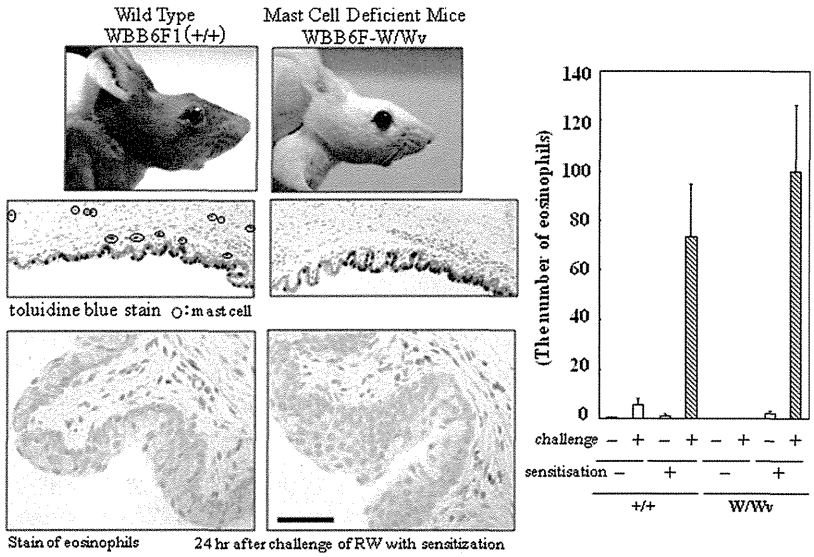

FIG. 8. Eosinophilic conjunctival inflammation in mast cell-deficient mice. Mast cell-deficient mice exposed to sensitization and eye drop challenge developed eosinophilic conjunctival inflammation similar to that seen in their congenic littermates. Adapted with permission from Ueta M, Nakamura T, Tanaka S, et al. Development of eosinophilic conjunctival inflammation at late-phase reaction in mast cell-deficient mice. *J Allergy Clin immunol* 2007;120;476–478. © 2010 by Elsevier Inc.

transcripts, including not only antiviral innate immune response-related genes but also allergy-related genes.

IKBZ AND OCULAR SURFACE INFLAMMATION WITH THE DISAPPEARANCE OF GOBLET CELLS

IκBζ is induced by diverse PAMPs and regulates nuclear factor (NF)-κB activity.[28,29] Thus, IκBζ is important for TLR/IL-1 receptor signaling, which is essential for an innate immune response. We previously reported that *IκBζ* KO mice exhibit severe, spontaneous ocular surface inflammation accompanied by the eventual loss of almost all goblet cells.[30] Moreover, balb/c background *IκBζ* KO mice exhibited not only spontaneous ocular surface inflammation but also spontaneous perioral inflammation (Fig. 11A).[31] Some *IκBζ* KO mice manifested ocular surface inflammation with

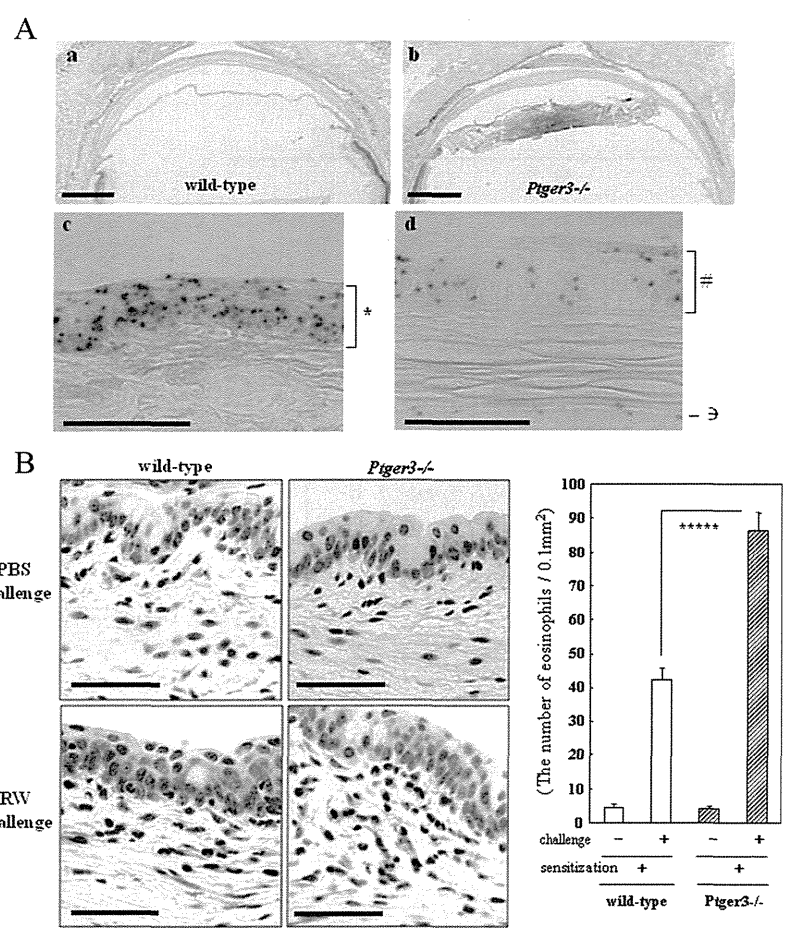

FIG. 9. (A) Expression and localization of EP3 in conjunctiva and cornea. Histochemical staining for EP3 (X-gal). Ocular surface tissues from *Ptger3*$^{-/-}$ mice expressing the β-galactosidase gene at the *Ptger3* locus was stained for β-galactosidase activity with the substrate X-gal. Sections of ocular surface tissues from *Ptger3*$^{-/-}$ mice (b, c, d) and from wild type mice (a) were counterstained with hematoxylin (*purple*) (a, b) or eosin (*red*) (c, d). Scale bars, 500 μm (a, b) or 50 μm (c, d). Positive signals (*blue*) were shown on *conjunctival epithelium (c), #corneal epithelium (d), and ∋corneal endothelium(d). Data are representative of three experiments. (B) Infiltration of eosinophils into the conjunctiva of wild-type and *Ptger3*$^{-/-}$ mice were detected by using Luna's method, which stained eosinophil granules with a distinctive red. Pronounced eosinophil infiltration was observed in *Ptger3*$^{-/-}$ mice compared with wild-type mice. Scale bars, 50 μm. The number of eosinophils in the lamina propria mucosae of the tarsal conjunctiva was quantified in wild-type and *Ptger3*$^{-/-}$ mice. The data are shown as mean ± SEM of samples from 19 animals, all the mice examined. *****$P<0.0005$. Reprinted with permission from Ueta M, Matsuoka T, Narumiya S, et al. Prostaglandin E receptor subtype EP3 in conjunctival epithelim regulates late-phase reaction of experimental allergic conjuctivitis. *J Allergy Clin immunol* 2009;123:466–471. © 2010 by Elsevier Inc.

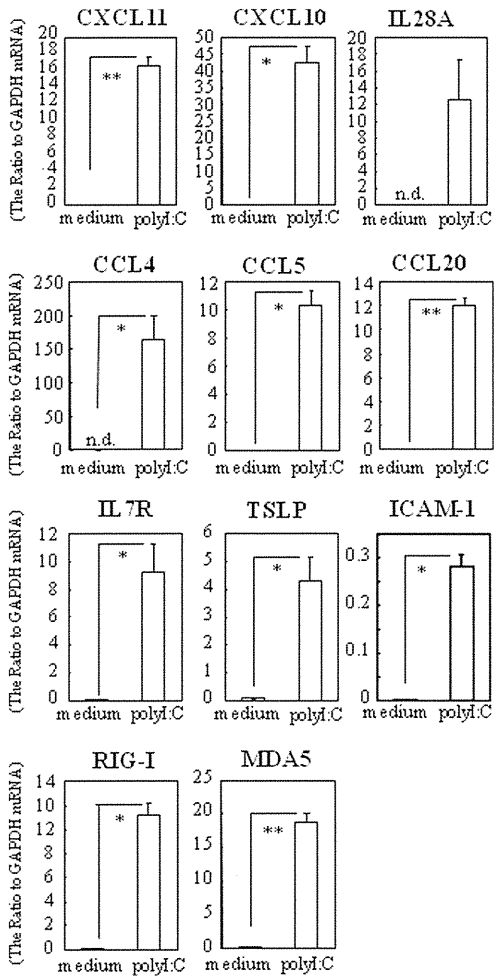

FIG. 10. The mRNA expression of the 11 transcripts in PHCEC exposed to 25 μg/mL polyI:C for 6 hours. The quantification data were normalized to the expression of the housekeeping gene GAPDH. Data are representative of three separate experiments and are given as the mean ± SEM from one experiment. (*P<0.05; **P<0.005; ***P<0.0005.)

