Original Article
Effect of FGF10 monoclonal antibody on psoriasis-like model in guinea pigs

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Abstract: Objective: To investigate the therapeutic effect of topical application of FGF10 monoclonal antibody on the guinea pig model with psoriasis. Methods: Blank group, model group, hydrocortisone butyrate treatment group and high-dose (0.188mg/ml), middle-dose (0.094mg/ml) and low-dose (0.063mg/ml) FGF10 antibody group were set, respectively. After two-week treatment, pathological changes of psoriasis-like models were observed by HE staining, and the difference in VEGF and PCNA expression levels among different groups was observed by immunohistochemical staining. Results: All the test indicators of each treatment group were lower than those of the model group, and there was a significant difference ($P<0.05$). The inflammatory cell count of the high-dose FGF10 antibody group was not statistically different from those of the blank group (t=0.77, $P=0.443$), and the counts of the rest treatment groups were significantly higher than those of the blank group and the high-dose FGF10 antibody group ($P<0.05$). The epidermal thickness of each FGF10 antibody treatment group was significantly higher than that of hydrocortisone butyrate treatment group ($P<0.05$), while no statistical difference was found in the epidermal thickness among the FGF10 antibody treatment groups ($P>0.05$). FGF10 monoclonal antibodies can reduce the PCNA and VEGF expression in psoriasis-like model of guinea pig's ear. Conclusion: FGF10 monoclonal antibodies can affect keratinocyte proliferation and division and can also significantly inhibit the inflammatory response in the psoriasis model. Meanwhile, FGF10 monoclonal antibodies can produce a therapeutic effect on psoriatic lesions by inhibiting the abnormal epidermis cell proliferation and neovascularization of the dermis in the psoriasis model.

Keywords: FGF10, FGF10 monoclonal antibodies, psoriasis, PCNA, VEGF

Introduction

Psoriasis is a kind of chronic inflammatory disease characterized by epidermal hyperplasia, and the incidence in natural population is approximately 1%-3% [1]. Its main pathological features include abnormal epidermal dysplasia, infiltration of a large number of inflammatory cells in the dermis and neovascularization. T cell and dendritic cell as well as cytokines and inflammatory mediums (e.g.: NF-α, IL- 8, IL- 12, IL- 22 and IL- 23) are all involved in the pathogenesis of psoriasis, and play an important role in inducing the proliferation of psoriatic keratinocytes [1, 2]. Indeed, the proliferation of keratinocytes is regulated by several cytokines, such as epidermal growth factor, transforming growth factor-a, fibroblast growth factors (FGFs) and so on. Among them, FGF10 and FGF7 are the key cytokines for regulating the proliferation and differentiation of keratinocytes, and

have an increased expression in psoriatic lesions [3]. Proliferating cell nuclear antigen (PCNA) is a cofactor of DNA polymerase δ in the process of DNA synthesis of eukaryotic cells. It is closely related with cell repair and proliferation and can detect the content of PCNA in cells. Thereby, it can be used as an indicator for assessment of the degree of cell proliferation [4]. Vascular endothelial growth factor (VEGF) is the strongest vascularization promoting factor currently, and it is secreted mainly by the epidermal keratinocytes and the vascular endothelial cells of the superficial dermis in the skin and overexpressed in the psoriatic lesions [5]. In this study, fibroblast growth factor-10 (FGF10) monoclonal antibody is used to perform the intervention in guinea pig model with psoriasis, thus observing the effect of FGF10 monoclonal antibody on the abnormal pathological changes and the expression of PCNA and VEGF in guinea pig model with psoriasis and exploring the therapeutic effect of FGF10 monoclonal antibody.

Materials and methods

Preparation of propranolol hydrochloride liniment and dilution of the antibody

5g propranolol hydrochloride was taken and dissolved in 50% ethanol. 5ml laurocapram-propanediol as the skin penetration enhancer and 5g polyvinylpyrrolidone (PVPK30) as the film-forming material were added into the solution above. The obtained solution was diluted to 100ml with 50% ethanol to prepare propranolol hydrochloride liniment [6] which was then stored in a refrigerator at 4 °C for use. The purified FGF10 monoclonal antibody (3.76mg/ml) was taken out from the refrigerator at -20 °C and recovered in a water bath at 37 °C. It was then blended into the pre-weighed Vaseline medium, and given 20-fold, 40-fold and 60-fold dilution. Finally, this solution was packaged individually and stored in a refrigerator at 4 °C for use.

Preparation of animal models

60 guinea pigs were pre-fed for a week (during the entire feeding period, ample supply of vegetables were provided) to adapt to the environment. After a week, in addition to the blank control group, the animal models of psoriasis were prepared as per the method in the literature [7], and the steps were as follows: the prepared 5% propranolol hydrochloride liniment was evenly applied onto the back of the ears in guinea pigs, qid, for consecutive 3 weeks. After 3 weeks, 6 guinea pigs were randomly sacrificed, and 12 auriculae of the ears were taken, embedded in paraffin and given HE staining. The histological changes were observed to determine whether the establishment of the models was successful. After a successful establishment of the models, the next step of the experiment can be conducted.

