regul Homeost Agents 2015; 29: 1-7.
22. Theoharides TC, Petra AI, Taracanova A, et al. Targeting IL-33 in autoimmunity and inflammation. J Pharmacol Exp Ther 2015; 354: 24-31.
23. Gu Y, Yang DK, Spinas E, et al. Role of TNF in mast cell neuroinflammation and pain. J Biol Regul Homeost Agents 2015; 29: 787-791.
24. Eskandari N, Tashrifi F, Bastan R, et al. Cyclic nucleotide phosphodiesterase isoforms in human basophils and mast cells. Int J Immunopathol Pharmacol 2016; pii: 0394632015626150.
25. Toniato E, Spinas E, Saggini A, et al. Immunomodulatory effects of vitamin d on skin inflammation. J Biol Regul Homeost Agents 2015; 29: 563-567.
26. Huh JY, Park YJ, Ham M, Kim JB. Crosstalk between adipocytes and immune cells in adipose tissue inflammation and metabolic dysregulation in obesity. Mol Cells 2014; 37: 365-371.
27. Bonnefoy JY, Gauchat JF, Life P, et al. Pairs of surface molecules involved in human IgE regulation: CD23-CD21 and CD40-CD40L. Eur Respir J Suppl 1996; 22: 63-66.
28. Falcone FH, Haas H, Gibbs BF. The human basophil: a new appreciation of its role in immune responses. Blood 2000; 96: 4028-4038.
29. Petra AI, Panagiotidou S, Stewart JM, et al. Spectrum of mast cell activation disorders. Expert Rev Clin Immunol 2014; 10: 729-739.
30. Sykora KW, Tomeczkowski J, Reiter A. C-kit receptors in childhood malignant lymphoblastic cells. Leuk Lymphoma 1997; 25: 201-216.
31. Theoharides TC, Kempuraj D, Tagen M, et al. Differential release of mast cell mediators and the pathogenesis of inflammation. Immunol Rev 2007; 217: 65-78.
32. Tan SL, Parker PJ. Emerging and diverse roles of protein kinase C in immune cell signalling. Biochem J 2003; 376: 545-552.
33. Zhang J, Shi GP. Mast cells and metabolic syndrome. Biochim Biophys Acta 2012; 1822: 14-20.
34. Walz P, Ladowski JS, Hines A. Distal revascularization and interval ligation (DRIL) procedure for the treatment of ischemic steal syndrome after arm arteriovenous fistula. Ann Vasc Surg 2007; 21: 468-473.
35. Simmons K, Michels AW. Lessons from type 1 diabetes for understanding natural history and prevention of autoimmune disease. Rheum Dis Clin North Am 2014; 40: 797-811.
36. Shi MA, Shi GP. Different roles of mast cells in obesity and diabetes: lessons from experimental animals and humans. Front Immunol 2012; 3: 7.
37. Chen GT, Han N, Li GF, et al. TNF-α mutation affects the gene expression profile of patients with multiple trauma. Eur J Inflamm 2015; 13: 109-116.
38. Tharp MD. The interaction between mast cells and endothelial cells. J Invest Dermatol 1989; 93: 107-112.
39. Papaccio G. Insulitis and islet microvasculature in type 1 diabetes. Histol Histopathol 1993; 8: 751-759.
40. Shinomiya M, Nadano S, Shinomiya H, Onji M. In situ characterization of dendritic cells occurring in the islets of nonobese diabetic mice during the development of insulitis. Pancreas 2000; 20: 290-296.
41. Möller E, Valugerdi MA, Ridderstad A. Specific and non-specific autoreactive immunity. J Autoimmun 1992; 5: 37-44.
42. Li CR, Baaten BJ, Bradley LM. Harnessing memory adaptive regulatory T cells to control autoimmunity in type 1 diabetes. J Mol Cell Biol 2012; 4: 38-47.
43. Milovanovic M, Volarevic V, Radosavljevic G. IL-33/ST2 axis in inflammation and immunopathology. Immunol Res 2012; 52: 89-99.