corneal opacity (Fig. 11A).[5] We considered *IκBζ* KO mice a suitable model for Stevens-Johnson syndrome (SJS), a severe, human ocular surface inflammatory disease, because these animals presented with ocular surface inflammation accompanied by a loss of goblet cells, and perioral inflammation is seen in patients with SJS (Fig. 11B).[5] *IκBζ* KO mice also manifested the airway inflammation and oral mucositis seen in human SJS (Fig. 11B).[5] Furthermore, *IκBζ/Stat6 double*-KO mice presented with severe dermatitis not only of the facial area but also of the abdominal skin; these animals also exhibited paronychia (Fig. 11C).[5,31] Our findings provide convincing evidence that *IκBζ* KO mice are a suitable model for SJS with ocular surface complications because patients with SJS present with ocular surface inflammation, perioral inflammation, and paronychia in the acute stage (Fig. 11D).[5]

IκBζ induced by diverse PAMPs regulates NF-κB activity, possibly to prevent excessive inflammation in the presence of bacterial components.[28] The spontaneous ocular surface inflammation observed in IκBζ KO mice suggested that dysfunction/abnormality of innate immunity can play a role in ocular surface inflammation.[5]

IκBζ mRNA was expressed in both corneal and conjunctival tissues from normal C57BL/6 mice.[30] When we compared the levels of *IκBζ* expression in murine tissues using RT-PCR, we found that *IκBζ* mRNA was intensely expressed in mucosal tissues such as the small intestine, trachea, cornea, and conjunctiva and slightly expressed in liver and kidney tissue.[30] Moreover, the predominant expression of *IκBζ* transcripts in the ocular surface tissue of the mice was localized spatially to corneal and conjunctival epithelia.[30] Human corneal and conjunctival epithelia also expressed human molecules possessing ankyrin-repeats induced by LPS (*MAIL*; similar to mouse *IκBζ*)-specific mRNA.[30]

To examine whether *MAIL* (similar to mouse *IκBζ*) can suppress the production of proinflammatory cytokines, we performed siRNA experiments to knockdown mRNA levels of *MAIL*. PHCECs were transfected with control- or *MAIL*-targeting siRNA and cultured for 24 hours. The knockdown of *MAIL* mRNA was confirmed by quantitative RT-PCR. The expression of *IL-6* and *IL-8* mRNA was enhanced in *MAIL*-knockdown PHCECs.[5] These results suggested that MAIL in the ocular surface epithelium may suppress the production of proinflammatory cytokines such as IL-6 and IL-8 and that the ocular surface epithelium might suppress inflammation via the expression of IκBζ.[5]

We also suggested that IκBζ exerts regulatory effects selectively not only on cytokines through NF-κB but also in a tissue- or cell type-specific manner (spatially orchestrated regulation).[31]

Furthermore, IκBζ$^{-/-}$ mice may provide further insight into the interplay between microorganisms and innate immune responses in the presence of ocular surface disorders because they may be a suitable model for SJS. Although the role of acquired immunity in the pathogenicity of SJS/toxic epidermal necrolysis (TEN) has been reported, it was not previously recognized that innate immunity plays a critical role in bridging the acute response to invading nonself molecules and chronic local immune inflammation in the pathogenicity of SJS/TEN.

SJS AND ABNORMALITY OF INNATE IMMUNITY

The SJS is an acute inflammatory vesiculobullous reaction of the skin and mucosa including the ocular surface. In individuals with extensive skin detachment and a poor prognosis, the condition is called TEN. Both SJS and TEN are commonly associated with infectious agents or inciting drugs or both,[32–34] and the pathophysiologic mechanisms of this disease have yet to be fully elucidated. In the acute stage, patients manifest vesiculobullous lesions of the skin and mucosa (especially that of the eyes and mouth), severe conjunctivitis, and persistent corneal epithelial defects because of ocular surface inflammation.[35,36] Oral involvement, including blisters, erosions, and bleeding of the mouth and lips, was observed in all patients with SJS/TEN with ocular surface complications.[35] Some patients with SJS/TEN manifested respiratory disorders such as mucous membrane damage of the trachea or bronchus, bronchiolitis obliterans, and pneumonia. Moreover, oral mucositis was noted in the acute stage of SJS/TEN, and almost all patients with SJS/TEN with ocular surface complications had lost their fingernails in the acute or subacute stage because of the occurrence of paronychia in the acute stage.[32,35] In the chronic stage, despite healing of the skin lesions, ocular surface complications including conjunctival invasion into the cornea, dry eye, symblepharon,

