

*Forum Minireview***Progress in Allergy Signal Research on Mast Cells:
Systemic Approach to Mast Cell Biology in Allergic Diseases**Hirohisa Saito^{1,*}¹*Department of Allergy and Immunology, National Research Institute for Child Health & Development,
2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan**Received November 5, 2007; Accepted December 12, 2007*

Abstract. At the end of the last century, microarray technology that examines the total genes and transcripts present in a cell became available as a laboratory tool. Mast cells are known to play a pivotal role in initiating allergic inflammation by releasing various mediators and cytokines. According to the recent microarray-based studies, mast cells have been found to be much more versatile functional molecules than we ever thought. Also, genes that are exclusively expressed in mast cells have been identified in comparison with other cell types. In this article, the outcome of microarray-based analyses on the role of mast cells in allergic inflammation will be reviewed by focusing on the mast cell-specific genes as drug targets.

Keywords: mast cell, microarray, asthma, allergy

Introduction

By complete reading of the genome sequence, functional genomics is rapidly developing. Among these technologies, microarray is considered to be one of the most revolutionary tools for understanding the total functional elements in a cell, that is, transcriptome or proteome (1). One of the final goals of functional genomics is considered by many researchers to simulate the human body in a computer. To understand the total functional machinery in the human body, however, we have to know the whole system in an organ. In order to do so, we have to examine the whole systemic functions in a cell. Integration of such genomic information regarding various cell types is expected as the first step for constructing the human body in the future. Thus, many researchers are now investigating transcriptomes and proteomes of various cell types, studies that are heading towards systems biology in the future (2, 3).

Mast cells are known to play a pivotal role in initiating allergic inflammation by releasing various mediators and cytokines. The recent microarray-based studies have provided convincing evidence that mast cells have more versatile functional molecules than we ever thought.

Also, genes that are exclusively expressed in mast cells have been identified in comparison with other cell types (4). In this article, the outcomes of microarray-based analyses on the role of mast cells in allergic inflammation will be reviewed by focusing on the mast cell-specific genes as drug targets.

Mast cell-specific genes as drug targets

Mast cells are known to play versatile roles such as evoking allergic reactions and controlling physiological reactions (5). However, functions of a substantial number of genes or molecules remain undiscovered. Novel genes that are highly expressed by mast cells may be easily found by examining the mast cell transcriptome database. By comparing it to transcriptomes expressed by other cell types, however, you may find that the mast cell-expressing genes are not mast cell-specific. Thus, elucidating the whole information related to the mast cell type-specific functions compared to the other cell types is important, especially when you are developing a new drug targeting the mast cell-specific gene because you may get side effects on physiologically important organs by using drugs targeting various organs. The safety of any candidate drug must be evaluated by comparing its efficacy on these granulocytes with its toxicity to physiologically important organs.

*Corresponding author. hsaito@nch.go.jp

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Eosinophils and basophils as well as mast cells are crucially involved in allergic reactions and inflammation (6). On the other hand, neutrophils kill bacteria and sometimes induce systemic vasculitis or multiple organ damage under certain conditions (7, 8). Mast cells, basophil-, and/or eosinophil-specific genes could be potential therapeutic targets for allergic diseases because these granulocytes play a crucial role in allergic inflammation (6). Activation of these cells is generally characterized by an influx of extracellular calcium (Ca^{2+}), which is essential for subsequent release of granule-derived mediators, newly generated lipid mediators, and cytokines (9). Flow of other ions plays an important role during granulocyte responses because they regulate cell membrane potential and thus influence Ca^{2+} influx (10). Treatment of mast cells and basophils with pertussis toxin inactivates the Gi-type of G-proteins and abolishes degranulation but not the influx of Ca^{2+} induced by non-immunological ligands such as thrombin and *N*-formylpeptide (11). Thus, the granulocyte degranulation pathway is sometimes Ca^{2+} -independent and is G protein-dependent. Indeed, the thrombin-activated receptors and formylpeptide receptors are classified as G protein-coupled receptors (GPR), having a seven transmembrane region (12). As such, ion channels and GPR both play essential roles in degranulation as well as other cellular functions important for granulocytes, and they are thought to be good targets of drug development (13). Receptor genes and ion-channel genes are found to be only 5% and 1.3% of all genes present in the human genome, respectively (14). However, receptors and ion channels are respectively 45% and 5% of the molecular targets of all known drugs (13, 15, 16).

