Hyperexpression of the High-Affinity IgE Receptor-β Chain in Chronic Allergic Keratoconjunctivitis

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Purpose. Although the existence of FcεRI-$\alpha\beta\gamma_2$ and FcεRI-$\alpha\gamma_2$ receptor subtypes was reported, there has been no direct evidence of these two subtypes of FcεRI in vivo. To investigate the existence of these two subtypes of FcεRI in vivo, the authors evaluated the expression of FcεRI-β in the giant papillae of chronic allergic conjunctivitis and compared the expression level of FcεRI-β with control conjunctivae using the anti-human FcεRI-β antibody.

Methods. FcεRI-β expression in giant papillae obtained from patients with atopic keratoconjunctivitis and vernal keratoconjunctivitis in control conjunctivae was evaluated by immunohistochemistry using anti-FcεRI-β, -α, -γ, and anti-human mast cell tryptase, anti-chymase, anti-basophil, and anti-CD1a antibodies.

Results. Statistical analyses revealed that the densities of FcεRI-β^+ cells, FcεRI-α^+ cells, tryptase$^+$ cells, and FcεRI-β^+/tryptase$^+$ cells were significantly increased in giant papillae compared with controls. There were two types of FcεRI ($\alpha\beta\gamma_2$ and $\alpha\gamma_2$) on the mast cells of the giant papillae. The ratio of the FcεRI-β^+ cell number/FcεRI-α^+ cell number in the giant papillae (0.69 ± 0.08 [mean ± SD]) was significantly higher than that of the controls (0.07 ± 0.16). FcεRI-β/tryptase double immunostaining revealed that 81% ± 13% of tryptase$^+$ cells expressed FcεRI-β. FcεRI-β^+ cells were preferentially localized within and around epithelial tissue. The authors also found that FcεRI-β was expressed by basophils but not by FcεRI-$\alpha\gamma_2$-positive Langerhans cells in the giant papillae samples.

Conclusions. Preferential FcεRI-β expression observed in the mast cells and basophils of giant papillae suggests important roles of FcεRI-β in the pathophysiology of atopic keratoconjunctivitis and vernal keratoconjunctivitis. (*Invest Ophthalmol Vis Sci.* 2009;50:2871–2877) DOI:10.1167/iovs.08-3022

Human high-affinity IgE receptor (FcεRI) exists in two isoform, a tetramer containing the β chain FcεRI-$\alpha\beta\gamma_2$ and a trimer lacking the β chain FcεRI-$\alpha\gamma_2$, depending on cell type.[1] The FcεRI-β gene (*MS4A2*) has been recognized as an atopy-related gene, initially discovered from a genetic linkage study[2] and also from a genetic association study[3] by our group, and the functional roles of FcεRI-β protein have been investigated extensively. For example, the FcεRI-β chain mediates intracellular signaling through the immunoreceptor tyrosine-based activation motif and is phosphorylated in response to antigen cross-linking of the receptor-bound IgE.[1] The human FcεRI-β chain acts as an amplifier for mast cell activation and cell surface expression of FcεRI.[4,5] Although the existence of the FcεRI-$\alpha\beta\gamma_2$ and FcεRI-$\alpha\gamma_2$ receptor subtypes has been reported,[6] there has been no direct evidence of these two subtypes of FcεRI in vivo at the protein level. Furthermore, the precise pathophysiological roles of the FcεRI-β chain in human atopic diseases remain unclear. Recently, we raised an antibody against human FcεRI-β that was useful for the in situ detection of the FcεRI-β protein.[7]

Atopic keratoconjunctivitis (AKC)[8,9] and vernal keratoconjunctivitis (VKC)[10] are the most severe forms of chronic allergic conjunctivitis. Massive infiltration of mast cells occurs, and serum and tear IgE levels are significantly higher than in healthy controls.[8,11,12] In addition, AKC and VKC tend to form giant papillae at the upper tarsal conjunctiva.[8,10,13] We resected giant papillae for therapeutic purposes[14] and carried out histopathologic analysis with the resected tissues using our newly generated anti-FcεRI-β-specific antibody. We reported previously that IgE-bearing FcεRI-α^+ mast cells were increased in the giant papillae of patients with VKC[15]; however, the expression of FcεRI-β has yet to be evaluated. We found preferential FcεRI-β expression in the mast cells of giant papillae samples compared with those of the control conjunctivae.

Materials and Methods

Antibodies

Rabbit antiserum against unique C-terminal sequences of human FcεRI-β (CYSELEDPGEMSPPIDL) was generated and the antiserum was purified on a protein-A column, as previously described.[7] Because this antibody was raised against the C-terminal region of human FcεRI-β protein, it did not recognize the truncated form of FcεRI-β protein described previously.[16] Other antibodies used in this study included Alexa 488-conjugated-goat anti-rabbit-F(ab')$_2$ and Alexa 594-conjugated goat anti-mouse IgG-F(ab')$_2$ (Invitrogen, Carlsbad, CA), Cy5-conjugated goat anti-mouse IgG1 antibody (Southern Biotechnology, Birmingham, AL), rabbit anti-FcεRI-γ polyclonal antibody (Upstate Biotechnology, Lake Placid, NY), phycoerythrin (PE)-conjugated mouse anti-FcεRI-α monoclonal antibody (clone CRA1; e-bioscience, Tokyo, Japan), mouse anti-chymase monoclonal antibody (clone CC1; LAB Vision, Fremont, CA), mouse anti-CD1a monoclonal antibody

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TABLE 1. Clinical Characteristics of Patients with AKC/VKC and FcεRI-β$^+$ Cell Numbers of Giant Papillae

Patient	Age (y)	Sex	Total IgE	Specific IgE	Diagnosis	FcεRI-β$^+$ Cells (mean ± SD)	Treatment
1	16	F	509	Positive	VKC	62.5 ± 20.0	Dex, CsA
2	22	M	89	Positive	VKC	53.9 ± 8.3	Dex
3	13	M	2319	Positive	VKC	20.2 ± 8.3	Dex
4	18	M	375	Positive	AKC	49.3 ± 22.0	Dex, CsA
5	17	M	17260	Positive	AKC	56.2 ± 21.2	Dex, CsA, oral steroid
6	21	M	1904	Positive	AKC	34.9 ± 18.0	Dex
7	16	M	3763	Positive	AKC	29.2 ± 17.0	Dex
8	19	M	124	Negative	VKC	49.4 ± 20.0	Dex
9	23	M	20328	Positive	AKC	78.3 ± 25.5	Dex
10	45	F	28	Negative	AKC	48.2 ± 12.0	Dex

Dex, 0.1% dexamethasone eyedrop; CsA, 0.1% cyclosporine eyedrop.

(clone O-10; Santa Cruz Biotechnology Inc., Santa Cruz, CA), and mouse anti-mast-cell tryptase monoclonal antibody (clone AA-1; Dako Japan, Kyoto, Japan). Mouse anti-basophil monoclonal antibody (clone BB-1) was generated as previously described.[17]

AKC/VKC Patient Selection and Giant Papillae Tissue Processing

Giant papillae were resected for therapeutic purposes[14] from six patients with AKC and four patients with VKC after obtaining informed consent (Table 1).AKC was defined as bilateral, chronic inflammation of the conjunctiva and lids associated with atopic dermatitis, and VKC was defined as bilateral, chronic inflammation of the conjunctiva associated with predisposition to atopy.[18] Patients who had atopic dermatitis or corneal stromal neovascularization were excluded from the VKC diagnosis. All patients with AKC or VKC were treated by topical dexamethasone eyedrops for at least 4 weeks before surgery. Some patients were also treated by an oral steroid (20 mg/day prednisolone) or by cyclosporine A eyedrops. Total serum IgE concentration and specific IgE titer against 26 common antigens (including house dust mite and Japanese cedar pollen) were measured by SRL, Inc. (Tokyo, Japan) using the fluorescence enzyme immunoassay method and the enzyme-linked immunosorbent assay (ELISA) method, respectively. Upper bulbar conjunctivae were resected from six patients with conjunctivochalasis and four patients with superior limbic keratoconjunctivitis (SLK)[19] for therapeutic purposes after informed consent was obtained (Table 2). Conjunctivochalasis was defined as a redundant conjunctiva typically located between the globe and the lower eyelid,[20] and SLK was defined according to the original clinical descriptions by Theodore.[21] Giant papillae were fixed with 4% paraformaldehyde (PFA)-phosphate buffered saline (PBS) for at least 4 hours and were then immersed in a 20% sucrose-PBS solution for 30 minutes, rapidly frozen in OCT compound (Sakura Finetek, Tokyo, Japan), and stored at −80°C. All procedures were approved by the ethics committee of Kyoto Prefectural University of Medicine, and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

