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Topical application of a new monoclonal antibody against fibroblast growth factor 10 (FGF 10) mitigates propranolol-induced psoriasis-like lesions in guinea pigs

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Abstract. – OBJECTIVES: Psoriasis is a chronic inflammatory skin disease characterized by excessive proliferation of keratinocytes. Fibroblast growth factor 10 (FGF10) acts as a growth factor for keratinocyte proliferation. The aim of this study is to investigate whether FGF10 blockage, a new monoclonal antibody against FGF10 we generated, could mitigate topical propranolol-induced psoriasis-like lesions in guinea pigs.

MATERIALS AND METHODS: The monoclonal anti-FGF10 was generated by a routine method and purified by affinity chromatography. The effect of FGF10 and anti-FGF10 on human keratinocyte HaCaT cell proliferation was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). The back of the ears of individual guinea pigs was topically exposed to 5% propranolol emulsion to induce psoriasis-like lesions and randomly treated topically with phosphate buffered saline (PBS), hydrocortisone butyrate, or different doses of anti-FGF10. The pathologic changes and the degrees of inflammation in the auricular areas of individual animals were examined histologically.

RESULTS: Characterization revealed that anti-FGF10 had a purity of 90% and a titer of 1:12800. We found that FGF10 stimulated HaCaT cell proliferation while treatment with different doses of anti-FGF10 inhibited FGF10-induced cell proliferation in a dose-dependent manner (100, 200 ng/ml, $p < 0.05$ vs. control; 400, 800, 1600 ng/ml, $p < 0.01$ vs. control). Compared to PBS-treated psoriatic animals, treatment with anti-FGF10, like hydrocortisone butyrate, greatly inhibited the severity of psoriasis-like lesions by reducing the Baker's scores, the thickness of epidermis, and the numbers of monocyte infiltrates in the dermis of animals.

CONCLUSIONS: The newly generated anti-FGF10 monoclonal antibody inhibited the proliferation of human keratinocytes *in vitro* and mitigated inflammation and pathogenic changes in propranolol-induced psoriasis-like lesions in animals. Therefore, these findings may provide a proof of principle that blockage of FGF-10 may inhibit psoriasis-related inflammation.

Key Words:
FGF10, Keratinocyte, Monoclonal antibody, Proliferation, Psoriasis.

Introduction

Psoriasis is a chronic inflammatory skin disease and approximately, affects 2% of the population in the world[1]. It is characterized by excessive growth and aberrant differentiation of keratinocytes in the skin lesions[2]. Currently, numerous therapeutic reagents are available including topical treatments (emollients, tar, dithranol, steroids, and vitamin D analogues), phototherapy (broadband or narrowband ultraviolet radiation B, laser), and systemic agents (anti-metabolites, oral retinoid acids, and immunosuppressants)[3]. However, the therapeutic efficacy of these treatments is limited. Many patients with psoriasis commonly do not respond to or develop tolerance to these therapies. Novel biologic agents such as anti-tumor necrosis factor (TNF) α, TNFα blocker, and anti-IL-12/IL-23, which inhibit autoimmunity and target specific molecular signals in the pathogenesis of psoriasis, are effective in the treatment of severe psoriasis[3]. However, the safety of these therapeutic reagents is of concern.

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It is well known that fibroblast growth factor 10 (FGF10) and keratinocyte growth factor (KGF) are crucial growth factors for the proliferation and differentiation of keratinocytes[4]. Among these factors, FGF10 serves as an important mediator of keratinocyte proliferation, differentiation, and migration[5,6]. FGF10 is predominantly secreted by fibroblasts, and it can bind to the IIIb isoform of FGF receptor II. A previous study has shown that the levels of FGF10 expression are elevated in the upper dermis of psoriatic skin and are correlated positively with the numbers of T cell infiltrates and the degrees of keratinocyte proliferation[7]. Moreover, mice with a deficiency in the FGF10 gene have abnormalities in epidermal morphogenesis, a decreased number of proliferating cells in the basal layer, the hypoplastic granular layer, and no distinctive keratohyaline granule and tonofibril[8]. Accordingly, FGF10 is an important factor of keratinocyte proliferation. Therefore, we hypothesized that blockage of FGF10 function by anti-FGF10 could inhibit keratinocyte proliferation and mitigate psoriasis-related inflammation.

