**ROLE OF MAST CELLS IN OBESITY**

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**Abstract**

Mast cells are critical effectors in the development of allergic diseases and in many immunoglobulin E-mediated immune responses. These cells play an important role in various immunological and metabolic diseases. The aim of present article is to explore the molecular targets to suppress the over expression of mast cells in obesity. The last 20 years literatures were collected to compile the data. The article also presents the existing research with mast cells to the area of metabolic diseases.

**1. Introduction:**

 Friedrich von Recklinghausen first observed mast cells as granular cells in frog mesenteries in 18631. About 12 years later, anatomist W. Waldeyer detected mast cells in a tissue spread of rat dura matter and named these cells “embryonal” or “plasma” cells2. In 1877, Waldeyer's medical student Paul Ehrlich stained mast cells with aniline-positive dyes in connective tissues and named them Mastzellen, meaning “well-fed cells” because they had high numbers of cytoplasmic granules3. Thirty years after the discovery of these “fat, well-fed” cells, he was awarded a Nobel Prize for his discoveries4. Many decades later, research on mast cell biology has continued, and these cells are becoming increasingly recognized as “cells without limits," able to elicit positive or negative effects on tissue and organ function.

 In the 1980s, Y. Kitamura suggested that mast cells were actually the progeny of hematopoietic stem cells (HSC) and derived from pluripotent hematopoietic stem cells in the bone marrow that leave and circulate as immature cells only to mature once they reach their destination5,6,7. Unlike other hematopoietic stem cell's offspring, such as neutrophils and erythrocytes—which circulate through the blood as mature forms—mast cells leave and circulate as immature cells only to mature once they reach their destination. Once released, mast cells undergo a maturation process that involves numerous factors, including the specific cytokine, stem cell factor (SCF) 7,8,9. The SCF receptor, c-Kit, is abundantly expressed in mature mast cells and plays a critical role in the maturation, development and secretory action of mast cells9,10. Mast cells like macrophages or T-cells are inflammatory cells but the exact mechanisms of mast cells in obesity are not fully understood.

**2. General Description of Mast Cells:** Mast cells (MCs) are immune cells produced by the bone marrow11. These cells pass the blood wall and quickly infiltrate most tissues, such as skin, mucous membranes, respiratory and gastrointestinal tracts, peritoneal cavity and meninges12. Mast cells are usually situated at the interface with host–environment (i.e., skin and mucosa), enabling them to respond rapidly to environmental stimuli. In oral mucosa and skin, they are distributed preferentially about the micro-vascular bed, being in close proximity to the basement membranes of blood vascular endothelial cells and nerves13. MCs act by degranulation14 and produce a plethora of mediators such as biogenic amines (histamine and serotonin), enzymes (acid hydrolases, phospholipases, chymase, tryptase and other proteases), cytokines (iterleukin-1 to interleukin-6, interferon, transforming growth factor (TGF), granulocyte microphage colony-stimulating factor, leukemia inhibitory factor; tumor necrosis factor TNF), lipid metabolites (leukotrienes, prostaglandins, platelet-activating factor), ATP (adenosine triphosphate), neuropeptides (vasoactive intestinal peptide), growth factors (nerve growth factor, NGF) and nitric oxide15.

 

 **Fig.1**: Structure of mast cell16

**3. Molecular targets on mast cells:**

**3.1. Crystallizable fragment's Epsilon Receptor 1 (Fc****R1): the high-affinity IgE receptor as a key modulator of mast cell activation**

FcRI, the high-affinity receptor for IgE, belongs to the Ig superfamily, and is expressed primarily on human mast cells and basophils as a tetramer composed of three subunits (2).The -subunit is responsible for IgE binding, the -subunit regulates receptor expression and signaling, and the -subunit, which forms a homodimer through disulfide linkage, is mainly responsible for signal transduction17,18,19. The extracellular part of α subunit contains two Ig-like domains that bind to the Fc domain of monomeric IgE with high affinity20. Moreover, a soluble form of the FcR1 also circulates in human serum free or bound to IgE21.

Once activated, the complete tetramer (αβγ2) becomes a key regulator of immediate allergic responses. The cytoplasmic tails of the β and γ Subunits of FcεR1 contain domains of immunoreceptor tyrosine-based activation motifs (ITAM) that can serve as docking sites for several members of the Sarcoma (Src) kinase family, such as Lyn and Fyn, as well as the kinase Syk22. The allergen cross linking of the IgE bound to the-subunit of the FcεRI activates the Lyn kinase that phosphorylates the immuno receptor tyrosine based activating motifs (ITAM) located on both β and γ chains of FcεRI.

