University of Zurich[UZH]

Zurich Open Repository and Archive
University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2023

Distinct and mutually exclusive Ca2+ flux- and adenylyl cyclase-inducing gene expression profiles of G-protein-coupled receptors on human antigen-specific B cells

Chang, Iris ; Kaushik, Abhinav ; Satitsuksanoa, Pattraporn ; Yang, Minglin ; Buergi, Laura ; Schneider, Stephan R ; Babayev, Huseyn ; Akdis, Cezmi A ; Nadeau, Kari ; van de Veen, Willem ; Akdis, Mübeccel

DOI: https://doi.org/10.1111/all.15858

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-252703
Journal Article
Published Version

The following work is licensed under a Creative Commons: Attribution-NonCommercial 4.0 International (CC BY-NC 4.0) License.

Originally published at:
Chang, Iris; Kaushik, Abhinav; Satitsuksanoa, Pattraporn; Yang, Minglin; Buergi, Laura; Schneider, Stephan R; Babayev, Huseyn; Akdis, Cezmi A; Nadeau, Kari; van de Veen, Willem; Akdis, Mübeccel (2023). Distinct and mutually exclusive Ca2+ flux- and adenylyl cyclase-inducing gene expression profiles of G-protein-coupled receptors on human antigen-specific B cells. Allergy, 78(11):3016-3019.
DOI: https://doi.org/10.1111/all.15858

CONFLICT OF INTEREST STATEMENT

Rebecca K. Martin and Anuj Tharakan own stock in Pleros Therapeutics Inc. which is currently of no value. The rest of the authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Anuj Tharakan[1]
Ankit Kumar[1]
Jeremy Allegood[2]
Lauren Ashley Cowart[2,3]
Daniel H. Conrad[1]
Rebecca K. Martin[1]

[1]*Department of Microbiology and Immunology, Virginia Commonwealth University, Richmond, Virginia, USA*
[2]*Department of Biochemistry and Molecular Biology, Virginia Commonwealth University, Richmond, Virginia, USA*
[3]*Hunter Holmes McGuire Veteran's Affairs Medical Center, Richmond, Virginia, USA*

Correspondence
Rebecca K. Martin, Department of Microbiology and Immunology, Virginia Commonwealth University, Richmond, VA, USA.
Email: rebecca.martin@vcuhealth.org

ORCID

Daniel H. Conrad https://orcid.org/0000-0002-4791-2694
Rebecca K. Martin https://orcid.org/0000-0001-9948-5463

REFERENCES

1. Kuruvilla ME, Lee FE, Lee GB. Understanding asthma phenotypes, Endotypes, and mechanisms of disease. *Clin Rev Allergy Immunol*. 2019;56:219-233.
2. Gowthaman U, Chen JS, Zhang B, et al. Identification of a T follicular helper cell subset that drives anaphylactic IgE. *Science*. 2019;365:eaaw6433.
3. Zhu Z, Lee PH, Chaffin MD, et al. A genome-wide cross-trait analysis from UK biobank highlights the shared genetic architecture of asthma and allergic diseases. *Nat Genet*. 2018;50:857-864.
4. Du X, Hu H. The roles of 2-Hydroxyglutarate. *Front Cell Dev Biol*. 2021;9:651317.
5. Donas C, Carrasco M, Fritz M, et al. The histone demethylase inhibitor GSK-J4 limits inflammation through the induction of a tolerogenic phenotype on DCs. *J Autoimmun*. 2016;75:105-117.
6. Clement RL, Daccache J, Mohammed MT, et al. Follicular regulatory T cells control humoral and allergic immunity by restraining early B cell responses. *Nat Immunol*. 2019;20:1360-1371.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

DOI: 10.1111/all.15858

Distinct and mutually exclusive Ca^{2+} flux- and adenylyl cyclase-inducing gene expression profiles of G-protein-coupled receptors on human antigen-specific B cells