TABLE 2. Clinical Characteristics of Control Patients

Patient	Age (y)	Sex	Diagnosis
1	39	F	SLK
2	49	F	SLK
3	70	F	Conjunctivochalasis
4	65	M	Conjunctivochalasis
5	71	F	Conjunctivochalasis
6	74	M	Conjunctivochalasis
7	53	F	Conjunctivochalasis
8	40	M	SLK
9	75	F	Conjunctivochalasis
10	59	F	SLK

Immunohistochemical Analysis of Giant Papillae

Seven-micrometer cryostat sections were made from the specimens and air dried. Sections were then postfixed with 4% PFA-PBS. After blocking with 1% bovine serum albumin (BSA) in PBS, the slides were reacted with anti-FcεRI-β or with anti-FcεRI-γ polyclonal antibodies for 1 hour and then with Alexa 488-conjugated anti-rabbit IgG antibody for 30 minutes. For double-staining with anti-tryptase, anti-FcεRI-α, anti-basophil, or anti-CD1a monoclonal antibodies, the slides were incubated simultaneously with FcεRI-β or FcεRI-γ polyclonal antibodies and with one of the monoclonal antibodies. In the case of double immunostaining with the anti-chymase antibody, the slides were incubated with the anti-chymase antibody overnight at 4°C, and then the FcεRI-β polyclonal antibody was added and further incubated for 1 hour at room temperature. Alexa 488-conjugated anti-rabbit IgG antibody and Alexa 594 conjugated anti-mouse IgG antibody were mixed and applied simultaneously as second antibodies. For triple immunostaining using the CD1a (class, mouse IgG1), FcεRI-α (class, mouse IgG2a), and FcεRI-β antibodies, the slides were incubated with the CD1a antibody and the FcεRI-β antibody for 1 hour at room temperature. After PBS washes, Alexa 488-anti-rabbit IgG antibody, Cy5-anti-mouse IgG_1 antibody, and PE-anti-FcεRI-α (class, mouse IgG2a) were applied simultaneously for another hour. As negative controls, normal rabbit IgG (Santa Cruz Biotechnology) was used instead of the FcεRI-β polyclonal antibody at the same concentration, or the FcεRI-β IgG antibodies were preabsorbed with a fivefold excess amount of the peptide used for immunization. These slides were then visualized with a confocal laser scanning microscope (FV1000; Olympus Corp., Tokyo, Japan).

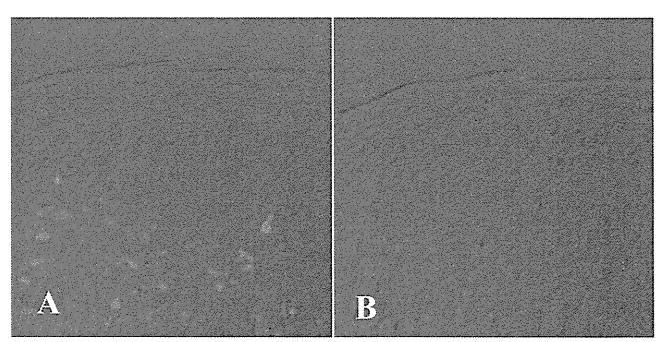

FIGURE 1. Anti-FcεRI-β immunostaining of giant papillae. Immunohistochemical staining was carried out with giant papillae specimens from patients with AKC or VKC using the anti-FcεRI-β antibody (**A**) and control rabbit IgG (**B**) at the same concentration. Original magnification, 200×. This is representative data obtained from 1 of 10 patients (patient 5 in Table 1).

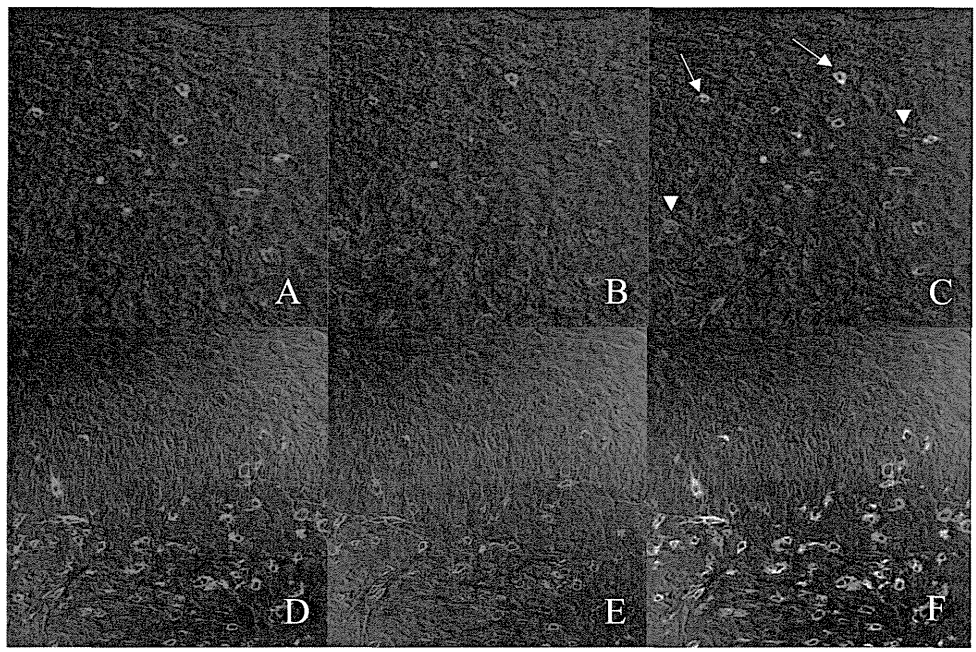

FIGURE 2. Two types of FcεRI$^+$ ($\alpha\beta\gamma_2$ and $\alpha\gamma_2$) cells in giant papillae. Immunohistochemical staining was carried out with giant papillae specimens from patients with AKC or VKC using anti-FcεRI-β (**A**, *green*) and anti-FcεRI-α (**B**, *red*) antibodies. FcεRI-β was merged with FcεRI-α (**C**). *Arrows* indicate FcεRI-α/β double-positive cells (*yellow*) and *arrowheads* indicate FcεRI-α single-positive (*red*) cells. A nearby section from the same patient was immunostained with anti-FcεRI-γ (**D**, *green*) and anti-FcεRI-α (**E**, *red*) antibodies. FcεRI-γ was merged with FcεRI-α (**F**). Original magnification, 400×. This is representative data obtained from 1 of 10 patients (patient 1 in Table 1).

Cell Counting

Numbers of FcεRI-β$^+$ and FcεRI-α$^+$ cells (membrane staining) and tryptase$^+$ cells (intracellular staining) were counted manually using 200× magnification immunostaining images. Positive cells, both in the epithelium and in the substantia propria, were counted per 1-mm unit length of the conjunctival surface as total. We counted three sections per each patient for FcεRI-β immunostaining and two sections for the remaining staining. All immunostained sections were evaluated by an observer who was blinded to the clinical data of the patients. We carried out two independent series of cell staining and counting, and we showed one representative result.