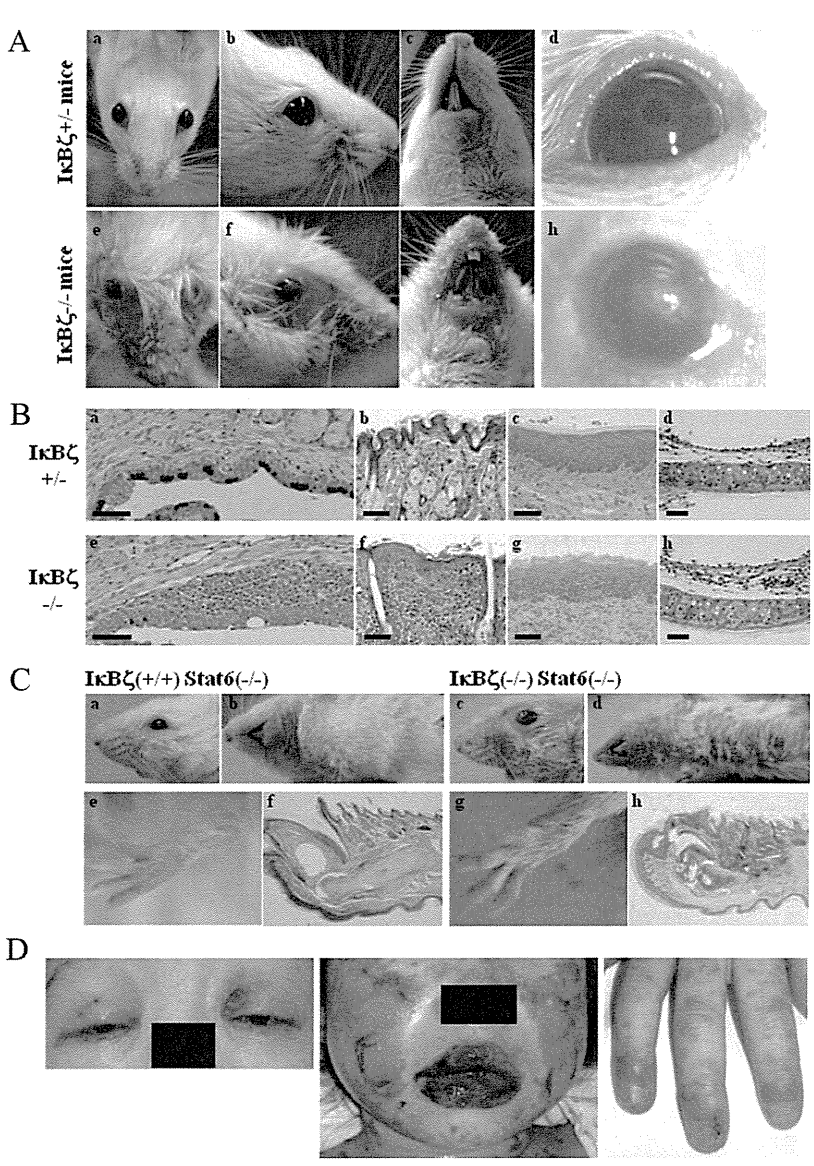

FIG. 11. (A) Phenotype of IκBζ KO mice. Photographs of the face including the perioral skin of 32-week-old $I\kappa B\zeta^{+/-}$ and an $I\kappa B\zeta^{-/-}$ mice taken 27 weeks after symptom onset. Although $I\kappa B\zeta^{+/-}$ mice were free of inflammation (a–d), $I\kappa B\zeta^{-/-}$ mice exhibited a severe inflammatory phenotype; the inflammation involved the ocular surface, the eyelids and the perioral skin (e–g). The $I\kappa B\zeta^{-/-}$ mouse also manifested corneal opacity with ocular surface inflammation (h). (B) Histologic findings on various tissues of $I\kappa B\zeta^{-/-}$ mice. Histologic findings on the palpebral conjunctiva, perioral skin, oral mucosa, and trachea of $I\kappa B\zeta^{+/-}$ and $I\kappa B\zeta^{-/-}$ mice. Histologic analysis of the palpebral conjunctiva of an $I\kappa B\zeta^{-/-}$ mouse (at 2 weeks after the onset of inflammatory symptoms) revealed heavy infiltration by inflammatory cells into the submucosa under the conjunctival epithelia and loss of goblet cells in the conjunctival epithelia (a). Histologic analysis of the perioral skin of an $I\kappa B\zeta^{-/-}$ mouse (at 2 weeks after the onset of inflammatory symptoms) revealed hyperplasia and spongiosis in the epidermis including the hair follicles, inter- and intracellular edema in the epidermis, and heavy infiltration of the dermis by inflammatory cells (b). Histologic analysis of the oral mucosa of an $I\kappa B\zeta^{-/-}$ mouse (at 9 weeks after the onset of inflammatory symptoms) revealed spongiosis in the epithelium, and infiltration by inflammatory cells into the submucosa under oral mucosal epithelia (c). Histologic analysis of the trachea of an $I\kappa B\zeta^{-/-}$ mouse (at 8 weeks after the onset of inflammatory symptoms) revealed infiltration of inflammatory cells into the submucosa under the tracheal epithelia (d). We observed no pathologic changes such as inflammatory phenotypes in $I\kappa B\zeta^{+/-}$ mice (e–h). Each bar represents a length of 50 μm. (C) Phenotype and histologic findings in an *IκBζ/Stat6* double-KO mouse. In the *IκBζ/Stat6* WKO mouse, severe inflammatory symptoms were elicited on the ocular surface and not only on the facial but also on the abdominal skin (c, d). The *IκBζ/Stat6* WKO mouse also manifested paronychia (g, h). No obvious dermatitis or paronychia was observed in *Stat6* single-KO mice (a, b, e, f). (D), Typical features of SJS/TEN in acute stage. Ocular surface inflammation with conjunctivitis and eyelids swelling (*left*). The face manifests swollen and crusted lips, blisters, and erosions of skin (*middle*). Paronychia (*right*). Reprinted with permission from Ueta M, Kinoshita S. Innate immunity of the ocular surface. *Brain Res Bull* 2010;81:219–228. © 2010 by Elsevier Inc.

ankyloblepharon, and in some instances, keratinization of the ocular surface, persist. Alopecia and trichiasis of the eyelashes were also observed.[37]

We considered the possibility of an association between SJS/TEN and a disordered innate immune response. Our reflections were based on an association between the onset of SJS/TEN and infections because many patients with SJS/TEN exhibited prodromata, including nonspecific fever, coryza, and sore throat—ailments that closely mimic upper respiratory tract infections commonly treated with antibiotics.[32] In addition, patients with SJS/TEN presented with opportunistic bacterial infections of the ocular surfaces, in particular methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *S. epidermidis* (MRSE). In fact, compared with individuals with other devastating ocular surface disorders, the detection rate of MRSA and MRSE was higher with respect to the ocular surfaces of patients with SJS/TEN.[38] Moreover, patients with SJS often have severe ocular surface inflammation when MRSA or MRSE reside on the ocular surface, although there is no inflammation on the ocular surface in normal contexts, despite resident commensal bacterium such as *S. epidermidis* and *P. acnes*. Notably, elderly people who are hospitalized have no ocular surface inflammation even when MRSA or MRSE reside on the ocular surface. The ocular surface inflammation of patients with SJS is also greatly reduced after treatment with antibiotics against MRSA or MRSE.[4,5] Finally, patients with SJS/TEN presented with persistent inflammation of the ocular surfaces harboring commensal bacteria.

Under the hypothesis of a disordered innate immune response in SJS/TEN, we performed gene expression analysis of monocytes, cells that are essential in innate immunity. First, we found differences in *IL4R* gene expression; on LPS stimulation, *IL4R* gene expression was downregulated in patients with SJS/TEN and slightly upregulated in the controls (Fig. 12A).[4,39] Second, after a 1-hour culture without LPS, the expression of *IL-1α* (Fig. 12B) and *IκBζ*-specific mRNA (Fig. 12C) was lower in monocytes from patients with SJS/TEN than in the

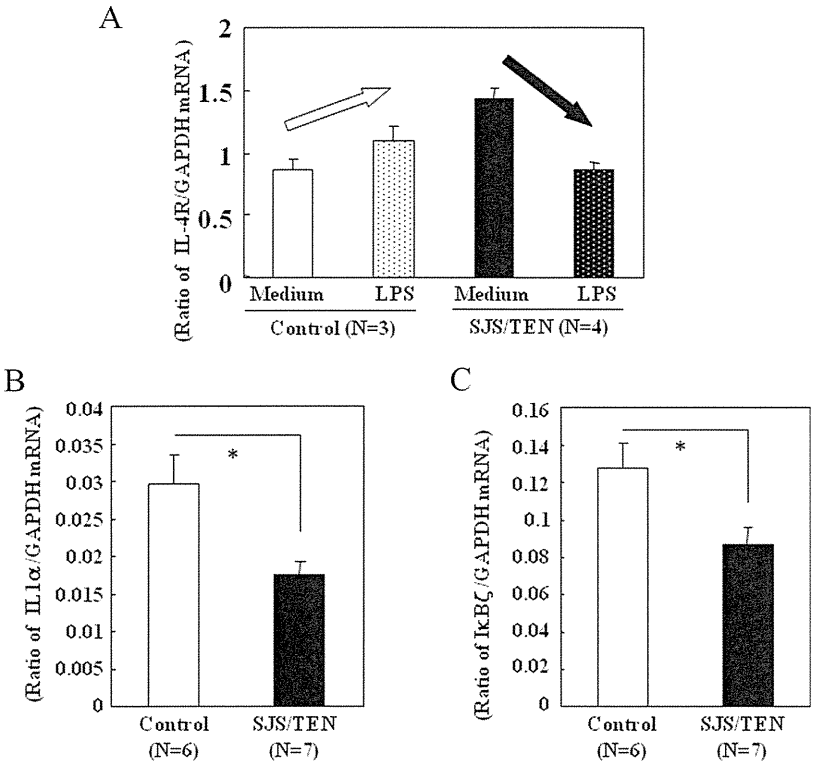

FIG. 12. (A), Difference of *IL4R* gene expression between patients with SJS/TEN and normal volunteers. $CD14^+$ cells from peripheral blood were subjected to gene expression analysis; the cells were cultured for 1 hour with or without LPS. SJS/TEN patients $N = 4$, normal volunteers $N = 3$. Low expression of IL-1α (B) and IκBζ (C) by isolated monocytes from patients with SJS/TEN after 1-hour culture. Quantitative RT-PCR assay confirmed that IL-1α (B) and IκBζ (C) gene expression was significantly lower in cultured monocytes from seven patients with SJS/TENthan the six controls. Data show the mean ± SEM. ($^*P<0.05$); evaluation was performed with Student *t* test using the Excel program. Reprinted with permission from Ueta M. Innate Immunity of the ocular surface and ocular surface inflammatory disorder. *Cornea* 2008;27(suppl 1):S31–S40. © 2008 by Lippincott Williams & Wilkins.

normal controls, suggesting that the reduced expression of *IL-1α* and *IκBζ* genes may play an important role in the pathophysiology of SJS/TEN.[4] According to Correia et al.,[40] IL-1α was significantly lower and sIL-2R was significantly higher in the blister fluid of patients with TEN than in that of patients with burn injury. Our study detected a significant difference between patients with SJS/TEN and controls with respect to the expression of *IL-1α* by $CD14^+$ monocytes. IκBζ is induced by diverse PAMPs regulates NF-κB activity, possibly to prevent excessive inflammation in the presence of bacterial components.[28] Our preliminary report pointed to the presence of ocular surface inflammation in *IκBζ* gene-disrupted mice.[5,30,31] We previously reported that virus dsRNA-mimic polyI:C, a TLR3 ligand, elicited increased expression of human *IκBζ*-specific mRNA in primary corneal epithelial cells.[32] Considering the induction of IκBζ by TLRs, the ocular surface inflammation seen in patients with SJS/TEN may be related to an innate PAMP-amplified immune response to microbes.

While SJS/TEN can be induced by drugs, not all individuals treated with these drugs developed SJS/TEN. Because the incidence of SJS/TEN is very low, we suspected a genetic predisposition and performed single-nucleotide polymorphism (SNP) association analysis using candidate genes associated with innate immunity,[4,32] allergy,[39,41] or apoptosis.[42]

For the SNP analysis, we enrolled 80 patients with SJS/TEN in the chronic or subacute phase; all presented with ocular surface complications. The controls were 160 healthy volunteers. All participants and volunteers were Japanese residing in Japan. The average age (mean ± SD) of the patients and controls was 45.3 ± 16.9 years and 36.2 ± 11.5 years, respectively. The male:female ratios in the patient and control groups were 35:45 and 57:103, respectively. SNP analysis was performed by direct sequencing.[4]

First, we examined the candidate genes associated with innate immunity, such as the *IL1α* genes (which differed between SJS/TEN and controls in our gene expression analysis), the *IκBζ* genes (which also differed between SJS/TEN and controls in our gene expression analysis and which lead to ocular surface and skin inflammation when disrupted), the *TLR2* genes (which are closely related to *S. aureus* and *S. epidermidis*, including MRSA and MRSE), and the *TLR3* gene (which is the one most highly expressed on ocular surface epithelium and responds to virus dsRNA-mimic polyI:C to generate proinflammatory cytokines and IFN-β).[4,32]