Once phosphorylated, these ITAMs can recruit Syk23 and Fyn24. Further, following spleen tyrosine kinase (SYK) binding, activation of mitogen activated protein kinases (MAPK), protein kinase C and phospholipase C takes place by intermediate phosphorylated events. This results in the rise of cyclic adenosine monophosphate (cAMP) that mediates the phosphorylation of mast cell granule membrane proteins and alters their permeability.

 

 **Fig.2**. the structure of the FcεRI receptor25

**3.2. Tyrosine protein kinase kit or Proto-oncogene Kit (c-Kit): the SCF receptor as a main regulator of mast cell development and function**

c-Kit (CD117), also referred to as a Stem Cell Factor (SCF) receptor, was identified in 198726. It is a type III receptor tyrosine kinase with a large extracellular portion containing five Ig like domains, a trans membrane domain, and a long cytoplasmic tyrosine kinase tail27. Binding stem cell factor (SCF) homo dimers to the c-KIT receptor on MC surfaces induces homodimerization and transphosphorylation of the receptor on several tyrosine residues; these in turn create docking sites for various signaling molecules and induce pathways essential for MC development, survival, proliferation, chemotaxis, and adhesion27,28. c-Kit is expressed in hematopoietic cells and on different non hematopoietic cells (i.e. melanocytes, interstitial cells of Cajal) and on some tumors29. Mast cell development and survival are dependent upon the c-Kit-mediated activation of (Phosphoinositide 3 Kinase) PI3K and its downstream target protein Kinase B. PI3K is crucial for SCF-mediated mast cell chemotaxis and adhesion, and SCF induced allergen-mediated mast cell degranulation and cytokine production30.



**Fig.3**: **Schematic representation of the structure of c-kit:** The extra-cellular domain consists of five Ig-like domains (D1-D5). The sequence GNNK (a tetrapeptide sequence) is either present or absent in the extra-cellular domain near the plasma membrane of c-kit (GNNK+ or GNNK-). The intracellular domain contains the tyrosine kinase domain, which is split into two parts by the amino acid residues insert sequence31.

**3.3. β-Tryptase**:

β Tryptase is a tetrameric serine proteinase, is the major protein within the secretory granules of mast cells. However, Basophils can contain a small amount of β-tryptase32,33. Human mast cells are so abundantly an asset with tryptase transcripts and protein that these have emerged as perhaps the most sensitive and specific means of detecting mast cells in tissues and biopsies. For example, tryptase mRNAs are among the most abundant transcripts in epithelial brushings and biopsiesin T helper 2 cell cytokine (“TH2 high”) asthma34, allergic rhinitis35, and eosinophilic esophagitis36, even though mast cells are a small fraction of cells retrieved in such samples. The pathophysiologic role of β-tryptase is not clear, but the enzyme has been associated with the promotion of inflammation and matrix remodeling32,37.

 

 **Fig.4**: Structure of β-Tryptase38

**3.4. Chymase**:

Chymase is a chymotrypsin-like serine proteinase stored in high quantities in the secretory granules within the cells with tryptase together with chymase. Carboxypeptidase and Cathepsin G are called MCTC type of MCs. Human genomes possess a single chymase gene (CMA1) encoding a serine-class endoprotease that is primarily chymotryptic, which is to say that it cleaves peptides after aromatic amino acids, especially phenylalanine and tyrosine37. In vitro, human chymase is not highly selective, and is capable of cleaving a variety of peptide and protein targets, both endogenous and exogenous (as from pathogens). Unlike tryptase, chymase can be inactivated by endogenous protease inhibitors, and therefore chymase is under the control of protease inhibitors in inflamed tissue39,40. If left uncontrolled by inhibitors, chymase is a potent enzyme that causes matrix destruction37,40 and inflammation, as well as producing angiotensin II from angiotensin I, suggesting a role in hypertension and cardiac failure37,41.

 

 **Fig.5**: Structure of Chymase42.

**3.5. Carboxypeptidase A3:** Carboxypeptidase A3 was termed mast cell carbox- ypeptidas43,44. However, as transcripts encoding this enzyme were discovered in basophils, its name was changed to reflect the broader expression. In basophils, it can be stored and accumulated in granules as it is in mast cells, in which carboxypeptidase A3 seems to be co-dependent on the presence of chymase and heparin proteoglycan45,46,47,48. Lack of chymase in basophils and/or low levels of heparin may explain weak storage of carboxypeptidase A despite the presence of transcripts, recently a selective knock in mutation rendering the carboxypeptidase get but still present as a “placeholder” and allowing preservation of granule structure and active carboxypeptidase A3 protects from toxic effects of endogenous endothelin and from endothelin-like sarafotoxin class of snake venins49. Similarly, chymase protects from toxic effects of Gilamonster and scorpion venoms50.