RESULTS

FcεRI-β Immunostaining of Giant Papillae and Control Conjunctivae

All the tested giant papillae samples (n = 10; Table 1) showed focal-positive immunostaining in the epithelium and in the substantia propria with anti-FcεRI-β (Fig. 1A), and the negative-control slide stained by normal rabbit IgG (Fig. 1B) and by the preabsorbed FcεRI-β antibody (data not shown) did not show any positive staining. In addition to anti-FcεRI-β staining (Fig. 2A), all the tested giant papillae showed positive staining with anti-FcεRI-α antibodies (Fig. 2B); there were FcεRI-α/FcεRI-β double-positive and FcεRI-α single-positive cells (Fig. 2C). Double-immunohistochemical staining of the nearby section shown in Figure 2A with anti-FcεRI-γ antibodies (Fig. 2D) and with anti-FcεRI-α antibodies (Fig. 2E) showed that all the FcεRI-α$^+$ cells were also FcεRI-γ$^+$ (Fig. 2F). Control upper bulbar conjunctivae from the conjunctivochalasis or SLK patients (n = 10; Table 2) showed a few FcεRI-α$^+$ cells (Figs. 3A, 3C) or a few tryptase-positive mast cells (Figs. 3B, 3D) in its substantia propria but a negligible number of FcεRI-β$^+$ cells (Fig. 3D; Table 3).

Immunolocalization and Quantification of FcεRI-β$^+$ Cells in Giant Papillae

The giant papillae were also double immunostained with anti-FcεRI-β and the antibodies to typical mast cell proteases (tryptase and chymase). FcεRI-β immunostaining was observed at the cell periphery of the tryptase$^+$ cells (Figs. 4C, 4G). Some of the tryptase$^+$ cells were FcεRI-β negative (Fig. 4C, 4G;

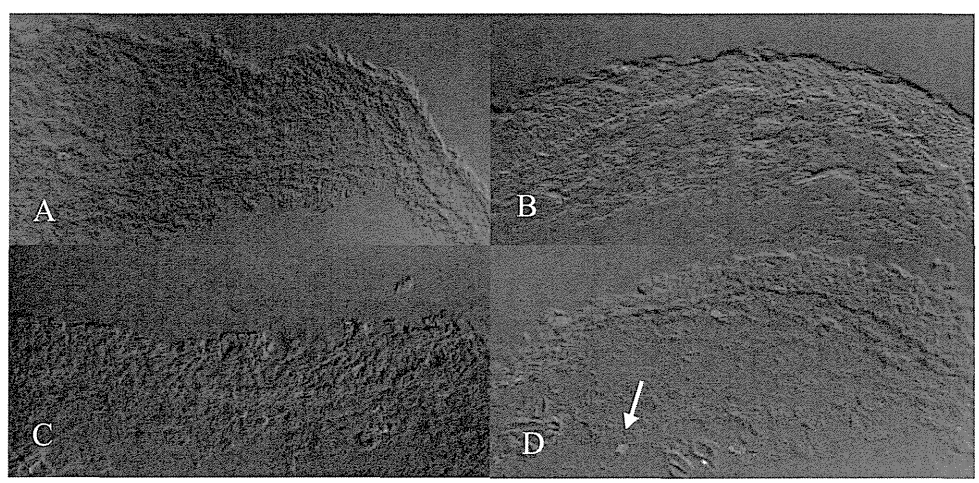

FIGURE 3. Expression of the FcεRI-β chain was almost negligible in control conjunctivae. Upper bulbar conjunctivae were obtained from conjunctivochalasis patients (**A**, **B**) and SLK patients (**C**, **D**). The conjunctivae were double immunostained with the pairs of anti-FcεRI-α (red) and anti-FcεRI-β (**A**, **C**, *green*) or anti-tryptase (*red*) and FcεRI-β (*green*) antibodies (**B**, **D**). (**D**) *Arrow* indicates FcεRI-β$^{\pm}$ tryptase$^+$ cells. Original magnification, 200×.

TABLE 3. Comparison of the FcεRI- and Tryptase-Positive Cells between Giant Papillae and Control Samples

	FcεRI-β^+ Cells (mean ± SD)	FcεRI-α^+ Cells (mean ± SD)	Tryptase$^+$ Cells (mean ± SD)	Ratio of FcεRI-β^+ and FcεRI-α^+ Cells (mean ± SD)	Ratio of FcεRI-β^+ and Tryptase$^+$ Cells (mean ± SD)
Giant papillae	55.9 ± 24.6*	99.0 ± 33.2†	71.1 ± 24.1‡	0.69 ± 0.08§	0.81 ± 0.13‖
Control	1.1 ± 2.3*	19.6 ± 16.9†	17.6 ± 9.8‡	0.07 ± 0.16§	0.06 ± 0.11‖

Student's t-test: *P = 0.0000007; †P = 0.0001; ‡P = 0.00005; §P = 0.00000007; ‖$P = 3 \times 10^{-9}$.

arrow); however, all the chymase$^+$ cells were FcεRI-β^+ (Fig. 4I, asterisks). We quantified the number of FcεRI-β^+ cells, FcεRI-α^+ cells, tryptase$^+$ cells, and FcεRI-β/tryptase double-positive cells. The numbers of FcεRI-β^+, FcεRI-α^+, and tryptase$^+$ cells were significantly higher in the giant papillae than in the control conjunctivae (Table 3). The ratio of the FcεRI-β^+ cells/FcεRI-α^+ cells in the giant papillae samples was 0.69 ± 0.08 (mean ± SD). That ratio was significantly higher than the ratio of the control samples (0.07 ± 0.16). Of tryptase$^+$ cells, 81% ± 13% expressed FcεRI-β, a rate also significantly higher than that of the control samples. Samples with hypertrophic epithelium showed FcεRI-β^+ cells predominantly at the epithelial layers (Figs. 4A, 4D, 4H). We found that intraepithelial FcεRI-β^+ cells were dominated by tryptase$^+$ and chymase$^-$ mast cells (MC_T; Figs. 4G, 4I).

We also found some FcεRI-β^+ cells within and around convoluted epithelium[22] and pseudotubules[23] (Figs. 5A, 5B; asterisks). Double immunostaining with FcεRI-β and tryptase (Figs. 5C, 5D) showed cytoplasmic tryptase staining (red) and membranous FcεRI-β staining (green). Double immunostaining with FcεRI-β and chymase (Figs. 5E, 5F) showed cytoplasmic chymase staining (red) at some of the FcεRI-β^+ cells (green). The results of the FcεRI-β^+ cell quantification are summarized in Table 3. Statistical analyses revealed that the densities of FcεRI-β^+ cells, and FcεRI-β^+-tryptase$^+$ mast cells were significantly increased in giant papillae compared with control conjunctivae. Although the average number of FcεRI-β^+ cells was higher for SLK (1.7 ± 0.7) than for conjunctivochalasis (0.7 ± 1.1) samples, the difference was not statistically significant (P = 0.38, Student's t-test), and the average number of FcεRI-β^+ cells in SLK samples was still significantly lower than the number of FcεRI-β^+ cells in giant papillae (P = 0.00001, Student's t-test).

FcεRI-β Expression in the Basophils of Giant Papillae Tissues but Not in Langerhans Cells (LCs)

During immunohistochemical analysis we found some tryptase$^-$-FcεRI-β^+ cells in the giant papillae sections, so we