To the Editor,

B cells play an essential role in allergies by producing allergen-specific IgE, which is a prerequisite for allergen-induced degranulation of mast cells (MCs) and basophils. MCs, basophils, dendritic cells and bacteria are capable of secreting inflammatory mediators including histamine.[1] Histamine is a bioactive amine that exerts its function through binding to histamine receptors (HRs), which are 7-transmembrane G-protein-coupled receptors (GPCRs). Histamine can regulate its function through four receptors (HR1-HR4), in which ligation of histamine with HR1 can trigger Ca^{2+} mobilization, whereas HR2 stimulates and increases cAMP concentrations.[2] Interestingly, *HRH1* and *HRH2* genes can show mutually exclusive expression pattern in B cells, with a differential antibody response as demonstrated in the clones. HR1+/HR2− increases Th1 response and HR1 deficient mice has increased antigen specific IgE, whereas HR1−/HR2+ mice has suppressed Th2 cytokines and induced tolerance and show suppressed antigen specific IgE.[2] Functionally, HR1 and HR2 GPCRs are well-known to generate a different set of downstream signaling

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.
© 2023 The Authors. *Allergy* published by European Academy of Allergy and Clinical Immunology and John Wiley & Sons Ltd.

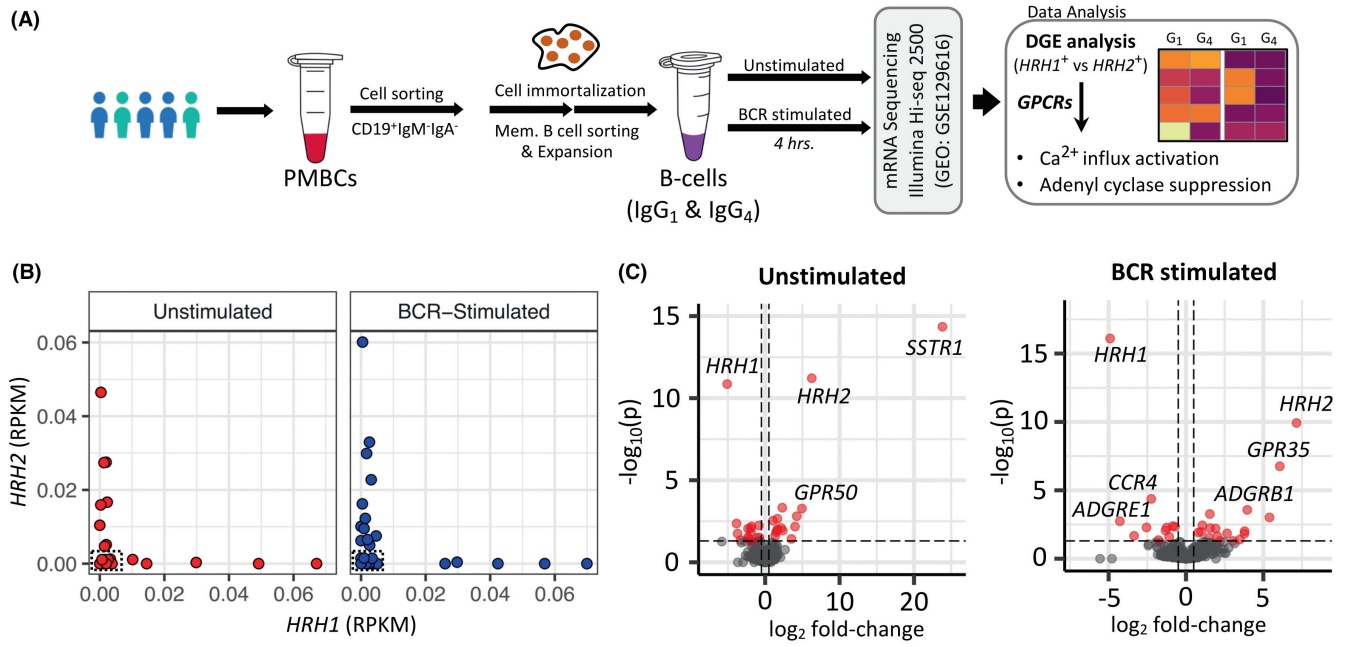

FIGURE 1 Study design and differential gene expression of histamine receptors. (A) The study design used for isolation and sorting of B cells clones for gene expression analysis and the data analysis workplan for identification and prioritization of GPCRs. (B) Mutually exclusive expression profile of *HRH1* and *HRH2* in both unstimulated and BCR-stimulated clones. The dotted box represents the threshold within which samples were considered as double negative, that is, *HRH1*−/*HRH2*−. (C) Volcano plots to highlight DE GPCR genes in *HRH1*+ versus *HRH2*+ samples in both unstimulated and BCR-stimulated samples. The red dots represent significantly differentially expressed genes (absolute logFC >0.5 & $p < .05$). Histamine receptor genes are represented as *HRH1* or *HRH2*, whereas their histamine receptor GPCR protein are represented as HR1 or HR2.

events in response to histamine. Therefore, to explore the response of B cells in allergic diseases, we analyzed the expression profile of HRs and other GPCRs in B cell clones. We hypothesized that the expression profile of HR genes (*HRH1*+ vs. *HRH2*+ B cell clones) could differentially affect the corresponding B cells response by triggering different intracellular events and downstream cascade of pathways in a GPCR-dependent manner.