In this present study, we generated a novel monoclonal antibody (mAb) against FGF10 (anti-FGF10) and examined the effect of anti-FGF10 in the suppression of keratinocyte proliferation *in vitro* and pathogenic changes in a guinea pig model of topical propranolol-induced psoriasis-like lesions. Our results may provide valuable insights into the role of FGF10 in the pathology of psoriasis and offer a novel approach for disease therapy.

Materials and Methods

Ethics Statement

Every effort was made to minimize the numbers and suffering of the animals used in the experiments. Animal study was performed in the Laboratory Animal Center, School of Basic Medical Sciences, Jilin University. The animal experiments were approved by the Animal Ethical Committee of the Jilin University.

Cell Culture

Sp2/0 mouse myeloma and human keratinocyte HaCaT cell lines were from the Institute of Biological Products in Changchun, China. Sp2/0 cells were maintained in RPMI-1640 medium (GIBCO, Shanghai, China) containing 10% fetal bovine serum (FBS, Zhejiang Tianhang Biological Technology, Hangzhou, China) and HaCaT cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM, GIBCO, Carlsbad, CA, USA) containing 20% FBS at 37°C in a 5% CO_2-humidified incubator.

Preparation and Identification of Anti-FGF10

Female BALB/c mice at 6 to 8 weeks of age were obtained from the Institute of Biological Products, Changchun, China. Animals were immunized with 20 μg FGF10 (the Engineering Research Center of Bioreactor and Pharmaceutical Development of Ministry of Education, Jilin Agricultural University, Changchun) in 50% complete Freund's adjuvant (CFA, GIBCO), and two weeks later, the mice were boosted with 20 μg FGF10 in 50% incomplete Freund's adjuvant (IFA, GIBCO) every ten days for two times. Two weeks after the last boosting, the mice were injected intravenously with 10 μg FGF10 and their blood samples were collected for the measurement of anti-FGF10 antibody titers at three days post the last intravenous chanlege. Subsequently, the mice were sacrificed and their splenic mononuclear cells were prepared. The prepared splenic mononuclear cells were fused with Sp2/0 cells at a ratio of 5:1 with polyethylene glycol (PEG) 4000. After the fusion, the cells were cultured in hypoxanthine-aminopterin-thymidine (HAT) medium and the supernatants of cultured hybridomas were harvested for the measurement of anti-FGF10 by enzyme-linked immunosorbent assay (ELISA). The positive hybridomas were selected and subjected to further cloning by limited dilution for three times. The generated hybridoma of 2G6 was injected into BALB/c nude mice to generate ascites. The anti-FGF10 antibody of 2G6 in the ascites was purified by affinity chromatography using Protein A beads (Invitrogen, Grand Island, NY, USA). The subclass of mAb of 2G6 was determined by ELISA using an Immunoglobin isotyping ELISA kit, according to the manufacturers' instruction (Sigma, St. Louis, MO, USA), and the purification of 2G6 was identified by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE).

MTT Assay

The impact of anti-FGF10 2G6 on human keratinocyte proliferation was tested by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Briefly, HaCaT cells (5×10^4 cells/well) were cultured overnight in a 96-

well plate and treated in quintuplicate with FBS-free DMEM medium supplemented with different concentrations of FGF10 alone (10, 50, 100, 200, 400, or 800 ng/ml) or 200 ng/ml of FGF10 and varying concentrations (100, 200, 400, 800, or 1600 ng/ml) of anti-FGF10 2G6 for 72 hrs. The control cells were cultured in medium alone. The cells were exposed to 20 µl of MTT (5 mg/mL) during the last 4-h incubation. The generated formazan was dissolved in 100 µl of dimethyl sulfoxide (DMSO) and measured for the absorbance at 490 nm (A490) using a microplate spectrophotometer. The average optical density (OD) was calculated.

