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640nm red light irradiation promotes transforming growth factor β induced collagen synthesis by MAPK cell pathway in human dermal fibroblasts

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Abstract: Purpose Transforming growth factor β is a key regulatory factor of collagen expression in human fibroblasts. 640nm red light can regulate the proliferation and transforming growth factor β expression of fibroblasts. Mitogen-activated protein kinase signaling pathway is involved in many physiological processes, such as cell proliferation, differentiation, and apoptosis. The study aims to investigate the effect of 640nm red light irradiation on collagen expression in fibroblasts and the specific regulatory mechanism of mitogen-activated protein kinase signaling pathway. Methods The cells were treated with 640 nm red light for different irradiation time. The effect of real-time fluorescence quantitative PCR detected gene expression of transforming growth factor β and collagen. The specific regulation mechanism of mitogen-activated protein kinase signaling pathway was assessed by western blotting. Results Red light irradiation at 640nm significantly up-regulated mRNA expression of transforming growth factor β, which promoted the expression of collagen mRNA. 640nm red light activated the protein phosphorylation of ERK and inhibited the phosphorylation level of P38 in mitogen-activated protein kinase signaling pathway, which promoting the proliferation of fibroblasts and the gene expression of collagen. Conclusion: 640nm red light irradiation can promote collagen synthesis through cell proliferation and the expression of transforming growth factor β and collagen. Phosphorylation of ERK and P38 promoted cell proliferation and up-regulates mRNA level of collagen.

Key words: Red Light Irradiation; Human Fibroblasts; Stretch Marks; Transforming Growth Factor β; Collagen; Mitogen-Activated Protein Kinase Pathway

1 Introduction

Skin is the largest organ of human body, which not only plays a role in protecting the body and regulating body temperature, but also affects people's appearance[1, 2]. Stretch marks are linear dermal skin lesions that occur during pregnancy[3]. Stretch marks firstly appear as dark red or purplish streaks, then become de-pigmented, flabby, shriveled, and finally stabilize as a white or silver wrinkled paper appearance[4]. Stretch marks are not harmful to physical health, but they cause great damage to the appearance of patients. Stretch marks bring great mental pressure and psychological burden to patients, and affect their quality of life[5]. Therefore, the treatment of stretch marks has been widely concerned and constantly explored.

The treatment of stretch marks mainly include drug therapy, laser therapy, minimally invasive surgery, red light therapy and so on[6]. However, there is no clear and unified treatment method. Recent years, more and more studies on the treatment of stretch marks have focused on red light therapy[7]. The wavelength of red light is generally between

600nm-700nm , and red light treatment mainly relies on photochemical action rather than energy action[8]. Presently, red light therapy is used in anti-inflammation[9], accelerating tissue repair[10], promoting fracture healing[11], and reducing scar[12]. 640nm is a small wavelength of red light, which is mainly used in the field of skin therapy[13]. Stretch marks are the marks left behind by skin lesions, and the effect of 640nm red light on stretch marks is unclear.

Although the causes of stretch marks are not well understood, the main believed causes of stretch marks are changes in skin tension and hormonal changes during pregnancy[14]. During pregnancy, the skin will be gradually stretched with the expansion of subcutaneous tissues such as fat and muscle[15]. Expansion of tissues results in dermal connective tissue damage, collagen fibers and elastic fibers broken, which induced the weakened extensibility and elasticity of the lesions, resulting in striped skin damage[16]. Hormone receptor expression and hormone levels also change dramatically during pregnancy. The surge of glucocorticoid can inhibit the activity and proliferation of fibroblasts, and reduce the synthesis of elastic fibers and collagen of fibroblasts, thus impeding the complete repair of the damaged connective tissue in the dermis[17, 18]. The stationary myofibroblasts of stretch marks are unable to synthesize collagen and elastin[19]. The regulation of collagen by fibroblasts is related to the differentiation status of cells. Mitogen-activated protein kinase (MAPK) signaling pathway is related to a variety of cell functions, and can be involved in a variety of physiological processes such as cell movement, apoptosis, growth and proliferation[20-22]. MAPK pathway has three levels of signaling: MAPK, MAPK kinase (MEK or MKK), and the kinase of MAPK kinase (MEKK or MKKK). Three kinases can be activated to regulate a variety of physiological/pathological effects of cells.

