



Different Roles of Mast Cells in Obesity and Diabetes: Lessons from Experimental Animals and Humans

Citation

Shi, Michael A., and Guo-Ping Shi. 2012. Different roles of mast cells in obesity and diabetes: Lessons from experimental animals and humans. *Frontiers in Immunology* 3:7.

Published Version

doi:10.3389/fimmu.2012.00007

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Different roles of mast cells in obesity and diabetes: lessons from experimental animals and humans

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Mast cells (MCs) play an important role in allergic hyperresponsiveness and in defending microorganism infections. Recent studies of experimental animals and humans have suggested that MCs participate in obesity and diabetes. MC distribution and activities in adipose tissues may vary, depending on the locations of different adipose tissues. In addition to releasing inflammatory mediators to affect adipose tissue extracellular matrix remodeling and to promote inflammatory cell recruitment and proliferation, MCs directly and indirectly interact and activate adipose tissue cells, including adipocytes and recruited inflammatory cells. Plasma MC protease levels are significantly higher in obese patients than in lean subjects. Experimental obese animals lose body weight after MC inactivation. MC functions in diabetes are even more complicated, and depend on the type of diabetes and on different diabetic complications. Both plasma MC proteases and MC activation essential immunoglobulin E levels are significant risk factors for human pre-diabetes and diabetes mellitus. MC stabilization prevents diet-induced diabetes and improves pre-established diabetes in experimental animals. MC depletion or inactivation can improve diet-induced type 2 diabetes and some forms of type 1 diabetes, but also can worsen other forms of type 1 diabetes, at least in experimental animals. Observations from animal and human studies have suggested beneficial effects of treating diabetic patients with MC stabilizers. Some diabetic patients may benefit from enhancing MC survival and proliferation – hypotheses that merit detailed basic researches and clinical studies.

Keywords: mast cell, obesity, diabetes, diabetic nephropathy, T cell, dendritic cell

INTRODUCTION

Mast cells (MCs) are inflammatory cells similar to macrophages, neutrophils, and lymphocytes, but they localize near surfaces exposed to the environment – such as the skin, airway, and gastrointestinal tract, where pathogens, allergens, and other environment agents frequently reside (Metcalf et al., 1997; Galli et al., 2005a). These cells therefore are first-line immune cells defending against bacterial and viral infections, and are essential in airway hypersensitivity, skin allergies, and food anaphylaxis. Recent studies, however, suggest that MCs appear in most tested tissues, and are more than just a first-line immune response. They are abundant in tumor tissues (Maltby et al., 2009), in atherosclerotic lesions and other vascular lesions (Kovanen, 2007; Sun et al., 2007a,b), and in inflamed white adipose tissue (WAT; Liu et al., 2009). MCs are derived from hematopoietic progenitor cells that migrate into virtually any tissue, where they complete their maturation (Metcalf et al., 1997). In the microenvironment, MCs require IL3 for early proliferation (Mekori et al., 1993) and stem cell factor (SCF) from stromal cells to maintain viability and maturation (Nocka et al., 1990; Irani et al., 1992).

Obesity and diabetes are considered chronic inflammatory diseases, largely due to several recent seminal discoveries of inflammatory cells in WAT – including macrophages (Ochi et al., 1988; Weisberg et al., 2003; Xu et al., 2003), B cells (Winer et al., 2011), CD4⁺ T cells (Winer et al., 2009), CD8⁺ T cells (Nishimura et al.,

2009), regulatory T cells (Treg; Feuerer et al., 2009), NK T cells (Ohmura et al., 2010), eosinophils (Wu et al., 2011), and MCs (Liu et al., 2009). These cells may interact directly through cell–cell contact, or indirectly by releasing cell mediators within adipose tissue. Relative to macrophages or lymphocytes, far fewer studies are available regarding MC functions in obesity and diabetes. This brief review summarizes what we have learned from experimental animals and observations from human studies.

MAST CELLS IN OBESITY

Adipose tissue, and WAT in particular, provides structural support and serves as a reservoir for energy surplus, but it also regulates metabolism, blood pressure, immune responses, coagulation, and functions of other endocrine organs (Trayhurn, 2005). A remarkable heterogeneity exists in the severity of WAT inflammation in different types of fat depots in obese subjects (Murano et al., 2008; Altintas et al., 2011a). MCs are myeloid hematopoietic cells derived from hematopoietic stem cells in the bone marrow. Progenitor MCs leave the bone marrow and differentiate into different MC subtypes, corresponding to the tissue compartments into which they home (Nakano et al., 1985). Recent discoveries demonstrated that WAT also harbors mast lineage cells that can home to organs such as intestine and skin, where they fulfill their roles (Poglio et al., 2010). For example, mouse inguinal fat pads contain c-Kit⁺Thy-1^{lo}Lin⁻Sca⁺ cells, which can differentiate into other cell types *in vitro*, such as functional mucosal MCs (Poglio et al., 2010).

Therefore, WAT harbors not only MC maturation, but also the whole process of MC differentiation.

MAST CELLS IN DIFFERENT ADIPOSE TISSUES

While WAT from obese humans and animals contains higher numbers of MCs than that from lean subjects in general, MC number, and functions can vary among fat pads from different locations. For example, whereas the difference in MC number in subcutaneous WAT between obese and lean subjects was not significant, MC numbers in visceral WAT increase significantly in obese mice compared with those in lean mice, and MC crown-like structures became prevalent in obese visceral WAT (Altintas et al., 2011a). The infrapatellar fat pad (IFP), also called Hoffa's fat pad, is an adipose tissue depot located intracapsularly and extrasynovially in the knee joint, to secrete inflammatory cytokines (Tilg and Moschen, 2006; Clockaerts et al., 2010). In a recent study among patients in the Netherlands, IFPs from patients with osteoarthritis contained higher amounts of IL6 and adipisin, and higher numbers of MCs, than those from subcutaneous WAT from the same patient population. IFP TNF- α levels, which may come from MCs, correlate with body-mass index (BMI) among this osteoarthritis patient population (Klein-Wieringa et al., 2011). Unlike subcutaneous WAT or visceral WAT, epididymal fat masses from mice fed a high-fat diet (HFD) for 20 weeks correlate inversely with body weight and liver mass. These fat tissues contain abundant dead adipocytes, as well as MCs, macrophages, and apoptotic cells. Therefore, mouse mast cell protease-6 (mMCP-6, human tryptase homolog), macrophage marker F4/80, cell apoptosis marker cleaved caspase-3, and the levels of the cytokines TNF- α and IL10 mRNA and of protein, all increased in obese mouse epididymal fat (Altintas et al., 2011b). Reduced epididymal fat mass in mice with long-standing obesity therefore is accompanied by divergent distribution of crown-like structures, apoptotic cells, MCs, and macrophages (Altintas et al., 2011b).