Besides their physiological importance, receptors including GPR and ion channels are considered to be marketable and targeting these molecules should be efficient for pharmaceutical development. In other words, we can concentrate on approximately 2,000 genes as practical drug targets, and we can forget about the 30,000 other genes present in the human genome. Thus, the cell type-selective transcriptome expression of 7 types of leukocytes (basophils, eosinophils, neutrophils, CD4^+ cells, CD8^+ cells, CD14^+ cells, and CD19^+ cells), platelets, fibroblasts, and mast cells were examined using high-density oligonucleotide probe arrays (GeneChip; Affymetrix, Santa Clara, CA, USA). Then, the expression of granulocyte-selective genes for ion channels, GPR, and other receptors were determined. It is estimated that approximately 50 genes are selectively expressed by mast cells, eosinophils, and basophils among all genes present in the human genome (17). The representative druggable genes, GPCRs, that were selectively expressed by mast cells, basophils, and/or

eosinophils using the Affymetrix U133A GeneChip (approximately 23,000 transcripts can be detected) were as follows: *HRH4* (histamine H_4 receptor), *PTGER3* (prostaglandin E receptor type 3a2), *ADORA3* (adenosine A_3 receptor), *P2RY2* (purinergic receptor), *GPR44* (chemoattractant receptor-homologous molecule expressed on Th2 cells: CTRH2), *EMR1* (egf-like module containing, mucin-like, hormone receptor-like sequence 1), *CCR3* (chemokine receptor 3), and *C3AR1* (C3a receptor). As such, analysis of cell type-selective druggable genes from database searches is expected to minimize the efforts required for drug discovery.

Systemic role of mast cells in allergic inflammation

Even before microarray techniques were developed, mast cells were known to produce multiple cytokines through transcription of these genes for inducing allergic inflammation, that is, tumor necrosis factor (TNF)- α (18), granulocyte-macrophage colony-stimulating factor (19); I-309/TCA-3 (CCL1, i.e., CC-chemokine ligand 1) (20); monocyte chemotactic peptide (MCP)-1 (CCL2) (21); macrophage inflammatory protein (MIP)-1 α (CCL3) (20, 22), MIP-1 β (CCL4) (20), and interleukin (IL)-3 (23); IL-4 (24), IL-5 (25), IL-6 (20, 26), IL-8 (20, 22), IL-9 (26), IL-10 (27), IL-13 (28, 29), and IL-16 (30) following IgE-dependent activation. A transcriptome assay for human mast cells seems to be of particular interest as to whether they can produce other unidentified cytokines. The two databases are now available regarding human mast cell transcriptome after IgE-mediated activation: http://genome-www5.stanford.edu/cgi-bin/publication/viewPublication.pl?pub_no=157 and http://www.nch.go.jp/imal/Mast/Blood_Dec1_2002sup.xls (31, 32). According to their microarray data, the results were not very surprising. Most of the cytokine/chemokine genes expressed by human mast cells after aggregation of $\text{Fc}\epsilon\text{RI}$ were identical to the previous reports using non-array methods (18–30). It was confirmed that Th1 cytokines and CXC-chemokines deriving Th1 cells are not expressed by activated human mast cells. Interesting findings among these microarray data may be up-regulation of some genes related to tissue remodeling such as IL-11 (31) and 4-1BB (32).

Mast cells express Toll-like receptors (TLR) that recognize various microbial components (33) and can be activated via challenge with these components. Mouse cultured mast cells express TLR2, TLR4, and TLR6 and produce a variety of cytokines including IL-13 in response to TLR ligands such as lipopolysaccharide (LPS) (34, 35) and release preformed mediators in response to peptidoglycan, a TLR2 ligand (36). Human

cord blood-derived cultured mast cells express TLR2 and TLR6 and produce a variety of cytokines such as GM-CSF (37, 38). On the other hand, adult peripheral blood progenitor-derived cultured mast cells do not significantly respond to TLR stimulation. However, after preincubation with IFN- γ , the expression of TLR4 is up-regulated, and LPS can induce a variety of transcripts in the peripheral blood-derived cultured mast cells. The transcriptome in LPS-stimulated and INF- γ -primed human mast cells are somewhat different from that in anti-IgE-stimulated human mast cells. These LPS-stimulated mast cells produce more TNF- α and RANTES (CXCL5) and produce less IL-5 (39).