The MAPK pathway has four main branching routes: the extracellular signal-regulated kinase (ERK) pathway[23], the c-Jun N-terminal kinase (JNK)/stress-activated protein (SAPK) pathway, the p38 MAPK pathway[24] and the ERK5/mitogen-activated protein kinase (BMK1) pathway[25]. Specially, JNK and p38 have similar functions, which related to inflammation, apoptosis and growth[26]. ERK pathway mainly channels the growth and differentiation of cells, and its upstream signal is the famous Ras/Raf protein. ERK protein include ERK1 (P44) and ERK2 (P42), which are essential for the transmission of signals from surface receptors to the nucleus. Each signal pathway is highly specific and has independent functions[27, 28]. To some extent, several signal pathways are cross-linked. Stretch marks are associated with the differentiation of fibroblasts[29]. The repair of stretch marks was accompanied by the proliferation and differentiation of dermal fibroblasts. The 640m red light could promote the repair of stretch marks. The regulatory mechanism of 640nm red light on collagen and the role of MAPK signaling pathway is still unclear. The study aims to explore whether 640nm red light regulates collagen expression by affecting MAPK signaling pathway, which to induce the the repair of stretch marks.

2 Materials and methods

1.1 Experimental materials

1.1.1 Cells: human dermal fibroblasts (Sciencel)

1.1.2 Reagents: Fibroblast culture media (Novozyme Bio-Tech Co Ltd., R401-01), trypsin EDTA (Solibol, T1300), Trizol (Thermofisher, 15596026), Reverse TranScripting Kit (Thermofisher, 4368813), Absolute Blue qPCR Mix, SYBR Green, Low Rox (Thermofisher,AB4323A), MAPK Family Antibody Sampler Kit (CST, 9926), Phospho-MAPK Family Antibody Sampler Kit (CST, 9910T), anti-β-actin murine monoclonal Antibody (Sigma, A5316), HRP-conjugated sheep anti-mouse second Antibody (Jackson, 515-005-003), HRP-conjugated sheep anti-rabbit second Antibody (Jackson, 111-005-003),Ripa Lysis and Extraction Buffer (Thermo, 89901), Pierce™ BCA Protein Assay Kit (Thermo, 23225), Pierce™ Fast Western Blot Kit, ECL Substrate (Thermo, 23500), ERK inhibitor (Selleck, S1013), JNK inhibitor (Selleck, S7794),P38 inhibitor (Selleck, S1076), AX-II X-ray photography cassette (Yuehua, 60015797), medical X-ray film (Carestream, X001), other chemical reagents are Sino pharmaceuticals.

1.1.3 Experimental materials: 6-well plate (Corning), 96-well plate (Corning), PCR eight-tube.

1.1.4 Experimental apparatus: carbon dioxide incubator (SANYO, MC0-15 ac), biological safety cabinet (haier,

HR40 - IIA2), centrifuge (Beijing times north, centrifuge, D75-2 b), enzyme standard instrument (Thermo Fisher, MULTISKAN FC), microscope (aurora borealis puca technology co., LTD., IM200), PCR instrument (biological technology co., LTD., Beijing dongsheng innovation ETC811), fluorescence quantitative PCR (ABI, Step One).

1.2 Methods

1.2.1 Cell culture: the resuscitated cells were gently shaken and melted in a water bath at 37℃ and transferred into a centrifuge tube containing 10ml dulbecco's modified eagle medium (DMEM); Centrifuge at 1000rpm /min for 5min, pour out the supernatant, add medium to the centrifuge tube and suspend it, then transfer it to the culture flask; The cells were proliferated to 80% density for passage.

1.2.2 Cell irradiation: After the cells were cultured to the third generation, the experiment groups were irradiated by 640nm red light for different irradiation time (30 min, 60 min, 120 min) respectively. Meanwhile, the non-irradiation group was set for comparison. After irradiation for different times, the cells were cultured and collected at 12 h, 24 h, 36 h, 48 h, 60 h and 72 h for detection of cell activity, growth status and gene expression level.