Establishment of Animal Model of Psoriasis-Like Lesions

Male guinea pigs at XX weeks of age were obtained from the Institute of Biological Products in Changchun, China, and housed in a specific pathogen free (SPF) facility with free access to food and water. An animal model of *psoriasis-like lesions* was established, as described previously[9]. At the beginning, six animals were treated topically with 5% propranolol emulsion (10 mg/mL, Shanxi Yunpeng Pharmaceutical, China) on the back of each ear four times per day for three or 21 consecutive days to induce psoriasis-like lesions. The pathological changes in the skin tissues were examined by histology. Subsequently, 45 animals were treated topically with 5% propranolol emulsion (10 mg/mL, Shanxi Yunpeng Pharmaceutical, China) on the back of each ear four times per day for 21 consecutive days to induce psoriasis-like lesions. Another nine animals were treated with phosphate buffered saline (PBS) and used as the healthy controls.

Treatment

One week after induction, these animals were randomized into six groups (nine animals per group) by a simple random sample using the SPSS software. Animals were treated topically with 100 µl of vehicle PBS as the model group, with 100 mg hydrocortisone butyrate (Tianjin Pharmaceuticals Group, China) as the hydrocortisone group, or with 0.188 mg/ml (high dose group), 0.094 mg/ml (medium dose group), or 0.063 mg/ml (low dose group) of anti-FGF10 2G6 on the back of the ears twice per day for 14 consecutive days. The healthy controls were treated with PBS. The animals were sacrificed one day after the last treatment, and their auricular areas were carefully removed for histological examination.

Histology

The ear tissues were fixed with buffered formalin, and the paraffin-embedded tissue sections (4 µM) were routinely stained with hematoxylin and eosin (H&E). The sections were examined under a light microscope and scored, according to Baker's score criteria[10] in a blinded fashion. The pathological changes in the corneous layer, epidermis, and dermis of the skin were analyzed and scored separately, as described in Table I. All the values of individual animals were summarized to obtain a total histopathological score for each animal (maximum score = 10). A lesion with a histopathological score of 4 was defined as a typical psoriasis-like lesion.

Statistical Analysis

Data are presented as the mean ± standard deviation (SD). The difference among the groups was determined using one-way analysis of variance (ANOVA), and the difference between two groups was analyzed by Fisher's least significant difference (LSD) test using the SPSS13.0 software (SPSS Inc., Chicago, IL, USA). A p value of < 0.05 was considered statistically significant.

Results

Anti-FGF10 Antagonizes FGF10-stimulated Human Keratinocyte Proliferation in vitro

FGF10 is a crucial growth factor of keratinocyte proliferation. We first tested the role of FGF10 in spontaneous keratinocyte proliferation. Human keratinocyte HaCaT cells were treated with different concentrations of recombinant FGF10 for 72 hrs, and the FGF10-stimulated HaCaT cell proliferation was determined by MTT. As shown in Figure 1A, treatment with 10-200 ng/mL of FGF10 stimulated HaCaT cell prolifer-

Table I. Histopathological score criteria.