Grouping of guinea pigs

The remaining 54 guinea pigs were randomized into six groups: blank group, model group, hydrocortisone butyrate treatment group, 20-fold dilution group (0.188mg/ml), 40-fold dilution group (0.094mg/ml) and 60-fold dilution group of FGF10 monoclonal antibody (0.063mg/ml), and 9 guinea pigs were included in each group. Except the model and blank group, all the other groups received the drug based on the grouping above. The drug was applied onto the back of ears in guinea pigs once in the morning and once in the evening for consecutive 2 weeks. After end of medication, guinea pigs were killed with 3% pentobarbital. The auriculae of the ears were taken, and fixed in 10% formalin for 24h and then embedded in paraffin.

HE staining and immunohistochemical staining

The tissue block embedded in paraffin was sectioned and then given HE staining and immunohistochemical staining, in which, the dropped primary antibodies were PCNA and VEGF.

Observations

The response of guinea pigs to the drugs for modeling and that for treatment was observed, and scratching and bending, hair and skin condition (smooth, coarse or scaly) were recorded.

One section was made for each auricula of the ears in each guinea pig. 3 visual fields were randomly selected under a light microscope (20×10), and Baker scoring was performed for the selected visual field [8]. Baker score is set based on the pathological changes of psoriasis, such as the absence and presence of hyperkeratosis, parakeratosis, micro-abscesses, acanthosis, granular layer thinning, vascular proliferation and inflammatory cell infiltration as well as their severity. Baker score is recorded as 0 without any changes above, and as 0.5-2 according to the severity in case of any changes above, and the maximum score is recorded as 10. IDA2000 digital image analysis system was adopted to perform inflammatory cell count and epidermal thickness measurement (mm).

Positive immunohistochemical staining showed faint yellow to sepia granules in the cytoplasm or nucleus. Under a 20×10 light microscope, 5 visual fields were selected randomly from the proximal to distal ear in guinea pigs (including the epidermis). 200 cells were counted for each visual field, and the results were expressed with the mean value. Scoring was performed according to the staining degree of the cytoplasm or nucleus, and the scores were recorded as follows: 0 score in the absence of color, 1 score in case of faint yellow, 2 scores in case of
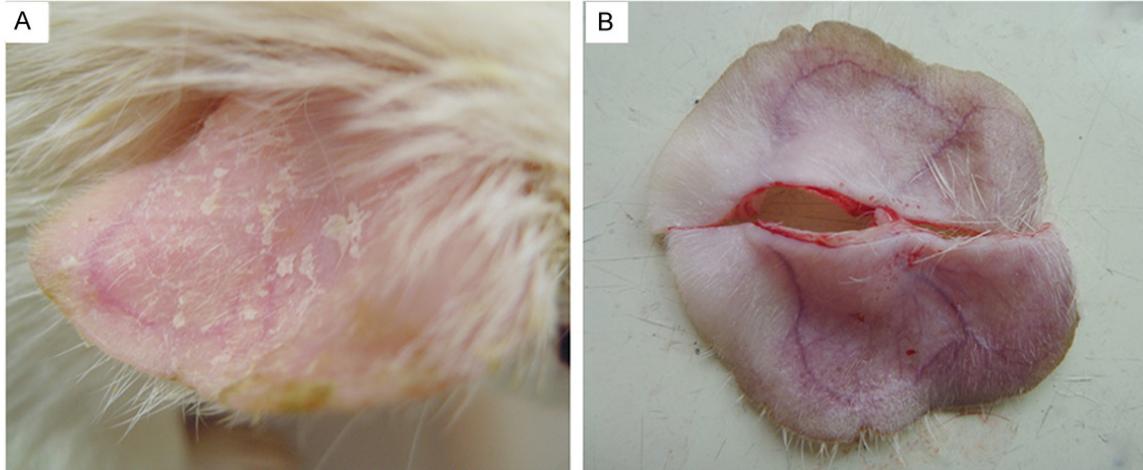
Figure 1. A: Large numbers of scales were found in the back skin of ears of guinea pigs at 3-week modeling and suspected as psoriasis. B: Psoriasis-like lesions disappeared in 20-fold dilution group of FGF10 monoclonal antibody after 2-week treatment.

brown orange, 3 scores in case of sepia and 4 scores in case of puce. Moreover, scoring was conducted based on the proportion of stained cells, and the scores were recorded as follows: 0 score when the proportion was 0-25%, 1 score when 26-50%, 2 scores when 50-75%, and 3 scores when 76-100%. The integrals of the two indexes above were summed, and the scores obtained were graded: 0-1 score was recorded as (-), 2-3 scores as (+), 4-5 scores as (++) and 6-7 scores as (+++).