To investigate *IκBζ*, we analyzed seven polymorphisms (rs.2305991, rs.622122, rs.14134, rs.3217713, rs.595788, rs.677011, and rs.3821727) in JSNP (the Japanese Single Nucleotide Polymorphisms database). The SNP rs.595788 showed a weak inverse association under a dominant model (rs.595788G/G vs. G/A+A/A: *P* value (χ^2) = 0.04, odds ratio [OR] = 0.55) (Fig. 13), although the results ceased to be significant when we corrected the *P* value for the number of alleles tested ($n = 7$).[4] There was no significant association in the other six polymorphisms.[4]

Regarding *IL1α*, we analyzed five SNPs (rs.1609682, rs.1894399, rs.2071373, rs.2071375, and rs.2071376) reported in JSNP. There was no significant association among these five SNPs.[4]

With regard to *TLR2*, we analyzed three SNPs (rs.3840100, rs.3840099, and rs.3840097) reported in JSNP. There was no significant association among these three SNPs.[4]

Regarding *TLR3*, we analyzed seven SNPs (rs.3775290, rs.3775291, rs.3775292, rs.3775293, rs.3775294, rs.3775295, and rs.3775296) reported in the JSNP database. The SNP rs.3775296 showed a significant association under a recessive model (rs.3775296 T/G + G/G vs. T/T, raw *P* value = 0.0001, corrected

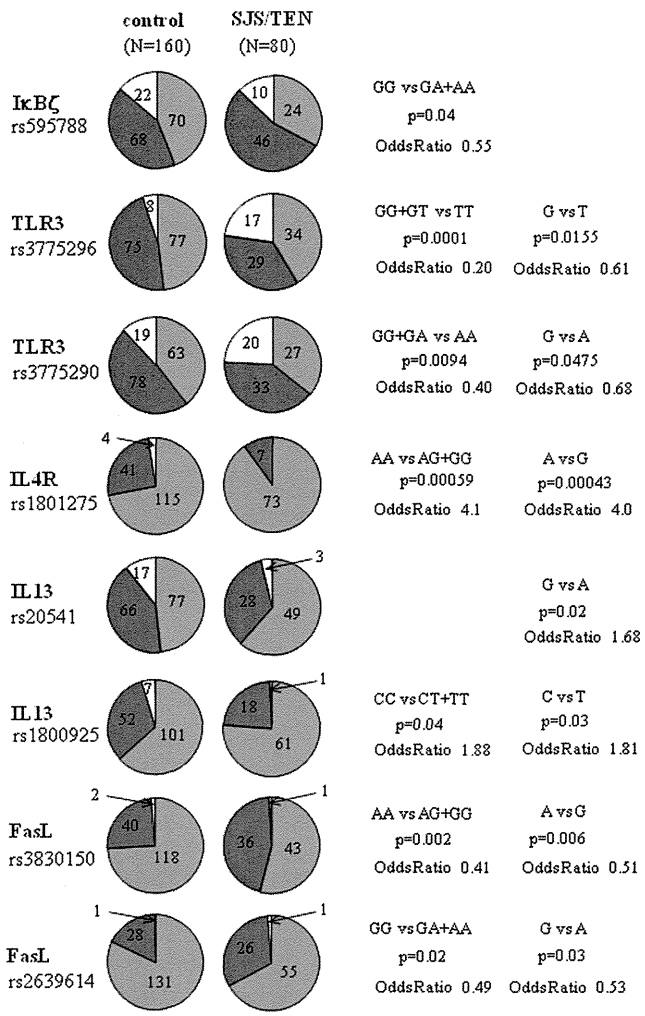

FIG. 13. The SNP association analysis using the candidate genes.

P value = 0.0007, OR = 0.20) and a weak inverse association with allele frequency (G vs. T, raw *P* value = 0.01, corrected *P* value = 0.07, OR = 0.6) (Fig. 13).[4,32] However, when we corrected the *P* value for the number of alleles tested (n = 7), the results ceased to be significant; SNP rs.3775290 also showed a significant association under a recessive model (rs.3775290 A/G + G/G vs. A/A, raw *P* value = 0.0094, corrected *P* value = 0.0658, OR = 0.40) (Fig. 13).[4,32] We also analyzed the genotype pattern of SNPs rs.3775296T/G and rs.3775290A/G and found that it (rs.3775290A/A–rs.3775296T/T) too strongly associated with SJS/TEN in Japanese patients (χ^2 test, *P*=0.00028, OR = 5.4, 95% CI, 2.0–14.8).[4,32] This association was stronger than observed for the single locus (rs.3775296). There was no significant association among other five SNPs. Our results suggest that polymorphisms in the *TLR3* gene may be associated with SJS/TEN in the Japanese population.[32] We hypothesized that viral infection or drugs or both may trigger a disorder in the host innate immune response and that this event is followed by aggravated inflammation of the mucosa, ocular surface, and skin.[4,32]

Next, we examined the candidate genes associated with allergy. We examined *IL4R* genes (in which there are differences between patients with SJS/TEN and controls as determined by our gene expression analysis). Notably, *IL4R* is essential for both IL-4 and IL-13 signaling because it is a component of IL-4 and IL-13 receptors. Regarding the *IL4R* gene, we analyzed polymorphisms of Ile50Val (rs.1805010), Ser478Pro (rs.1805015), and Gln551Arg (rs.1801275) in the *IL4R* gene to compare Japanese patients with SJS/TEN and Japanese healthy volunteers. Among three SNPs in *IL4R*, Gln551Arg showed a significant association with allele frequency (A vs. G, raw *P* value = 0.00043, corrected *P* value = 0.00129, OR = 3.95) and the dominant model (A/A vs. A/G + G/G, raw *P* value = 0.00059, corrected *P* value = 0.00177, OR = 4.1) (Fig. 13).[4,39,41] We also investigated *IL4* and *IL13* (which are ligands of IL4R). Regarding the *IL4* gene, we analyzed polymorphisms of promoter −590C/T (rs.2243250) related to higher IgE levels, and we found no significant association between SJS/TEN and controls.[41] With regard to the *IL13* gene, we analyzed polymorphisms of the promoter −1111C/T SNP (rs.1800925) and Gln110Arg SNPs (rs.20541) in the *IL13* gene among Japanese patients with SJS/TEN and Japanese healthy volunteers. There was a weak association of the promoter −1111C/T SNP in the *IL13* gene related to asthma with allele frequency (C vs. T, raw *P* value = 0.029, corrected *P*(*Pc*) value = 0.057, OR = 1.8); correction of the *P* value for the number of alleles detected (n = 2) showed that the results were not significant (Fig. 13).[41] Gln110Arg SNPs in *IL13* exhibited a significant association with allele frequency (G vs. A, raw *P* value = 0.021, corrected *P* value = 0.042, OR = 1.7) even when we corrected the *P* value for the number of alleles detected of *IL13* SNPs (n = 2) (Fig. 13).[41] These findings contrast with those of Heinzmann et al.[43] who reported that Gln110 was significantly increased in human asthma. We detected a significant increase in Arg110 in our patients with SJS/TEN.

Finally, we examined the candidate genes associated with apoptosis, the *FasL* genes (which reported to manifest increased serum levels in patients with SJS/TEN in the acute stage). We examined four SNPs of *FasL* (rs.929087, rs.2639614, rs.2859247, and rs.3830150) reported in JSNP and found that rs.3830150 A/G (intron) showed a significant inverse association with allele frequency (A vs. G, raw *P* value = 0.006, corrected *P* value = 0.024, OR = 0.5) and the dominant model (A/A vs. A/G + G/G, raw *P* value = 0.0019, corrected *P* value = 0.0075, OR = 0.4) (Fig. 13). SNP rs.2639614 G/A had a significant inverse association with allele frequency (G vs A, raw *P* value = 0.03; OR = 0.53) and with the dominant model (G/G vs G/A + A/A, raw *P* value = 0.02; OR = 0.49), although the results ceased to be significant when we corrected the p-value for the number of alleles tested (n=4) (Fig. 13). Analysis of the genotype pattern of SNPs rs.3830150 and rs.2639614 (rs.3830150 A/A - rs.2639614 G/G) also manifested a strong inverse association with SJS/TEN in Japanese patients (*P* value = 0.0016, OR = 0.4). There was no significant association among other two SNPs.

In summary, we found that *TLR3* rs.3775296 SNP and *IL4R* SNP rs.1801275 (Gln551Arg) were strongly associated (*P*<0.0005), *FasL* rs.3830150 SNP was mildly associated (*P*<0.005), and *IL13* rs.20541 (Arg110Gln) and *IκBζ* SNP rs.595788G/A exhibited a weak association (*P*<0.05) with SJS/TEN with ocular surface complications (Fig. 14A).