A total of 27 IgG1 and IgG4 expressing B cell clones were isolated for gene expression analysis under unstimulated and BCR stimulated conditions, respectively (Figure 1A and Data S1). Interestingly, we observed B cell clones with mutually exclusive expression profile of *HRH1* and *HRH2* genes (Figure 1B), with more *HRH1*+ B cell clones in BCR-stimulated samples than unstimulated samples. The subsequent *HRH1*+ versus *HRH2*+ differential gene expression analysis (Figure 1C), reveal 28 differentially expressed (DE) GPCRs in unstimulated samples, with upregulated *P2RY13* and *C5AR1 genes* in *HRH2*+ B cell clones (Figure 2A,B), which are associated with the cAMP signaling and suppressive pathway.[3,4] To further prioritize the DE GPCRs specifically associated with Ca^{2+} and cAMP signaling pathways, we reconstructed the co-expression networks and performed the weighted degree analysis across *HRH1*+ versus *HRH2*+ clones. The analysis reveals that the purinergic receptor family of GPCRs (i.e., *P2RY1*, *P2RY13*) and complement component 5a receptor family of genes (i.e., *C5AR1* and *C5AR2*) share highest degree of interactions. These genes are upregulated in *HRH2*+ samples and are well-known to affect cAMP signaling pathway[3,4] (Figure S1A). Intriguingly, we also observed upregulation of *GPR35* in *HRH2*+ B cells, which is associated in maintaining a low baseline Ca^{2+} level.[5] Similarly, we also observed upregulation of *GPR68 and GPR171* in *HRH1*+ B cells; both are known to stimulate Ca^{2+} flux (Data S1).

Similarly, 27 GPCRs were DE in BCR-stimulated samples (Figure 2C,D), including higher expression of serotonin receptor type 1A (*HTR1A*) and *HCAR1* (or *GPR81*) in *HRH2*+ samples, with a cAMP-linked suppressive function. In addition, we also observed upregulation of complement component 5a receptor family of genes (i.e., *C5AR1* and *C5AR2*) and *GPR35*, in agreement with the trend observed in unstimulated *HRH2*+ B cell clones. Surprisingly, we observed a higher expression of prostaglandin E2 receptor subtype EP4 (*PTGER4*) and adenosine A2A receptor (*ADORA2A*) in *HRH2*+ samples,[4,6] which are known to be associated with activation of cAMP production and share the highest strength of interactions with the cAMP signaling sub-network (Figure S1B). Among the upregulated genes in *HRH1*+ samples, we found three Ca^{2+} mobilizing genes, that is, *GPR34*, *P2RY10*, and *PTAFR*.

The results reported in this study provide data for a novel hypothesis suggesting investigation of co-expressed genes that may play important synergistic or antagonistic regulatory roles in B cell function.

AUTHOR CONTRIBUTIONS

Iris Chang: Writing, review & editing, formal analysis; Abhinav Kaushik: Writing, review & editing, software and formal analysis;

13989995, 2023, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.15858 by Universitatsbibliothek Zuerich, Wiley Online Library on [10/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