Statistical analysis

SPSS 13.0 was adopted for statistical analysis. The rank sum test was used for comparison of independent ranked data in multiple groups. ANOVA was employed for comparison of mononuclear cell count and epidermal thickness. The least significant difference (LSD) was used for pairwise comparison of the mean values of the multiple samples. The data rank conversion, homogeneity test of variances and LSD test were performed in sequence for intergroup pairwise comparison of the integral of immunohistochemical staining results. $P<0.05$ was considered statistically significant. Measurement data were expressed as $\overline{X}\pm s$.

Results

Gross observations

Response to the drug for modeling: after applying propranolol liniment, the guinea pigs showed scratching and bending reactions frequently on the day, and had a higher local skin temperature. Moreover, the obvious hair loss and escharosis of the auricula was found after three days, and after one week, the psoriasis-like lesions, significant desquamation, angiotelectasis and thickened skin were found in the auricula of guinea pigs. The above-mentioned changes in the auricula of guinea pigs were still sustained until the end of three-week model establishment (**Figure 1A**).

Response to the drug for treatment: the frequency of scratching and bending reactions significantly reduced during treatment. After applying FGF10 antibody and hydrocortisone butyrate for a week, the auricular skin of guinea pigs became obviously smooth, and desquamation reduced or even disappeared compared with the model group. After treating for two weeks, the psoriasis model disappeared in the auricular skin of guinea pigs by visual inspection (**Figure 1B**).

HE staining

Under a light microscope, no Munro's microabscess and parakeratosis were found in all the experiment groups, but the pathological changes were not consistent. In the blank group, spinous layer included 3-6 layers in thickness, and granular layer included 1-3 layers; trochanterellus was flat, and the mononuclear cells were few in the epidermis (**Figure 2A**). In the model group, hyperkeratosis and reduced granular
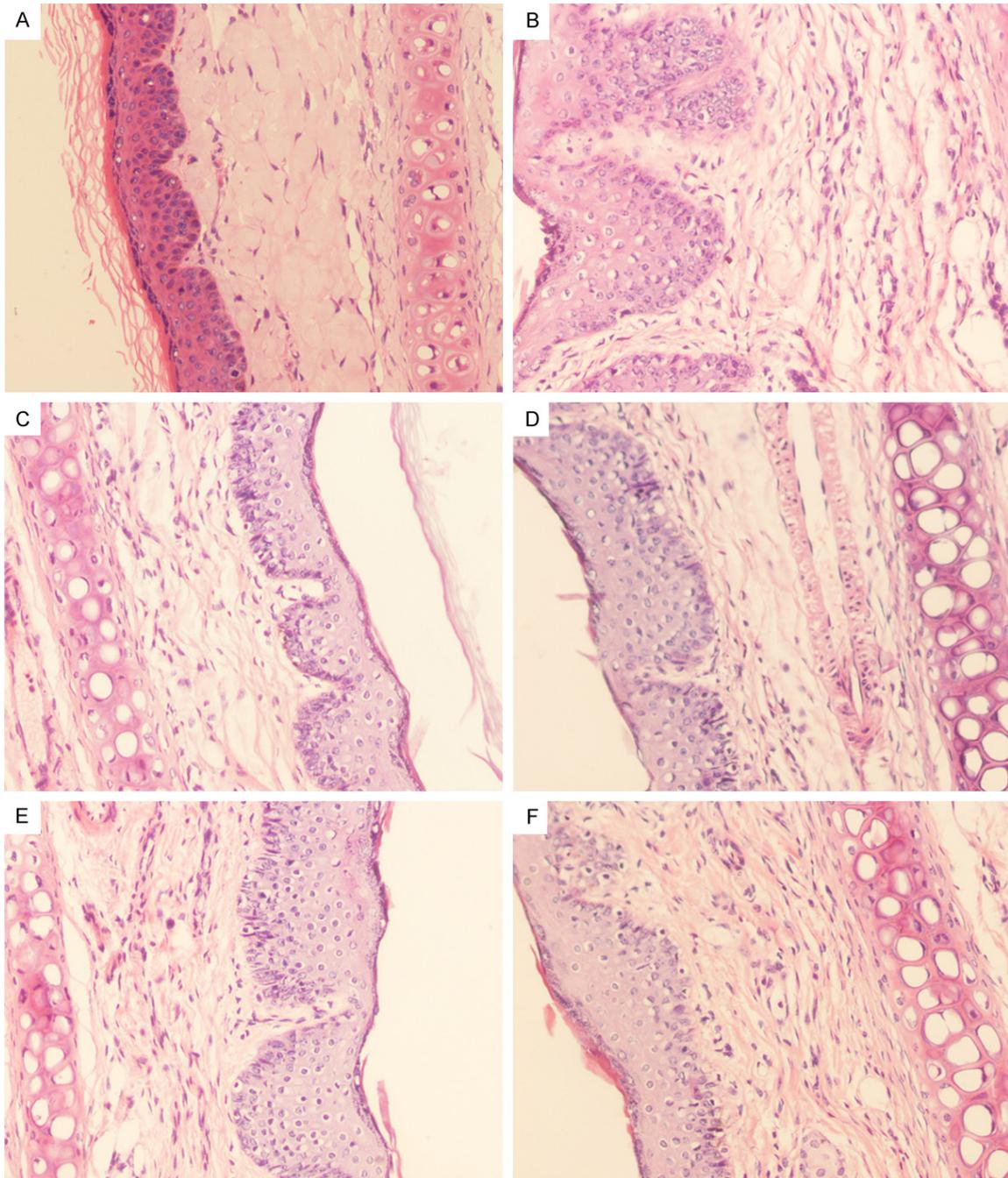
Figure 2. A: In the blank group, spinous layer included about 3-6 layers in thickness, and granular layer included 1-3 layers; trochanterellus was flat, and the mononuclear cells were less in the epidermis (HE×200). B: In the model group, thickened epidermis, prolonged obviously trochanterellus and obvious inflammatory cell infiltration in the dermis were found (HE×200). C: In hydrocortisone butyrate treatment group, the lower epidermis thickening degree compared with the model group, flat epithelium and alleviated inflammatory cell infiltration (HE×200). D: In 20-fold dilution group of FGF10 antibody, the epidermal thickness was in the middle between the model group and hydrocortisone butyrate treatment group, and the epithelium became flat, and the inflammatory cell infiltration was fewer (HE×200). E: In 40-fold dilution group of FGF10 antibody, the epidermal thickness was in the middle between the model group and hydrocortisone butyrate treatment group, and the epithelium became flat, and the inflammatory cell infiltration increased compared with 20- fold dilution group (HE×200). F: In 60-fold dilution group of FGF10 antibody, the epidermal thickness was in the middle between the model group and hydrocortisone butyrate treatment group, and the became flat, and the inflammatory cell infiltration increased compared with 40-fold dilution group (HE×200).