Furthermore, we examined human leukocyte antigen (HLA)-class I (*HLA-A, HLA-B,* and *HLA-C*) and HLA II (*DRB1* and *DQB1*) antigens in 71 Japanese patients with SJS/TEN with ocular complications and 113 healthy volunteers. We found that *HLA-*

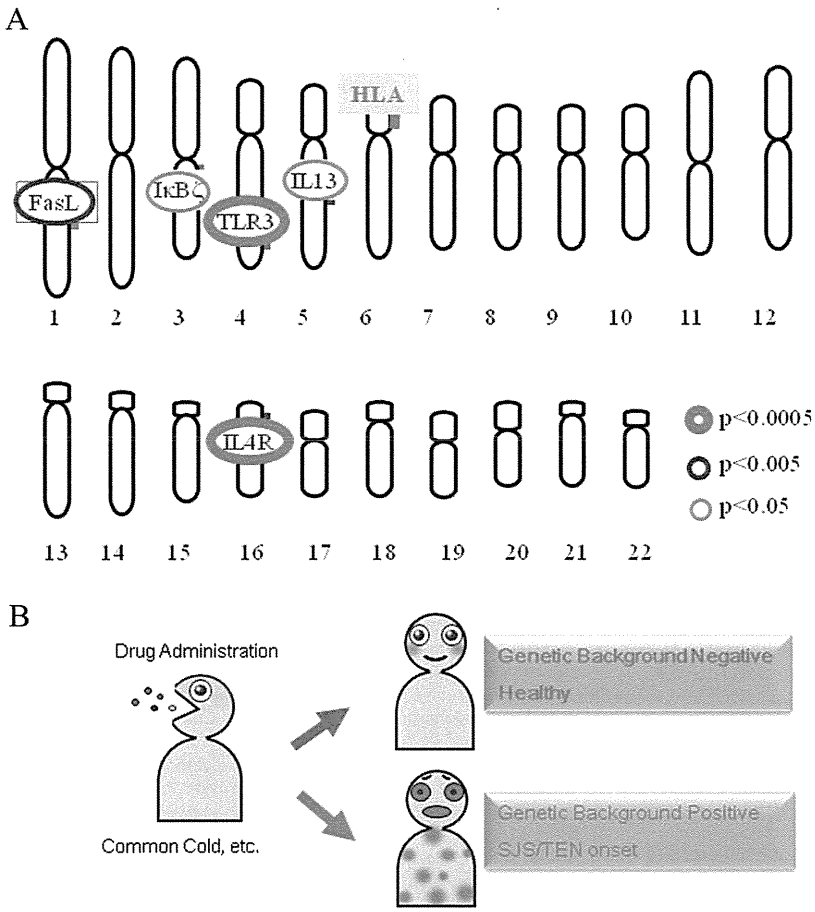

FIG. 14. Conclusions of SNP association analysis. (A) *TLR3* rs.3775296 SNP and *IL4R* SNP rs.1801275 (Gln551Arg) were strongly associated ($P<0.0005$), *FasL* rs.3830150 SNP was mildly associated ($P<0.005$), and *IL13* rs.20541 (Arg110Gln) and *IκBζ* SNP rs.595788G/A exhibited a weak association ($P<0.05$) with SJS/TEN with ocular surface complications. (B) Not only environmental but also genetic factors may play a role in an integrated etiology of SJS/TEN.

*A*0206* was strongly associated with SJS/TEN with ocular complications (carrier frequency: $P<0.00005$, corrected P value <0.0005, OR = 4.1; gene frequency: $P<0.0005$, corrected P value <0.005, OR = 3.2) and that HLA-A*1101 was inversely associated (carrier frequency: $P<0.01$, corrected P value = 0.078, OR = 0.23; gene frequency: $P<0.005$, corrected P value <0.05, OR = 0.22), although there was no association with HLA-class II.[44,45] The onset of SJS with ocular complications was associated with putative viral syndromes or the administration of drugs, a finding that coincided with that of Mondino.[46] Although the *HLA-B12* antigen was significantly increased in white patients with SJS,[46–48] we found no association with *HLA-B12* in Japanese patients with SJS. This result is likely because in whites, the *HLA-B12* antigen is primarily coded for by *HLA-B*4402*, whereas in Japanese, it is almost exclusively coded for by *HLA-B*4403*.[49] On the other hand, *HLA-A*0206* is strongly associated with SJS/TEN with ocular complications in Japanese individuals. This association is absent in whites. We detected no significant association between SJS/TEN and *HLA-DQB1*0601*, although *HLA-DQB1*0601* was associated with ocular complications in white patients with SJS.[50]

Thus, our findings suggest strong ethnic differences in the association of SJS/TEN with HLA. Because SJS/TEN is rare and probably has a complex genetic inheritance background, specific combinations of genes and certain environmental factors may be required for the manifestation of this rare phenotype. Interestingly, HLA class I has been reported to be related to immune responses to virus.

Not only environmental but also genetic factors may play a role in an integrated cause of SJS/TEN (Fig. 14B). A possible association exists between SJS/TEN and disordered innate immunity. Agendas for future research are further examination of the involvement of disordered innate immunity in SJS and investigation of the mechanism of ocular surface inflammation in SJS, especially the correlation with ocular surface involvement.

ACKNOWLEDGMENT

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A survey of Borsuk-Ulam type theorems for isovariant maps

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ABSTRACT. In this article, we shall survey isovariant Borsuk-Ulam type theorems, which are interpreted as nonexistence results on isovariant maps from the viewpoint of equivariant topology or transformation group theory. We also discuss the existence problem of isovariant maps between representations as the converse of the isovariant Borsuk-Ulam theorem.

1 Introduction – backgrounds

Ever since K. Borsuk [5] proved the celebrated antipodal theorem, called the Borsuk-Ulam theorem, this theorem has attracted many researchers and has been generalized as Borsuk-Ulam type theorems, because it is not only beautiful but also has many interesting applications in several fields of mathematics like topology, nonlinear analysis and combinatorics. The original Borsuk-Ulam theorem is stated as follows:

Proposition 1.1. *For any continuous map $f : S^n \to \mathbb{R}^n$, there exists a point $x \in S^n$ such that $f(x) = f(-x)$.*

Let C_2 be a cyclic group of order 2. Consider C_2-spheres S^m and S^n on which C_2 acts antipodally. By means of equivariant topology, the Borsuk-Ulam theorem is restated as follows:

Proposition 1.2. *If there is a C_2-map $f : S^m \to S^n$, then $m \leq n$. In other words, if $m > n$, then there is no C_2-map from S^m to S^n.*

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Thus, in the context of equivariant topology, Borsuk-Ulam type theorems are thought of as nonexistence results on G-maps. Such results are implicitly and explicitly applied in several mathematical problems; for example, a Borsuk-Ulam type result plays an important role in the proof of Furuta's 10/8-theorem [14] in 4-dimensional topology. Lovász [21] succeeded in proving Kneser's conjecture in combinatorics using the Borsuk-Ulam theorem. Matoušek [27] also illustrates several applications to combinatorics. Clapp [9] applied a Borsuk-Ulam type theorem to a certain problem in nonlinear analysis. Further results and applications on the Borsuk-Ulam theorem can be found in excellent survey articles [46], [47].

Wasserman [49] first considered an isovariant version of the Borsuk-Ulam theorem. Nagasaki [31], [33], [34] and Nagasaki-Ushitaki [38] also studied isovariant Borsuk-Ulam type theorems. For example, Wasserman's results imply the following.

Proposition 1.3. *Let G be a solvable compact Lie group and V, W real G-representations. If there exists a G-isovariant map from V to W, then the inequality*

$$\dim V - \dim V^G \leq \dim W - \dim W^G$$

holds. Here V^G denotes the G-fixed point set of V.

In this article, we shall survey isovariant Borsuk-Ulam type theorems and related topics, in particular, we shall discuss the existence or nonexistence problem for isovariant maps between G-representations or more general G-spaces. This article is organized as follows. In Section 2, after recalling some *equivariant* Borsuk-Ulam type theorems, we shall show the isovariant Borsuk-Ulam theorem for semilinear actions which is a generalization of Proposition 1.3. In Section 3, we shall discuss the question of determining for which groups the isovariant Borsuk-Ulam theorem holds. In Section 4, we shall discuss the existence of an isovariant map between representations. Finally, in Section 5, other topics, in particular, the isovariant Borsuk-Ulam theorem for pseudofree S^1-actions and its converse are discussed.

2 Isovariant Borsuk-Ulam type theorems

We first recall some definitions and notations in transformation group theory. Let G be a compact Lie group and X a G-space. For any $x \in X$, the isotropy subgroup G_x

at x is defined by $G_x = \{g \in G \mid gx = x\}$. We denote by $\mathrm{Iso}\, X$ the set of the isotropy subgroups. A subgroup of G always means a closed subgroup. The notation $H \leq G$ means that H is a subgroup of G, and $H < G$ means that H is a proper subgroup of G. As usual X^H denotes the H-fixed point set: $X^H = \{x \in X \mid hx = x \ (\forall h \in H)\}$. All G-equivariant maps (G-maps for short) are assumed to be continuous. A G-map $f : X \to Y$ is called *G-isovariant* if f preserves the isotropy subgroups, i.e., $G_x = G_{f(x)}$ for all $x \in X$. The notion of isovariance was introduced by Palais [41] in order to study a classification problem on orbit maps of G-spaces. Moreover isovariant maps often play important roles in classification problems of G-manifolds or equivariant surgery theory, for example, see [7], [44], [50]. For the study of these maps from the viewpoint of homotopy theory, see [12].

