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Letter to the Editor

Modulation of human basophil activation by resveratrol

Dear Editor

Recent experimental findings have shown that basophils may be highly important in anaphylaxis or IgE-mediated very-late-phase skin inflammation.¹ Activation of basophils by immunological stimuli is known to be modified by various exogenous substances having anti-allergic properties. Bisphenols appear to have such properties; several chemicals belonging to bisphenols, including quercetin and curcumin, are reported to down-regulate activation of basophils or other allergic effector cells and to suppress allergic inflammation.² Recently, resveratrol—another bisphenol—has attracted researchers' attention since it is included in red wine and is thought to improve various indices of French peoples' health status.³ Although resveratrol is suspected to share a variety of anti-oxidant properties with quercetin, its precise biological actions have not been fully elucidated.

In this study, we assessed the effect of resveratrol on basophil activation, detected as release of histamine and leukotriene C₄ (LTC₄). Basophils were obtained from non-allergic volunteers by dextran sedimentation of venous blood (purity ~1%). In some experiments, highly purified basophils prepared by Percoll gradient centrifugation plus negative MACS selection were used.⁴ Cells were preincubated with resveratrol (Wako Pure Chemicals, Osaka, Japan) for 30 min at 37 °C, washed and then stimulated with secretagogues for 45 min.⁴ Histamine and LTC₄ in the supernatant were measured using an autoanalyzer and ELISA kits (Cayman Chemical, Ann Arbor, MI, USA), respectively.

Histamine release from basophils in response to treatment with each of polyclonal anti-IgE antibody (MBL, Nagoya, Japan), phorbol myristate acetate (PMA) (Sigma, St. Louis, MO, USA) and calcium ionophore A23187 (Sigma) was significantly suppressed by preincubation of the cells for 30 min with resveratrol at 30 or 100 μM (Fig. 1a). Similar results were obtained for highly purified basophils (purity > 80%), suggesting that resveratrol acts directly on basophils (Fig. 1b). Resveratrol did not cause apparent damage to basophils, since basophil preparations pretreated with this substance at 100 μM for 2 h had a normal histamine content and showed histamine releasability similar to that of 30-min-pretreated basophils (data not shown). In the next experiments, dextran-sedimented basophils were pretreated with serial concentrations of resveratrol for 30 min and a basophil-priming cytokine, IL-3, for 15 min before stimulation with anti-IgE antibody (Fig. 1c). Resveratrol significantly down-regulated histamine

release from basophils treated with all the tested concentrations of IL-3. Next, the effect of resveratrol on basophil LTC₄ release was assessed (Fig. 1d). Basophils stimulated with anti-IgE antibody released LTC₄, and this was augmented by pretreatment with IL-3. Resveratrol at 100 μM strongly suppressed LTC₄ secretion from anti-IgE-antibody-stimulated basophils. Lastly, basophils were pretreated with resveratrol or quercetin, washed and stimulated with anti-IgE antibody (Fig. 1e). Quercetin at 100 μM significantly suppressed histamine release, and the effect of quercetin was slightly more potent than that of resveratrol.

Our results clearly indicate that resveratrol down-regulates basophil mediator release induced by IgE-mediated and non-IgE-mediated stimulation. These findings are in line with previous reports showing that this substance suppresses activation of rodent mast cells and human eosinophils at concentrations similar to those used in the present study.^{5,6} Resveratrol can thus be regarded as negative regulators of allergic inflammatory cell activation. It will be interesting to assess whether, and to what extent, dietary supplementation of resveratrol affects our immunological status.⁷ The serum concentration of resveratrol (~10 μM) is close to the effective dose in our study, suggesting that modulation of basophil functions might also take place *in vivo*.

Various activities of resveratrol are being unveiled through recent experimental approaches. Rodent studies demonstrated that this compound is able to suppress allergic reactions in the airways.^{8–10} Resveratrol can also suppress tissue-damaging or stress-related responses via anti-oxidant or other signal-modifying mechanisms.³ Various *in vivo* studies found that resveratrol exerts organ-protective effects. In addition, the broad action of this compound improves the outcome of diabetes mellitus and cancer.³ We surmise that allergic diseases may also be important targets of resveratrol. Although the *in vivo* significance of our findings and the overall import of the immunological actions of resveratrol remain unclear, elucidation of the precise roles of this unique compound in various allergic disorders is strongly warranted.

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Conflict of interest

The authors have no conflict of interest to declare.