 

**Fig.6:** General structure of carboxypeptidase A. Alpha-helices in blue, beta-sheets in red, Zn2+ ion in yellow, active site side chains in cyan51

**3.6. Cathepsin C:** Cathepsin C (gene name CTSC), also known as dipeptidylpeptidase, I, is a cysteine exopeptidase that is expressed in many cells but is especially abundant in mast cells52. It is a potential pharmaceutical target because of its role as an upstream activator of tryptases, chymases, and cathepsin G, from which it removes N-terminal pro-dipeptides from the zymogen forms of these proteases.

**3.7. Histamine and histamine receptors:** Histamine, a preformed mediator in MCs/Bs, has long been proven to be a critical factor in the cause and therefore, treatment of allergy. Histamine has 4 distinct G protein–coupled receptors, histamine receptors 1-4 (H1-H4 receptors) and blocking drugs is one of the great milestones in the history of medicine. This breakthrough was marked by two Nobel Prize awards in the field of histamine research, Daniel Bovet,in 1957, for the discovery of an H1R antagonist53 and Sir James Black*,* in 1988, for the development of an H2R antagonist54. Mast cells and basophils are well established prominent sources of preformed histamine in humans, and through this, mediators play an important role in causing the symptoms of allergy, acting on target organs such as lungs, skin and intestine. In humans, mast cells express H1R, H2R and H4R while the expression of H3R is limited to brain mast cells. Histamine binding to H1R on mast cells leads to the activation of phospholipase A2 and phospholipase D and downstream of the transcription factor NF-B through Gq/11 and Gβγ55. The activation of H1R *via* histamine stimulates the further release of histamine and other mediators, increases the expression of adhesion molecules and chemotaxis of eosinophils and neutrophils, enhances the antigen-presenting cell capacity, increases the costimulatory activity of B cells, and downregulates IgE production56.

H1-antihistamines are inverse agonists and are currently the most-used antiallergic drugs, such as in patients with urticaria, atopic dermatitis, allergic rhinitis, and conjunctivitis, as well as in asthmatic patients. At high doses, H1-antihistamines can also reduce mast cell functions, acting as MC stabilizers57,58,59. H4R antagonists/inverse agonists are plausible new drugs for treating allergic diseases60.



 **Fig.7**: Histamine H1 receptor in complex with theantagonist61

**3.8. De novo–synthesized lipid mediators:**

Upon activation of mast cells by various stimuli, including Immunoglobulin E and antigen, various lipid mediators are synthesized de novo. Arachidonic acid is released from the perinuclear membrane and endoplasmic reticulum and processed into several eicosanoids62. Among these are prostaglandin D2 (PGD2) (the major prostanoid product in MCs), prostaglandin E2 (PGE2)63, and the leukotrienes C4 (LTC4) and leukotrienes B4 (LTB4)64,65 leukotrienes C4(LTC4), which appears to play an important role in allergic inflammation and MC proliferation, is synthesized de novo in MCs/Bs from arachidonic acid through the consecutive action of 5-lipoxygenase (5-LO) and LTC4 synthase, followed by conversion to leukotrienes D4 (LTD4) and leukotrienes E4 (LTE4). LTC4 and LTD4 are potent bronchoconstrictors and play an important role in asthma through binding to cysteinyl leukotriene receptor (cysLTR) 1 and 2. Several specific cysLTR1 antagonists, including zafirlukast, pranlukast, and montelukast have been developed66,67. Prostaglandin D2 (PGD2) is another soluble lipid mediator produced de novo predominantly by MCs and in small amounts also by Bs68, 69, 70, 71. The characterization of PGD2 receptors, namely D-type prostanoid receptor (DP) 1 and 2 (also known as CRTH2) and the thromboxane receptor, has uncovered novel roles for PGD2 in allergic inflammation given their expressions on endothelial and airway smooth muscle cells, as well as on eosinophils, TH2 cells, and Bs. PGD2 induces bronchoconstriction through Thromboxane receptors on airway smooth muscle cells, vasodilatation through DP1 receptors in endothelial cells, and activation of immune cells through DP269,70,72.