MAST CELL-T CELL INTERACTIONS IN WAT

White adipose tissue contains CD4⁺, CD8⁺, Treg, and NK T cells (Feurerer et al., 2009; Nishimura et al., 2009; Winer et al., 2009; Ohmura et al., 2010). We recently showed that CD8⁺ T cells and MCs localize together in mouse visceral WAT (Xu and Shi, 2012). Physical proximity between MCs and T cells proposes a bidirectional functional relationship between the two cell types (Mekori, 2004; Kalesnikoff and Galli, 2008). MCs degranulate in response to direct contact with T cells or T cell membrane preparations, and release MC mediators, such as TNF- α , IL8, and oncostatin M (Baram et al., 2001; Salamon et al., 2008). Separation of the two cell populations by a semipermeable porous membrane prevents MC activation (Inamura et al., 1998), suggesting that T cells activate MCs not necessarily by small molecule protein peptides, but instead by using membrane transfer as a mode in intercellular communication. Many cells, including monocytes (Shi and Shi, 2010) and T cells (Al-Nedawi et al., 2009; Théry et al., 2009), release microvesicles. A recent study using Centricon filtration, high-speed centrifugation, identification by electron microscopy, FACS (Annexin staining), and expression of integrin lymphocyte function-associated antigen 1 (LFA-1) demonstrated that human peripheral blood T cells use such microvesicles to activate human cord blood MC mitogen-activated protein kinase (MAPK) signaling pathway, followed by MC degranulation and release of IL8 and oncostatin M (Shefler et al., 2010). MC activation then boosts T cell proliferation by MC surface molecule LFA-1 (Sayed and Brown, 2007; Shefler et al., 2010; **Figure 1**).

Regulatory T cells influences the inflammatory state of WAT, thereby increasing insulin sensitivity in mice (Feurerer et al., 2009). Although there is no direct evidence that Treg interacts with MCs in WAT, interaction between OX40 on Treg and OX40L on MCs suppresses MC degranulation and allergic responses (Gri et al., 2008; Piconese et al., 2009). *In vitro* interactions between human and mouse MCs and CD4⁺CD25⁺Foxp3⁺ Treg reduced

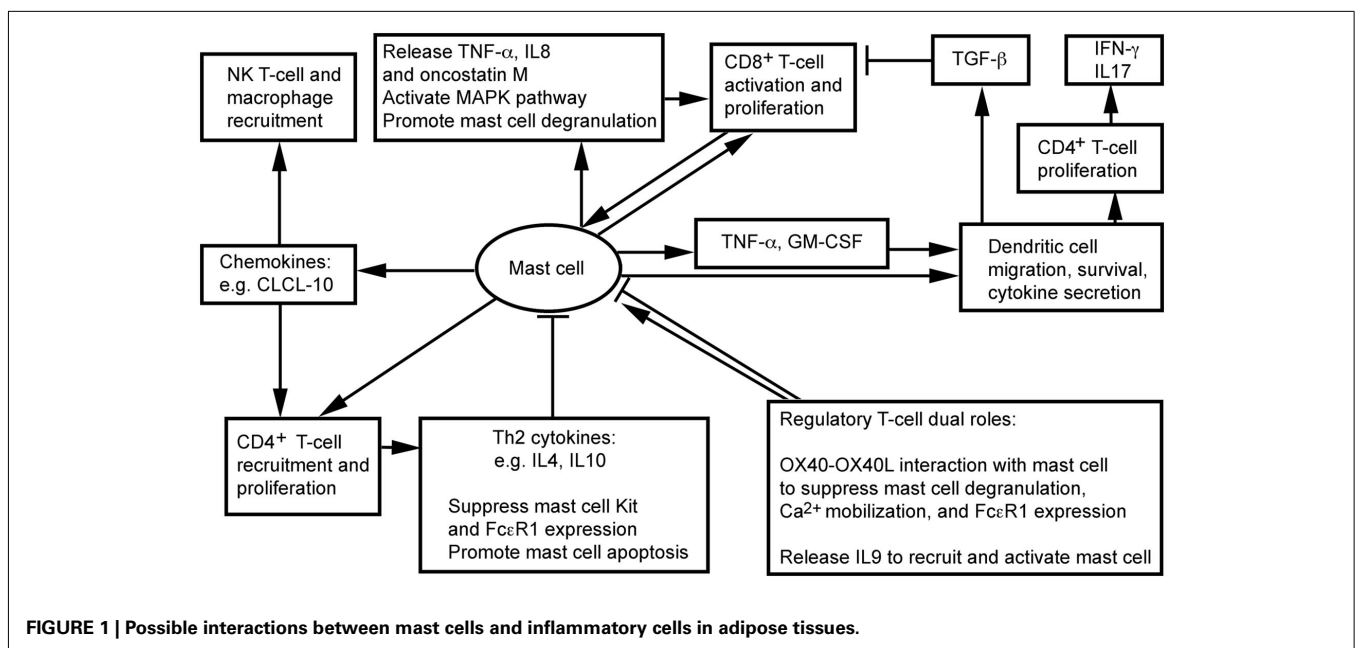


FIGURE 1 | Possible interactions between mast cells and inflammatory cells in adipose tissues.

MC degranulation and Ca^{2+} mobilization, without affecting overall cytokine secretion (Frossi et al., 2011). Anti-OX40L antibody blocks Treg-mediated MC stabilization (Gri et al., 2008). Treg also suppress MC expression of high-affinity IgE receptor FcεR1 (Kashyap et al., 2008). Treg may interact with MCs differently, however, under a different environment. In an allograft tolerance model, where MCs are essential in $\text{CD4}^+\text{CD25}^+\text{Foxp3}^+$ Treg-dependent peripheral tolerance, Treg plays an immunosuppressive role by recruiting and activating MCs. When MC-deficient $\text{Kit}^{\text{W-sh/W-sh}}$ mice do not induce tolerance, Treg produces IL9 to recruit and activate MCs in tolerant tissues to mediate regional immunosuppression. Anti-IL9 antibody neutralization leads to allograft rejection (Lu et al., 2006). In WAT, therefore, whether Treg activates MCs for immunosuppression or suppresses MC degranulation remains unknown.