	Pathological change	Score
Corneous layer	Parakeratosis	1.0
	Hyperkeratosis	0.5
	Munro abscess	2.0
Epidermis	Lengthening of rete ridges	0.5-1.5
	Acanthosis	1.0
	Lack of granular layer	1.0
Dermis	Lymphocytic infiltrate	0.5-2.0
	Thinning above papillae	0.5
	Papillary papillae congestion	0.5

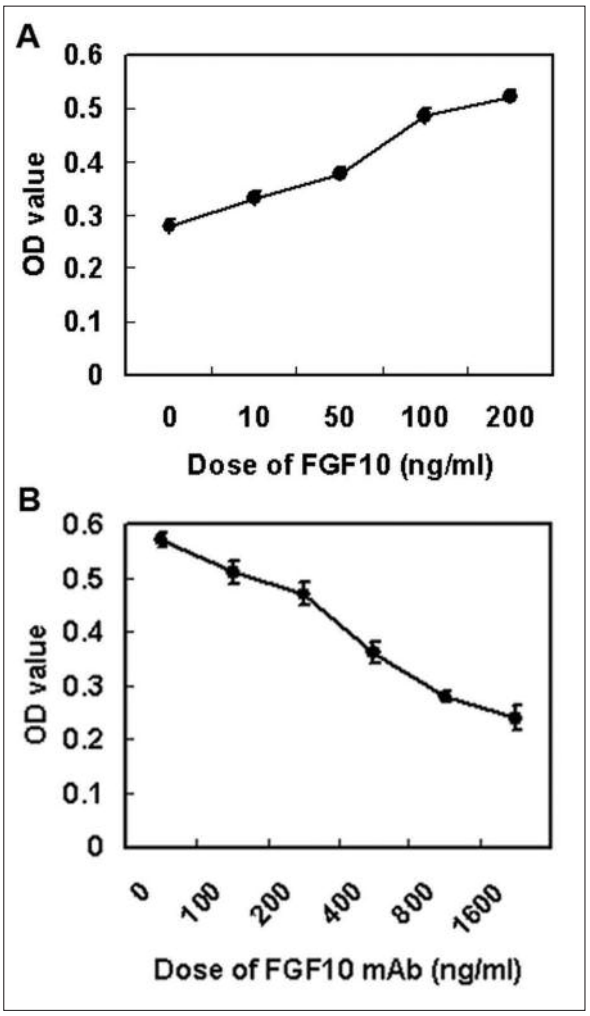

Figure 1. Anti-FGF10 inhibits HaCaT cell proliferation *in vitro*. HaCaT cells were treated in triplicate with the indicated doses of FGF10 or with 200 ng.ml of FGF10 in the presence or absence of different doses of anti-FGF10 for 72 h. The cell proliferation was measured by MTT assays. The average optical density (OD) value was expressed as the mean ± SEM of each group of cells from five separate experiments. ***A,*** FGF10 stimulated HaCaT cell proliferation in vitro. ***B,*** Anti-FGF10 inhibited the FGF10-stimulated HaCaT cell proliferation *in vitro*. *$p < 0.05$, **$p < 0.01$ vs. the control cells without FGF10 or without anti-FGF10 treatment.

ation in a dose-dependent manner. Furthermore, we stimulated HaCaT cells with 200 ng/mL of FGF10 in the presence or absence of different concentrations of anti-FGF10 2G6. We found that treatment with different doses of anti-FGF10 2G6 inhibited FGF10-stimulated HaCaT cell proliferation also in a dose-dependent manner (Figure 1B). Treatment with 100 or 200 ng/ml anti-FGF10 treatment significantly inhibited FGF10-stimulated HaCaT cell proliferation ($p < 0.05$ vs. the cells treated with FGF10 alone), and treatment with a higher dose (400, 800, or1600 ng/ml) of anti-FGF10 resulted in more significant inhibition of HaCaT cell proliferation ($p < 0.01$ vs. the cells treated with FGF10 alone). Therefore, the 2G6 mAb has potent anti-FGF10 activity *in vitro.*

Anti-FGF10 Mitigates Inflammation and Pathogenic Changes in Chemical-Induced Psoriasis-Like Lesions in Guinea Pig

Keratinocyte over-proliferation is associated with the pathogenesis of psoriasis. Next, we tested the hypothesis that treatment with anti-FGF10 2G6 after chemical induction of psoriasis-like lesions could mitigates inflammation and pathogenic changes in chemical-induced psoriasis-like lesions in guinea pig. Guinea pigs were topically exposed to 5% propranolol emulsion on the back of their ears, and control animals were exposed to control vehicle. We observed that the auricular areas of experimental animals displayed slight desquamation three days after induction, and eschar one week after induction. These areas presented with a typical psoriasis-like lesion and with edema, telangiectasia, dry skin/desquamation, and increased skin thickness (Figure 2A). Histological examination showed increased thickness of epidermis and many inflammatory infiltrates in the lesions at three weeks post induction.