1.2.3 Fluorescence staining: Cell slides were dipped and washed with PBS for 3 times, 3min/ time; It was fixed with 4% paraformaldehyde for 15min, then washed with PBS for 3 times, 3min/ time; 0.5%TritonX-100 penetration for 20min, PBS washed for 3 times, 3min/ time; The goat serum was sealed at room temperature for 30min, and the primary antibodies were incubated overnight at 4℃. PBST was washed for 3 times, 3min/ time. Fluorescence labeled sheep anti-rabbit labeled IgG was incubated for 1h. PBST was washed for 3 times, 3min/ time. DAPI was used to stain the core and seal the film, and the images were observed and collected.

1.2.4 Preparation of cDNA: Cells were collected to mix with 500uLTRIZOL, and then lysed for 5min; Add 100ul chloroform, blowing and mixing with the tip of a gun at room temperature for 10min, and centrifuge at 12000rpm at 4℃ for 15min. Transfer the supernatant to a new tube, add isopropanol of equal volume, blow and mix, stand for 10min at room temperature, and centrifuge for 5min at 12000rpm at 4℃. The supernatant was discarded and added with 1mL of anhydrous ethanol, rinsed and precipitated gently, and centrifuged at 6000rpm at 4℃ for 5min. The supernatant was dried at room temperature, then 30uL water was added to dissolve RNA and stored at -80℃. RNA was transcribed into cDNA according to the reverse transcription kit and stored at -20℃.

1.2.5 Quantitative real-time PCR (RT-PCR) amplification of the target gene, and preparation of RT-PCR reaction solution: 2× Master mix 10.0 (ul), Forward Primer 1.0 (ul), Reverse Primer 1.0 (ul), nuclease-free H2O 1.0 (ul), Total per Reaction 18.0 (ul); The PCR reaction solution was divided into eight PCR tubes and 2ul cDNA prepared was added. The difference of gene expression was detected by fluorescence quantitative PCR.

1.2.6 Western Blot assay

(1) Cell collection: Cells were cultured to the density reached 80%, cells were scraped with a plastic scraper and collected in a centrifuge tube. (2) Protein extraction: wash twice with PBS and discard as much as possible residual PBS. The cells were resuspended with an appropriate volume of RIPA lysate, and then the cells were cleaved with ultrasonic apparatus for 10sec. Pyrolysis liquid centrifuged with 13000rpm at 4°C for 20min, the supernatant was transferred to a new tube, the protein content was determined by BCA method and diluted to the same concentration. The different treated samples with the same total protein content were mixed at 1： 3 and 4× Loading buffer, denaturated at 100℃ for 5min, and stored at -20°C. (3) Gel preparation and electrophoresis: SDS-polyacrylamide gel electrophoresis was prepared. The concentrated gel was compressed at 60V, and the separation gel was separated at 120V for 1.5~2h. (4) Film transfer: after electrophoresis, remove and cut the glue, cut the film of the appropriate size according to the size, one layer of filter paper on each side, glue and film in the middle, glue in the negative electrode, film in the positive electrode, using full wet film transfer, constant current 0.25A to 1.5h~2.5h. (5) Red dyeing and sealing: the membrane was immersed in red dyeing solution, dyed for 1-2min, washed with distilled water, labeled protein, cut off the target strip, washed with PBST for 5min, and sealed with 5% skim milk powder at 37°C for 1h. (6) Antibody incubation: discard the blocking solution, dilute the primary antibody in the blocking solution, incubate at room temperature for

1~2h, or incubate overnight at 4°C; PBST was purified for 10min×5, the secondary antibody was diluted with the blocking solution and incubated in a shaker at room temperature for 1h. After the reaction, the secondary antibody was discarded and washed with PBST for 10min×5. (7) X-ray film is developed in a darkroom.

3 the results

3.1 Effect of 640nm red light on TGF-β and COL-I gene expression in fibroblasts

The fusion curves of GAPDH, TGF-β, COL, SAM, FN and Vim were credible, indicating that the amplification of target gene by primers was normal. Previous experimental results showed that there was significant cytotoxic effect of 640nm red light irradiation for 120min, so 30min and 60min irradiation intensities were selected for qPCR detection.