NK T cells participate in WAT inflammation. Absence of NK T cells protects mice from diet-induced obesity (DIO), whereas NK T cell activation with α -galactosylceramide exacerbates glucose intolerance, macrophage infiltration, and WAT inflammatory cytokine expression (Ohmura et al., 2010). Although not tested in WAT, in mice infected with dengue virus, MCs express chemokine CXCL10 to trigger NK1.1^+ cell infiltration to dengue virus-infected footpads – a mechanism of MC control viral infection within tissues – and limit viral spread to draining lymph nodes. Recruitment of NK1.1^+ cells facilitates viral clearance (St. John et al., 2011). MCs may control NK T cell infiltration to WAT. We have shown that MC inactivation reduces macrophage infiltration to WAT (Liu et al., 2009). MCs also stimulate CD4^+ T cell migration (Kashyap et al., 2008) and proliferation (Kotani et al., 2007), and enhance antigen-specific CD8^+ T cell activation and proliferation – a process requiring direct interaction between MCs and T cells (Stelekati et al., 2009). While CD8^+ T cells increased in obese WAT and exhibited adverse effects in obesity and diabetes (Nishimura et al., 2009), CD4^+ T cells decreased in obese WAT (Winer et al., 2009). Th2 cytokines, such as IL4 and IL10, reduce the expression of Kit (SCF receptor) and FcεR1 (Ryan et al., 1998; Mirmonsef et al., 1999) in MCs, and promote MC apoptosis (Yeatman et al., 2000; **Figure 1**). High numbers of Th2 cells and low numbers of MCs therefore occur in WAT from lean subjects (Liu et al., 2009; Winer et al., 2009).

MAST CELL–DENDRITIC CELL INTERACTIONS

Dendritic cells (DCs) are the most effective professional antigen-presenting cells that prime T cells. DCs play an important role in atherogenesis (Tedgui et al., 2011), but their functions in obesity and diabetes remain unknown. Several lines of experiments – though most not related to obesity – suggest a controversial role of DCs in inflammation. DCs from obese mice show impaired antigen-presenting activity to activate CD8^+ T cells, due to secretion of immunosuppressive transforming growth factor- β (TGF- β ; Macia et al., 2006; Smith et al., 2009). Murine peritoneal MCs, however, directly contact immature DCs and induce their maturation with enhanced expression of DC co-stimulatory molecules. Co-culture of DCs and MCs releases the T cell modulating cytokines IFN- γ , IL2, IL6, and TGF- β . MCs also synergistically increase endotoxin-induced DC secretion of these

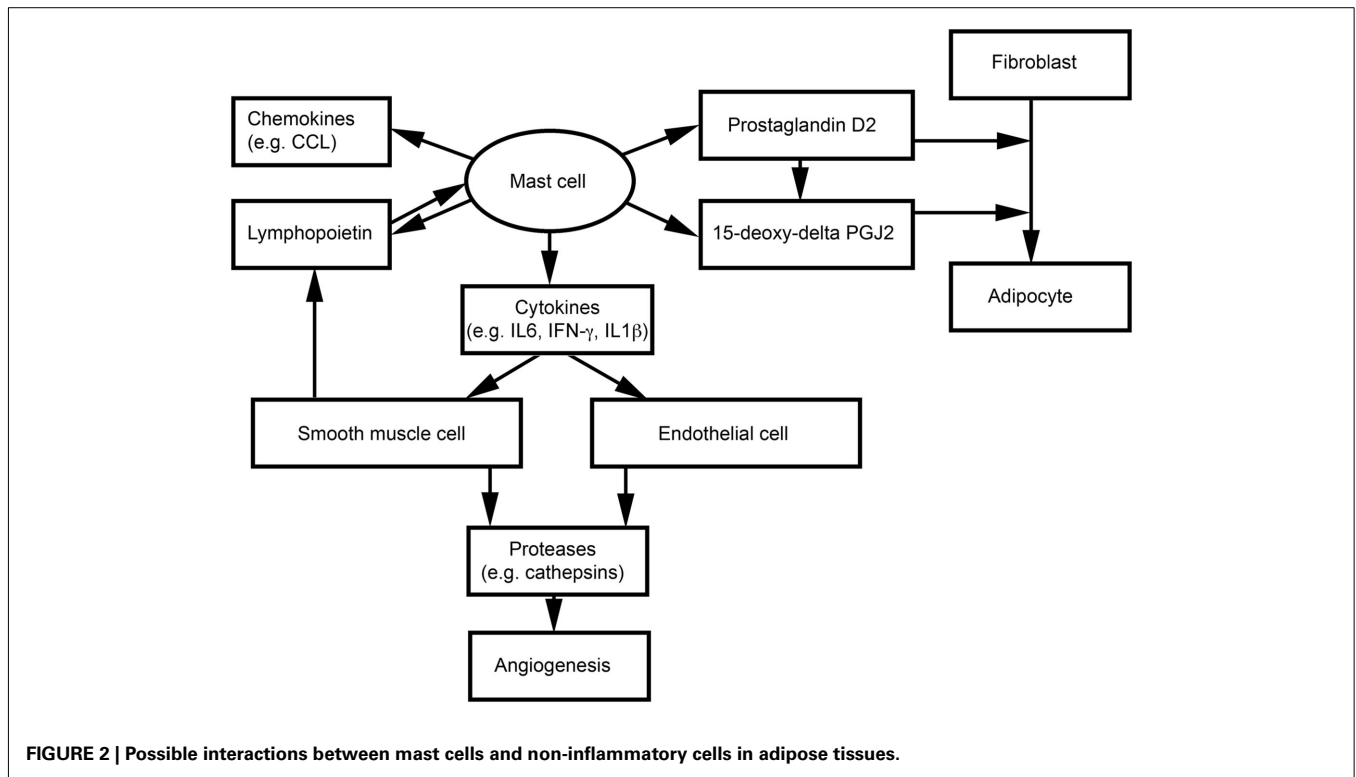
cytokines, thereby inducing CD4^+ T cell proliferation and the release of high levels of IFN- γ and IL17. MCs thus may indirectly promote Th1 and Th17 responses (Dudeck et al., 2011; **Figure 1**). In addition to affecting DC maturation, MCs release TNF- α to mediate DC migration (Suto et al., 2006). In a hapten FITC-induced cutaneous allergic contact hypersensitivity mouse model, MC deficiency ($\text{Kit}^{\text{W-sh/W-sh}}$ mice) suppressed contact hypersensitivity, which can be repaired by local transfer of MCs from wild-type (WT) mice, but not those from $\text{Tnfr}^{-/-}$ MCs. In the same model, FITC DC migration to draining lymph nodes or airway DC migration to local lymph nodes are impaired in $\text{Kit}^{\text{W-sh/W-sh}}$ mice or $\text{Tnfr}^{-/-}$ mice. In a mouse skin allograft tolerance model, MCs increased TNF- α -dependent DC accumulation in draining lymph nodes. MC production of GM-CSF also controls graft-derived DC survival. DCs that migrate from tolerant allografts to draining lymph nodes are tolerogenic and can suppress T cell responses (de Vries et al., 2011). MCs in WAT therefore may also regulate DC recruitment, maturation, and survival directly and indirectly (**Figure 1**). Consistent with this hypothesis, peripheral blood DC contents are significantly higher in obese patients with type 2 diabetes than in those without diabetes or lean patients, and DCs from obese and diabetic patients adhere much more efficiently to coronary smooth muscle cells (SMCs; Musilli et al., 2011).