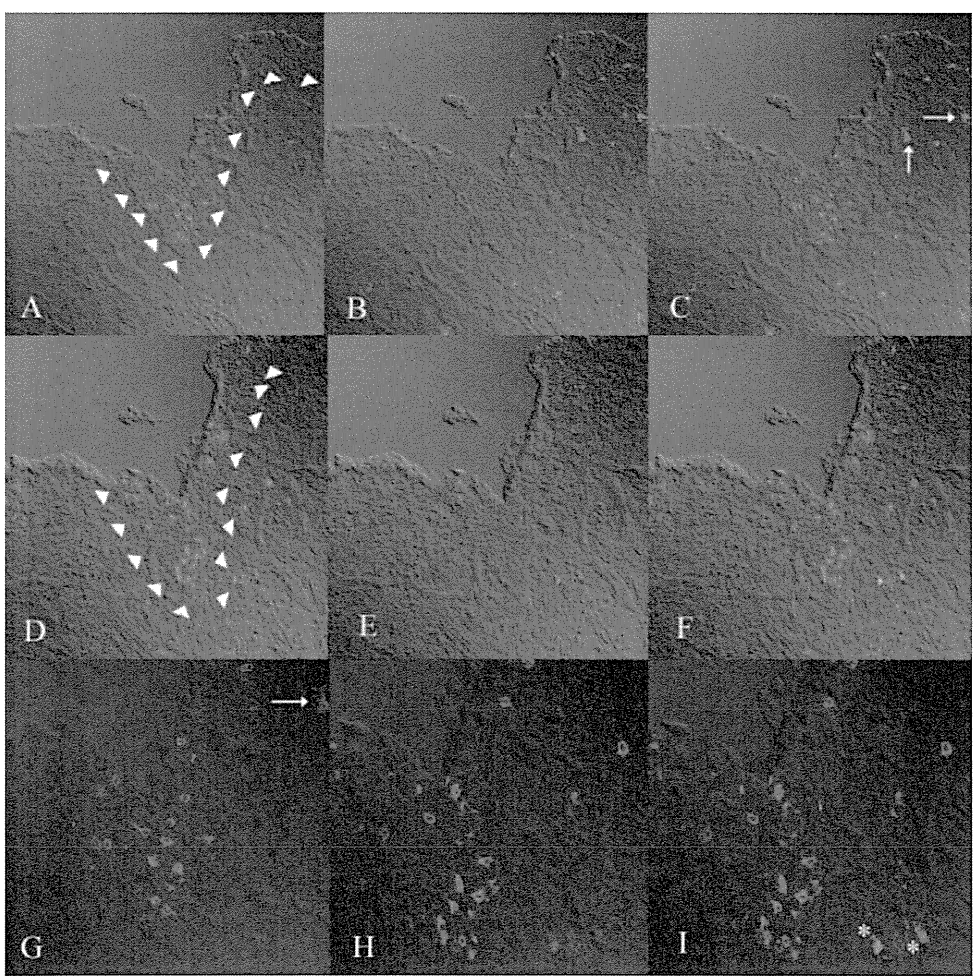

FIGURE 4. Localization of FcεRI-β^+ cells in hypertrophic epithelium of giant papillae. Giant papillae with hypertrophic epithelium were double immunostained with anti-FcεRI-β (**A**, *green*) and anti-tryptase (**B**, *red*) antibodies. FcεRI-β was merged with tryptase (**C**). Adjacent section was also double immunostained with anti-FcεRI-β (**D**, *green*) and anti-chymase (**E**, *red*) antibodies, FcεRI-β was merged with chymase (**F**). *Arrowheads* indicate the boundary line between epithelium and substantia propria. FcεRI-β immunostaining of the hypertrophic epithelial region is shown at higher magnification (**H**), and merged with tryptase (**G**) and with chymase (**I**). *Arrows* and *asterisks* indicate FcεRI-β^--tryptase$^+$ cells (**C**, **G**) and FcεRI-β^+-chymase$^+$ cells (**I**), respectively. Original magnification, 100× (**A**–**F**); 400× (**G**–**I**). This is representative data obtained from 1 of 10 patients (patient 10 in Table 1).

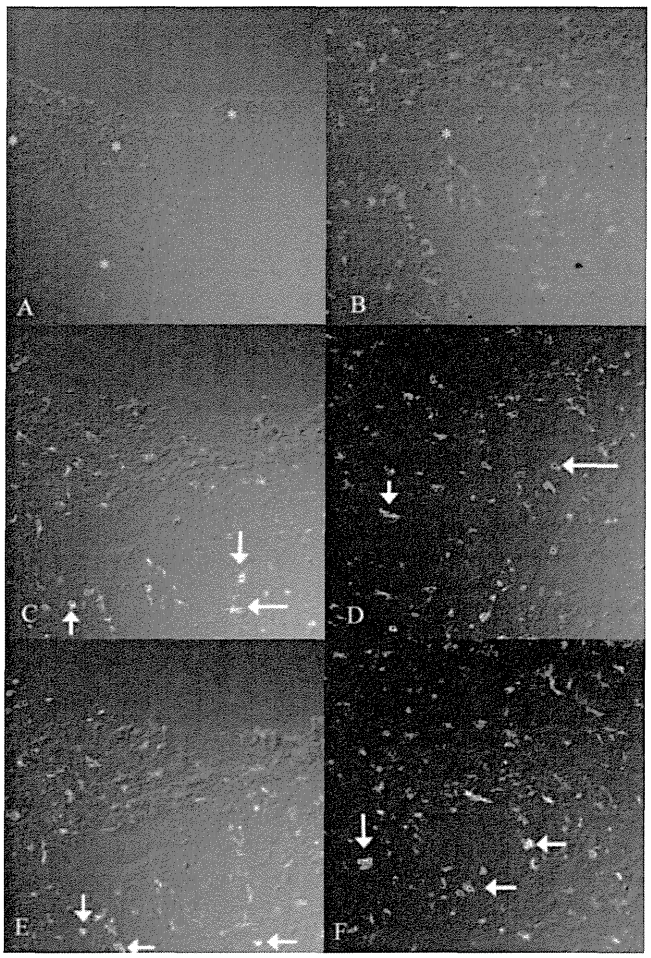

FIGURE 5. Localization of FcεRI-β^+ cells in convoluted epthelium and pseudotubules. Giant papillae with convoluted epithelium were immunostained with the anti-FcεRI-β antibody (**A**, *green*). *Asterisks* indicate convoluted epithelium and pseudotubules. The staining around convoluted epithelium (**B**, **C**, **E**) and pseudotubules (**D**, **F**) is shown at higher magnification. Some slides were double immunostained with anti-tryptase (**C**, **D**, *red*), and FcεRI-β was merged with them. *Arrows* indicate FcεRI-β^+-tryptase$^+$ cells. Adjacent sections were double immunostained with anti-chymase (**E**, **F**, *red*), and FcεRI-β was merged with them. *Arrows* indicate FcεRI-β^+-chymase$^+$ cells. Original magnifications, 100× (**A**); 200× (**B**–**F**). This is representative data obtained from 1 of 10 patients (patient 2 in Table 1).

speculated that the FcεRI-β^+ cells included basophils. Positive basophil staining was observed at the substantia propria of the giant papillae (Fig. 6A). Double immunostaining using anti-FcεRI-β and anti-basophil antibodies showed FcεRI-β immunostaining (green) at the periphery of the basophil (red) (Fig. 6C). To examine the FcεRI-receptor subtype in LCs of the giant papillae, immunostaining with CD1a and FcεRI-α/FcεRI-β antibodies was carried out. Double-staining did not reveal any CD1a$^+$/FcεRI-β^+ cells (Figs. 7A, 7C, 7E). On the other hand, two CD1a$^+$ cells were FcεRI-α^+ cells (Figs. 7B, 7C, 7D; arrows). By triple-immunohistochemical staining, we confirmed the existence of FcεRI-α^+/CD1a$^+$/FcεRI-β^- LCs (Fig. 7E, arrow) and of FcεRI-α^+/FcεRI-β^+/CD1a$^-$ mast cells (Fig. 7E, arrowhead).

