Allergy Asthma Immunol Res. 2021 Sep;13(5):819-821
https://doi.org/10.4168/aair.2021.13.5.819
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Letter to the Editor

PD-1 Regulates Passive Anaphylaxis: A Possible Role of the Mast Cell Intracellular Inhibitory Signal

Tatsuya Ogawa,[1] **Yosuke Ishitsuka**,[1,2*] **Yoshiyuki Nakamura**,[1] **Rei Watanabe**,[1,2] **Naoko Okiyama**,[1] **Yasuhiro Fujisawa**,[1] **Manabu Fujimoto** [1,2]

[1]Department of Dermatology, Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki, Japan
[2]Department of Dermatology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

Received: Jan 5, 2021
Revised: Feb 11, 2021
Accepted: Feb 23, 2021

Correspondence to
Yosuke Ishitsuka, MD, PhD
Department of Dermatology, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan.
Tel: 81-6-6879-3031
Fax: 81-6-6879-3039
E-mail: ishitsuka@derma.med.osaka-u.ac.jp

ORCID iDs
Tatsuya Ogawa
https://orcid.org/0000-0003-1124-4572
Yosuke Ishitsuka
https://orcid.org/0000-0002-1733-5427
Yoshiyuki Nakamura
https://orcid.org/0000-0003-0166-2658
Rei Watanabe
https://orcid.org/0000-0001-8254-9176
Naoko Okiyama
https://orcid.org/0000-0002-5398-0773
Yasuhiro Fujisawa
https://orcid.org/0000-0003-3010-8496
Manabu Fujimoto
https://orcid.org/0000-0002-3062-4872

Dear Editor,

Antigen engagement on immunoreceptors initiates a series of intracellular phosphorylation/dephosphorylation events and regulates immune effector functions located downstream. Src-family protein tyrosine kinases phosphorylate the immunoreceptor tyrosine-based *activation* motif (ITAM), while protein tyrosine phosphatase non-receptor type 11 (SHP-2) dephosphorylates the immunoreceptor tyrosine-based *inhibitory* motif (ITIM) or the immunoreceptor tyrosine-based switch motif (ITSM). ITIM/ITSM in the cytoplasmic tail of programmed cell death-1 (PD-1)[1] dampens immune effector functions following the engagement of T-cell receptor (TCR)[2] or B-cell receptor (BCR).[3]

The mast cell (MC) can serve as a critical effector of adaptive immune responses; analogous to TCR/BCR signaling pathways, the high-affinity immunoglobulin E (IgE) receptor (FcεRI) signaling pathway involves ITAM-or ITIM/ITSM-mediated immune signaling.[4] Although the MC reportedly does not express PD-1 on its surface,[5] ligation of this receptor does lead to phosphorylation of SHP-1/SHP-2 in a mast cell line,[5] suggesting that the presence of receptor cytoplasmic tail-mediated inhibitory signaling is conserved across the cell lineage.[2,3] Given that PD-1 interacts with SHP-2 even without the engagement of its own receptor in T cells *in vitro*,[2] we hypothesized that FcεRI signaling is inhibited through the cytoplasmic tail. To this end, we employed an IgE-mediated passive anaphylaxis model to assess MC effector function *in vivo*.

In contrast to the results of MC-specific SHP-2 deletion,[6] the number of the cutaneous or peritoneal MC populations of PD-1 knockout (PD-1KO) mice were not significantly altered (**Supplementary Fig. S1A and B**, **Supplementary Data S1**). This discrepancy suggests that PD-1 is dispensable for the KIT proto-oncogene/SHP-2 axis-mediated development of the tissue MC lineage.[6] PD-1KO mice exhibited a significantly greater decline in temperature than wild-type (WT) mice (**Figure A**). Likewise, in passive cutaneous anaphylaxis, PD-1KO mice exhibited a significantly greater degree of ear swelling than WT mice (**Figure B**). However, monoclonal antibody (mAb)-mediated PD-1 blockade did not produce such an exacerbated anaphylactic response (**Figure C-E**). Conversely, during active anaphylaxis that solely depends on adaptive immunity, PD-1KO mice exhibited a decline in temperature comparable to WT mice (data not shown). These results suggest that exacerbated passive anaphylaxis is not necessarily attributable to broad immunologic abnormalities in PD-1KO mice.