MAST CELL INTERACTIONS WITH NON-INFLAMMATORY CELLS

Adipocytes, endothelial cells (ECs), and SMCs also are important components of WAT. We have shown that MCs release inflammatory cytokines to induce vascular EC and SMC expression of cysteinyl cathepsins, and therefore may promote angiogenesis and WAT growth in obese mice (Sun et al., 2007a,b; Liu et al., 2009; **Figure 2**). MCs and SMCs express thymic stromal lymphopoietin, which activates MCs to release inflammatory cytokines (e.g., IFN- γ , TNF- α , and IL1 β) and a series of CCL chemokines (Kaur et al., 2011; **Figure 2**). Earlier studies showed that nerve growth factor and cyclooxygenase mediate prostaglandin D₂ (PGD) production from MCs and T cells, respectively, and that PGD influences the differentiation of human fibroblasts into adipocytes (Marshall et al., 1999; Feldon et al., 2006). PGD can be metabolized into a final metabolite 15-deoxy-delta-12,14-prostaglandin J₂ (15-deoxy-delta PGJ₂), which is a major endogenous ligand of peroxisome proliferator-activated receptor- γ (PPAR γ ; Kliewer et al., 1995; Herlong and Scott, 2006). Recent studies demonstrated that MC supernatant contains 15-deoxy-delta PGJ₂ that induces pre-adipocyte 3T3-L1 cell adipogenesis (**Figure 2**). The specific PPAR γ antagonist GW9662 blocks this MC activity (Tanaka et al., 2011). Using MC-deficient $\text{Kit}^{\text{W/W}^v}$ mice, the investigators showed that reduced body weight in $\text{Kit}^{\text{W/W}^v}$ mice can be reversed by WT bone marrow-derived mast cell (BMMC) transplantation, but not by transplantation of BMMC from hematopoietic PGD synthase (H-PGDS)-deficient mice. H-PGDS-deficient BMMC also failed to induce 3T3-L1 differentiation (Tanaka et al., 2011).

ROLE OF MAST CELLS IN EXPERIMENTAL OBESE ANIMALS

Increased inflammation and MC infiltration in obese WAT suggest an essential role of MCs in obesity and its associated complications. As discussed earlier, MCs may interact with inflammatory



and non-inflammatory cells by direct cell–cell contact or by releasing inflammatory mediators. TNF- α , for example, is an important mediator of MCs (Zhang et al., 2011a,b) and is increased in obese rodents. Neutralization of TNF- α with a soluble TNF- α receptor-immunoglobulin G chimeric protein ameliorated insulin resistance (Hotamisligil et al., 1993), and obese mice lacking TNF- α demonstrated improved insulin sensitivity (Uysal et al., 1997). Hypoadiponectinemia associates with obesity and insulin resistance (Weyer et al., 2001). Adiponectin mRNA levels were increased in WAT from MC-null mice fed an HFD, although serum levels did not change (Tanaka et al., 2011).

Using *Kit*^{W-sh/W-sh} and *Kit*^{W/W^v} mice, we (Liu et al., 2009) and others (Tanaka et al., 2011) proved that MCs participate directly in obesity. While WT mice became obese after consuming an HFD, *Kit*^{W-sh/W-sh} and *Kit*^{W/W^v} mice were protected from DIO. Adoptive transfer of BMDC from WT or *Tnf*^{-/-} mice, but not those from *Il6*^{-/-}, *Ifng*^{-/-}, or H-PGDS-deficient mice, partially reversed body weight gain in *Kit*^{W-sh/W-sh} and *Kit*^{W/W^v} mice. Pharmacological MC inactivation using cromolyn and ketotifen, two common MC stabilizers, yielded similar results. Both drugs not only prevented WT mice from DIO, but also reduced pre-established obesity (Liu et al., 2009), revealing a possible therapy for obese humans.

MAST CELL-DERIVED MOLECULES IN OBESE PATIENTS

The role of MCs in human obesity has not been examined, but epidemiological studies consistently have shown a positive association between obesity and the risk of asthma (Beuther, 2009; Shore, 2010), and low-grade inflammation associated with obesity

could be a pathogenetic mechanism linking obesity to asthma (Hersoug and Linneberg, 2007). In a Danish study, serum MC tryptase levels, skin prick test reactivity (atopy), methacholine bronchial hyperresponsiveness (BHR), BMI, and serum lipid levels were determined in 1216 patients. Serum tryptase levels were much higher in obese patients (BMI > 30) than in lean patients [BMI < 25; 4.4 (3.0–6.1; 25th–75th percentile) μ g/L vs. 3.3 (2.3–4.9; 25th–75th percentile) μ g/L, $P < 0.0001$]. Among this population, serum tryptase levels associated positively with male sex and smoking, and inversely with alcohol consumption. Tryptase levels, however, did not associate with atopy or BHR but positively associated with the symptoms of allergic respiratory disease and obesity (OR = 1.98, 95% CI = 1.25–3.14). Increasing BMI therefore associates with serum tryptase levels and the prevalence of allergic respiratory disease symptoms, and MC activity did not affect the association between BMI and asthma and rhinitis symptoms (Fenger et al., 2011). Similar conclusions were made in a Spanish study of 420 patients. Among those patients, serum tryptase associated positively with age and serum IgE levels, but inversely with female sex and heavy alcohol use. Tryptase levels appear significantly higher in non-atopic patients, overweight patients, or patients with metabolic syndromes, compared with those were atopic, of normal weight, or without metabolic syndrome.