Table 1. Baker score, mononuclear cell count and epidermal thickness ($\bar{X}\pm s$)

Groups	n	Baker score	Mononuclear cell count (/5.79mm^2)	Epidermal thickness (mm)
Blank group	18	2.25±0.26	76.00±9.82	65.21±11.62
Model group	18	6.31±0.73[a]	114.57±8.77[a]	128.95±10.73[a]
Hydrocortisone butyrate group	18	4.53±0.67[a,c]	89.85±12.12[b,c]	97.60±19.56[a,c]
20-fold dilution group of FGF10	18	4.83±0.75[a,c]	73.82±8.82[c,e]	115.26±17.35[a,d,e]
40-fold dilution group of FGF10	18	4.94±0.68[a,c]	90.37±14.84[a,c,f]	118.52±16.21[a,d,e]
60-fold dilution group of FGF10	18	5.17±0.75[a,c,e]	97.56±13.62[a,c,e,f]	109.40±12.84[a,c,e]

Footnote: compared with the blank group, [a]$P<0.01$, [b]$P<0.05$; compared with the model group, [c]$P<0.01$, [d]$P<0.05$; compared with the hydrocortisone butyrate group, [e]$P<0.05$; and compared with 20-fold dilution group of FGF10 monoclonal antibody, [f]$P<0.01$.

layer (≤1) were found, and the spinous layer was significantly thickened to 13-24 layers; in addition, trochanterellus was prolonged obviously, and the mononuclear cells and angiotelectasis in the epidermis increased (**Figure 2B**). In the hydrocortisone butyrate treatment group, the epidermal thickness was significantly thinner than that in the model group, and the number of the mononuclear cells declined (**Figure 2C**). In the FGF10 treatment group, different biological activities were reflected due to different concentrations (**Figure 2D-F**, **Table 1**).

Difference in Baker score of the experiment groups

As shown in the experiment results, the maximum and minimum Baker scores were found in the model group and the blank group, respectively, and the Baker score in the treatment groups was between them. The rank sum test showed that the score of the model group significantly increased than that of the blank group, and the difference was significant ($P<0.01$, t=13.16). It also suggested that the score of each treatment group (20-fold dilution group, 40-fold dilution group and 60-fold dilution group of FGF10 monoclonal antibody as well as the hydrocortisone butyrate treatment group) was lower than that of the model group, and the difference was statistically significant ($P<0.01$, t=6.01, t=5.47, t=4.28 and t=7.33); moreover, the scores of the treatment groups were higher than that of the blank group, and there was a significant difference ($P<0.01$, t=7.14, t=7.68, t=8.87 and t=5.83). The differences increased gradually between 20-fold dilution group, 40-fold dilution group with 60-fold dilution group of FGF10 monoclonal antibody and the hydrocortisone butyrate treatment group ($P>0.05$, t=1.32; $P>0.05$, t=1.86;

$P<0.05$, t=3.04, respectively), and the Baker scores gradually declined with the increase of the concentrations of FGF10 monoclonal antibody.