The experimental animals were randomly treated topically with PBS, hydrocortisone butyrate, or different doses of anti-FGF10 daily beginning at one week post induction and continually for two weeks. We found that in comparison with that in the PBS-treated animals, treatment with hydrocortisone butyrate or anti-FGF10 greatly reduced the psoriasiform-related edema, telangiectasia, and dry skin/desquamation in the tested areas at three weeks post induction (Figure 2B). However, there was no parakeratosis or munro abscess in the lesions of different groups of animals.

Histological analysis indicated that the skin tissues form the healthy controls showed a regular length of rete ridges, granular cell layer (1-3 layers), and acanthosis (3-6 layers) with a few monocytes in the dermis, the tissue samples from the PBS-treated model group of animals displayed hyperkeratosis, reduced numbers of granular cell layers (≤ 1 layer), increased thickness of acanthosis (13-24 layers) and irregular

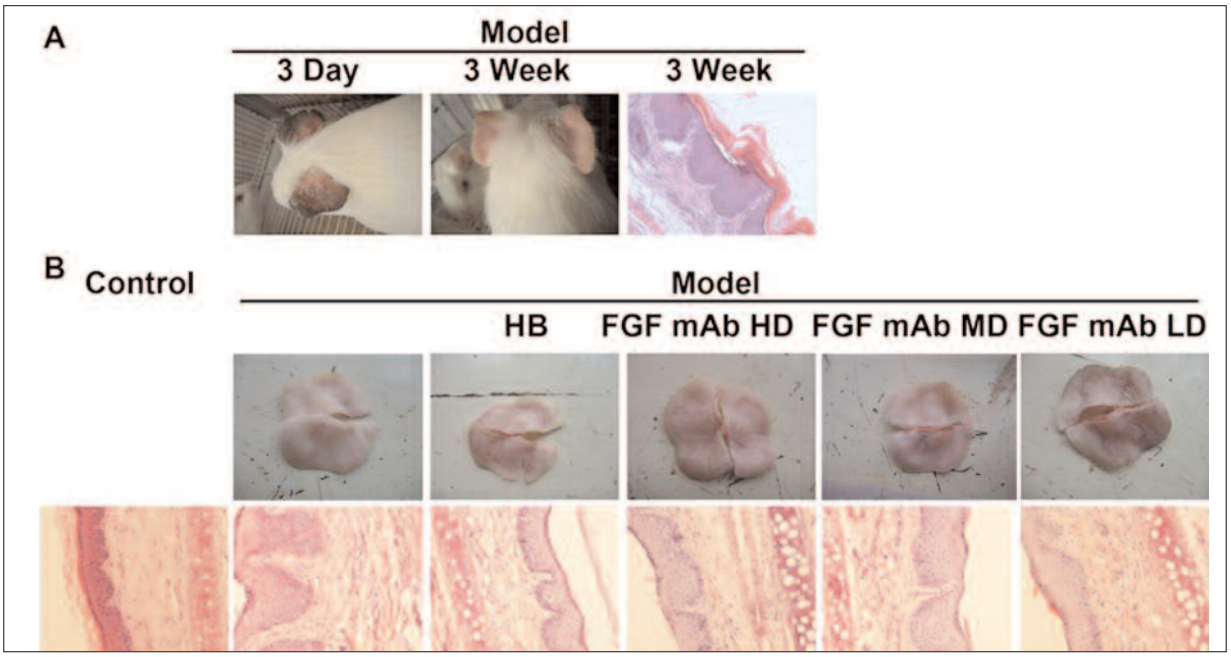

Figure 2. Pathologic examination of psoriasis-like lesions. Guinea pigs were topically treated with 5% of propranolol emulsion on the back of their ears to induce psoriasis-like lesions and randomly treated topically with PBS, hydrocortisone butyrate, or different doses of anti-FGF10. The pathologic changes and the degrees of inflammation in the auricular areas of individual animals were examined histologically. ***A,*** The morphology of auricular psoriasis-like lesions was examined at 3 days or 3 weeks post propranolol treatment, and tissue sections were examined at 3 weeks post induction (magnification: ×100). ***B,*** The gross and histological examination of psoriasis-like lesions at two weeks post treatment (magnification: ×200). The upper panels (a-e): the gross tissues; The low panels (f-k): histological examination (Magnification: ×200). HB, hydrocortisone butyrate group; HD, high dose (0.188 mg/ml); MD, medium dose (0.094 mg/ml); LD, low dose (0.063 mg/ml). n = 4-5 for each group at each time point. The monocyte infiltrates are indicated by arrowheads and the thickness of epidermis is indicated by arrows.