Discussion

To the best of our knowledge, this study is the first to demonstrate the existence of both FcεRI-$\alpha\beta\gamma_2$and FcεRI-$\alpha\gamma_2$ receptor subtypes in the giant papillae of patients with chronic allergic conjunctivitis. FcεRI-β staining (Figs. 1, 2) showed a membranous staining pattern at the giant papillae. This staining pattern is consistent with our previous in vitro study using cultured human mast cells.[7] FcεRI-α staining of the same slide showed a broader expression at the conjunctiva than that of FcεRI-β (Fig. 2C), and all the FcεRI-α^+ cells were FcεRI-γ^+ (Fig. 2F). These findings showed the existence of FcεRI-$\alpha\beta\gamma_2$ mast cells and FcεRI-$\alpha\gamma_2$ mast cells in the giant papillae. In our previous study, we quantified FcεRI-β protein expression in human mast cells using flow cytometry.[7] We found monophasic rather than biphasic FcεRI-β expression pattern in human mast cells,[7] and Western blotting showed that the sensitivity of the FcεRI-β antibody is approximately 100 pg in the recombinant FcεRI-β protein (Matsuda A, unpublished data, 2008). These results suggested that there are various levels of FcεRI-β expression in each mast cell, and we identified an area of the mast cell population that expresses the FcεRI-β protein past the threshold as FcεRI-β-positive cells. We could not deny the possibility that FcεRI-$\alpha\beta\gamma_2$ and FcεRI-$\alpha\gamma_2$ receptor subtypes could be coexpressed in one mast cell. Nevertheless, we could conclude that there were at least two types of mast cells dominated by FcεRI-$\alpha\beta\gamma_2$ or by FcεRI-$\alpha\gamma_2$ receptors. We further examined FcεRI-β expression in the conjunctivae of two nonatopic conjunctival diseases as controls. We selected patients with conjunctivochalasis because relatively large upper bulbar conjunctivae samples could be obtained at the time of surgery. We examined patients with SLK as controls for two reasons:

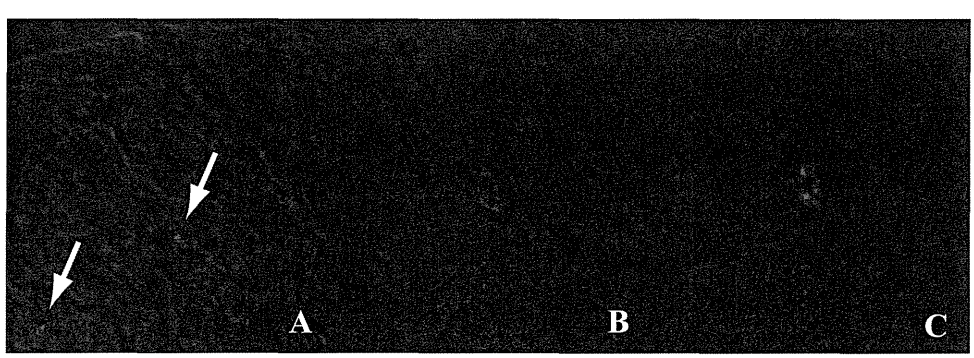

FIGURE 6. Expression of FcεRI-β in basophils of giant papillae. Giant papillae specimens from a patient with AKC (patient 6 in Table 1) were immunostained with the anti-basophil antibody (**A**; *arrows* indicate areas of positive staining). The same sections were stained with anti-FcεRI-β antibody and are shown in higher magnification (**B**). Double immunostaining using anti-FcεRI-β and anti-basophil antibodies is shown in (**C**). FcεRI-β immunostaining (*green*) was observed at the periphery of the anti-basophil-positive (*red*) cells. Original magnifications, 200× (**A**); 1000× (**B**, **C**).

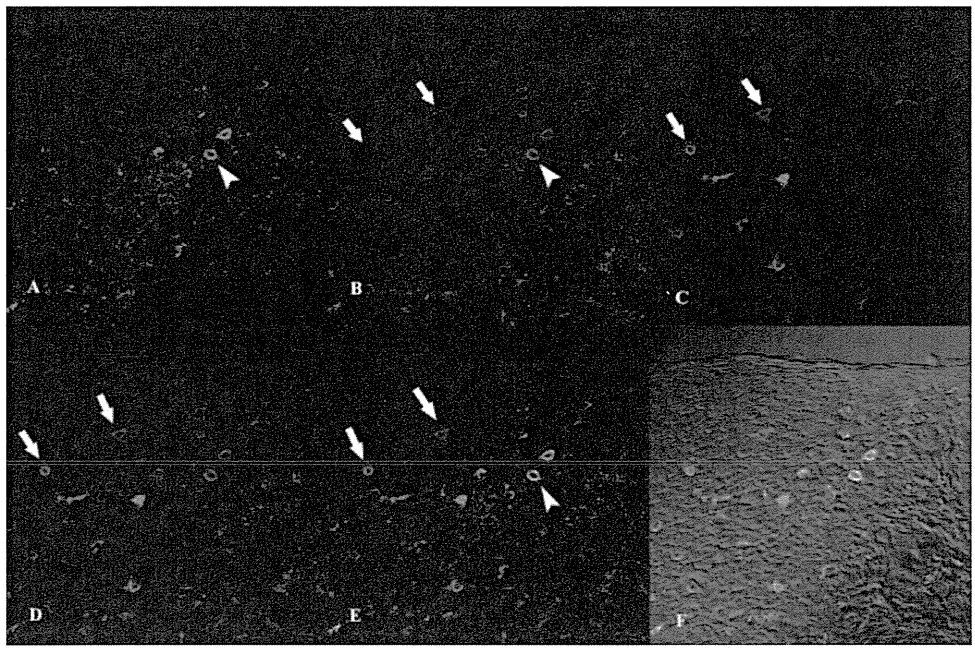

FIGURE 7. Langerhans cells in giant papillae expressing the FcεRI-$\alpha\gamma_2$ subtype. Giant papillae from a patient with AKC (patient 4 in Table 1) was stained with the anti-FcεRI-β antibody (**A**), anti-FcεRI-α antibody (**B**), and anti-CD1a antibody (**C**). Double immunostaining with the anti-FcεRI-α antibody and CD1a antibody (**D**) showed two CD1a/FcεRI-α double-positive cells (**D**; *arrows*). Triple immunostaining using CD1a (*silver*), FcεRI-α (*red*), and FcεRI-β (*green*) antibodies showed no existence of FcεRI-β/CD1a double-positive cells. CD1a$^+$/FcεRI-α^+/FcεRI-β^- LCs and FcεRI-β^+/FcεRI-α^+ mast cells (**E**, *arrows* and *arrowhead*, respectively). Merged image using a differential contrast microscope (**F**). Original magnification, 400×.

because an increased number of mast cells has been reported in the SLK conjunctivae[24] and to avoid bias from the very low number of the mast cells in the conjunctivochalasis samples. In addition, we excluded allergic conjunctivitis by careful slit-lamp examinations in these cases. The increased number of FcεRI-β^+ cells and the higher ratio of FcεRI-β^+/FcεRI-α^+ cells number in giant papillae samples suggested the preferential expression of FcεRI-β protein in chronic allergic conjunctivitis.

Double immunohistochemical staining with anti-FcεRI-β and anti-tryptase/anti-chymase antibodies showed that 81% of tryptase$^+$ cells were FcεRI-β^+, and all the chymase$^+$ cells were FcεRI-β^+ (Figs. 4, 5; Table 3). The FcεRI-β^+ rate among chymase-positive mast cells was higher than it was among among tryptase-positive mast cells; the reason for this is unknown and requires further investigation. During the analysis of double immunostaining with anti-FcεRI-β and anti-tryptase antibodies, we found the preferential localization of FcεRI-β^+ mast cells within and around hypertrophic or convoluted epithelium and epithelial pseudotubules (Figs. 4, 5). It was reported that antigen challenge in sensitized animals induced mast cell infiltration in esophageal epithelium.[25] Kitaura et al.[26] reported that a combination of antigen and IgE could stimulate mast cell migration by autocrine/paracrine secretion of chemokines. They also showed that Lyn, a signal transduction molecule associated with FcεRI-β immunoreceptor tyrosine-based activation motif,[27] plays an essential role for the antigen-IgE-induced mast cell migration. We considered the possibility that the accumulation of FcεRI-β^+ mast cells in the hypertrophic epithelium could be a reflection of increased antigen stimulation at the ocular surface of AKC/VKC eyes. Furthermore, Galli et al.[28] reported that mast cells could induce airway epithelial cell proliferation in mouse asthma models in response to antigen stimulation; hence, it is possible that the infiltrating FcεRI-β^+ mast cells themselves play some roles in epithelial hypertrophy.

This is the first study to show the existence of FcεRI-$\alpha\beta\gamma^{2+}$ basophils (Fig. 6) and FcεRI-$\alpha\gamma_2^+$ LC (Fig. 7) at the protein level in giant papillae. Recently, it was reported that basophils play major roles in delayed-phase allergic reaction, independently of T cells and mast cells.[29] We are now investigating the role of FcεRI-β^+ basophils in the pathophysiology of AKC/VKC. The existence of FcεRI-$\alpha\gamma_2^+$ LC is consistent with previous findings in mRNA levels,[30] and FcεRI-$\alpha\gamma_2^+$ LCs play important roles for enhanced antigen presentation in atopic disorders.

