Commentary   **Open Access**

Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ) Agonist Troglitazone Suppresses Collagen Synthesis via Expression of the Downstream Target MiRNAs A Novel Strategy to Treat Skin Fibrosis?

Hua-yu Zhu[1], **Wen-dong Bai**[2], **Hong-tao Wang**[1], **Jun-tao Han**[1] and **Da-hai Hu**[1*]

[1]Department of Burns and Cutaneous Surgery, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, P.R China

[2]Department of Clinical Laboratory Center, Xinjiang Command General Hospital of Chinese People's Liberation Army, Urumqi, Xinjiang, P.R China

[*]**Corresponding author:** Da-hai Hu, Department of Burns and Cutaneous Surgery, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi, P.R China, Tel: +86-29-84775293; E-mail: zzhuhy@aliyun.com

Abstract

Nuclear receptor peroxisome proliferator-activated receptor-γ (PPAR-γ) activity has been identified as an important endogenous anti-fibrotic defense mechanism. Troglitazone, a PPAR-γ agonist, has been used to suppress the formation of keloids and growth of hypertrophic scar fibroblasts. Indeed, the PPAR-γ agonist was able to inhibit collagen I expression in hypertrophic scar fibroblasts, which clearly demonstrates its therapeutic potential, and clarification of the underlying molecular mechanisms could further indicate the usefulness of the PPAR-γ agonists in the treatment of keloids. Moreover, increasing evidence has suggested that aberrant expression of miRNAs leads to the development and progression of fibrosis diseases. Thus, fully understanding the biological functions and molecular mechanisms of miRNAs in the regulation of fibrosis could provide insight for advancements in the diagnosis and treatment of fibrosis. This commentary briefly summarizes the current evidence for the ability of PPAR-γ agonist troglitazone to suppress collagen synthesis and regulate miRNA expression and downstream targets in cells.

Keywords: Troglitazone; Benign tumor; Keloid; miRNAs; PPAR-γ agonist
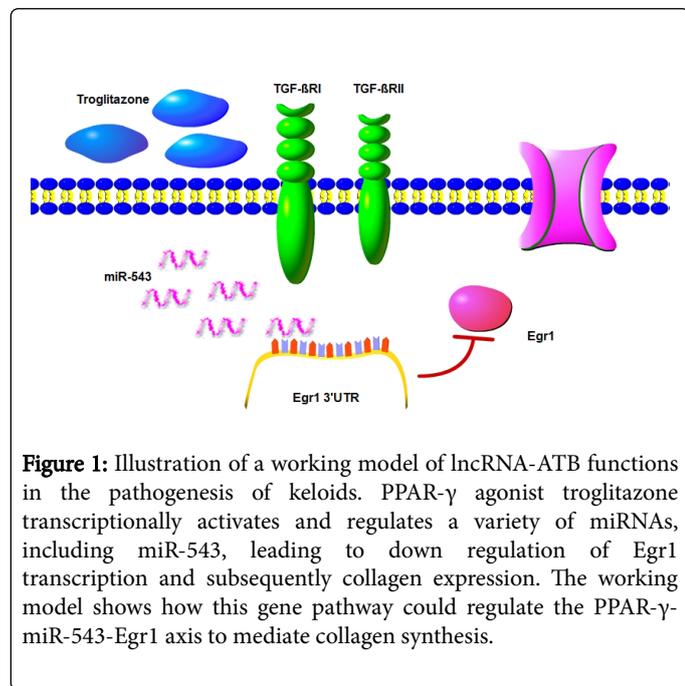
Introduction

Keloids result from uncontrolled growth and fibrosis of granulation tissue after skin injury [1]. Histologically, keloids are benign fibroproliferative tumors that characterized by an overabundant accumulation of extracellular matrix components, especially collagen, in the dermis and subcutaneous tissue that extends beyond the confined original wound site [1]. The etiology of keloids is not defined, but ethic and genetic background may contribute to keloid formation [1]. To date, the treatment of keloids is multiple and age-dependent and surgical resection remains the mainstay for keloid treatment. However, when used as the sole form of therapy, lesions recur in 70-100% of patients, often leading to more robust collagen accumulation and formation of a larger lesion [2]. Other treatments, such as radiation, chemotherapy, anti-metabolite agents, or cortisol can result in harmful side effects [3]. Thus, keloid treatment continues to pose a significant challenge to clinicians in daily practice. Previous research evaluated a combination of surgery with several adjuvant therapies, such as pulsed-dye laser ablation, CO_2 laser ablation, radiation, pressure therapy, interferon, 5-fluorouracil, imiquimod, tacrolimus, sirolimus, bleomycin, doxorubicin, transforming growth factor-beta (TGF-β), epidermal growth factor, verapamil, retinoic acid, tamoxifen, botulinum toxin A, onion extract, silicone-based camouflage, hydrogel scaffold, and/or skin tension offloading device [2]. Some keloid lesions were effectively treated and controlled with these treatments, but others still led to various degrees of recurrence [2]. However, conclusive results are difficult to ascertain because of a number of factors, most notably the limited patient cohort size in individual studies [2]. In this commentary, we summarize and review novel approaches and strategies in the treatment of keloids.