In a multivariate analysis, the significance of metabolic syndrome association with tryptase levels dropped from $P = 0.08$ to $P = 0.008$ after adjusting for age, sex, atopy status, IgE, alcohol use, and smoking (Gonzalez-Quintela et al., 2010). These human studies strongly suggest a role of MC activation in obesity, but this hypothesis has not been tested directly.

ROLE OF MAST CELLS IN DIABETES AND DIABETIC COMPLICATIONS

MAST CELLS IN TYPE 2 DIABETES

We first reported that MCs participate directly in type 2 diabetes mellitus (T2DM). DIO mice also developed glucose intolerance and insulin resistance, which did not appear in *Kit*^{W^{sh}/W^{sh} and *Kit*^{W^{Wv} MC-deficient mice. MC stabilization with either cromolyn or ketotifen had results similar to those from MC-deficient mice. Genetic deficiency and pharmacological inactivation of MCs therefore prevented diet-induced T2DM in mice (Liu et al., 2009). Mechanistically, we found that MC-derived IL6 and IFN- γ were critical to both obesity and diabetes. Reduced T2DM symptoms (serum glucose, leptin, insulin levels, and glucose tolerance and insulin sensitivity) in MC-deficient mice can be reversed partially by adoptive transfer of BMMC from WT or *Tnf*^{-/-} mice, but not those from *Il6*^{-/-} and *Ifng*^{-/-} mice. But different mechanisms may exist – for example, long-term culture in high-glucose medium augments IgE-induced MC activation (Anderson et al., 2010). Although not tested in our study, MC activation may be elevated in DIO mice. The most important finding of our study is that MC stabilization with cromolyn or ketotifen improved glucose tolerance and insulin sensitivity in DIO mice with pre-established T2DM. This finding has been confirmed in a patient with T2DM; less than 6 months of treatment with cromolyn reduced both plasma glucose and hemoglobin A1c levels to normal ranges (Shi, personal communication).}}

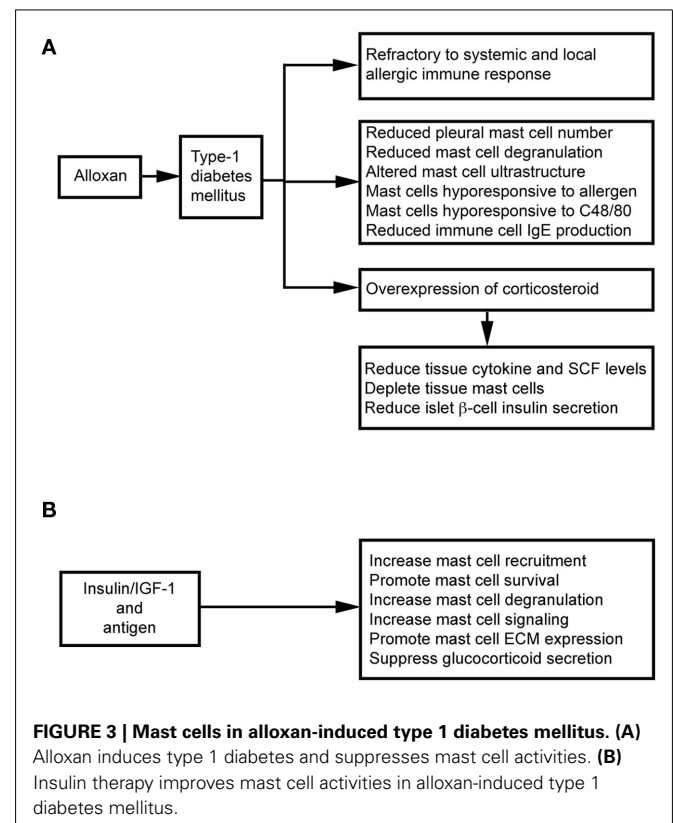
MAST CELLS IN TYPE 1 DIABETES

Although MC function in human type 1 diabetes mellitus (T1DM) has not been studied, several animal models have demonstrated rather complicated roles of MCs in T1DM. While accumulation of MCs is detrimental in animals with some T1DM models, MC depletion is an important mechanism of T1DM development in different experimental models.

Intravenous administration of alloxan induces T1DM in rats. These animals show decreased microvascular responses to inflammatory histamine (Fortes et al., 1983), decreased leukocyte–EC interaction (Fortes et al., 1991), and reduced MC degranulation (de Oliveira Barreto et al., 2003; Cavalher-Machado et al., 2004), but increased leukocyte apoptosis (Ottom et al., 2004). These diabetic rats therefore are refractory to systemic anaphylactic shock, and show a selective reduction in the number of pleural MCs – a phenomenon also observed after treatment with the alternative diabetogenic agent streptozotocin (STZ; Diaz et al., 1996). Diabetic sensitized animals are clearly resistant to local and systemic allergic inflammatory responses (Carvalho et al., 2005). It was hypothesized that autoimmune T1DM is Th1-dependent and that allergic responses are Th2-dependent. The susceptibility to one disease might lead to refractoriness to the other (Huang, 1999). Children with T1DM and their siblings, therefore, are partially protected against asthma (Douek et al., 1999), but several studies suggest that this refractoriness associates with MC depletion or the inability to activate MCs, and overexpression of endogenous corticosteroids (Diaz et al., 1997; Carvalho et al., 2003). MC depletion in the intestinal tissue is important in the refractoriness of diabetic rats to anaphylactic shock. In alloxan-treated rats, ovalbumin (OVA) sensitization reduces total cell yield in lavage fluid

after antigen challenge (Vianna and Garcia-Leme, 1995). In the same experimental model, bronchial segments from diabetic rats showed reduced contraction to OVA, and accompanied with a 50% reduction in degranulated MCs and histamine release, in addition to changes in MC ultrastructure (Ozsoy and Gül, 2005). Diabetes also influences immune cell production of IgE. Total and antigen-specific IgE augmentation was suppressed in diabetic sensitized rats (Carvalho et al., 2003). After transfer of spleen and lymph node immune cells from naïve mice to diabetic mice, immune cells lose their ability to form IgE. In contrast, immune cells from diabetic mice regain their ability to generate IgE after transfer to non-diabetic recipients (Ptak et al., 1983), suggesting that some factor(s) in the blood of diabetic mice affect immune cell IgE production. Diabetes also directly affects MC activities. Rats with alloxan-induced diabetes mount weaker allergen-evoked pleural MC degranulation and plasma leakage paralleled with reduction of MCs in the pleural cavity. Transfer of MCs from sensitized non-diabetic rats can restore allergen-evoked pleural protein extravasation in diabetic rats. In contrast, transfer of MCs from sensitized diabetic rats to naïve rats leads to a lower allergen-induced protein exudation. *In vitro*, purified MCs from diabetic rats are hyporesponsive to antigen and C48/80 stimulation (de Oliveira Barreto et al., 2003; **Figure 3A**).