**3.9. Cytokines, Chemokines and Growth factors:** Both MCs and Bs synthesize and release a variety of cytokines and chemokines32,73. MCs can produce TNF-α on stimulation by many factors, including IgE, antigen, and bacterial products74,75,76 and biological drugs (eg, infliximab, adalimumab, and etanercept) that target TNF-α are well established in the therapy of patients with psoriasis, rheumatoid arthritis, and other chronic inflammatory conditions. Upon activation, peripheral MCs release stable heparin-based particles containing preformed TNF-α and other proteins. These complexes, by trafficking to the draining lymph nodes where they can deliver TNF-α, enable communication between peripheral sites of inflammation and secondary lymphoid tissues77.

 IL-6 is another proinflammatory cytokine that is produced by MCs/ Bs and numerous other cell types78, 79. IL-6 plays a substantial role in toll-like receptor (TLR)-2-mediated inhibition of tumor growth in mice80. MC-derived IL-6 and IFN-γ can also mediate diet-induced obesity and diabetes in mice81.

**4. Structural/biochemical features:**

**Table 1: Molecular targets and pharmacological description of mast cells**:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Molecular Targets | Agonist | Antagonist | Animal | Activity | Reference |
| Chymase | mast cell protease (MCP)-1 | BCEAB,NK3201 | Mice | Angiotensin-II synthesis; Chymotryptic, leuase | Caughey 200437, Li et al., 200481 |
| Carboxype-ptidase A3 | Sodium butyrate or trichostatin A | p21(WAF1/CIP1) | Mice | Exopeptidase (aromatic, neutral),Peptide processing | Feyerabend et al.,201145; Lilla et al., 201183; [Huang H](https://www.ncbi.nlm.nih.gov/pubmed/?term=Huang%20H%5BAuthor%5D&cauthor=true&cauthor_uid=10383164) et al., 199984 |
| Cathepsin C | Mast cell protease 4 and FY01 | Cyclic thiocarbamate | Mice | Dipeptidyl amino-peptidase | Methot N, Rubin J, Guay D85, et al., 2007 |
| Histamine receptor (H1) | Methylhistaprodifen | Cyproheptadine | Rats | Allergy, infla-mmation | Canonica GW, Blaiss M,201186; Fujimoto K et al., 199387; Seifert R et al., 200388; Moguilevsky N et al., 199489 |
| Histamine receptor (H2) | Amthamine | Ranitidine | Rats | Gastric acid secretion, regulate GIT motility | Kraus A et al., 200990; Leurs R et al.,199491 |
| Histamine receptor (H3) | Immethridine | Iodophenpropit | Mice | Control of satiety | Kitbunnadaj R et al.,200492; Lovenberg TW et al., 200093; Attoub S et al.,200194 |
| Histamine receptor (H4) | Clobenpropit | Thioperamide | Mice | Mast cell [chemotaxis](https://en.wikipedia.org/wiki/Chemotaxis) | Lim HD et al., 200595;; Gutzmer R et al.,201160; Hofstra CL et al.,200396; Liu C et al., 200197 |
| β –Tryptase | PAR SFLLR-NH2, TFLLRN-NH2 | Bis (5-amidino-2-benzimidazolyl) methane, APC-366 | Mice | Tryptic, inflammation | Tao Li and Shaoheng He, 200698; Hallgren J and Pejler G,200699 |