Difference in mononuclear cell count of the experiment groups

The maximum and minimum mononuclear cell count infiltrated in the dermis was found in the blank group and the model group, respectively, and the mononuclear cell count infiltrated in the dermis in the treatment groups was between them. The results of pairwise comparison of the mean value for multiple samples by LSD method showed that the mononuclear cell count of the treatment groups was lower than that of the model group, and the difference was significant ($P<0.01$, t=10.73, t=6.25, t=4.39 and t=6.52), indicating that hydrocortisone butyrate and FGF10 monoclonal antibody can reduce the mononuclear cell count infiltrated in the dermis in the animal model of psoriasis. There was not a statistical difference in the mononuclear cell count between 20-fold dilution group of FGF10 monoclonal antibody and the blank group (t=0.77, $P<0.05$), indicating that FGF10 monoclonal antibody after 20-fold dilution can reduce the mononuclear cell count infiltrated in the dermis to the normal level.

Difference in epidermal thickness of the experiment groups

The minimum and maximum epidermal thickness was found in the blank group and the model group, respectively, and the epidermal thickness in the treatment groups was between them. The results by LSD method showed that the epidermal thickness of all the treatment groups became thinner than that of the model
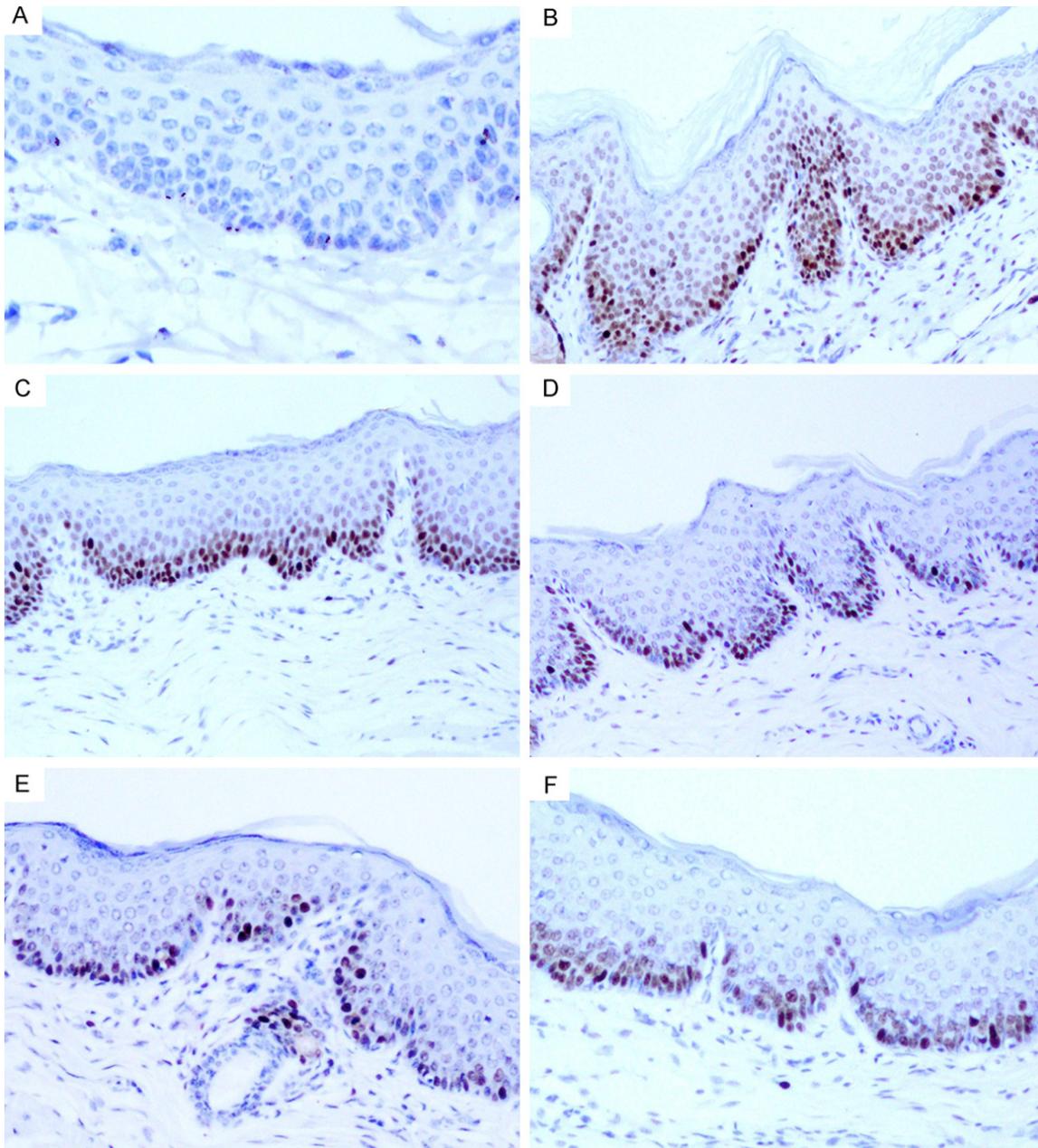
Figure 3. A: PCNA expression in the blank group: only a small amount of PCNA expression occurred in the basal layer, and little expression occurred in the spinous layer (DAB×200). B: PCNA expression in the model group: PCNA expression occurred widely in the entire epidermis layer with a deeper staining (DAB×200). C: PCNA expression in 60-fold dilution of FGF10 antibody: PCNA expression occurred in the basal layer and the lower spinous layer (DAB×200). D: PCNA expression in 40-fold dilution of FGF10 antibody: PCNA expression occurred in the basal layer and the lower spinous layer (DAB×200). E: PCNA expression in 20-fold dilution of FGF10 antibody: PCNA expression occurred only in the basal layer (DAB×200). F: PCNA expression in hydrocortisone butyrate group: PCNA expression occurred in the basal layer and the lower spinous layer (DAB×200).