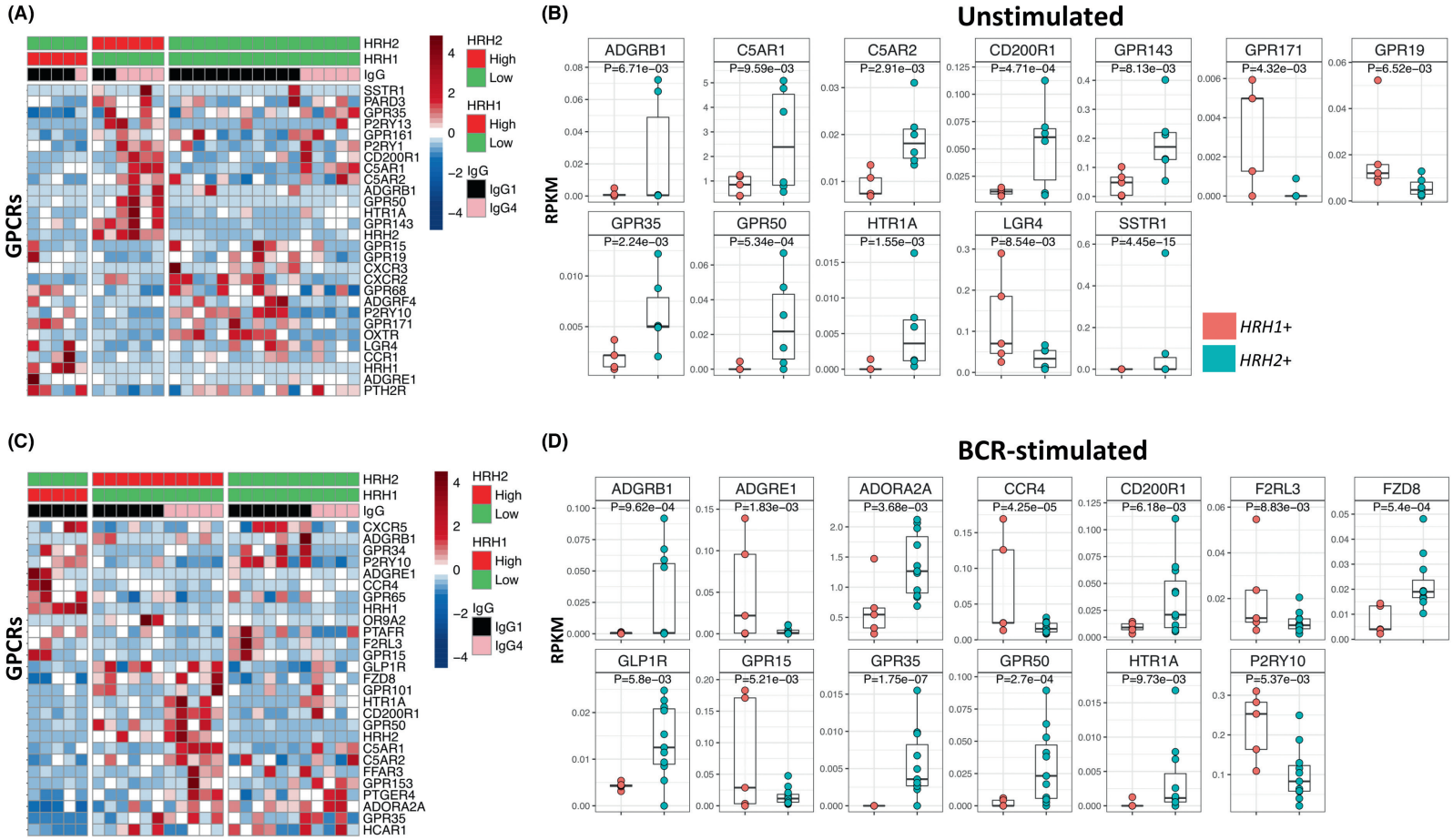

FIGURE 2 Differentially expressed (DE) GPCRs in *HRH1*+ versus *HRH2*+ samples. (A) Heatmap showing expression profile of DE GPCR genes in all the unstimulated samples, including double negative samples. The top two panels represent the *HRH1*+ and *HRH2*+ status of each sample. (B) The boxplot showing topmost significantly DE GPCR genes in (absolute logFC >0.5 & $p < .001$) in unstimulated samples. (C) Heatmap showing expression profile of DE GPCR genes in all the BCR-stimulated samples. The annotations are same as (A). (D). The boxplot showing topmost significantly DE GPCR genes in (absolute logFC >0.5 & $p < .001$) in BCR-stimulated samples. Histamine receptor genes are represented as *HRH1* or *HRH2*, whereas their histamine receptor GPCR protein are represented as HR1 or HR2.