lengths of rete ridges, accompanied by many inflammatory infiltrates in the dermis, increased thickness of epidermis, and telangiectasia in the lesions (Figure 2B, Table II). Quantitative analyses revealed that treatment with hydrocortisone butyrate or anti-FGF10 at any of the doses significantly reduced the thickness of epidermis, the number of inflammatory infiltrates (monocytes) in the dermis, and Baker's scores, as compared with that in the model group ($p < 0.05$, Table II). It was notable that the numbers of inflammatory infiltrates in the dermis in the anti-FGF10-treated mice were similar to that of the healthy controls ($p > 0.05$), suggesting that anti-FGF10 may suppress the proliferation and migration of inflammatory cells and the release of inflammatory cytokines. These observations indicate that anti-FGF10 mitigates inflammation and pathogenic changes in chemical-induced psoriasis-like lesions in guinea pig.

Table II. The pathological changes of the corneous layer, epidermis and dermis in the lesions from different groups of animals.

Groups	Baker's Score	The number of monocytes	Thickness of epidermis (mm)
Control	2.25 ± 0.26	76.00 ± 9.82	65.21 ± 11.62
Model	6.31 ± 0.73**	114.57 ± 8.77*	128.95 ± 10.73**
Model + HB	4.53 ± 0.67**.##	89.85 ± 12.12*.##	97.60 ± 19.56**.#
Model + FGF mAb HD	4.83 ± 0.75**.##	73.82 ± 8.82##	115.26 ± 17.35**.#
Model + FGF mAb MD	4.94 ± 0.68**.##	90.37 ± 14.84*.##	118.52 ± 16.21**.#
Model + FGF mAb LD	5.17 ± 0.75**.##	97.56 ± 13.62*.##	109.40 ± 12.84**.#

HB: hydrocortisone butyrate group; HD: high dose (0.188 mg/ml); MD: medium dose (0.094 mg/ml); LD: low dose (0.063 mg/ml). *$p < 0.05$, **$p < 0.01$ vs. the healthy control; #$p < 0.05$, ##$p < 0.01$ vs. the model group. n = 9 for each group.

Discussion

It is well known that excessive growth and aberrant differentiation of keratinocytes contribute to the pathological process of psoriasis[2]. Previous studies have shown that FGF10 is an important regulator of keratinocyte proliferation, differentiation, and migration[5,6], and its over-production is associated with the development of psoriasis[11]. To further study the function of FGF10 in keratinocyte proliferation and psoriasis formation, we generated a new mAb against FGF10 with a titer of 1:12800. The successful production of anti-FGF10 provides a unique reagent for studying the function of FGF10 blockage in keratinocyte proliferation *in vitro* and the development of psoriasis-like lesions *in vivo*.