Recent studies have also indicated that the role of the FcεRI-β protein in mast cells depends on the amount of IgE-specific antigen, with the low concentration of antigen FcεRI-β chain working as an amplifier[31] but with a supraoptimal amount of antigen FcεRI-β chain acting as an inhibitory molecule for degranulation and cytokine expression.[31,32] In this study we showed preferential FcεRI-β expression in the giant papillae samples in AKC/VKC, suggesting the involvement of an FcεRI-β-mediated mechanism for amplifying reactions against chronic low concentration of antigens. Additional functional studies will be necessary for investigating the roles of the FcεRI-β chain; this antibody will be a useful tool for in situ analysis.

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THE BORSUK-ULAM THEOREM IN A REAL CLOSED FIELD

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Abstract

Let C_p be a cyclic group of order p. We prove the definable C_p-version of the Borsuk-Ulam theorem in an o-minimal expansion $\mathcal{N} = (R, +, \cdot, <, ...)$ of a real closed field R.

1. Introduction

Any definable category is a generalization of the semialgebraic category. Many results in semialgebraic geometry hold true in the more general setting of an o-minimal expansion $\mathcal{M} = (\mathbb{R}, +, \cdot, <, ...)$ of the standard structure $\mathcal{R} = (\mathbb{R}, +, \cdot, <)$ of the field $\mathbb{R}$ of real numbers. See also [5], [7], [16] for other examples and constructions of them. General references on o-minimal structures are [4], [6], [23], and there exist uncountably many o-minimal expansions of $\mathcal{R}$ [22].

Let $\mathcal{N} = (\mathbb{R}, +, \cdot, <, ...)$ be an o-minimal expansion of a real closed field R including $\mathbb{R}$. In this paper "definable" means "definable with parameters in $\mathcal{N}$", everything is considered in $\mathcal{N}$, each definable map is continuous and every simplicial complex K has the definably compact realization $|K|$ unless otherwise stated.

For a non-negative integer n, let $\mathbb{S}^n$ denote the n-dimensional unit sphere of the $(n+1)$-dimensional Euclidean space $\mathbb{R}^{n+1}$. Then it has the antipodal action of a cyclic group C_2 of order 2. The Borsuk-Ulam theorem states that if there exists a continuous C_2-map $f : \mathbb{S}^m \to \mathbb{S}^n$, then $m \leq n$ (e.g. P141 [15]). It is generalized to the case where a cyclic group C_p of order p acts on the odd dimensional sphere $\mathbb{S}^{2n-1} \subset \mathbb{C}^n$ by $g(z_0, ..., z_n) = (e^{2\pi i/p} z_0, ..., e^{2\pi i/p} z_n)$, where g generates C_p ([13], [14]). There are several equivalent statements of it and many related generalizations (e.g. [2], [17], [18], [19], [20]).

In this paper, we prove the definable C_p-version of the Borsuk-Ulam theorem in $\mathcal{N}$.

For a non-negative integer n, the n-dimensional unit sphere S^n in R^{n+1} is defined by $S^n = \left\{(x_1, ..., x_{n+1}) \in R^{n+1} \mid \sum_{i=1}^{n+1} x_i^2 = 1\right\}$. Then clearly S^n is a definable C^∞-manifold.

A *definable* $C^\infty C_p$*-manifold* is a pair (X, ϕ) consisting of a definable C^∞-manifold X and a group action $\phi : C_p \times X \to X$ which is a definable C^∞-map. We simply write X instead of (X, ϕ).

We consider the C_p-action on R^2 defined by

$$g\begin{bmatrix} x \\ y \end{bmatrix} = \begin{bmatrix} \cos 2\pi/p & -\sin 2\pi/p \\ \sin 2\pi/p & \cos 2\pi/p \end{bmatrix}\begin{bmatrix} x \\ y \end{bmatrix},$$

where g generates C_p. Considering the diagonal action, we have a definable $C^\infty C_p$-action on R^{2m+2}. Then S^{2m+1} is C_p-invariant. Thus S^{2m+1} is a free definable $C^\infty C_p$-manifold.

Theorem 1.1 (Definable Borsuk-Ulam Theorem). (1) *Suppose that* $p \geq 3$ *and that* S^{2m+1} *and* S^{2n+1} *have the above* C_p*-actions. If there exists a definable* C_p*-map* $f : S^{2m+1} \to S^{2n+1}$, *then* $m \leq n$.

(2) *If* S^m *and* S^n *have the antipodal* C_2*-actions and there exists a definable* C_2*-map* $f : S^m \to S^n$, *then* $m \leq n$.

In Theorem 1.1(1), we cannot drop the condition that C_p acts freely on spheres. Even if $\mathcal{N} = \mathcal{R}$, there is a counterexample (see Proposition 2.10). Theorem 1.1 may be extensible to the case where spheres have general free definable C_p-actions.

2. Equivariant Definable Simplicial Complexes

By [4], every definable set X admits a finite partition into definable cells. Using cell decompositions, the Euler characteristic $\chi(X)$ of X is

defined by the alternating sum of the number of i-dimensional cells. This number does not depend on the choice of definable cell decomposition and it is a definable bijective invariant (4.2.4 [4]).

On the other hand, the definable simplicial homology is introduced in [25]. For any definable set X, one can define the Euler characteristic $\chi(X)$ of X in a definable homological way. If X is definably compact, then these two definitions coincide [8]. If X is not definably compact, then they do not necessarily coincide. For example, if $X = [0, 1) \subset R$, then $\chi(X)$ in the first definition is 0 and $\chi(X)$ in the second definition is 1.

Let G be a finite group and $\Phi : G \to O_n(R)$ be a group homomorphism. A *representation* Ω of G means R^n with the orthogonal G-action induced by Φ. A G-invariant definable set X in a representation Ω of G is a *definable G-set* if X is G-invariant. In this paper, every representation is assumed to be orthogonal.

Proposition 2.1 (e.g. 10.2.18 [4]). *Let G be a finite group and X be a definable G-set. Then X/G is a definable subset of some R^n and the orbit map $p : X \to X/G$ is a surjective definably proper definable map.*

In $\mathcal{N}$, we can define equivariant simplicial complexes as follows when G is a finite group.

A *simplicial G-complex* consists of a simplicial complex K together with a G-action $\psi : G \times K \to K$ such that $\psi_g = \psi(g, \cdot) : K \to K$ is a simplicial homeomorphism for any $g \in G$.

Definition 2.2. A simplicial G-complex is an *equivariant simplicial complex* if the following two conditions are satisfied.

(1) For any subgroup H of G, if $\Delta = \langle v_0, ..., v_n \rangle$ and $\Delta' = \langle h_0 v_0, ..., h_n v_n \rangle$ are simplexes of K for $h_i \in H$, then there exists an $h \in H$ such that $hv_i = h_i v_i$ for all i.

(2) For every simplex Δ^n of K, the vertices $v_0, ..., v_n$ of Δ^n can be ordered with $G_{v_n} \subset \cdots \subset G_{v_0}$.

Note that the second barycentric subdivision of any simplicial G-complex is an equivariant simplicial complex [10].

Definition 2.3. Let X be a definable G-set.

(1) An *equivariant definable triangulation* (L, ϕ) of X consists of an equivariant simplicial complex L and a definable G-homeomorphism ϕ from X to a G-invariant union of open simplexes of L.

(2) Let $X_1, ..., X_k$ be G-invariant definable subsets of X. An equivariant definable triangulation (L, ϕ) of X is *compatible with* $X_1, ..., X_k$ if each $\phi(X_i)$ is a G-invariant union of open simplexes of K.

Equivariant simplicial complexes and equivariant definable triangulations are introduced in [11] when $\mathcal{N} = \mathcal{M}$ and in [21] when $\mathcal{N} = \mathcal{R}$.