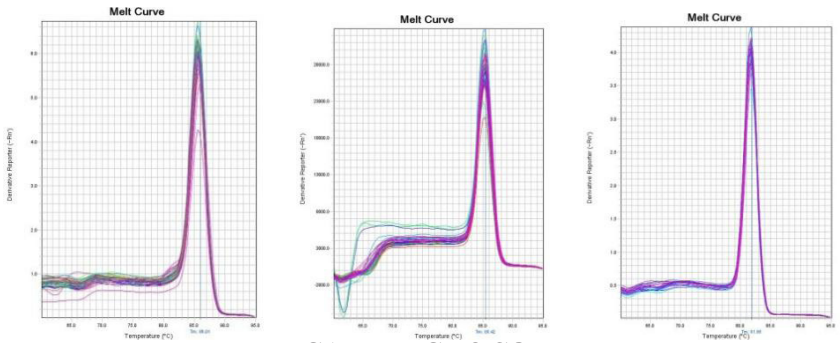

Figure 3-1. Fusion curves of TGF-β, Col-I; FN, SAM and VIM target genes

TGF-β gene expression was the most active in the control group after 24 hours of red light irradiation, and the mRNA expression of TGF-β was gradually down-regulated with irradiation time. TGF-β gene expression was gradually up-regulated in the 640nm red light irradiation group, and reached at the maximum level at 48h. Among them, 60min irradiation intensity had the most significant upregulation effect on TGF-β gene expression.

Compared with the control group, the 30min irradiation intensity increased the expression of Col-I at 24h, and down-regulated Col-I expression level after 48h. The 60min radiation intensity down-regulated the expression of Col-I at 48h, but significantly up-regulated the expression at 72h.

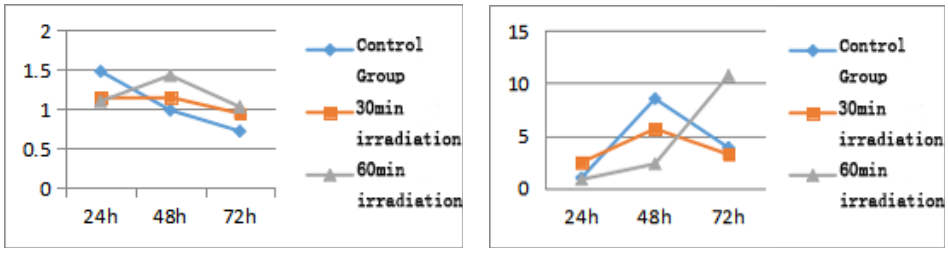

Figure 3-2 Effect of red light irradiation on TGF-β(left) and Col(right) gene expression in fibroblasts

3.2 Effect of 640nm red light on extracellular matrix

At the same time, the mRNA expression levels of different extracellular matrix were detected. The results showed that the expressions of SAM, Vim and FN genes were down-regulated in the different intensity of red light irradiation groups, and there was no difference of genes expression between the red light irradiation groups and the control group after 72h.