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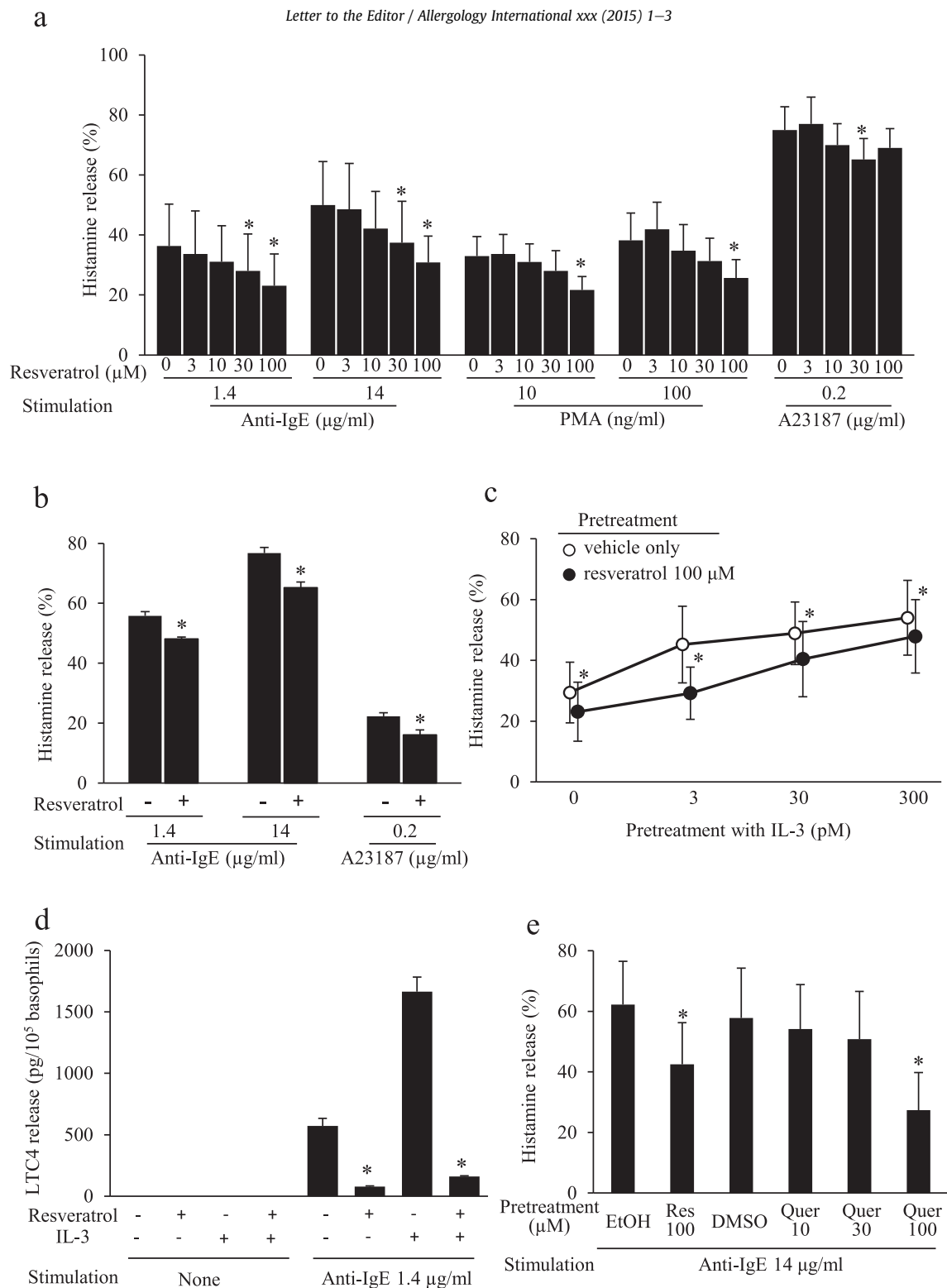


Fig. 1. Modulation of basophil mediator release by resveratrol. **(a)** Basophil preparations were preincubated with and without various concentrations of resveratrol for 30 min at 37 °C and then stimulated with secretagogues for 45 min. Histamine release was expressed as a percentage of the total cellular histamine after subtracting spontaneous release (usually < 5%). Data are the mean $\pm$ SEM of four separate experiments. * p < 0.05, versus corresponding values of cells not preincubated with resveratrol, assessed by one-way ANOVA followed by Tukey post-hoc test. **(b)** Resveratrol at 100 μ M affects histamine release from highly purified basophils. Data are the mean $\pm$ SEM (n = 4). * p < 0.05, versus corresponding cells not preincubated with resveratrol. **(c)** Effects of resveratrol and IL-3 on basophil degranulation. Cells were preincubated with and without resveratrol at 100 μ M for 30 min, washed and then incubated with and without IL-3 for 15 min before stimulation with anti-IgE antibody at 1.4 μ g/ml. Data are the mean $\pm$ SEM (n = 3). * p < 0.05, versus the corresponding value of cells not preincubated with resveratrol. **(d)** Effect of resveratrol on basophil LTC4 release. Data are the mean $\pm$ SEM (n = 3). * p < 0.05, versus the corresponding value of cells not preincubated with resveratrol. **(e)** Stock solutions were prepared and stored at -80 °C for resveratrol at 50 mM in ethanol and quercetin at 50 mM in DMSO. Basophils were preincubated with and without diluted resveratrol or quercetin for 30 min at 37 °C, washed and then stimulated with anti-IgE antibody for 45 min. Percentages of histamine release by cells preincubated with vehicle are also shown. Data are the mean $\pm$ SEM (n = 4). * p < 0.05, versus the corresponding value of vehicle-pretreated cells. Res: resveratrol; Quer: quercetin.

Yusuke Tanaka ^a, Masao Yamaguchi ^{a,*}, Maho Suzukawa ^b,
Hidenori Arai ^a, Hiroyuki Nagase ^a, Ken Ohta ^{a,b}

^a Division of Respiratory Medicine and Allergology, Department of Medicine, Teikyo University School of Medicine, Tokyo, Japan

^b National Hospital Organization Tokyo National Hospital, Tokyo, Japan

* Corresponding author. Division of Respiratory Medicine and Allergology, Department of Medicine, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan.

E-mail address: myama@med.teikyo-u.ac.jp (M. Yamaguchi).

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