As mentioned in the Introduction, the Borsuk-Ulam theorem can be stated in the context of equivariant topology or transformation group theory. In this context, there are very rich researches and results on Borsuk-Ulam type theorems, see, for example, [1], [3], [4], [9], [11], [13], [15], [16], [17], [19], [20], [26], [43]. Here we present the following generalization of the Borsuk-Ulam theorem for free G-spaces.

Theorem 2.1 ([3], [37]). *Let C_k be a cyclic group of order k. Let X be an arcwise connected free C_k-space and Y a Hausdorff free C_k-space. If there exists a positive integer n such that $H_q(X; \mathbb{Z}/k) = 0$ for $1 \leq q \leq n$ and $H_{n+1}(Y/C_k; \mathbb{Z}/k) = 0$, then there is no continuous C_k-map from X to Y. Here this homology means the singular homology.*

Remark. This result can be deduced from a more general result of [3] and therein the Borel cohomology and spectral sequence arguments are used. On the other hand, in [37], the Smith homology is used. The advantage of the latter method is that the proof is still valid in the category of definable sets with the o-minimal structure over a real closed field, see [36], [37].

Theorem 2.1 implies a well-known Borsuk-Ulam type theorem.

Corollary 2.2 (mod p Borsuk-Ulam theorem). *Let C_p be a cyclic group of prime order p. Assume that C_p acts freely on mod p homology spheres Σ^m and Σ^n. If there is a C_p-map $f : \Sigma^m \to \Sigma^n$, then $m \leq n$. In other words, if $m > n$, then there is no C_p-map from Σ^m to Σ^n.*

In addition, one can see the following.

Corollary 2.3. *Let S^1 be a circle group. Assume that S^1 acts smoothly and fixed-point-freely on rational homology spheres Σ^m and Σ^n. If there is an S^1-map $f : \Sigma^m \to \Sigma^n$, then $m \leq n$.*

Proof. One can take a large prime number p such that C_p ($\leq S^1$) acts freely on Σ^m and Σ^n, and that Σ^m and Σ^n are mod p homology spheres. □

Thus Borsuk-Ulam type theorems are thought of as nonexistence results of G-maps. In this direction, we discuss the nonexistence of G-isovariant maps; namely, the isovariant Borsuk-Ulam theorem. We here recall a linear action or a homologically linear action on a (homology) sphere. Let V be a real representation of G, i.e., V is a (finite dimensional) real vector space on which G acts linearly. Since every representation of compact Lie group G is isomorphic to an orthogonal representation [2], we may suppose that the representation is orthogonal. Since, then, the G-action on V preserves the standard metric, it induces linear G-actions on the unit sphere SV and the unit disk DV. A G-manifold which is G-diffeomorphic to SV [resp. DV] is called a linear G-sphere [resp. a linear G-disk].

A *homologically linear* action on a homology sphere is defined as follows. Let G be a compact Lie group. Set

$$R_G = \begin{cases} \mathbb{Z}/|G| & \text{if } \dim G = 0 \\ \mathbb{Z} & \text{if } \dim G > 0. \end{cases}$$

Let Σ be an R_G-homology sphere, i.e., $H_*(\Sigma; R_G) \cong H_*(S^m; R_G)$, where $m = \dim \Sigma$. Suppose that G acts smoothly on Σ.

Definition.

(1) The G-action on Σ is called *homologically linear* if for every subgroup H of G, the H-fixed point set Σ^H is an R_G-homology sphere or the empty set.

(2) The G-action on Σ is called *semilinear* or *homotopically linear* if for every subgroup H of G, the H-fixed point set Σ^H is a homotopy sphere or the empty set. (Hence Σ itself must be a homotopy sphere.)

(3) We call a smooth closed manifold Σ with homotopically linear [resp. semilinear] G-action a homotopically linear [resp. semilinear] G-sphere.

Let $\mathcal{H}_G$ denote the family of homologically linear G-spheres and $\mathcal{S}_G$ the family of semilinear G-spheres. We also denote by $\mathcal{L}_G$ the family of linear G-spheres.

Remark. Clearly $\mathcal{L}_G \subset \mathcal{S}_G \subset \mathcal{H}_G$, but the converse inclusions are not true in general. For semilinear actions on spheres, see [29], [30], [32].

Lemma 2.4. *Let $\mathcal{F}_G = \mathcal{H}_G$, $\mathcal{S}_G$ or $\mathcal{L}_G$.*

(1) *Let H be a subgroup of G. If $\Sigma \in \mathcal{F}_G$, then $\Sigma \in \mathcal{F}_H$ by restriction of the action.*

(2) *Let H be a normal subgroup of G. If $\Sigma \in \mathcal{F}_G$, then $\Sigma^H \in \mathcal{F}_{G/H}$.*

Proof. (1) Since Σ^K, $K \leq H$, is an R_G-homology sphere (or the empty set), it is also an R_H-homology sphere (or the empty set).

(2) Since $(\Sigma^H)^{K/H} = \Sigma^K$ is an R_G-homology sphere (or the empty set), it is also an $R_{G/H}$-homology sphere (or the empty set). □

Now we state the isovariant Borsuk-Ulam theorem for homologically linear actions.

Theorem 2.5 (Isovariant Borsuk-Ulam theorem). *Let G be a solvable compact Lie group. If there is a G-isovariant map $f : \Sigma_1 \to \Sigma_2$ between homologically linear G-spheres Σ_i, $i = 1, 2$, then the inequality*

$$\dim \Sigma_1 - \dim \Sigma_1^G \leq \dim \Sigma_2 - \dim \Sigma_2^G$$

holds.

A convention: if Σ_i^G is empty, then we set $\dim \Sigma_i^G = -1$. To prove the theorem, we make the following definition.

Definition. We say that G has the IB-property in $\mathcal{F}_G$, where $\mathcal{F}_G = \mathcal{L}_G$, $\mathcal{S}_G$ or $\mathcal{H}_G$ if G has the following property: If there is a G-isovariant map $f : \Sigma_1 \to \Sigma_2$, $\Sigma_i \in \mathcal{F}_G$, then the inequality

$$\dim \Sigma_1 - \dim \Sigma_1^G \leq \dim \Sigma_2 - \dim \Sigma_2^G$$

holds.

We first show the following fact.

Lemma 2.6 ([49], [31]).

(1) *Let H be a normal subgroup of G. If H and G/H have the IB-properties in $\mathcal{F}_H$ and $\mathcal{F}_{G/H}$ respectively, then G also has the IB-property in $\mathcal{F}_G$.*

(2) *Let $\mathcal{F}_G = \mathcal{S}_G$ or $\mathcal{L}_G$. If G has the IB-property in $\mathcal{F}_G$, then G/H also has the IB-property in $\mathcal{F}_{G/H}$.*

Proof. (1) Let $f : \Sigma_1 \to \Sigma_2$ be any G-isovariant map between Σ_1 and Σ_2 in $\mathcal{F}_G$. Then $\mathrm{res}_H f : \Sigma_1 \to \Sigma_2$ is H-isovariant and $f^H : \Sigma_1^H \to \Sigma_2^H$ is G/H-isovariant. It follows from Lemma 2.4 that Σ_1, $\Sigma_2 \in \mathcal{F}_H$ and Σ_1^H, $\Sigma_2^H \in \mathcal{F}_{G/H}$. By assumption, we have

$$\dim \Sigma_1 - \dim \Sigma_1^H \leq \dim \Sigma_2 - \dim \Sigma_2^H,$$

$$\dim \Sigma_1^H - \dim \Sigma_1^G \leq \dim \Sigma_2^H - \dim \Sigma_2^G.$$

Hence we obtain

$$\dim \Sigma_1 - \dim \Sigma_1^G \leq \dim \Sigma_2 - \dim \Sigma_2^G.$$

(2) Suppose that $f : \Sigma_1 \to \Sigma_2$ is a G/H-isovariant map between Σ_1 and $\Sigma_2 \in \mathcal{F}_{G/H}$. Via the projection $G \to G/H$, the G/H-action lifts to a G-action. Hence Σ_i, $i = 1, 2$, are thought of as in $\mathcal{F}_G$ and then f is a G-isovariant map. Thus we have $\dim \Sigma_1 - \dim \Sigma_1^{G/H} \leq \dim \Sigma_2 - \dim \Sigma_2^{G/H}$, since $\dim \Sigma_i^{G/H} = \dim \Sigma_i^G$. □

Proof of Theorem 2.5. We show that a solvable compact Lie group has the IB-property in $\mathcal{H}_G$. Suppose that $f : \Sigma_1 \to \Sigma_2$ is a G-isovariant map. Since G is solvable, there is a normal series of closed subgroups:

$$1 = H_0 \lhd H_1 \lhd \cdots \lhd H_r = G$$

such that H_i/H_{i-1}, $1 \leq i \leq r$, is isomorphic to C_p (p: some prime) or S^1.