Alloxan administration induces glucocorticoid overexpression, which induces MC depletion in the skin, lungs, and intestines (Pipkorn et al., 1989; Goldsmith et al., 1990; Finotto et al., 1997). MC depletion and increased endogenous glucocorticoids are closely related (Diaz et al., 1997). Glucocorticoids exhibit



anti-inflammatory activity by inhibiting tissue cytokine and SCF expression (Schleimer, 1993; Finotto et al., 1997), therefore participating in MC depletion in the intestines and other organs in diabetic rats (Pipkorn et al., 1989; Goldsmith et al., 1990; Finotto et al., 1997). Treatment with steroid receptor agonist RU486 (Carvalho Vde et al., 2009) or surgical bilateral adrenalectomy (Diaz et al., 2001) increases intestinal MC numbers and IL3 staining and IgE formation in diabetic mice – suggesting a negative correlation between MC–IgE system and serum glucocorticoid levels. Glucocorticoids also inhibit insulin secretion effectively through pancreatic β cells (Ludvik et al., 1993), and insulin treatment in alloxanated rats impairs the increase of systemic corticosterone. A balance between glucocorticoid and insulin is essential to T1DM (Diaz et al., 2001; **Figure 3A**).

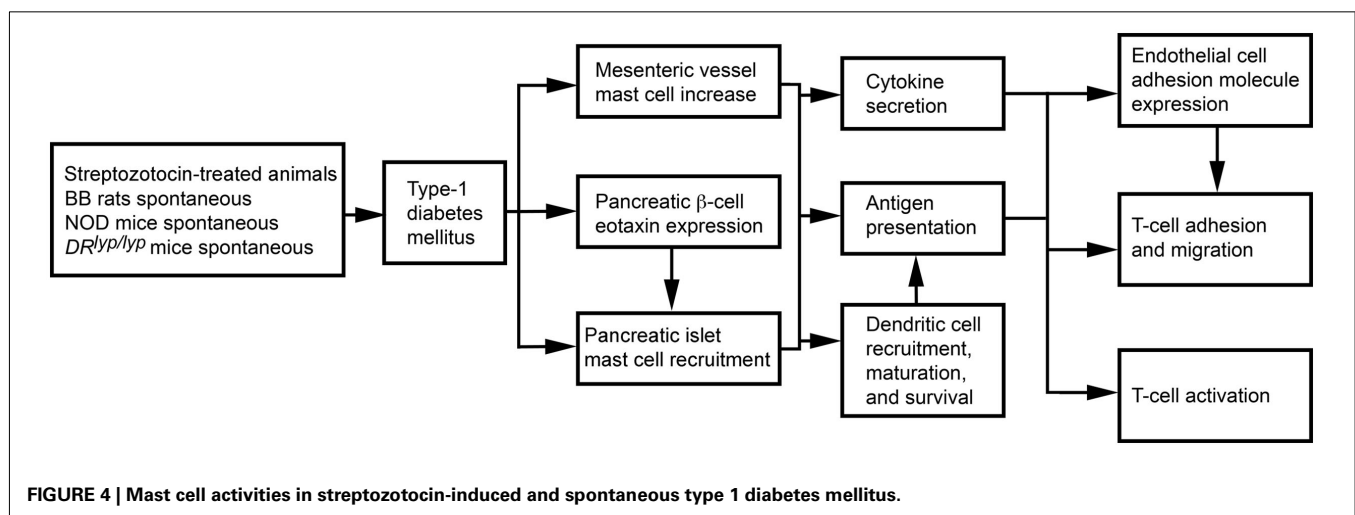
Insulin therapy not only suppresses glucocorticoid secretion, but also stimulates several MC signaling pathways, including Lyn, Syk, Fyn, adapter protein Gab2, Akt, JNK, p38 kinase, SHIP1, and protein kinase C- θ . Antigen and insulin or insulin-like growth factor-1 (IGF-1) synergistically increased antigen-induced MC degranulation and cytoskeletal rearrangement and promoted MC survival in the absence of IL3 (Lessmann et al., 2006; Kettner et al., 2010). In diabetic rats, subcutaneous administration of insulin revealed an important role of insulin in MC extracellular matrix protein (ECM; e.g., laminin, fibronectin, and collagen) expression and MC recruitment (de F Carvalho et al., 2008; **Figure 3B**). MCs express integrin-type ECM receptors to mediate their activation and increase responses to antigen stimulation (Kitaura et al., 2005). Interaction between MCs and ECM is important to MC migration and distribution in tissues (Hamawy et al., 1994). Insulin treatment reverses alloxan-induced reductions in MC numbers, histamine production, and IgE release (Vianna and Garcia-Leme, 1995; Cavalher-Machado et al., 2004).

The role of MCs in T1DM can also vary by T1DM models. In 3-week-old rats with STZ-induced diabetes, the disease associates with increased mesenteric vessel fibrosis and MC numbers. Both mesenteric vessel fibrosis and chymase-positive MC numbers were reduced after rats received tranilast (Jones et al., 2004), suggesting a causative role of MCs in STZ-induced diabetes. Biobreeding (BB) rats and non-obese diabetic (NOD) mice spontaneously develop