Human keratinocyte line, HaCaT, has been widely used as a model of a highly proliferative epidermis[12], and we cultured HaCaT cells to evaluate the potential effect of anti-FGF10. We found that treatment with different doses of FGF10 stimulated HaCaT cell proliferation in a dose-dependent manner, consistent with previous findings[5,6]. Given that FGF10 is produced by keratinocytes[13], FGF10 may stimulate keratinocyte proliferation in an autocrine fashion. More importantly, we found that treatment with varying doses of anti-FGF10 inhibited the FGF10-stimulated human keratinocyte proliferation also in a dose-dependent manner. These data demonstrated that anti-FGF10 effectively neutralized the activity of FGF10 and inhibited keratinocyte proliferation *in vitro*.

It is well known that FGF10 expression is upregulated in the upper dermis of psoriatic skin and that the levels of FGF10 in the lesions are correlated with keratinocyte proliferation and the severity of inflammatory infiltrates in the lesions[7]. On the other hand, $FGF10^{-/-}$ mice display abnormal epidermal morphogenesis[8]. Apparently, FGF10 may promote the growth of keratinocytes in psoriasis and aberrant keratinocyte proliferation contributes to the development of psoriasis-like lesions. We tested the potential therapeutic effect of anti-FGF10 on the propranolol-induced psoriasis-like lesions and we found that treatment with anti-FGF10, like hydrocortisone butyrate, greatly inhibited the severity of psoriasis-like lesions by reducing the Baker's scores, the thickness of epidermis, and the numbers of monocyte infiltrates in the dermis of the animals. To the best of our knowledge, this was the first study to demonstrate that treatment with anti-FGF10 effectively mitigated inflammation and propranolol-induced psoriasis-like lesions in animals. The significant reduction in the numbers of inflammatory infiltrates in the lesions may stem from inhibition of FGF-10-promomted chemokine production and inflammatory cell migration in this model. Indeed, significantly higher levels of serum tumor necrosis factor α (TNF-α), interferon-γ (IFN-γ), interleukin (IL)-6, IL-8, IL-12, and IL-18 are detected in active psoriatic patients, related to that in controls[14]. Treatment with anti-TNF-α mAb markedly decreases the clinical activity of psoriasis lesions[15]. It is well known that many inflammatory factors contribute to the development and progression of psoriasis and these factors may synergistically promote the development of psoriasis[16]. Indeed, both IL-17a and TNF-α can synergistically induce the production of CXCL8 and β-defensin 2 (BD2) during the development of psoriasis lesions[17]. Treatment with anti-FGF10 alone inhibited inflammation and partially reduced inflammation-related epidermal thickness in this model. It is possible that anti-FGF10 may neutralized FGF10 and inhibit its effect on promoting keratinocyte proliferation, leading to less amount of cytokine and chemokine production. Therefore, anti-FGF10 may be used as an adjuvant therapeutic reagent, in combination with other drugs, such as glucocorticoids and retinoic acids. We are interested in further investigating the combination therapies for the intervention of psoriasis-like lesions, how neutralization of FGF10 by anti-FGF10 affects cytokine and chemokine production in keeratinocytes and the potential mechanisms by which anti-FGF10 inhibits inflammatory cell infiltration in the psoriasis-like lesions.

Conclusions

We have successfully generated mouse mAb against FGF10 and found that treatment with anti-FGF10 inhibited FHF10-stimulated keratinocyte proliferation in a dose-dependent manner *in vitro*. Furthermore, we found that topical treatment with anti-FGF10 effectively mitigated inflammation and propranolol-induced psoriasis-like lesions in animals. Our findings may provide a proof of principle that the blockage of local FGF10 can inhibit keratinocyte proliferation and mitigate propranolol-induced psoriasis-like lesion. These observations may offer new basis to design new immunotherapies for the intervention of psoriasis in the clinic.

Acknowledgements

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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