By Lemmas 2.4 and 2.6, the proof is reduced to the cases of C_p and S^1; moreover, the case of S^1 is also reduced to the case of C_p, since there exists some cyclic subgroup C_p of S^1 such that $\Sigma_i^{S^1} = \Sigma_i^{C_p}$, $i = 1, 2$, in fact, $\Sigma_i \in \mathcal{H}_G$ has only finitely many orbit types [6], [18].

In the case of C_p, the proof proceeds as follows. Let $G = C_p$. Since f is G-isovariant, it follows that $f(\Sigma_1 - \Sigma_1^G) \subset \Sigma_2 - \Sigma_2^G$. Set $N_i := \Sigma_i - \Sigma_i^G$. Since Σ_i and Σ_i^G

are mod p homology spheres, by Alexander duality, one can see that $N_i := \Sigma_i - \Sigma_i^G$ has the same mod p homology groups as a sphere S^{n_i}, where $n_i = \dim \Sigma_i - \dim \Sigma_i^G - 1$. Since $G = C_p$ acts freely on N_i and $f|_{N_1} : N_1 \to N_2$ is a G-map, it follows from Theorem 2.1 that $n_1 \leq n_2$, and hence

$$\dim \Sigma_1 - \dim \Sigma_1^G \leq \dim \Sigma_2 - \dim \Sigma_2^G.$$

Thus C_p has the IB-property in $\mathcal{H}_{C_p}$. □

This theorem implies Proposition 1.3.

Proof of Proposition 1.3. Let $f : V \to W$ be a G-isovariant map between representations. Let $V^{G^\perp}$ denote the orthogonal complement of V^G in V, and then V decomposes as $V = V^G \oplus V^{G^\perp}$. Similarly W decomposes as $W = W^G \oplus W^{G^\perp}$. Then the composition map $g := p \circ f \circ i : V^{G^\perp} \to W^{G^\perp}$ is a G-isovariant map, where $i : V^{G^\perp} \to V$ is the inclusion and $p : W \to W^{G^\perp}$ is the projection. Since $g^{-1}(0) = \{0\}$, g induces a G-isovariant map $g_0 : V^{G^\perp} \setminus \{0\} \to W^{G^\perp} \setminus \{0\}$. By normalizing, one has a G-isovariant map $g_1 : S(V^{G^\perp}) \to S(W^{G^\perp})$. Since G has the IB-property in $\mathcal{H}_G$, one has

$$\dim S(V^{G^\perp}) + 1 \leq \dim S(W^{G^\perp}) + 1,$$

which leads to the inequality

$$\dim V - \dim V^G \leq \dim W - \dim W^G.$$

□

The following is obtained from Smith theory [6], [18].

Corollary 2.7. *Let G be a finite p-group. Let Σ_i, $i = 1, 2$, be mod p homology spheres with G-actions. If there is a G-isovariant map $f : \Sigma_1 \to \Sigma_2$, then*

$$\dim \Sigma_1 - \dim \Sigma_1^G \leq \dim \Sigma_2 - \dim \Sigma_2^G$$

holds.

Proof. Smith theory shows that for every subgroup H, the H-fixed point set Σ_i^H is a mod p homology sphere or the empty set. Hence the G-action on Σ_i is homologically linear and $\Sigma_i \in \mathcal{H}_G$. □

The singular set $N^{>1}$ of a G-manifold N is defined by

$$N^{>1} = \bigcup_{1 \neq H \leq G} N^H.$$

The following is a variant of the isovariant Borsuk-Ulam theorem, which is a generalization of a result in [33].

Corollary 2.8. *Let G be a finite group and W a representation of G. Let M and N be homologically linear G-spheres and assume that G acts freely on M. If there is a G-isovariant map $f : M \to N$, then the inequality*

$$\dim M + 1 \leq \dim N - \dim N^{>1}$$

holds.

Proof. Since $\dim N^{>1} = \max\{\dim N^H \mid 1 \neq H \leq G\}$, there is a subgroup $H \neq 1$ such that $\dim N^H = \dim N^{>1}$. Taking a cyclic subgroup $C_p \leq H$ of prime order, one has $\dim N^{C_p} = \dim N^{>1}$. By restricting to the C_p-action, it turns out that f is a C_p-isovariant map. Hence, by the isovariant Borsuk-Ulam theorem, one has

$$\dim M + 1 \leq \dim N - \dim N^{C_p} = \dim N - \dim N^{>1}.$$

□

Remark. Not all finite groups can act freely on a (homology) sphere. For details, see [8], [23], [24], [25].

3 Which groups have the IB-property?

As seen in the previous section, a solvable compact Lie group has the IB-property in $\mathcal{F}_G$, i.e., the isovariant Borsuk-Ulam theorem holds in $\mathcal{F}_G$. In this section, we discuss the question: Which compact Lie groups have the IB-property in $\mathcal{F}_G$? First we consider the case of $\mathcal{F}_G = \mathcal{H}_G$ or $\mathcal{S}_G$. In this case, a complete answer is known.

Theorem 3.1 (cf. [31]). *The following statements are equivalent.*

(1) *G has the IB-property in $\mathcal{H}_G$.*

(2) *G has the IB-property in $\mathcal{S}_G$.*

(3) *G is a solvable compact Lie group.*

Proof. We have already seen the implication (3) $\Rightarrow$ (1), and trivially (1) $\Rightarrow$ (2). To see (2) $\Rightarrow$ (3), we show that there is a counterexample to the isovariant Borsuk-Ulam theorem when G is nonsolvable. According to Oliver [40, Theorem 4], there exists a disk D with a smooth G-action such that D^H is also a disk if H is a solvable subgroup, and the empty set if H is a nonsolvable subgroup. The boundary of this G-disk D is clearly a semilinear G-sphere. Note also that $D^G = \emptyset$ since G is nonsolvable. Set $\Sigma_n = \partial(D \times D(\mathbb{R}^n))$, where $D(\mathbb{R}^n)$ is an n-dimensional disk with trivial G-action. Then Σ_n is a semilinear G-sphere without G-fixed points. For any positive integer n, take a map $h_n : D(\mathbb{R}^n) \to D(\mathbb{R}^1)$ such that $h_n(D(\mathbb{R}^n)) \subset \partial D(\mathbb{R}^1)$, and define a G-map

$$g_n := id \times h_n : D \times D(\mathbb{R}^n) \to D \times D(\mathbb{R}^1).$$

Then one can easily see that g_n is a G-isovariant map and g_n maps the boundary $\partial(D \times D(\mathbb{R}^n))$ into the boundary $\partial(D \times D(\mathbb{R}^1))$. Hence we obtain a G-isovariant map $f_n := g_{n|\Sigma_n} : \Sigma_n \to \Sigma_1$. Since $\dim \Sigma_n > \dim \Sigma_1$ for $n > 1$, this f_n gives a counterexample to the isovariant Borsuk-Ulam theorem. □

Remark. The semilinear G-sphere Σ_1 in the above proof is equivariantly embedded in some linear G-sphere SW [6]. Hence there is an isovariant map $f_n : \Sigma_n \to SW$ such that $\dim \Sigma_n + 1 > \dim SW - \dim SW^G$ for some large n.

In the case $\mathcal{F}_G = \mathcal{L}_G$, the problem is more difficult; in fact, a complete answer is unfortunately unknown to the best of the author's knowledge. However some partial answers are known. We present them here without proof.

To state Wasserman's result, we recall the *prime condition* for a finite group G.

Definition. We say that a finite simple group G satisfies the prime condition if for every element $g \in G$,

$$\sum_{p|o(g)} \frac{1}{p} \leq 1$$

holds, where $o(g)$ denotes the order of g, and p is a prime dividing $o(g)$.

We say that a finite group G satisfies the prime condition if every simple factor group in a normal series of G satisfies the prime condition as a simple group.

Theorem 3.2 ([49]). *Every finite group satisfying the prime condition has the IB-property in $\mathcal{L}_G$.*

This theorem provides nonsolvable examples of having the IB-property in $\mathcal{L}_G$.

Example 3.3. The alternating groups $A_5, A_6, \ldots, A_{11}$ satisfy the prime condition, and hence A_i has the IB-property in $\mathcal{L}_{A_i}$, $i = 5, 6, \ldots, 11$.

Remark. The alternating groups A_n, $n > 11$, do not satisfy the prime condition. However, the author does not know whether A_n has the IB-property for $n > 11$.

Another partial answer is a weak version of the isovariant Borsuk-Ulam theorem.