autoimmune T1DM (Kikutani and Makino, 1992; Wallis et al., 2009). $DR^{lyp/lyp}$ rats also develop spontaneous T1DM. Unless insulin is administered, death follows after T1DM onset as a result of hyperglycemia and ketoacidosis (Mordes et al., 1996). In BB rats, islet β cells express eotaxin (Geoffrey et al., 2006), which leads to infiltration of CCR3-expressing neutrophils and MCs to the pancreatic islets (Kukreja and Maclaren, 1999; Hessner et al., 2004). Treatment of $DR^{lyp/lyp}$ rats with cromolyn significantly delayed onset of T1DM relative to saline-treated control rats (Kukreja and Maclaren, 1999; Geoffrey et al., 2006). Mechanistically, MCs present antigens to activate T cells in major histocompatibility complex class I and class II pathways in rodents and humans (Frandji et al., 1993). T cells are primary mediators of human and rodent T1DM (Green et al., 1998; Mathis et al., 2001; Groen et al., 2003). In NOD mice and BB rats, early thymectomy prevents T1DM (Green et al., 1998; Mathis et al., 2001; Groen et al., 2003). MCs also promote T cell migration to inflammatory sites by producing chemokines or indirectly by increasing EC adhesion molecule expression (Galli et al., 2005b; Zhang et al., 2011b). As discussed earlier, MCs also affect DC maturation, migration, and activity, providing another pathway for T cell activation (Galli et al., 2005b; **Figure 4**). In NOD mice, however, anti-Fc ϵ R1 antibody delayed T1DM onset. Anti-Fc ϵ R1 was proposed to activate basophil and MC release of IL4 and histamine. Anti-Fc ϵ R1 antibody lost its ability to delay T1DM in $I14^{-/-}$ NOD mice, but this ability was not affected by histamine receptor blocker. Basophils, therefore, were proposed to play a role in T1DM in NOD mice (Hübner et al., 2011).

MC FUNCTIONS IN DIABETIC COMPLICATIONS

Long-term diabetes associates with numerous complications, including nephropathy (Fowler, 2008) – a multistage clinical syndrome characterized by thickening of the glomerular basement membrane and mesangial expansion, with progression into glomerulosclerosis, tubular necrosis, and interstitial fibrosis, ultimately resulting in renal failure (Wolf and Ziyadeh, 1999, 2007). MCs are most abundant in the kidneys of diabetic patients with nephropathy (Okon and Stachura, 2007). An increase in renal MCs associates with fibrosis and ECM accumulation in the kidneys



of diabetic nephropathy patients (Rüger et al., 1996). In kidneys from glomerulonephritis patients, MCs are clustered with T cells and macrophages in the interstitial (not in the glomerulus) and associate with α -SMA-positive interstitium and percentage of the interstitial fibrotic areas, suggesting a role of MCs in renal fibroproliferation and interstitial fibrosis (Tóth et al., 1999).

Mast cells produce TGF- β (Metcalfe, 2008), chymase, tryptase, cathepsin G, renin (Silver et al., 2004), and TNF- α (Bissonnette et al., 1995), as summarized in **Figure 5**. TGF- β is a fibrogenic cytokine linked to diabetic nephropathy in both animals and humans (Bollineni and Reddi, 1993; Sato et al., 1998). Elevated TGF- β has been implicated in the pathogenesis of diabetic nephropathy (Goldfarb and Ziyadeh, 2001). Treatment with an anti-TGF- β antibody (1D11; Benigni et al., 2006) or a soluble TGF- β type II receptor (aT β RII.Fc; Russo et al., 2007) reduced proteinuria, inhibited renal fibrosis, and produced renoprotective effects in rats with diabetic nephropathy. MC proteases contribute to renal fibrosis directly or indirectly. In diabetic nephropathy patients, MC chymase increases and associates with glomerulosclerosis, tubulointerstitial fibrosis, and vascular fibrosis (Ritz, 2003; Huang et al., 2007). MC chymase and cathepsin G convert angiotensin (Ang)-I to Ang-II, thereby activating TGF- β (Metcalfe et al., 1997; Doggrel and Wanstall, 2005; Helske et al., 2006). MC chymase and cathepsin G also activate MMP-9 (Ishida et al., 2008) to promote TGF- β signaling (Wilson et al., 2009). MC tryptase participates in the development of renal interstitial fibrosis by increasing ECM production (Kondo et al., 2001). MCs release histamine and tryptase to differentiate fibroblasts into α -smooth muscle actin-positive myofibroblasts (Gailit et al., 2001). *In vitro*, treatment of rat cardiac fibroblasts with MC tryptase induced fibroblast proliferation and collagen synthesis (Levick et al., 2009). Renin, also known as angiotensinogenase, converts angiotensinogen into Ang-I and regulates TGF- β expression in rat kidney mesangial cells, independent of Ang-II (Huang et al., 2007). Patients with diabetic nephropathy have elevated renin levels (Deinum et al., 1999). The renin inhibitor aliskiren attenuates

glomerulosclerosis in diabetic transgenic (mRen-2) 27 rats with advanced diabetic nephropathy (Kelly et al., 2007). MC histamine stimulates H2 receptor-mediated release of renin from rat kidneys (Schwertschlag and Hackenthal, 1982), indirectly affects renal Ang-II production, and induces diabetic nephropathy. TNF- α expression increases in the glomeruli of rats and humans with diabetic nephropathy (Nakamura et al., 1993; Mahmoud et al., 2004). TNF- α overexpression induces renal hypertrophy (Navarro et al., 2003) and microalbuminuria (Kalantarinia et al., 2003) in rats with diabetic nephropathy. The TNF- α agonist TNFR:Fc prevents renal hypertrophy (Navarro et al., 2003). The soluble TNF- α receptor infliximab reduced urine albumin excretion in rats with diabetic nephropathy (Moriwaki et al., 2007).

MAST CELL PROTEASES AND IGE IN DIABETIC PATIENTS

Although MC functions in T1DM can be complicated, we anticipate a detrimental role of MCs in T2DM, based on our prior animal studies (Liu et al., 2009). Patients with T2DM are expected to have increased levels of plasma biomarkers of MC proteases and associated activation markers. We tested this hypothesis in our recent community screening study (Wang et al., 2012). In this study, we screened 3163 volunteers 55–75 years of age, from three neighborhood communities in Zhejiang Province, China. Of those, 1197 accepted the invitation for fasting plasma glucose (FPG) and 2-h oral glucose tolerance test (2 h-OGTT). Among the subjects, 807 had normal glucose tolerance (FPG < 5.6 mmol/L, 2 h-OGTT < 7.8 mmol/L), 267 had pre-diabetes (FPG \geq 5.6 and < 7.0 mmol/L or 2 h-OGTT \geq 7.8 and < 11.1 mmol/L), and 123 had T2DM (FPG \geq 7.0 mmol/L or 2 h-OGTT \geq 11.1 mmol/L). The Kruskal–Wallis test revealed significant differences in plasma IgE levels among patients with different glucose tolerance status ($P = 0.008$). A linear regression test showed significant correlations between plasma chymase ($P = 0.030$) and IgE ($P = 0.022$) and diabetes mellitus. Ordinal logistic regression analysis demonstrated that IgE was a significant risk factor of pre-diabetes and T2DM before (odds ratio: 1.674, $P = 0.034$) or after adjustment