13989995, 2023, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.15858 by Universitaetsbibliothek Zuerich, Wiley Online Library on [10/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Pattraporn Satitsuksanoa, Laura Buergi, Stephan R. Schneider: review & editing; Minglin Yang: formal analysis; Kari Nadeau: supervision, review & editing; Willem van de Veen: review & editing, conceptualization, method, provide data; Huseyn Babayev: software and formal analysis; Cezmi A. Akdis and Mübeccel Akdis: review & editing, conceptualization, supervision.

ACKNOWLEDGMENTS

M.A. has received research support from the Swiss National Science Foundation No. 310030-201053/320030-159870 and the Sean N Parker Center for Allergy and Asthma Research at Stanford University. C.A.A. is employed by the Swiss Institute of Allergy and Asthma Research, University of Zurich; has research grants from the Swiss National Science Foundation No. 310030-156823, and the Christine Kühne—Center for Allergy Research and Education (CK-CARE). W.V. received research grant from Promedica Stiftung. M.S. received research grants from the Swiss National Science Foundation (No. 310030_189334/1) and the GSK, and Novartis. K.N. has received the funding from NIAID grants U19AI104209, U01AI140498, and R01AI140134 and the Sean N. Parker Center for Allergy and Asthma Research at Stanford University.

CONFLICT OF INTEREST STATEMENT

Authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article

Iris Chang[1,2,3]
Abhinav Kaushik[1,2,4]
Pattraporn Satitsuksanoa[1]
Minglin Yang[1]
Laura Buergi[1]
Stephan R. Schneider[1]
Huseyn Babayev[1,5]
Cezmi A. Akdis[1]
Kari Nadeau[2,4]
Willem van de Veen[1]
Mübeccel Akdis[1]

[1]*Swiss Institute of Allergy and Asthma Research (SIAF), University of Zürich, Davos, Switzerland*
[2]*Sean N. Parker Center for Allergy and Asthma Research, Department of Medicine, Stanford University, Palo Alto, California, USA*
[3]*Stem Cell Transplantation and Regenerative Medicine, Department of Pediatrics, Stanford University School of Medicine, Palo Alto, California, USA*
[4]*Department of Environmental Health, Harvard T. H. Chan School of Public Health, Boston, Massachusetts, USA*
[5]*Department of Microbiology, Institute of Graduate Studies, Bolu Abant Izzet Baysal University, Bolu, Turkey*

Correspondence
Mübeccel Akdis, Swiss Institute of Allergy and Asthma Research (SIAF), University of Zürich, Davos, Switzerland.
Email: akdism@siaf.uzh.ch

Iris Chang and Abhinav Kaushik contributed equally.

ORCID

Iris Chang https://orcid.org/0009-0007-1971-8513
Abhinav Kaushik https://orcid.org/0000-0001-5682-0209
Cezmi A. Akdis https://orcid.org/0000-0001-8020-019X
Kari Nadeau https://orcid.org/0000-0002-2146-2955
Mübeccel Akdis https://orcid.org/0000-0003-0554-9943

REFERENCES

1. Barcik W, Pugin B, Westermann P, et al. Histamine-secreting microbes are increased in the gut of adult asthma patients. *J Allergy Clin Immunol*. 2016;138(5):1491-1494.e7.
2. Jutel M, Watanabe T, Klunker S, et al. Histamine regulates T-cell and antibody responses by differential expression of H1 and H2 receptors. *Nature*. 2001;413(6854):420-425.
3. Li XX, Lee JD, Massey NL, et al. Pharmacological characterisation of small molecule C5aR1 inhibitors in human cells reveals biased activities for signalling and function. *Biochem Pharmacol*. 2020;180:114156.
4. Thompson RJ, Sayers I, Kuokkanen K, Hall IP. Purinergic receptors in the airways: potential therapeutic targets for asthma? *Front Allergy*. 2021;2:677677.
5. Schneditz G, Elias JE, Pagano E, et al. GPR35 promotes glycolysis, proliferation, and oncogenic signaling by engaging with the sodium potassium pump. *Sci Signal*. 2019;12(562):eaau9048.
6. Kim HJ, Kim SH, Kim M, et al. Inhibition of 15-PGDH prevents ischemic renal injury by the PGE(2)/EP(4) signaling pathway mediating vasodilation, increased renal blood flow, and increased adenosine/a(2A) receptors. *Am J Physiol Renal Physiol*. 2020;319(6):F1054-F1066.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

13989995, 2023, 11, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/all.15858 by Universitatsbibliothek Zuerich, Wiley Online Library on [10/01/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License