International Immunopharmacology 40 (2016) 362–384

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Targeting mast cells: Uncovering prolific therapeutic role in myriad diseases

Jatinder Singh [1], Ramanpreet Shah [1], Dhandeep Singh *

Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala 147002, Punjab, India

ARTICLE INFO

Article history:
Received 27 August 2016
Received in revised form 16 September 2016
Accepted 22 September 2016
Available online 29 September 2016

Keywords:
Cytokine receptors
G-protein coupled receptors
Mast cells
MRGPRX2
Ligand gated ion channels

ABSTRACT

The mast cells are integral part of immune system and they have pleiotropic physiological functions in our body. Any type of abnormal stimuli causes the mast cells receptors to spur the otherwise innocuous mast cells to degranulate and release inflammatory mediators like histamine, cytokines, chemokines and prostaglandins. These mediators are involved in various diseases like allergy, asthma, mastocytosis, cardiovascular disorders, etc. Herein, we describe the receptors involved in degranulation of mast cells and are broadly divided into four categories: G-protein coupled receptors, ligand gated ion channels, immunoreceptors and pattern recognition receptors. Although, activation of pattern recognition receptors do not cause mast cell degranulation, but result in cytokines production. Degranulation itself is a complex process involving cascade of events like membrane fusion events and various proteins like VAMP, Syntaxins, DOCK5, SNAP-23, MARCKS. Furthermore, we described these mast cell receptors antagonists or agonists useful in treatment of myriad diseases. Like, omalizumab anti-IgE antibody is highly effective in asthma, allergic disorders treatment and recently mechanistic insight of IgE uncovered; matrix mettaloprotease inhibitor marimistat is under phase III trial for inflammation, muscular dystrophy diseases; ZPL-389 (H4 receptor antagonist) is in Phase 2a Clinical Trial for atopic dermatitis and psoriasis; JNJ3851868 an oral H4 receptor antagonist is in phase II clinical development for asthma, rheumatoid arthritis. Therefore, research is still in inchoate stage to uncover mast cell biology, mast cell receptors, their therapeutic role in myriad diseases.

Contents

1. Introduction . . . 363
   1.1. Mast cell normal body functions . . . 363
2. Mast cell development and differentiation . . . 363
3. Mast cell receptors . . . 364
   3.1. G-protein coupled receptors . . . 364
   3.2. Ligand gated ion channel . . . 365
   3.3. Pattern recognition receptors . . . 365
   3.4. Immunoreceptors . . . 366
4. Mast cell degranulation and its effects . . . 366
   4.1. G-protein coupled receptors (CXCR, H4, $CRTH_2$, NK_3R) . . . 366
   4.2. Ligand gated ion channels ($P2X_7$, K^+, Cl^-, $TRPV_2$) . . . 367
   4.3. Pattern recognition receptors (TLRs) . . . 367
   4.4. Immunoreceptors: FcεR1(αβγγ) . . . 368

Abbreviations: AP1, Activator protein 1; cAMP, Cyclic adenosine monophoshate; CXCR, Cytokine receptors; CRTH2, Chemoattractant receptor-homologous molecule expressed on Th2 cells; DAMPs, Damage-associated molecular pattern; EtBr, Ethidium Bromide; IgE, Immunoglobulin E; IKK, IκB kinase; IRF3, Interferon regulatory factor 3; LAT, linker for activation of T cells; LYN, Tyrosine-protein kinase; MAP3Ks, Mitogen-activated protein kinase kinase kinases; NFκB, Nuclear factor kappa B; NTAL, Non-T-cell activation linker; PGs, Prostaglandins; PLCβ, Phospholipase C- beta; PIP_3, Phosphatidylinositol trisphosphate; TBK1, Serine/threonine-protein kinase TBK1; TRAF6, TNF receptor associated factor; TRAK1, Trafficking kinesin-binding protein 1; TRIF, TIR-domain-containing adapter-inducing interferon-β.

* Corresponding author.
E-mail address: ddd300@gmail.com (D. Singh).