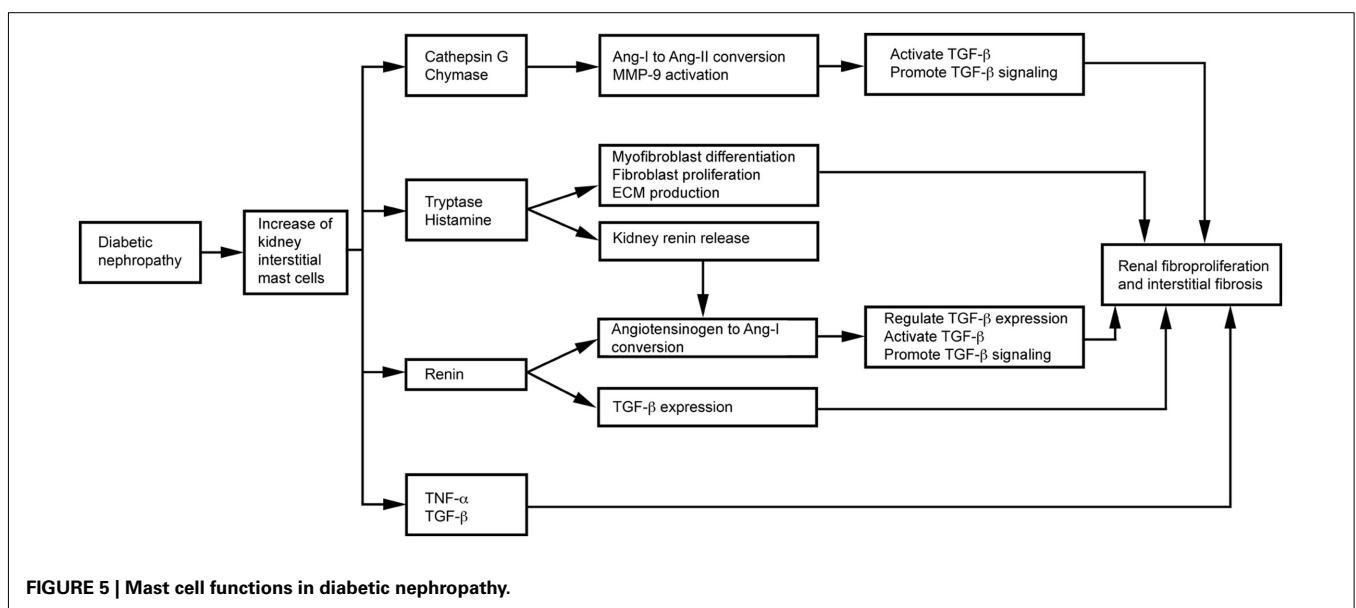


FIGURE 5 | Mast cell functions in diabetic nephropathy.

(odds ratio: 1.866, $P=0.015$) of all tested T2DM risk factors. Although not statistically significant, plasma tryptase levels were also higher in T2DM patients than in those with pre-diabetes or with normal glucose levels (Wang et al., 2012). More sophisticated studies are required to test a role of MCs in diabetes or obesity, but this human study inspired us to explore MC participation in these metabolic diseases.

PERSPECTIVE

Observations from experimental animals and diabetic patients strongly suggest a direct participation of MCs in both obesity and diabetes, although the mechanisms by which MCs contribute to the pathogenesis of these metabolic diseases are rather complicated. Our animal study, using both cromolyn and ketotifen to treat pre-established obesity and T2DM in mice, encouraged us to develop novel medications for patients with those metabolic diseases by inactivating MCs. Indeed, in an early study to evaluate cromolyn applications in asthma patients, stabilization with a cromolyn nasal spray reduced body weight by more than 3 pounds in less than 3 months (Clarke and May, 1980). But other potential actions of cromolyn are unknown; reduced body weight (Clarke and May, 1980) or improved T2DM (Shi, personal communication) in humans do not necessarily relate only to MCs. Tranilast, for example, was developed as a MC stabilizer (Koda et al., 1985), and it reduces tubulointerstitial fibrosis, tubular atrophy, and albuminuria in rats with diabetic nephropathy (Mifsud et al., 2003) and retards the progression of advanced diabetic nephropathy in humans (Soma et al., 2002). But these tranilast activities may not result from MC stabilization only. In STZ-treated diabetic rats, tranilast reduced mesenteric weight, superior mesenteric artery wall-to-lumen ratio, matrix

deposition, and expression of TGF- β , epidermal growth factor (EGF), and collagens – therefore attenuating vascular hypertrophy (Bonnet et al., 2003). In these mice, both ECs and MCs express endothelin, which constricts blood vessels. The endothelin_{A/B} receptor antagonist bosentan had the same effects as tranilast, but bosentan did not prevent TGF- β overexpression in diabetic rats (Gilbert et al., 2000). Tranilast, therefore, may target cells other than MCs – such as ECs. Indeed, tranilast inhibits EC protein kinase C and nuclear factor- κ B activities (Koyama et al., 1999; Spiecker et al., 2002). Tranilast also inhibits TGF- β release from fibroblasts and monocytes/macrophages (Suzawa et al., 1992; Yamada et al., 1994), and suppresses insulin secretion and induces glucose uptake from glucose-induced rat islets and a tolbutamide-treated rat islet cell line (INS-1E) without affecting their glucose transporter (Glut2) expression (Taguchi et al., 2008). We showed that MCs release inflammatory cytokines to induce EC adhesion molecule expression (Zhang et al., 2011b). MCs also interact with macrophages and induce expression of prostaglandin E2 and 6-keto-prostaglandin F1 during immediate hypersensitivity reactions (Jakschik et al., 1987). Tranilast activities, therefore, may associate indirectly with MC activity inhibition. More basic and clinical studies in this field will benefit greatly to patients suffering from these social diseases.

ACKNOWLEDGMENTS

I thank Ms. Sara Karwacki for editorial assistance. Studies cited in this article are supported by National Institutes of Health grants HL60942, HL81090, and HL88547; and by an Established Investigator Award (0840118N) from the American Heart Association to Guo-Ping Shi.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 14 December 2011; accepted: 09 January 2012; published online: 25 January 2012.

Citation: Shi MA and Shi G-P (2012) Different roles of mast cells in obesity and diabetes: lessons from experimental animals and humans. *Front. Immun.* 3:7. doi: 10.3389/fimmu.2012.00007

This article was submitted to *Frontiers in Inflammation*, a specialty of *Frontiers in Immunology*.

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