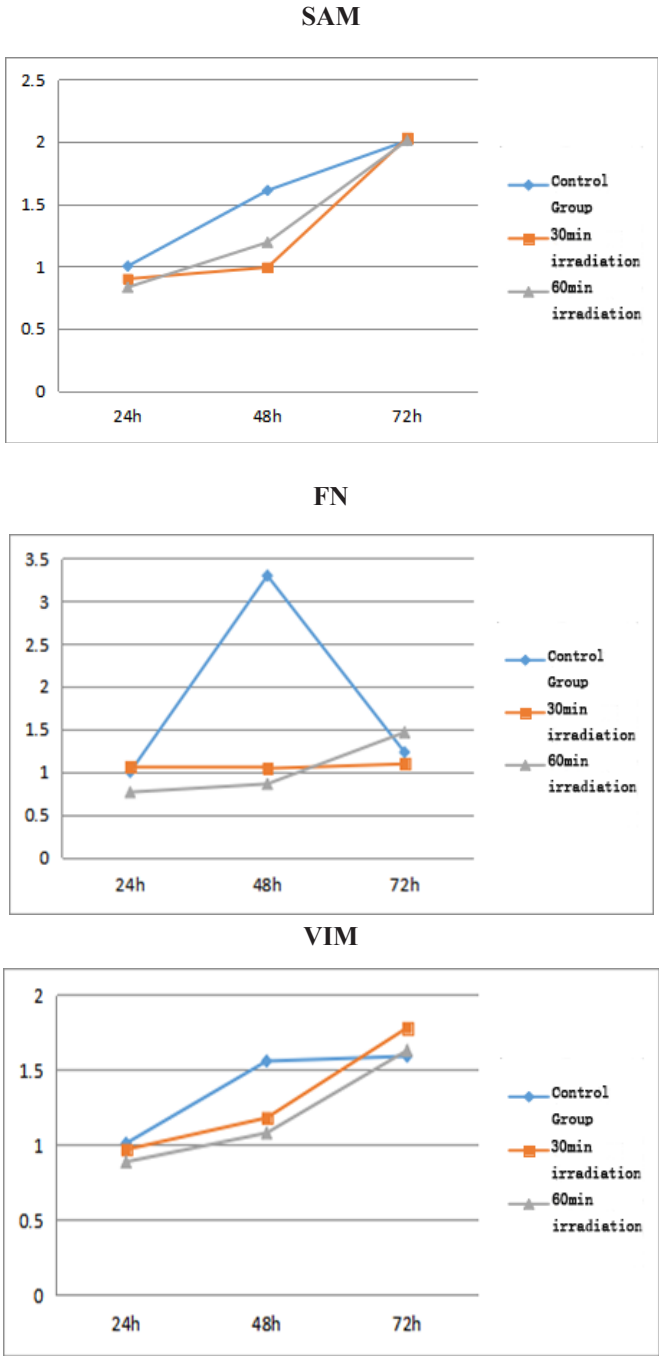

Figure 3-3 Effect of red light irradiation on SAM, FN and VIM gene expression in fibroblasts

3.3 Effect of 640nm red light on MAPK signaling pathway

MAPK is involved in multiple signaling pathways such as cell differentiation, proliferation and apoptosis. Regulation of three key proteins mediated by MAPK signaling pathway mainly includes ERK-mediated cell proliferation, JNK and p38 mediated inflammatory response under stress conditions, cell apoptosis and

immunomodulation processes. 60min 640nm red light irradiation enhanced the phosphorylation level of P42, had no significant effect on the phosphorylation level of JNK protein, and significantly inhibited the phosphorylation level of P38.

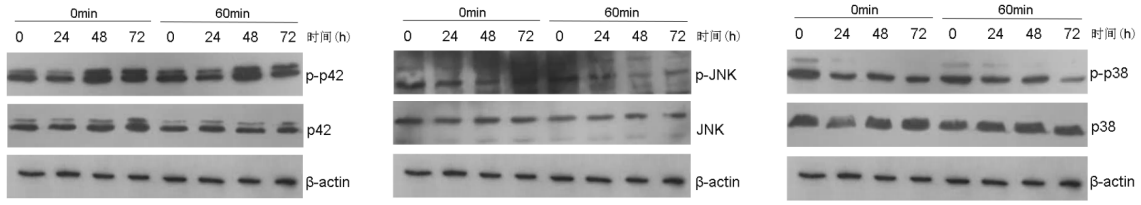

Figure 3-4 Effect of red light irradiation on MAPK signaling pathway

3.4 Influence of ERK on MAPK signaling pathway regulated by 640nm red light

To further investigate whether the increase of ERK signaling pathway induced by 640nm red light promotes fibroblast proliferation. In this study, ERK signaling pathway inhibitors were used to intervene. ERK inhibitors inhibited P42 phosphorylation, while ERK inhibitors and JNK inhibitors did not..