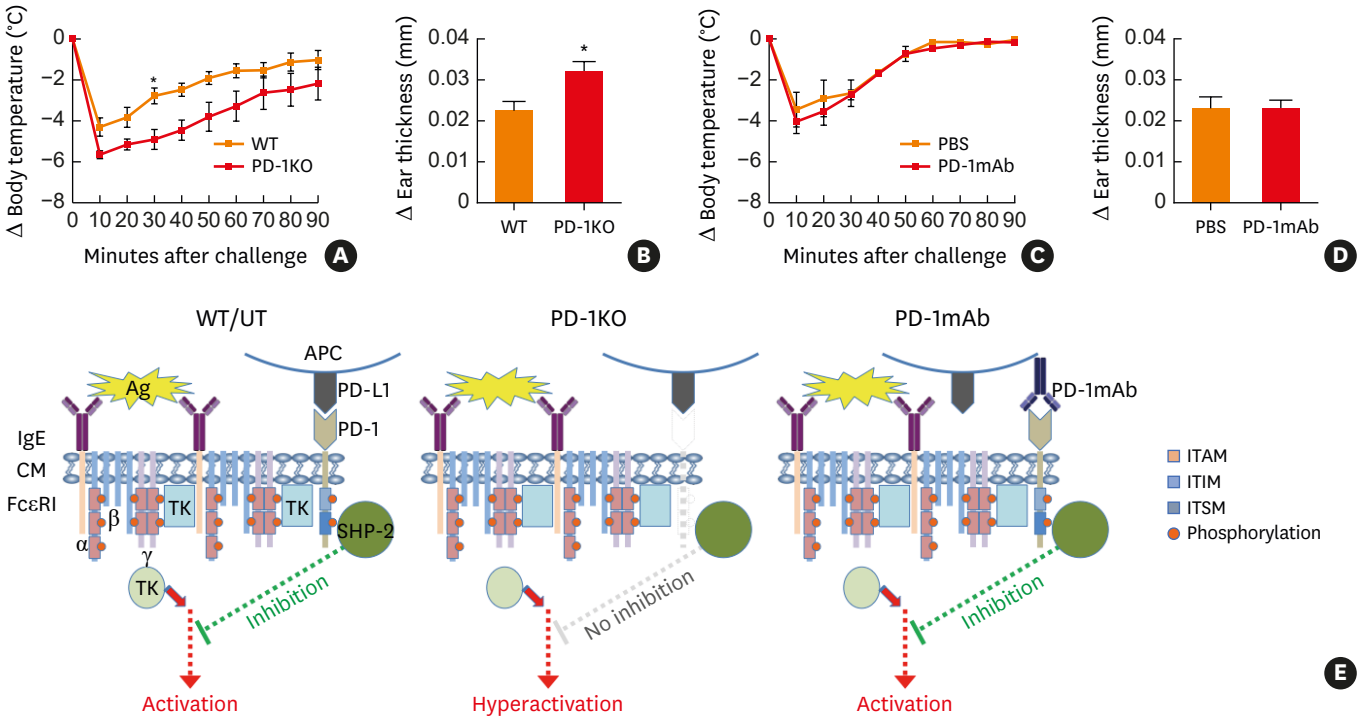

Figure. Enhanced passive anaphylaxis in PD-1KO, but not in mAb-mediated PD-1 blockade.
(A) Both WT and PD-1KO mice were injected intraperitoneally (20 μg of anti-DNP IgE) and intravenously (1 mg of DNP-human serum albumin). Rectal temperature was monitored for 90 minutes following the challenge (n = 4, two-way ANOVA). (B) Both WT and PD-1KO mice were injected intravenously (2 μg of anti-DNP IgE), and their ear pinnae were painted (20 μL of 0.3% 1-fluoro-2,4-dinitrobenzene). Ear thickness was measured 24 hours after the challenge (*n* = 6, Welch's *t* test). (C) Administration of anti-PD-1mAb to WT mice preceded the induction of passive systemic anaphylaxis. Rectal temperature was monitored for 90 minutes following the challenge (n = 4, two-way ANOVA). (D) Administration of anti-PD-1mAb to WT mice preceded the induction of passive cutaneous anaphylaxis. Ear thickness was measured 24 hours after the challenge (n = 6, Welch's *t* test). (E) A possible role for intracytoplasmic PD-1 signaling in mast cells. Multivalent antigen-binding causes aggregation of mast cell surface FcεRI. Subsequently, cytoplasmic tyrosine kinases phosphorylate ITAMs in the immunoreceptor tail, resulting in the rapid release of soluble mediators from preformed granules.
Wild-type/Untreated (WT/UT): ITSM-containing PD-1 cytoplasmic tail recruits SHP-2 to oppose phosphorylation events.
PD-1 knockout (PD-1KO): Complete deletion of PD-1 abrogates interaction with SHP-2 (and thus opposition to phosphorylation events).
PD-1 blockade (PD-1mAb): Because the PD-1 cytoplasmic tail remains intact, FcεRI activation overcomes receptor engagement-dependent opposition to phosphorylation events.
PD-1KO, programmed cell death-1 knockout; mAb, monoclonal antibody; PD-1, programmed cell death-1; DNP, dinitrophenyl; IgE, immunoglobulin E; ANOVA, analysis of variance; WT, wild-type; FcεRI, high-affinity IgE receptor; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; PBS, phosphate-buffered saline; Ag, antigen; APC, antigen presentation cell; CM, cell membrane; PD-L1, programmed death-ligand 1; SHP-2, protein tyrosine phosphatase non-receptor type 11; TK, tyrosine-protein kinase.
*$P < 0.05$.

Disclosure

There are no financial or other issues that might lead to conflict of interest.