group, and the difference was statistically significant ($P<0.05$ t=2.72, t=2.07, t=3.89 and t=6.23); the epidermal thickness of 20-fold dilution group, 40-fold dilution group and 60-fold dilution group of FGF10 monoclonal antibody was thickened compared with the hydrocortisone butyrate group, and the difference was statistically significant ($P<0.05$, t=3.51, t= 4.16 and t=2.35). However, the comparison among the different FGF10 monoclonal

Table 2. PCNA expression of each group

Groups	Frequency	Grade			
		(-)	(+)	(++)	(+++)
Blank group	18	15	3	0	0
Model group	18	0	3	5	10
Hydrocortisone butyrate group	18	1	16	1	0
Treatment with high-dose FGF-10	18	13	5	0	0
Treatment with middle-dose FGF-10	18	0	15	2	1
Treatment with low-dose FGF-10	18	0	11	6	1
Total	108	29	53	14	12

antibody groups showed that the difference was not statistically significant (*P*>0.05), indicating that FGF10 monoclonal antibody at different concentrations did not produce different impacts in improving the epidermal thickness.

Expression of PCNA in the experiment groups

PCNA expression occurs in the nucleus. PCNA expression in the blank group mainly occurred in the basal layer, and the expression amount was lower in the spinous layer (**Figure 3A**). The expression significantly increased in the model group and treatment groups (**Figure 3B-F** and **Table 2**). The inter-group pairwise comparison by LSD method showed that the PCNA expressions of the blank group and the treatment groups were all lower than that of the model group, and the difference was statistically significant (all *P*<0.05); the comparison among the treatment groups with different doses of FGF10 antibody showed that PCNA had a lower expression in the high dose group compared with the low dose group, and the difference was statistically significant (*P*=0.000, *P*=0.000, *P*=0.013 and *P*<0.05, respectively). The comparison in PCNA between the high dose of FGF10 monoclonal antibody and the blank group showed that the results were not statistically different (*P*=0.123), indicating that the proliferation degree of keratinocyte decreased significantly (**Table 2**).

Expression of VEGF in the experiment groups

VEGF expression occurs in the cytoplasm. VEGF expression was not found in the blank group or only fewer expressions existed in the basal layer (**Figure 4A**). The expression significantly increased in the model group and treatment groups (**Figure 4B-F** and **Table 3**). The inter-group pairwise comparison by LSD method

showed that the VEGF expressions of the blank group and the treatment groups were all lower than that of the model group, and the differences were statistically significant (all P<0.05); VEGF had a lower expression in the high dose group compared with the low dose group, and the difference was statistically significant (P<0.05). The comparison in VEGF between the high dose group and the middle dose group as well as the low dose group and hydrocortisone butyrate group showed that the results were not statistically different (P>0.05). All the results indicated that, after establishment of the model, VEGF expression in the model increased obviously and decreased after treatment, and FGF10 monoclonal antibody had a negative effect on the VEGF expression in psoriasis-like guinea pig model (**Table 3**).