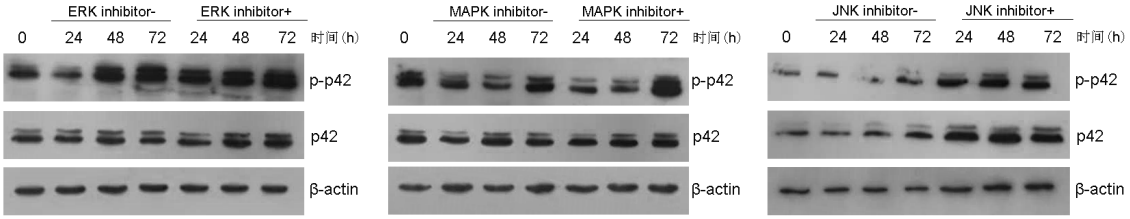

Figure 3-5 Influence of ERK on MAPK signaling pathway regulated by red light irradiation

3.5 Influence of JNK on MAPK signaling pathway regulated by 640nm red light

With the growth of cells, the phosphorylation level of JNK protein was not significantly affected by 640nm red light irradiation. Meanwhile, the JNK signaling pathway inhibitors did not affect the protein expression of the JNK signaling pathway. 640nm red light irradiation May not activate the JNK signaling pathway, which not affect the MAPK signaling pathway through the JNK pathway.

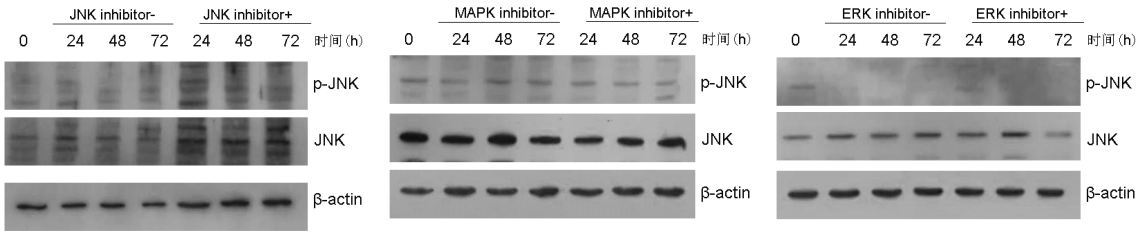

Figure 3-6 Influence of JNK on MAPK signaling pathway regulated by red light irradiation

3.6 Influence of P38 on MAPK signaling pathway regulated by 640nm red light

Phosphorylation of P38 was inhibited in the control group and the 60min irradiation group, and the 60min irradiation group significantly inhibited the activity of phosphorylated P38. Compared with the control group, P38 inhibitors upregulated the phosphorylation level of P38, while ERK inhibitors and JNK inhibitors did not. 640nm red light irradiation was also played a key role by affecting the P38 pathway of MAPK.

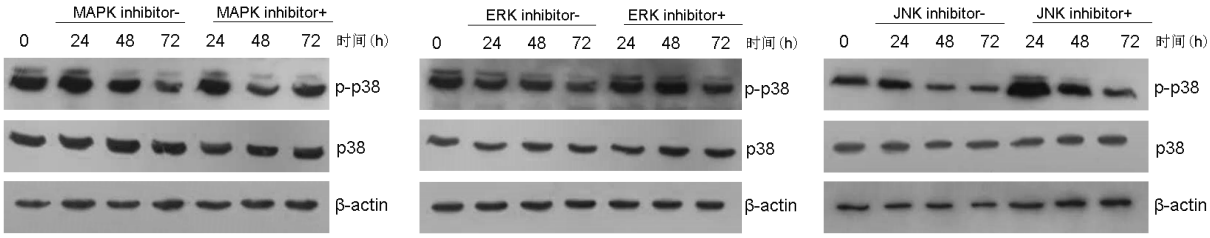

Figure 3-6 Influence of P38 on MAPK signaling pathway regulated by red light irradiation