**Table 2: Molecular targets and pharmacological description of mast cells:**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Targets | Agonist | Antagonist | Activity | Reference |
| TNF-α | TNF-R55 | Infliximab, Adalimumab | Inflammation, Psoriasis, Rheumatoid Arthritis | Kunder et al.,200977; F Mackay et al.,1993100 |
| IgE | FcεRI | Omalizumab | Allergy | Johansson SG, Haahtela T, and O’Byrne PM., 2002101; Schulman ES, 2001102 |
| IL-1 | IL-1β | Anakinra | Arthritis | Eisenberg S.P et al., 1991103; John N. Fain, 2006104 |
| IL-6 | IL-6 receptor | Sirukumab,BMS945429 | Obesity Diabetes, Atherogenesis | Liu et al., 200981 |
| IFN-γ | MHC-II | Olsalazine | Obesity, Diabetes, Atherogenesis, Leucocyte proliferation | Liu et al., 200981;Steimle V et al.,1993105 |
| IL-17 | IL-23 | Secukinumab, Lxekizumab | Autoimmune disease, Leucocyte migration | [Zhu S](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhu%20S%5BAuthor%5D&cauthor=true&cauthor_uid=22324470), [Qian Y](https://www.ncbi.nlm.nih.gov/pubmed/?term=Qian%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=22324470),2012106.; Kenna TJ.,2013107; Starnes T et al., 2002108 |
| IL-13 | IL-13R-α1 and IL-4R -α | CAT-354 | Allergy,AtopicDermatisis | Eric B. ,Umasundari,2011109; May RD et al., 2012110; Sheikh F et al., 2015111 |
| IL-12 | S-27609 | Ustekinumab | Inflammation, Pain | Engel T, Kopylov U,2016112; Christie L, et al., 2003113 |
| IL-8 (CXCL8) | TNF-α | Anti-IL-8 mAb | Psoriasis, Chemoattractant | Skov L et al.,2008114; Tabrizi W et al., 2010115; Gibbs BF, 2012; Iwabe T et al., 2000117 |
| CXCR2 | Corticotropin Releasing hormone | MK-7123 | Adhesion expression | Hallgren, J. et al.,2007118; Nair P et al., 2012119 |
| CXCR3 | CXCL11 | AMG 487 | Rheumatoid Arthritis | Ruschpler P et al., 2003120;Henne KR et al., 2012121; Stroke I.L et a., 2006122 |
| CXCR4 | SDF-1α | AMD3100 | Control Neutrophill release | Hendrix, C. W et al., 2004123; Heveker, N. et al., 1998124 ; Link D, 2005125 |

Abbreviations used: 5-LO: 5-Lipoxygenase, FLAP: 5-Lipoxygenase–activating protein, 15-LO-1: 15-Lipoxygenase-1, LTC4: Leukotriene C4 ,LTD4:Leukotriene D4, cysLTR: Cysteinyl leukotriene receptor, DP: D-type prostanoid receptor, PGD2: Prostaglandin D2, H1R: Histamine Receptor1, H2R: Histamine Receptor 2, H4R: Histamine Receptor 4

**5. Role of Mast cells in Obesity:**

 Obesity becomes a major area of concern over a worldwide. In U.S., one-third of U.S. adults are categorized as overweight or obese. Inflammation is now considered to have a pivotal role on the development of obesity. There are two types of adipose tissue essentially involve in metabolic functions. White Adipose Tissue (WAT), which regulates energy balance126, and it also regulate metabolism, blood pressure, immune responses, coagulation, and functions of other endocrine organs127 and brown adipose tissue (BAT), which affects sensitivity to insulin and susceptibility to weight gain128.

 White Adipose Tissue, which consists of Adipocytes, which involved in production of adipocytokines129 such as IL-6130 and adiponectin and leptin secretion as well as insulin resistance129. Obese adipose tissue shows the signs of chronic inflammation, with massive leukocyte recruitment and accumulation of macrophages in WAT131,132, While WAT from obese humans and animals contains higher numbers of MCs than that from other lean subjects. In general, MC number, and functions can vary among fat pads from different locations. For example, the difference in Mast Cell number in subcutaneous WAT between obese and lean subjects was not significant, whereas the MC numbers in visceral WAT increase significantly in obese as compared to lean subjects133.

 The participation of mast cells in obesity was established using mast cell-deficient KitW-sh/W-sh mice. KitW-sh/W-sh mice, fed a Western diet for 12 weeks gained significantly fewer body weight, had improved glucose intolerance and had reduced adipose tissue inflammation with reduced leptin and insulin levels in the circulation, compared with congenic wild-type controls; in addition, serum and WAT levels of inflammatory cytokines, chemokines and proteases were reduced as glucose homeostasis and energy expenditure improved81.

 MC contributes to obesity by affecting energy expenditure, adipose tissue angiogenesis, and preadipocyte differentiation. Mast cells are often localized next to microvessels in WAT. The numbers of microvessels correlated with the increase in mast cell numbers during the development of obesity. At molecular level, Mast cell's acts as reservoirs for inflammatory cytokines to stimulate vascular cells134 and adipocytes81to release cysteinyl cathepsins—an important proteases that can catabolize ECM protein fibronectin to promote adipogenesis, and degrade intracellular insulin receptor and glucose transporter (Glut)-4, leading to impaired insulin and glucose sensitivities135,136. It directly the same cathepsins along with their unique chymases and tryptases, all of which can regulate neovascularization and cell survival that are essential for WAT growth81 (Fig. 9).

**Conclusion:** The article enlisted the various targets and possible mechanism to suppress the obesity induced immune response. The available drugs are not much as an effective or promisable response against the suppression of mast cells in obesity. The present work may help the researchers to overcome the various loop h in this area.

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