Discussion

Psoriatic lesions are induced mainly by the abnormal keratinocyte proliferation and division. Besides T cells, dendritic cell and cytokines, fibroblasts in the dermis also play an important regulating role in keratinocyte proliferation [9-11]. These cells can maintain the epithelial morphology and resist the ultraviolet injury by producing FGFs which is then combined with keratinocyte growth factor receptor (KGFR). However, when the pathological FGFs increases, excessive proliferation and activation of keratinocyte may be caused [12]. Activated keratinocytes can further express vascular endothelial growth factor (VEGF) to participant in the early angiogenesis of psoriasis model, which is an indispensable precipitating factor of the pathogensis of psoriasis [13, 14]. FGF10 and FGF7 of FGFs family are the two most important factors for regulating keratinocyte growth and differentiation and play an important role in the skin damage and repair [3]. Studies have found that FGF10 has an obviously increased expression in the lesions of psoriasis vulgaris patients, and it is inferred that FGF10 may be involved in the abnormal proliferation of epidermal cells in the psoriatic lesions [15]. Proliferating Cell Nuclear Antigen (PCNA) can be referred to measure the level of
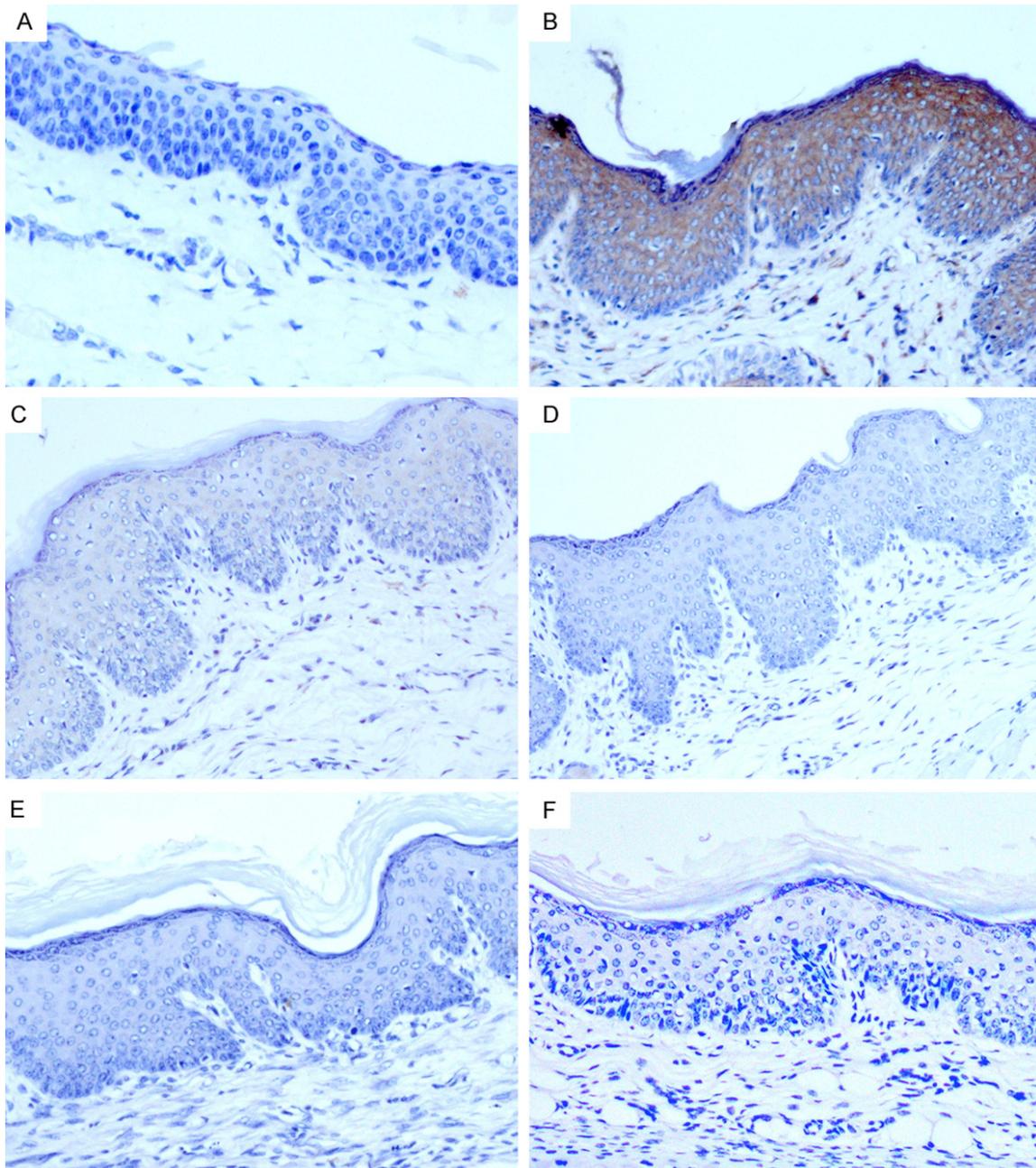
Figure 4. A: VEGF expression in the blank group Little VEGF was expressed (DAB×200). B: VEGF expression in the model group VEGF was expressed in the entire epidermis layer with a deeper staining (DAB×200). C: VEGF expression in 60-fold dilution of FGF10 antibody VEGF was expressed mainly in the middle to upper spinous layer with a lighter staining (DAB×200). D: VEGF expression in 40-fold dilution of FGF10 antibody VEGF was expressed mainly in the middle to upper spinous layer with a lighter staining (DAB×200). E: VEGF expression in 20-fold dilution of FGF10 antibody. A small amount of VEGF was expressed in the upper spinous layer with a lighter staining (DAB×200). F: VEGF expression in hydrocortisone butyrate treatment group. A small amount of VEGF was expressed in the upper spinous layer with a lighter staining (DAB×200).