4 discuss

Stretch marks are caused by a decrease in the number of fibroblasts or collagen production. TGF-β is a major regulator of collagen synthesis in fibroblasts[30]. On the one hand, it regulates the transcription, translation and secretion levels of collagen in fibroblasts, and on the other hand, it can inhibit collagen degradation and accelerate collagen deposition by selectively inhibiting collagenase activation and expression[30]. TGF-β also regulates the expression and secretion levels of other extracellular matrix, such as hyaluronic acid, fibro connection and receptors, laminin, proteoglycan and so on[31]. Promoting the growth and proliferation of fibroblasts and contraction of collagen fibers are the main ways to treat stretch marks. At present, red light therapy is widely used in anti-inflammatory, accelerating tissue repair, promoting fracture healing, reducing scar and other fields[32]. 640nm is a small wavelength of red light, which is mainly used in the field of skin therapy. However, the therapeutic effect of 640nm red light on stretch marks is still unclear, and the specific regulatory mechanism is rarely studied.

In this study, fibroblasts were irradiated with different intensities of red light to promote the proliferation of cultured fibroblasts in vitro and induce the secretion of TGF-β, and the irradiation intensity of 60min had the most obvious regulation effect on TGF-β gene expression. TGF-β is the main regulatory factor of human skin procollagen production, which can promote the proliferation and division of fibroblasts cultured in vitro and the synthesis of collagen[33]. Red light irradiation at 640nm can significantly up-regulate the mRNA expression of collagen in human fibroblasts. There was no significant difference in the SAM, Vim and FN genes in extracellular matrix gene expression.

MAPK signaling pathway is related to a variety of cell functions, and can be involved in a variety of physiological processes such as cell movement, apoptosis, differentiation, growth and proliferation[34]. This pathway mainly contains three key protein regulatory roles: ERK mediated cell proliferation, JNK and p38 mediated inflammatory response under stress conditions, cell apoptosis and immune regulation. In order to further explore the role of MAPK signaling pathway in the regulation of TGF-β secretion by 640nm red light irradiation, western blotting detected the protein expression differences of three major signaling pathways of MAPK signaling pathway, namely JNK, ERK, and P38. Compared with the control group, 640nm red light plays a significant regulatory role in ERK and P38 signaling pathways, which mainly promoted the phosphorylation level of P42 protein and inhibited the phosphorylation level of P38 protein, thereby regulating the MAPK signaling pathway and further regulating the expression of downstream target genes. ERK inhibitors can down-regulate the phosphorylation level of P42 protein induced by red light irradiation at 640nm, while JNK inhibitors and MAPK inhibitors do not have this effect. The results indicate that red light irradiation at 640nm promotes the proliferation of fibroblasts by affecting the ERK pathway. Red light irradiation at 640nm had no effect on the expression of JNK pathway proteins, nor did ERK, JNK and MAPK inhibitors. Red light irradiation at 640nm did not regulate MAPK through JNK signaling pathway. Red light irradiation at 640nm significantly inhibited the phosphorylation level of P38 protein, while P38 inhibitors reversed the down-regulation effect, while ERK inhibitors and JNK inhibitors could not play this role. The results showed that red light irradiation at 640nm regulates the downstream pathways by affecting the P38 pathway of MAPK, thereby regulating the expression of collagen in fibroblasts. Three signaling pathway has its own characteristics. Different or completely opposite biological effects can

be produced by the coordination and integration of signals between different subclasses of stimulus factors such as cell culture time and red light irradiation intensity. Therefore. Further study still needs to explore parallel signaling pathways between mutual coordination and regulation mechanism.

In conclusion, this study found that 640 nm red light irradiation therapy was time- and dose dependence. After 48-72h of 60min irradiation, irradiation group significantly promoted the proliferation of human fibroblasts and increased mRNA level of TGF-β. 640 nm red light promote the synthesis of collagen by increasing cell proliferation and TGF-β gene expression, which further to improve the repair of skin stretch marks. 60min red light irradiation promotes the proliferation of fibroblasts by promoting the phosphorylation level of ERK protein of the MAPK family molecule, and further promotes the gene expression and secretion of collagen. 60min red light irradiation inhibited the P38 signaling pathway and reduced the inflammatory response of fibroblasts, thus promoting the proliferation and differentiation of fibroblasts. The 60min red light can promote the expression of collagen in fibroblasts by regulating the MAPK signaling pathway, which is expected to be a noninvasive and effective treatment for stretch marks repair.

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