Let X be a definable G-set. A definable triangulation (L, ϕ) of the orbit space X/G is *compatible with the orbit types* if for any orbit type (H), $\phi \circ \pi(X(H))$ is a union of open simplexes of L, where $\pi : X \to X/G$ denotes the orbit map and $X(H) = \{x \in X \mid (G_x) = (H)\}$.

Theorem 2.4. *Let G be a finite group. Let X be a definable G-set in a representation Ω of G and $X_1, ..., X_k$ be G-invariant definable subsets of X. Then there exists an equivariant definable triangulation (K, ϕ) of X compatible with $X_1, ..., X_k$ and the orbit types. In particular, if X is definably compact, then $\phi(X) = |K|$.*

The following two results are the definable triangulation theorem (8.2.9 [4]) and piecewise triviality (9.1.7 [4]).

Theorem 2.5 (8.2.9 [4]). (*Definable triangulation theorem*) *Let X be a definable set and $X_1, ..., X_k$ be definable subsets of X. Then there exists a definable triangulation (M, τ) of X compatible with $X_1, ..., X_k$, namely M is a simplicial complex and τ is a definable homeomorphism from X to a union of open simplexes of M such that each $\tau(X_i)$ is a union of open simplexes of M. In particular, if X is definably compact, then $\tau(X) = |M|$.*

A definable map $f : X \to Y$ is *definably trivial* if there exist a point $y \in Y$ and a definable homeomorphism $H : X \to Y \times f^{-1}(y)$ such that $f = p \circ H$, where $p : Y \times f^{-1}(y) \to Y$ denotes the projection.

Theorem 2.6 (9.1.7 [4]). *(Piecewise triviality) Let X, Y be definable sets and $f : X \to Y$ be a definable map. Then there exists a finite partition $\{V_j\}_{j=1}^{u}$ of Y into definable sets such that each $f | f^{-1}(V_j)$ is definably trivial.*

Proof of Theorem 2.4. Let (H_1), ..., (H_l) be orbit types of X.

First we prove the case where X is definably compact. Note that for each orbit type (H_i) of X, $X(H_i) = \{x \in X \mid G_x$ is conjugate to $H_i\}$ is G invariant. Since every $X(H_i)$ is a definable G-set and the orbit map $\pi : X \to X/G$ is a definable map, $\pi(X(H_i))$ is a definable subset of X/G. By Theorem 2.6, we have a finite partition $\{V_j\}_{j=1}^{u}$ of X/G such that each $\pi | \pi^{-1}(V_j)$ is definably trivial. Since X is definably compact and $\pi : X \to X/G$ is definable, X/G is definably compact. By Theorem 2.5, there exists a definable triangulation (M, τ) of X/G compatible with $\pi(X_1)$, ..., $\pi(X_k)$, $\pi(X(H_1))$, ..., $\pi(X(H_l))$, V_1, ..., V_u.

Replacing M by its barycentric subdivision, if necessary, for each $\Delta \in M$, $\pi^{-1}(\tau^{-1}(\mathrm{Int}\Delta))$ is a definable G-set in Ω and there exists a definable section $s_\Delta : \tau^{-1}(\Delta) \to X$ such that:

(1) $s_\Delta(\tau^{-1}(\mathrm{Int}\Delta))$ is a definable set in Ω.

(2) $s_\Delta | \tau^{-1}(\mathrm{Int}\Delta) : \tau^{-1}(\mathrm{Int}\Delta) \to s_\Delta(\tau^{-1}(\mathrm{Int}\Delta))$ is a definable homeomorphism, where Int Δ denotes the interior of Δ.

Note that $s_\Delta(\tau^{-1}(\Delta)) = (\pi^{-1}(\tau^{-1}(\Delta)))^H$ and

$$s_\Delta(\tau^{-1}(\mathrm{Int}(\Delta))) = (\pi^{-1}(\tau^{-1}(\mathrm{Int}(\Delta))))^H,$$

where (H) is the orbit type of $\tau^{-1}(\mathrm{Int}\Delta)$.

Let L' be a finite abstract simplicial complex whose simplexes are $\{gs(\tau^{-1}(\Delta)) \mid \Delta \in K, g \in G\}$. Then L' is an abstract G-complex with the following G-action. For a simplex $\{hs(v_0), ..., hs(v_n)\}$ in L' and $g \in G$, we define $\phi_g(\{hs(v_0), ..., hs(v_n)\}) = \{ghs(v_0), ..., ghs(v_n)\}$. Now let L be the realization of L' and $\langle\langle gs(v_0), ..., gs(v_n)\rangle\rangle$ denote the corresponding simplex to $\{gs(\tau(v_0)), ..., gs(\tau(v_n))\}$ for $\Delta = \langle v_0, ..., v_n\rangle \in M$. Then L is an equivariant simplicial complex with the action induced by L'. For any $g \in G$, $\Delta = \langle v_0, ..., v_n\rangle$ in M and a section s on Δ, we define a linear homeomorphism $\prod_{\langle\langle gs(\Delta)\rangle\rangle}: \langle\langle gs(v_0), ..., gs(v_n)\rangle\rangle \to \Delta$ by $\prod_{\langle\langle gs(\Delta)\rangle\rangle}(gs(v_i)) = v_i$. Define $\prod = \cup \prod_{\langle\langle gs(\Delta)\rangle\rangle}: L \to M$. Then Π is a well-defined simplicial map. Note that $\prod: L \to M$ is the orbit map and $L/G = M$.

Define a map $\eta : |L| \to X$ by $\eta|\langle\langle gs(\Delta)\rangle\rangle = gs \circ \tau^{-1} \circ \prod |\langle\langle gs(\Delta)\rangle\rangle : \langle\langle gs(\Delta)\rangle\rangle \to gs(\tau(\Delta))$, $\Delta \in M$, $g \in G$. Then η is a well-defined definable G-map. For each simplex $\Delta = \langle\langle gs(\Delta)\rangle\rangle$ of L, we have $\eta(\mathrm{Int}(\Delta)) = gs(\tau^{-1}(\mathrm{Int}(\Delta)))$. Moreover $\eta|\langle\langle gs(\mathrm{Int}(\Delta))\rangle\rangle$ is a definable G-homeomorphism from $\langle\langle gs(\mathrm{Int}(\Delta))\rangle\rangle$ onto its image because it is the composition of a linear isomorphism $\prod |\langle\langle gs(\mathrm{Int}\,\Delta)\rangle\rangle$, and definable homeomorphism $\tau^{-1}|\mathrm{Int}(\Delta)$ and gs_Δ. Therefore, (L, η^{-1}) is the required triangulation.

We now prove the general case. We can identify Ω with $\Omega \times \{1\} \subset \Omega \times R =: \Omega'$. Replacing Ω by Ω', we may assume that $0 \notin X$. Let $\theta : \Omega - \{0\} \to \Omega - \{0\}$ be $\theta(x) = \dfrac{x}{\|x\|^2}$. Then it is a Nash G-diffeomorphism because G acts on Ω orthogonally, where $\|x\|$ denotes the standard norm of Ω. Replacing X by $\theta(X)$, we may assume that X is bounded. Let $\overline{X}$ be the closure of X in Ω. Then $\overline{X}$ is a definably compact definable G-set in Ω. Apply $(\overline{X}, X, X_1, ..., X_k)$ to the definably compact case, we have an equivariant definable triangulation (K, ϕ') of $\overline{X}$ compatible with $X, X_1, ..., X_k$. Let $\phi = \phi'|X$. Then (K, ϕ) is the required triangulation. □

Using the proof of 5.22 [12] and Theorem 2.4, we obtain the following.

Theorem 2.7. *If a finite group G acts freely on a definably compact definable G-set X, then $\chi(X) = |G|\chi(X/G)$.*

By TR3. P786 [1], $H_0(S^n, \mathbb{Z}) \cong H_n(S^n, \mathbb{Z}) \cong \mathbb{Z}$ and for any i with $0 < i < n$, $H_i(S^n, \mathbb{Z}) \cong 0$. Thus $\chi(S^{2n}) = 2$. Therefore, a finite group whose order exceeds 3 cannot act freely on an even dimensional sphere. Thus it is justified to consider only odd-dimensional spheres in Theorem 1.1(1).