Mast cell-specific genes in airway tissue remodeling

Increasing evidence indicates that airway remodeling plays an important part in asthma pathogenesis. However, mechanisms underlying airway remodeling are not yet fully elucidated. Plasminogen activator inhibitor (PAI)-1 is the main inhibitor of the fibrinolytic system and is known to play an essential role in tissue remodeling. Recent evidence indicates that chronic asthma may lead to tissue remodeling such as subepithelial fibrosis and extracellular matrix deposition in the airways. Recently, mast cells were found to be a major source of PAI-1 by using microarray technology, and a large number of mast cells expressing PAI-1 are infiltrated in the airways of patients with severe asthma (40).

Wang et al. (41) and Okumura et al. (42) used oligonucleotide microarrays to examine the up-regulated

genes expressed by activated mast cells. These two groups separately identified amphiregulin as a transcript that is markedly increased following aggregation of Fc ϵ RI. Amphiregulin induced tissue remodeling, that is, proliferation of lung fibroblasts and marked induction of MUC5AC transcripts in a human respiratory epithelial cell line. Both groups showed that amphiregulin-positive mast cells were increased in the airways of asthmatics. These investigators employed culture-derived human mast cells for microarray as the first screening and they confirmed the *in vivo* expression and function of this up-regulated gene. Figure 1 illustrates the typical strategy for identifying a novel biomarker, amphiregulin in this case, by using microarrays as coincidentally employed in two independent studies (41, 42).

Gene expression profiles of human mast cell subsets

For a long time, we had not been able to obtain the substantial amount of human mast cells necessary for genome-wide comprehensive analyses such as an analysis of the transcriptome. We have established, however, the method of generating a substantial number of human mast cells from umbilical cord blood (43) and from adult peripheral blood (44). By the development of microarray technology, it became possible to examine the levels of whole transcripts present in a cell using approximately 10^5 cells. Thus, now we can examine the small cell populations such as tissue-derived mast cells or blood basophils. Several years ago, the expression levels of >10,000 transcripts in cultured human mast

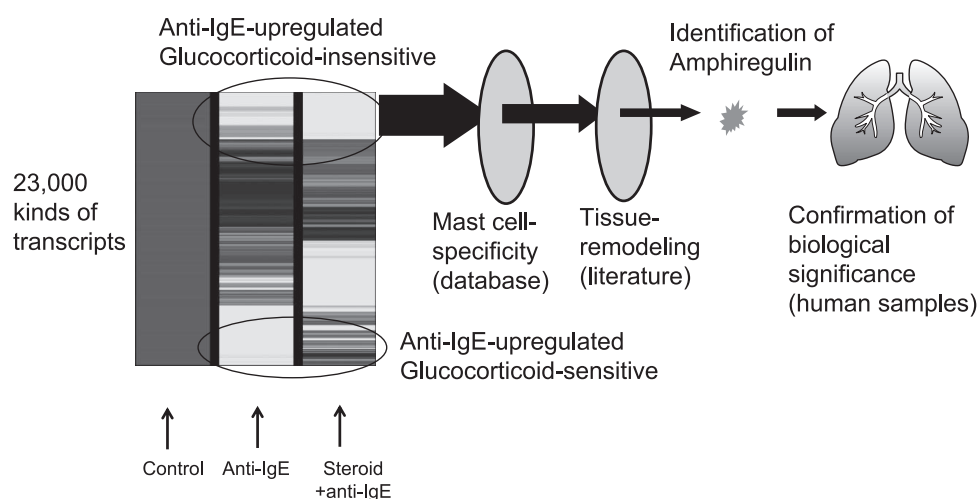


Fig. 1. The strategy to identify amphiregulin as a glucocorticoid-resistant mast cell-specific molecule. In references 41 and 42, the authors used the Affymetrix GeneChip® to find an anti-IgE-upregulated and glucocorticoid-resistant gene cluster. Then, amphiregulin was selected as one of target molecules by filtering with mast cell specificity and descriptions regarding tissue remodeling. Finally, biological significance was confirmed by demonstrating the selected expression in lung mast cells obtained from asthmatics.