the cell proliferation, and PCNA synthesis and expression level is a more sensitive indicator for reflecting cell proliferation. We adopted FGF10 monoclonal antibody to intervene the guinea pig model of psoriasis, and the results suggested that this antibody can improve the psoriatic lesion, inhibit the inflammatory cell infiltration and keratinocytes proliferation in

Table 3. VEGF expression in each group

Groups	Frequency	Grade			
		(-)	(+)	(++)	(+++)
Blank group	18	16	2	0	0
Model group	18	0	2	6	10
Hydrocortisone butyrate group	18	1	2	12	3
Treatment with high-dose FGF-10	18	2	11	5	0
Treatment with middle-dose FGF-10	18	0	13	5	0
Treatment with low-dose FGF-10	18	0	7	10	1
Total	108	19	37	38	14

the psoriatic lesion and produce a negative effect on the PCNA and VEGF expression in the dermis by the topical method.

Some previous experimental studies confirmed that the expression of KGF and KGFR increased in psoriatic lesions, and the expression of fibroblast growth factor receptor KGFR was down-regulated by UVB irradiation to the psoriatic lesion, thus better improving the psoriasis state [12]. In the present study, it was found that FGF10 monoclonal antibody can significantly improve the lesion state of the guinea pig model of psoriasis, which may be related with decreased combination of FGF10 and the receptor. Baker score indicated that FGF10 monoclonal antibody had a similar effect on psoriasis as hydrocortisone butyrate, and it was found that FGF10 monoclonal antibody had a dose-dependent improvement on the model of psoriasis, that is, the improvement effect on psoriasis was more obvious with an increase of the concentration. However, interestingly, for the effect on psoriasis-like lesion, the epidermal thickness changes in FGF10 monoclonal antibody group was statistically different from those in the model group, but the improvement of the epidermal thickness was weaker than that in hydrocortisone butyrate treatment group, and a dose-dependent improvement was not exhibited among all the FGF10 monoclonal antibody groups. This result indicated that FGF10 monoclonal antibody was beneficial to improvement of the epidermal thickness in psoriasis animal, but it alone was not enough to improve the epidermal thickness on the one hand. On the other hand, FGF10 monoclonal antibody had an overall dose-dependent improvement on the model of psoriasis, indicating that it can not only inhibit the keratinocyte growth, but also improve the pathological changes in psoriasis animal from other

aspects. Some experiments suggested that FGF10 was mainly expressed in the connective tissues at the dermal-epidermal junction and fewer expressions occurred in keratinocytes; meanwhile, most FGF10 expressions showed a sustained increase after seven days, which also suggested that FGF10 had other effects [16]. In the present study, we also found that FGF10 monoclonal antibody can significantly decrease the number of inflammatory cells in the dermis in a dose-dependent manner, and its inhibitory effect on inflammatory cells was stronger than that of hydrocortisone butyrate. It was also found that the inflammatory cell count in the model of psoriasis can be reduced to the normal level through increasing the concentration of FGF10 monoclonal antibody in this study. In addition, the immunohistochemical results of this experiment showed that PCNA and VEGF expression of psoriasis-like lesion model in guinea pig was down regulated after treatment with FGF10 monoclonal antibody. Decreased PCNA expression is the effective indicator reflecting that FGF10 monoclonal antibody can significantly inhibit the epidermal hyperplasia. However, VEGF of the skin is mainly secreted by the epidermal keratinocytes and the vascular endothelial cell of the superficial dermis, and decrease of VEGF expression may be attributed to this inhibitory effect of FGF10 monoclonal antibody on keratinocyte proliferation. From the experimental results, VEGF expression of the high- and medium-dose FGF10 monoclonal antibody group was better than that of hydrocortisone butyrate group, but the inhibitory effect of only the high dose group on PCNA was better than that of hydrocortisone butyrate group, suggesting that the concentration of FGF10 monoclonal antibody had an important impact on the efficacy. These results suggested that FGF10 monoclonal antibody had a certain intervention effect on keratinocyte proliferation, inflammatory reaction and angiogenesis at the lesions.

Psoriasis is difficult to cure in clinic. The biological treatments provide more options for psoriasis patients. In this text, the animal experiment confirmed that FGF10 monoclonal antibody has an improvement role in psoriasis model, provid-

ing a theoretical basis for topical treatment of psoriasis with FGF10 monoclonal antibody. However, it is also found in the study that FGF10 monoclonal antibody can improve the thickness of psoriatic lesion, but it can not make the thickness return to the normal level, suggesting that the topical application of FGF10 monoclonal antibody has a certain limitation, suggesting that it needs to combine with other drugs for comprehensive treatment clinically.

Acknowledgements

Disclosure of conflict of interest

None.

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