Immune checkpoint inhibitors can evoke immune-related adverse events (irAEs).[7] Analogous to TCR signaling,[2] our results suggest that an augmented IgE humoral immune response requires complete deletion of PD-1, while PD-1 blockade is dispensable. Furthermore, our results indicate that PD-1 has co-evolved with other inhibitory immunoreceptors to regulate the adaptive immune response at the effector phase,[7] and may additionally correlate with clinical observations; although urticarial eruptions are a common form of cutaneous irAE, its systemic counterpart–anaphylaxis–is rarely reported in this context. Our results may be an important guide for medical oncology practice in that the PD-1 blockade would hardly aggravate IgE-mediated anaphylaxis. Further studies are needed to elucidate PD-1 functions on MC.

https://doi.org/10.4168/aair.2021.13.5.819

ACKNOWLEDGMENT

This research was supported in part by the JSPS KAKENHI Grant; Grant-in-Aid for Research Activity Start-up 16H06663 and Early-Career Scientists (18K16018) to YI. We thank Ms. Yuriko Hirota for technical assistance with the passive systemic anaphylaxis and Ono Pharmaceutical Co., Ltd. (Osaka, Japan) for kindly providing the PD-1mAb.

SUPPLEMENTARY MATERIALS

Supplementary Data S1
Materials and methods

Click here to view

Supplementary Fig. S1
Unaltered mast cell homeostasis in the absence of PD-1.

Click here to view

REFERENCES

1. Shinohara T, Taniwaki M, Ishida Y, Kawaichi M, Honjo T. Structure and chromosomal localization of the human PD-1 gene (PDCD1). Genomics 1994;23:704-6.
PUBMED | CROSSREF
2. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.
PUBMED | CROSSREF
3. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98:13866-71.
PUBMED | CROSSREF
4. Izawa K, Kitaura J, Yamanishi Y, Matsuoka T, Kaitani A, Sugiuchi M, et al. An activating and inhibitory signal from an inhibitory receptor LMIR3/CLM-1: LMIR3 augments lipopolysaccharide response through association with FcRγ in mast cells. J Immunol 2009;183:925-36.
PUBMED | CROSSREF
5. Kataoka TR, Fujimoto M, Moriyoshi K, Koyanagi I, Ueshima C, Kono F, et al. PD-1 regulates the growth of human mastocytosis cells. Allergol Int 2013;62:99-104.
PUBMED | CROSSREF
6. Sharma N, Kumar V, Everingham S, Mali RS, Kapur R, Zeng LF, et al. SH2 domain-containing phosphatase 2 is a critical regulator of connective tissue mast cell survival and homeostasis in mice. Mol Cell Biol 2012;32:2653-63.
PUBMED | CROSSREF
7. Ogawa T, Ishitsuka Y, Saito A, Nakamura Y, Watanabe R, Okiyama N, et al. Immune microenvironment controls the outcome of PD-1 blockade in cutaneous immune response. Allergy 2019;74:2257-61.
PUBMED | CROSSREF