[1] Both authors contributed equally.

http://dx.doi.org/10.1016/j.intimp.2016.09.019
1567-5769/

5. Mast cells disorders . . . 369
5.1. Primary mast cell disorders . . . 370
5.1.1. Mastocytosis . . . 370
5.1.2. Monoclonal mast cell activation syndrome . . . 371
5.2. Secondary mast cell activation disorders . . . 371
5.3. Miscellaneous mast cell diseases . . . 372
6. Mast cell receptors antagonists or agonists . . . 373
7. G-protein coupled receptors antagonists . . . 374
7.1. CRTH2 antagonists . . . 374
7.1.1. Phenylacetic acid derivatives . . . 375
7.1.2. Ramatroban analogs [126] . . . 375
7.1.3. Pyridiminyl acetic acid derivative . . . 375
7.1.4. Isoquinoline indole acetic acid derivatives . . . 376
7.1.5. Tetrahydro-γ-carboline derivative . . . 376
7.1.6. Diazine derivative . . . 376
7.1.7. Sulfonyl indole acetic acid derivative . . . 376
7.1.8. H4 antagonists [133] . . . 376
7.2. CXCR4 (chemokine receptor) inhibitors) [142] . . . 377
7.3. Mrgprb2 . . . 378
7.4. N-formyl-peptide receptor 1 (FPRL1) receptor . . . 378
7.5. Endocannabinoids . . . 378
7.6. Adenosine receptors . . . 378
7.7. Corticotricotropin releasing hormone receptors . . . 378
7.8. Ligand gated ion channel antagonists: 5.2.1 $P2X_7$ inhibitors . . . 378
7.8.1. Adamantyl derivatives [168,169] . . . 379
7.8.2. TRPV2 (transient receptor potential vanilloid 2 channel) antagonist . . . 379
7.8.3. Ca^{2+} release–activated Ca^{2+} channels (CRAC) . . . 379
7.9. Immunoreceptors antagonists and anti-IgE antibody . . . 379
7.9.1. FCεR1 inhibitors . . . 379
7.9.2. Anti-IgE (immunoglobulin E) antibody . . . 379
7.10. Pattern recognition receptor agonists . . . 380
7.10.1. Toll-like receptors agonists [47] . . . 380
7.10.2. TL-7 agonists . . . 380
7.10.3. TLR-8 agonists . . . 380
7.10.4. TLR-9 agonists . . . 380
7.10.5. TLR-2 agonist . . . 380
7.11. Mast cell enzymes inhibitors . . . 380
7.11.1. Chymase inhibitors [195] . . . 380
7.11.2. Tryptase inhibitors [196] . . . 380
7.11.3. Protease inhibitors [201] . . . 380
8. Conclusion . . . 380
Acknowledgement . . . 381
References . . . 381

1. Introduction

The Mast Cells (MCs) origin could be traced to a leukocyte ancestor operating as primitive local innate immunity, which primarily functioned as phagocytic action and pathogens killing activity. Since, from the beginning this type of defensive cell, the MC phylogenetic progenitor progressively evolved into a tissue regulatory cell, which later on might have been incorporated into the networks of recombinase activating genes (RAG)-mediated adaptive immunity in the Cambrian era, about 550 million years ago. Perhaps the early MCs appeared about 450–500 million years ago, albeit we shared them with lamprey, hagfish, and sharks (our last common ancestor) [1]. Furthermore, developmental biological data, alluded that the PGD_2 pathway of arachidonic acid metabolism developed before the LTC_4 pathway during evolution, that heparin evolved to store histamine and varied enzymatically active serine proteases in the MC's secretory granules, and that heparin expressing MCs appeared >500 million years ago, before the inception or development of adaptive immunity [2]. Hence, mast cell originates, diversify after millions year of evolution.

1.1. Mast cell normal body functions

Mast cells are integral part of immune system and they have pleiotropic physiological functions in our body including protective ones. Because of mast cells close vicinity with blood vessels, allows them to have a crucial sentinel role in host defence [3]. Mast cells have been reported in the regulation of innate and adaptive immune responses: including tolerance to skin graft rejection [4,5], in settings of T cell and antibody mediated autoimmunity [6], in protective immunity against viral [7], and microbial pathogens [8]. Furthermore, they play crucial role in tissue remodelling, wound healing [9], angiogenesis [10], protection from cancer by participation in tumor stroma [11]. Mast cells also limit UV-B induced inflammation, and injury [12]. Indeed, mast cells inactivate, neutralize honeybee, and viper venom. [13]. Thus, mast cells are not responsible for incendiary effects, but also plays pivotal role in protective body functions.

In this review we try uncover human and rodent mast cells development, differentiation, and receptors differences. Furthermore, we also uncover mast cell disorders, mast cells receptors mechanism, targeting mast cells with receptor antagonists and mast cell enzyme inhibitors.

2. Mast cell development and differentiation

The considerable differences exist between murine and human mast cells development and differentiation. In human two major types of MCs have been reported: MCs containing only tryptase (MC_T), mostly found in mucosal tissues (lamina propria, in the airways), and MCs containing tryptase, chymase and carboxypeptidase A (MC_{TC}) chiefly