cells derived from umbilical cord blood progenitors and from adult peripheral blood progenitors have been investigated (45). It was found that the transcript for Fc ϵ receptor α -chain is selectively down-regulated in cord blood-derived human mast cells compared to adult peripheral blood progenitor-derived mast cells. This down regulation may be controlled by epigenetic mechanisms present in hemopoietic progenitors since the expression level of Fc ϵ receptor α -chain was down-regulated even under the same culture conditions. Indeed, neonatal cord and adult peripheral blood hemopoietic progenitors can produce cell types having somewhat different profiles (46, 47).

Kashiwakura et al. have reported (48) the transcriptome analysis of human tonsillar mast cells, which locate in the interfollicular areas and may interact with T cells. A large fraction of the gene expression profiles of cultured tonsillar mast cells were comparable to other mast cells including cultured lung mast cells. However, MIP-1 α (CCL3) and MIP-1 β (CCL4) were expressed in resting cultured tonsillar mast cells but not in resting cultured lung mast cells. TNF- α expression was also up-regulated in tonsillar mast cells following Fc ϵ RI aggregation. It has been reported that CCL3 and CCL4 have the ability to recruit T cells into lymph nodes and mast cells are one of the major sources of CCL4 (49) and that both TNF- α concentration and the recruitment of circulating T cells were increased within draining lymph nodes following peripheral mast cell activation (50). T cells thus may be recruited by tonsillar mast cells. In agreement with the results of chymase expression of tissue mast cells (51), cultured tonsillar mast cells also showed higher intensity of the expression than cultured lung mast cells. It is of particular interest that the tissue-specific nature of human mast cells persists after a long period of culture. Kambe et al. have reported a similar observation regarding human skin-derived cultured mast cells (52). Reactivity toward substance P of the human skin-derived cultured mast cells was not lost even after extensive proliferation of the mast cells under the standard serum-free culture system supplemented with stem cell factor (SCF). Bradding et al. have reported (53) that human skin-derived cultured mast cells express somewhat different types of ion channel profiles in comparison with lung and cord blood-derived mast cells, although the transcriptome profiles of these mast cells were mostly identical. More recently, we used the hierarchical clustering method to understand the global gene expression profiles of human mast cell subtypes. All the transcripts subjected to this clustering analysis were classified into two large clusters, that is, mast cell-preferential or non-mast cell-preferential, indicating that mast cells are distinct from lymphocytes,

monocytes, and granulocytes including basophils. These mast cells from tonsil, lung, and skin had been cultured for more than several weeks to obtain highly viable and pure cell populations. Most of the transcripts were commonly expressed by these mast cell subtypes. However, tonsil-derived mast cells and skin-derived mast cells but not lung-derived mast cells expressed high levels of chymase (*CMA1*). These *CMA1*-high mast cells and *CMA1*-low mast cells respectively expressed distinct sets of transcripts as small gene clusters even after being cultured in the absence of tissue environment. These results suggest that the two types of mast cells can be regarded as differentiated mast cell subtypes (54).

These reports indicate that cultured mast cells retain some of their characteristics derived from the original tissues, even after proliferation at 15-fold increased number of mast cells under the standard culture conditions. Although the microenvironment can change the characterization of mast cells (55), some effects of microenvironment may last long after removal of the environmental factors. These findings may suggest that mast cell progenitors committed to a certain mast cell subtype might be selectively recruited to the tissue. Alternatively, the tissue-specific characters of mast cells may be determined by epigenetic alteration that occurred in their progenitors. The mast cell progenitors may be epigenetically influenced by environmental factors during their stay in the tissue. Environmental conditions sometimes modify the composition of genomic structure or nucleic acid molecules such as CpG methylation, and this modification sometimes lasts for a long time, even beyond generations (56).

Conclusions

The microarray analyses that have been performed so far have provided us with both information about gene expression profiling and some novel pathogenic mechanisms regarding mast cells in allergic diseases. After discovery of all player molecules present in mast cells in the future, we will know the systemic function of the cell.

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