44. Starska K, Brzezińska-Błaszczyk E. The role of stromal mast cells in the modification of CD4+CD25+Foxpł regulatory T cells, Th17 lymphocytes and cytotoxic lymphocytes Tc1 in the development and progression of tumor. Postepy Hig Med Dosw (Online) 2010; 64: 408-416.
45. Sia C, Hänninen A. Functional alterations of proinflammatory monocytes by T regulatory cells: implications for the prevention and reversal of type 1 diabetes. Rev Diabet Stud 2010; 7: 6-14.
46. Noble JA, Johnson J, Lane JA, Valdes AM. HLA class II genotyping of African American type 1 diabetic patients reveals associations unique to African haplotypes. Diabetes 2013; 62: 3292-3299.
47. Lukic ML, Mensah-Brown E, Wei X, et al. Lack of the mediators of innate immunity attenuate the development of autoimmune diabetes in mice. J Autoimmun 2003; 21: 239-246.
48. Conti P, Reale M, Barbacane RC, et al. Intramuscular injection of hrRANTES causes mast cell recruitment and increased transcription of histidine decarboxylase in mice: lack of effects in genetically mast cell-deficient W/Wv mice. FASEB J 1998; 12: 1693-1700.
49. Hattersley AT, Thorens B. Type 2 diabetes, SGLT2 inhibitors, and glucose secretion. N Engl J Med 2015; 373: 974-976.
50. Zhang J, Shi GP. Mast cells and metabolic syndrome. Biochim Biophys Acta 2012; 1822: 14-20.
51. Ikeda T. The pathogenesis of vitreoretinal diseases from the standpoint of molecular biology. Nippon Ganka Gakkai Zasshi 2003; 107: 785-812.
52. Lee M, Calabresi L, Chiesa G, et al. Mast cell chymase degrades apoE and apoA-II in apoA-I-knockout mouse plasma and reduces its ability to promote cellular cholesterol efflux. Arterioscler Thromb Vasc Biol 2002; 22: 1475-1481.
53. Conti P, Shaik-Dasthagirisaheb YB. Mast cell serotonin immunoregulatory effects impacting on neuronal function: implications for neurodegenerative and psychiatric disorders. Neurotox Res 2015; 28: 147-153.
54. Hübner MP, Larson D, Torrero MN. Anti-FcεR1 antibody injections activate basophils and mast cells and delay Type 1 diabetes onset in NOD mice. Clin Immunol 2011; 141: 205-217.
55. Shi GP, Bot I, Kovanen PT. Mast cells in human and experimental cardiometabolic diseases. Nat Rev Cardiol 2015; 12: 643-658.
56. Woolley DE. The mast cell in inflammatory arthritis. N Engl J Med 2003; 348: 1709-1711.
57. Qin L, Zhao D, Xu J, et al. The vascular permeabilizing factors histamine and serotonin induce angiogenesis through TR3/Nur77 and subsequently truncate it through thrombospondin-1. Blood 2013; 121: 2154-2164.
58. Au RY, Al-Talib TK, Au AY, et al. Avocado soybean unsaponifiables (ASU) suppress TNF-alpha, IL-1beta, COX-2, iNOS gene expression, and prostaglandin E2 and nitric oxide production in articular chondrocytes and monocyte/macrophages. Osteoarthritis Cartilage 2007; 15: 1249-1255.
59. Kohlgruber A, Lynch L. Adipose tissue inflammation in the pathogenesis of type 2 diabetes. Curr Diab Rep 2015; 15: 92.
60. Antonelli A, Ferrari SM, Giuggioli D, et al. Hepatitis C virus infection and type 1 and type 2 diabetes mellitus. World J Diabetes 2014; 5: 586-600.

61. Tonnel AB, Gosset P, Molet S, et al. Interactions between endothelial cells and effector cells in allergic inflammation. Ann N Y Acad Sci 1996; 796: 9-20.
62. Uysal KT, Wiesbrock SM, Marino MW, Hotamisligil GS. Protection from obesity-induced insulin resistance in mice lacking TNF-alpha function. Nature 1997; 389: 610-614.