We now construct a counterexample of Theorem 1.1 when $\mathcal{N} = \mathcal{R}$ and G acts non-freely.

Let p, q be two distinct primes and $g = e^{\frac{2\pi}{pq}i}$. Then g generates a cyclic group C_{pq} of order pq. For any $k \in \mathbb{Z}$, let U_k be the complex plane $\mathbb{C}$ with the C_{pq}-action $g \cdot z = g^k z$ and U_k^t be the t-fold direct sum of U_k. Then for any $r, s \in \mathbb{Z}$, $t, u \in \mathbb{N} \cup \{0\}$, $U_r^t \oplus U_s^u$ is a representation of C_{pq}. Let $S(U_r^t \oplus U_s^u)$ denote the unit sphere of $U_r^t \oplus U_s^u$.

Theorem 2.8 [24]. *For any $t \in \mathbb{N}$, there exists a continuous C_{pq}-map $f : S(U_1^t) \to S(U_p \oplus U_q)$.*

Using the polynomial approximation theorem, existence of a Nash C_{pq}-tubular neighborhood of $S(U_p \oplus U_q)$ in $U_p \oplus U_q$ and averaging of the Haar measure, we have the following proposition.

Proposition 2.9. *Every continuous C_{pq}-map $f : S(U_1^t) \to S(U_p \oplus U_q)$ is G-homotopic to a definable $C^\infty C_{pq}$-map $h : S(U_1^t) \to S(U_p \oplus U_q)$.*

Note that C_{pq} acts freely on $S(U_1^t)$ and non-freely on $S(U_p \oplus U_q)$. By Proposition 2.9, we have the following proposition.

Proposition 2.10. *For any $t \in \mathbb{N}$, there exists a definable $C^\infty C_{pq}$-map $h : S(U_1^t) \to S(U_p \oplus U_q)$. In particular, there exists a definable C_{pq}-map from $S(U_1^t)$ to $S(U_p \oplus U_q)$.*

3. Proof of Theorem 1.1

Since $H_n(S^n, \mathbb{Z}) \cong \mathbb{Z}$, fix a generator x of $H_n(S^n, \mathbb{Z})$. For a definable map $f : S^n \to S^n$, it induces the homomorphism $(f_*)_n : H_n(S^n, \mathbb{Z}) \to H_n(S^n, \mathbb{Z})$. The degree of f is defined to be the integer deg f such that $(f_*)_n(x) = (\deg f)x$.

We prove the following theorem to prove Theorem 1.1.

Theorem 3.1. *Let G be a finite group acting freely on S^n. For every definable G-map $f : S^n \to S^n$, $\deg f \equiv 1 \bmod |G|$.*

Let $f : S^n \to S^n$ be a definable map. The Lefschetz number $L(f)$ of f is defined by $L(f) = \sum_{i=0}^{n} (-1)^i \mathrm{tr}(f_*)_i$, where $\mathrm{tr}(f_*)_i$ is the trace of the induced homomorphism $(f_*)_i : H_i(S^n, \mathbb{Z}) \to H_i(S^n, \mathbb{Z})$. The Lefschetz number $L(f)$ of f over $\mathbb{Q}$ is introduced in [8]. Since $H_0(S^n, \mathbb{Z}) \cong H_n(S^n, \mathbb{Z}) \cong \mathbb{Z}$ and for any i with $0 < i < n$, $H_i(S^n, \mathbb{Z}) \cong 0$, $L(f) = 1 + (-1)^n \deg f$. Thus we can easily obtain Theorem 3.1 from the following theorem.

Theorem 3.2. *Let G be a finite group acting freely on S^n. For every definable G-map $f : S^n \to S^n$, $L(f) \equiv 0 \bmod |G|$.*

For any equivariant simplicial complex X and for any $k \in \mathbb{N} \cup \{0\}$, let X_k denote the k-skeleton of X_k. A definable G-map $h : X \to Y$ between equivariant simplicial complexes is a *definable G-cellular map* if for each $k \in \mathbb{N} \cup \{0\}$, $h(X_k) \subset Y_k$.

Proposition 3.3 (4.1.6 [4]). *Let $h : X \to Y$ be a definable map between definable sets. Then* $\dim h(X) \leq \dim X$.

Under the assumption of Theorem 3.2, by Theorem 2.4, we may assume that S^n is an equivariant simplicial complex. Since f is a

definable G-map, for each simplex σ, $f(\sigma)$ is a definable subset of S^n and $f(G\sigma)$ is a G-invariant definable subset of S^n. Thus using Theorem 2.4 and Proposition 3.3, we have the following lemma.

Lemma 3.4. *Let G be a finite group acting freely on S^n. For every definable G-map $h : S^n \to S^n$, after replacing some subdivision of S^n, we may assume that h is a definable G-cellular map $S^n \to S^n$.*

Let K be a simplicial complex of dimension n. For any i with $0 \leq i \leq n$, we define the i-dimensional chain complex $C_i(K)$ to be $H_i(K_i, K_{i-1})$ and the boundary homomorphism $\partial_i : C_i(K) \to C_{i-1}(K)$ to be the boundary homomorphism $\partial_* : H_i(K_i, K_{i-1}) \to H_{i-1}(K_{i-1}, K_{i-2})$ in the homology exact sequence. Then by Section V.6. [3], $\partial_i \circ \partial_{i+1} = 0$ and $C(X) = \{C_i(K), \partial_i\}$ is a free chain simplex. We call this the *chain complex* of the simplicial complex K. This chain complex defines the homology group of X.

By a way similar to P157 [9], we have the following.

Theorem 3.5. *Let X be a definably compact definable set. Then the definable homology group of X is isomorphic to the homology group defined from the chain complex of X.*

Proof of Theorem 3.2. By Lemma 3.4, we may assume that $f : S^n \to S^n$ is a definable G-cellular map. Thus f induces the homomorphism $f_* : C_i = H_i(S_i^n, S_{i-1}^n) \to C_i = H_i(S_i^n, S_{i-1}^n)$. By Theorem 3.5, $L(f) = \sum_{i=0}^{n} (f_*)_i$. Since G acts freely on S^n, for any i with $0 \leq i \leq n$, $C_i(S^n)$ is a free $\mathbb{Z}G$-module, namely $C_i(S^n) = \mathbb{Z}g_1e_{i1} \oplus \cdots \oplus \mathbb{Z}g_te_{i1} \oplus \cdots \oplus \mathbb{Z}g_1e_{il_i} \oplus \cdots \oplus \mathbb{Z}g_te_{il_i}$, where $G = \{g_1, ..., g_t\}$ and $e_{i1}, ..., e_{il_i}$ denote i-dimensional simplexes. For any u, v, let $(f_*)_i(g_ue_{iv}) = \sum_{u,v} a_{i_uv}g_ue_{iv}$. Then since G acts freely on S^n, for any v, $a_{i_1v} = \cdots = a_{i_tv}$. Thus the trace of $(f_*)_i$ is a multiple of $|G|$. Therefore, $L(f) \equiv 0 \bmod |G|$. □

Proof of Theorem 1.1. Suppose that $m > n$ and $i : S^{2n+1} \to S^{2m+1}$ is the inclusion. Since S^{2n+1} and S^{2m+1} have the actions as in introduction, i is a definable C_p-map. Thus $i \circ f : S^{2m+1} \to S^{2m+1}$ is a definable C_p-map. By Theorem 3.1, $\deg(i \circ f) \equiv 1 \bmod |G|$. In particular, $\deg(i \circ f) \neq 0$. On the other hand, $(i \circ f)_* = i_* \circ f_* = 0 : H_{2m+1}(S^{2m+1}, \mathbb{Z}) \to H_{2m+1}(S^{2m+1}, \mathbb{Z})$. It implies $\deg(i \circ f) = 0$. This contradiction proves Theorem 1.1. □

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A Note on the Existence Problem of Isovariant Maps between Representation Spaces

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