Theorem 3.4 ([31]). *For an arbitrary compact Lie group G, there exists a weakly monotone increasing function $\varphi_G : \mathbb{N}_0 \to \mathbb{N}_0$ diverging to ∞ with the following property.*

(WIB) *For any pair of representations V and W such that there is a G-isovariant map $f : SV \to SW$, the inequality*

$$\varphi_G(\dim V - \dim V^G) \leq \dim W - \dim W^G$$

holds.

Here $\mathbb{N}_0$ denotes the set of nonnegative integers.

The above result does not hold for G-equivariant maps even if $SV^G = SW^G = \emptyset$. For example, when G is a cyclic group C_{pq} of order pq, where p, q are distinct primes, a Borsuk-Ulam type theorem does not hold as can be seen below.

Let U_k $(= \mathbb{C})$ be the representation of $C_n = \langle g \rangle$ for which g acts by $g \cdot z = \xi^k z$, $z \in U_k$, where $\xi = \exp(2\pi\sqrt{-1}/n)$.

Proposition 3.5 (cf. [48]). *Let $C_{pq} = \langle g \rangle$ be a cyclic group of order pq, where p, q are distinct primes. For any positive integer r, there is a C_{pq}-map $f : S(rU_1) \to S(U_p \oplus U_q)$, where rU_1 is the direct sum of r copies of U_1.*

Proof. Set $G = C_{pq}$. By a result of [48], there is a self G-map $h : S(U_p \oplus U_q) \to S(U_p \oplus U_q)$ with $\deg h = 0$; hence h is (nonequivariantly) nullhomotopic. Since G acts freely on $S(rU_1)$, $S(rU_1)$ has a G-CW complex structure consisting of free G-cells. We put $S(rU_1) = \bigcup_k X_k$, where X_k is the k-skeleton. A G-map from $S(rU_1)$

to $S(U_p \oplus U_q)$ is inductively constructed as follows. Suppose that one has a G-map $f_{k-1} : X_{k-1} \to S(U_p \oplus U_q)$. Then f_{k-1} can be extended to a G-map $f' : X_{k-1} \cup_\phi G \times D^k \to S(U_p \oplus U_q)$. Indeed, since $h \circ \phi_{|\{1\} \times S^{k-1}} : S^{k-1} \to S(U_p \oplus U_q)$ is nullhomotopic, $h \circ \phi_{|S^{k-1}}$ is extended to a map $g : D^k \to S(U_p \oplus U_q)$, and next g is equivariantly extended to a G-map $g' : G \times D^k \to S(U_p \oplus U_q)$. By gluing g' to f_{k-1}, one obtains a G-map $f' : X_{k-1} \cup_\phi G \times D^k \to S(U_p \oplus U_q)$. Repeating this procedure, one has a G-map $f_k : X_k \to S(U_p \oplus U_q)$. □

Remark. More generally, Bartsch [1] shows that a weak version of the Borsuk-Ulam theorem holds for linear G-spheres of a finite group G if and only if G has prime power order.

Combining this proposition with the isovariant Borsuk-Ulam theorem, we obtain another Borsuk-Ulam type result.

Corollary 3.6. *For any C_{pq}-map $f : S(rU_1) \to S(U_p \oplus U_q)$, $r \geq 2$, the image of f meets the Hopf link $SU_p \coprod SU_q$ in $S(U_p \oplus U_q)$.*

Proof. Suppose that $f^{-1}(SU_p \coprod SU_q) = \emptyset$. Then f is a G-isovariant map, since G acts freely on $S(U_p \oplus U_q) \setminus (SU_p \coprod SU_q)$. Furthermore $\mathrm{Res}_{C_p} f$ is a C_p-isovariant map. By the isovariant Borsuk-Ulam theorem, it follows that

$$2r = \dim S(rU_q) + 1 \leq \dim S(U_p \oplus U_q) - \dim S(U_p \oplus U_q)^{C_p} = 2.$$

This is a contradiction. □

Remark. Another equivalent statement of the original Borsuk-Ulam theorem is: For any C_2-map $f : S^n \to \mathbb{R}^n$, the image of f meets the origin in $\mathbb{R}^n$, where the C_2-actions on S^n and $\mathbb{R}^n$ are both given by multiplication by -1.

4 The converse of the isovariant Borsuk-Ulam theorem

The isovariant Borsuk-Ulam theorem is interpreted as a nonexistence result of isovariant maps, and it produces several inequalities, which give a necessary condition for the existence of an isovariant map. In several cases, it is also sufficient. In this section, we shall present such examples for the existence of an isovariant map and

discuss the converse of the isovariant Borsuk-Ulam theorem. The materials are taken from [34], [35], [38], [39].

As a special case of Corollary 2.8, we consider the case $N = SW$, a linear G-sphere. Then, the inequality

$$\dim M + 1 \leq \dim SW - \dim SW^{>1}$$

holds if there is a G-isovariant map $f : M \to SW$. In this case, we show that the converse is true.

Proposition 4.1. *Let G be a finite group and M a compact G-manifold with free G-action. Let W be a representation of G. If $\dim M + 1 \leq \dim SW - \dim SW^{>1}$, then there exists a G-isovariant map $f : M \to SW$.*

We define the free part SW_{free} of SW by $SW_{\text{free}} = SW \setminus SW^{>1}$. Set $d = \dim SW - \dim SW^{>1}$.

Lemma 4.2. *The free part SW_{free} is $(d-2)$-connected.*

Proof. Since $\dim S^k \times I + \dim SW^{>1} < \dim SW$ for $k \leq d-2$, any homotopy into SW deforms to a homotopy into SW_{free} by a general position argument. Hence every map from S^k to SW_{free} is nullhomotopic for $k \leq d-2$. □

Proof of Proposition 4.1. Since G acts freely on M and SW_{free}, it suffices to show the existence of a G-map from M to SW_{free}. Since M has a G-CW complex structure, we may put $M = \bigcup_k X_k$, where X_k is the k-skeleton of M. The inequality means $k \leq d-1$. A G-map into SW_{free} is inductively constructed as follows. Suppose that f_{k-1} is constructed as a G-map from X_{k-1} to SW_{free}; then f_{k-1} is extended on $X_{(k-1)} \cup_\phi G \times D^k$; indeed, since SW_{free} is $(d-2)$-connected, the map $f_{k-1} \circ \phi_{|\{1\} \times S^{k-1}} : S^{k-1} \to SW_{\text{free}}$ is extended to a map $g : D^k \to SW_{\text{free}}$ and then g is equivariantly extended to a G-map $\tilde{g} : G \times D^k \to SW_{\text{free}}$. By gluing $\tilde{g}$ to f_{k-1}, one can obtain a G-map $f'_{k-1} : X_{k-1} \cup_\phi G \times D^k \to SW_{\text{free}}$. Repeating this procedure, we obtain a G-map from the k-skeleton X_k to SW_{free}, and finally we obtain a G-map $f : M \to SW_{\text{free}}$. □

Thus, in this situation, the existence problem is solved as follows.

Corollary 4.3. *Let M be a mod $|G|$ homology sphere with free G-action and W a representation of G. There exists a G-isovariant map from M to SW if and only if*

$$\dim M + 1 \leq \dim SW - \dim SW^{>1}.$$

Next we consider the existence problem of an isovariant map between (real) representations. Let G be a finite solvable group. Let $f : V \to W$ be a G-isovariant map between representations V and W. Take any pair (H, K) of subgroups of G with $H \lhd K$. Then $f^H : V^H \to W^H$ is considered as a K/H-isovariant map. Since K/H is solvable, the isovariant Borsuk-Ulam theorem implies the inequality

$$\dim V^H - \dim V^K \leq \dim W^H - \dim W^K.$$

From this observation, we consider the following condition for a pair of representations V and W of a solvable group G:

$(C_{V,W})$ $\dim V^H - \dim V^K \leq \dim W^H - \dim W^K$ for every pair (H, K) with $H \lhd K$.

Moreover the condition $(I_{V,W})$: $\operatorname{Iso} V \subset \operatorname{Iso} W$ is obviously necessary for the existence of an isovariant map.

Definition. We say that a finite solvable group G has the *complete IB-property* if, for every pair (V, W) of representations satisfying conditions $(C_{V,W})$ and $(I_{V,W})$, there exists a G-isovariant map from V to W.

Remark. If G is nilpotent, then $(C_{V,W})$ implies $(I_{V,W})$ [34].

Which solvable groups have the complete IB-property? A complete answer is not known; however, some examples that have the complete IB-property are known.

Theorem 4.4 ([34], [35]). *Let p, q, r be distinct primes. The following finite groups have the complete IB-property:*

(1) *abelian p-groups,*

(2) *$C_{p^m q^n}$: cyclic groups of order $p^m q^n$,*

(3) *C_{pqr}: cyclic groups of order pqr,*

(4) *D_3, D_4 and D_6: dihedral groups of order 6, 8 and 12, respectively.*