63. Reber LL, Sibilano R, Mukai K, Galli SJ. Potential effector and immunoregulatory functions of mast cells in mucosal immunity. Mucosal Immunol 2015; 8: 444-463.
64. Toniato E, Spinas E, Saggini A, et al. Immunomodulatory effects of vitamin d on skin inflammation. J Biol Regul Homeost Agents 2015; 29: 563-567.
65. Xu Y, Chen G. Mast cell and autoimmune diseases. Mediators Inflamm 2015; 2015: 246126.
66. Wesolowski J, Paumet F. The impact of bacterial infection on mast cell degranulation. Immunol Res 2011; 51: 215-226.
67. Rodewald HR, Feyerabend TB. Widespread immunological functions of mast cells: fact or fiction? Immunity 2012; 37: 13-24.
68. Ryba-Stanisławowska M, Stanisławowski M, Myśliwska J. Effector and regulatory T cell subsets in diabetes-associated inflammation. Is there a connection with ST2/IL-33 axis? Perspective. Autoimmunity 2014; 47: 361-371.
69. Manti S, Chimenz R, Salpietro A, et al. Atopic dermatitis: expression of immunological imbalance. J Biol Regul Homeost Agents 2015; 29 (2 Suppl 1): 13-17.
70. Shin JS, Abraham SN. Co-option of endocytic functions of cellular caveolae by pathogens. Immunology 2001; 102: 2-7.
71. Sandig H, Bulfone-Paus S. TLR signaling in mast cells: common and unique features. Front Immunol 2012; 3: 185.
72. Avila M, Gonzalez-Espinosa C. Signaling through Toll-like receptor 4 and mast cell-dependent innate immunity responses. IUBMB Life 2011; 63: 873-880.
73. Abella V, Scotece M, Conde J, et al. The novel adipokine progranulin counteracts IL-1 and TLR4-driven inflammatory response in human and murine chondrocytes via TNFR1. Sci Rep 2016; 6: 20356.
74. Dvorak AM. New aspects of mast cell biology. Int Arch Allergy Immunol 1997; 114: 1-9.
75. Garozzo MT, Cuppari C, Filippelli M, et al. Relation of body mass index with ige levels, allergic sensitization and lung function in asthmatic children: our experience and revision of literature. J Biol Regul Homeost Agents 2015; 29: 89-95.
76. Masaki T, Yoshimatsu H. Neuronal histamine and its receptors in obesity and diabetes. Curr Diabetes Rev 2007; 3: 212-216.
77. Woolley DE. The mast cell in inflammatory arthritis. N Engl J Med 2003; 348: 1709-1711.
78. Aronin N, Leeman SE, Clements RS Jr. Diminished flare response in neuropathic diabetic patients. Comparison of effects of substance P, histamine, and capsaicin. Diabetes 1987; 36: 1139-1143.
79. Sismanopoulos N, Delivanis DA, Alysandratos KD, et al. Mast cells in allergic and inflammatory diseases. Curr Pharm Des 2012; 18: 2261-2277.
80. Takai S, Jin D, Miyazaki M. Multiple mechanisms for the action of chymase inhibitors. J Pharmacol Sci 2012; 118: 311-316.
81. Theoharides TC, Conti P. Mast cells: the Jekyll and Hyde of tumor growth. Trends Immunol 2004; 25: 235-241.
82. Li Z, Zhou J, Zhu D, et al. Role of endogenous TNF-α in cardiomyocyte apoptosis induced by bacteria lipoprotein and the protective effect of IL-10. Eur J Inflamm 2015; 13: 117-125.
83. Zhang C, Liu X, Zhan H, Chen D. Role of dexmedetomide in IL-4 and IFN-γ expression in rats with multiple organ dysfunction syndrome induced by postpartum bleeding. Eur J Inflamm 2015; 13: 164-172.

Address for correspondence

Pio Conti
Postgraduate Medical School
Università G. d'Annunzio, Italy
viale Unità d'Italia
66100 Chieti, Italy
e-mail: pconti@unich.it