Peroxisome proliferator-activated receptor-gamma (PPAR-γ) was reported to inhibit the growth of various tumor cells [4] and to suppress human dermal fibroblast production of extracellular matrix [5]. PPAR-γ can be activated by both natural and synthetic ligands and fulfills the functions in cells and tissues. Troglitazone, a class of thiazolidinediones developed by Japanese researchers in 1988, is an antidiabetic and anti-inflammatory drug designed to enhance insulin sensitivity. It was the first thiazolidinedione antidiabetic agent approved by the US Food and Drug Administration in 1997, but it was withdrawn from the market in 2000 due to serious idiosyncratic hepatotoxicity [3]. Novel troglitazone derivatives were therefore developed and have shown anti-proliferative activity in breast cancer cell lines [6]. Troglitazone also was found to be effective at treating fibrotic diseases [7,8], and a further study reported that troglitazone suppresses deposition of extracellular matrix and lowers scar development in a rat model of chronic cholestasis [9]. At the gene level, troglitazone inhibits the synthesis and expression of collagen type I with or without induction of TGF-β1. These studies suggest a novel therapeutic approach in the treatment of dermal fibrosis, including keloids [10,11].

Recently, troglitazone was shown to activate PPAR-γ and, in turn, to inhibit collagen synthesis in human keloid fibroblasts [5]. Indeed, troglitazone was found to be a synthetic PPAR-γ agonist [3]. To further explore the molecular mechanism of the troglitazone-suppressed deposition of extracellular matrix and scar development, our study revealed that Troglitazone was able to modulate the expression of miR-543 and its target gene Egr1 in human keloid fibroblasts. This study could provide a novel gene pathway, i.e., the PPAR-γ-miR-543-

Egr1 axis after treatment of human keloid fibroblasts with the PPAR-γ agonist troglitazone, to control collagen synthesis and keloid formation (Figure 1).

Figure 1: Illustration of a working model of lncRNA-ATB functions in the pathogenesis of keloids. PPAR-γ agonist troglitazone transcriptionally activates and regulates a variety of miRNAs, including miR-543, leading to down regulation of Egr1 transcription and subsequently collagen expression. The working model shows how this gene pathway could regulate the PPAR-γ-miR-543-Egr1 axis to mediate collagen synthesis.

Indeed, miRNAs are a class of naturally occurring non-coding small sized RNAs that posttranscriptionally silence expression of target genes to regulate cell growth, differentiation, apoptosis, and carcinogenesis [12]. Aberrant miRNA expression was also demonstrated to play a critical role in the initiation and progression of fibrosis and fibrogenic diseases [13]. Thus, a better understanding of miRNA biology, functions, and molecular mechanisms could support significant advancements in the diagnosis and treatment of fibrosis and fibrogenic diseases [14]. Our previous study of the ability of troglitazone to control keloids revealed that miR-543 was transcriptionally activated upon troglitazone treatment and, in turn, inhibited collagen synthesis via the PPAR-γ-miR-543-Egr1 signaling axis in keloid fibroblasts [5]. Thus, detection of miRNA expression could potentially be used to assess the risk of keloid progression (prognostic information), monitor treatment response, or identify therapeutic targets and resistance mechanisms as well as to better understand the biology of keloid development. For example, our research revealed overexpression of miR-543 in keloid fibroblasts and demonstrated that miR-543 mediated the transcriptional or posttranscriptional regulation of multiple target genes in coordination to inhibit fibrosis. Thus, further study of miRNAs in fibrosis could provide novel knowledge about the underlying mechanisms of fibrosis development and progression, and therefore, provide novel strategies for the treatment of fibrosis and keloids [15].

Conclusion

Effective treatment of keloids is a challenge in clinical practice, and natural and synthetic PPAR-γ ligands could provide a potentially novel strategy for the control of keloid formation and progression. In this context, a synthetic PPAR-γ agonist troglitazone showed promising action against keloid formation in *in vitro* and *in vivo* experiments [12-14].

Troglitazone could activate PPAR-γ to inhibit the synthesis and expression of collagen in keloid fibroblasts [5]. At the gene level, troglitazone treatment was able to modulate miR-543 expression and its downstream targets, namely, the PPAR-γ-miR-543-Egr1 axis, to inhibit keloid formation and progression. Such data could provide a novel therapeutic potential for keloids, although there are still many unresolved questions surrounding the gene-regulatory networks. It is also necessary to point out that the main pharmacodynamically idiosyncratic hepatotoxicity effects of troglitazone and other drugs could include inhibition of hepatic drug transporters, hypersensitivity reaction associated with troglitazone hepatotoxicity, mitochondria-mediated toxicity, kinase-mediated cell toxicity, and protein translation-associated toxicity. However, these may not block the development and use of troglitazone for keloid treatment, if troglitazone is administered separately from other hepatotoxic drugs. In addition, novel troglitazone derivatives and other PPAR-γ ligands could overcome the problems associated with troglitazone in addition to directly target miRNAs or their targeting genes. Such treatments may have to be carefully tailored to be tissue- and target gene-specific to minimize side effects, although this is a great challenge in medical research at present [16]. Our current study is only proof-of-principle, and further research is needed to fully develop PPAR-γ ligands for the control of keloid formation and progression in clinical practice.

References

1. Andrews JP, Marttala J, Macarak E, Rosenbloom J, Uitto J (2016) Keloids: The paradigm of skin fibrosis - Pathomechanisms and treatment. Matrix Biol 51: 37-46.

2. Berman B, Maderal A, Raphael B (2016) Keloids and Hypertrophic Scars: Pathophysiology, Classification, and Treatment. Dermatol Surg.

3. Arno AI, Gauglitz GG, Barret JP, Jeschke MG (2014) Up-to-date approach to manage keloids and hypertrophic scars: a useful guide. Burns 40: 1255-1266.

4. Kole L, Sarkar M, Deb A, Giri B (2016) Pioglitazone, an anti-diabetic drug requires sustained MAPK activation for its anti-tumor activity in MCF7 breast cancer cells, independent of PPAR-Î³ pathway. Pharmacol Rep 68: 144-154.

5. Zhu HY, Bai WD, Wang HT, Xie ST, Tao K, et al. (2016) Peroxisome proliferator-activated receptor-Î³ agonist inhibits collagen synthesis in human keloid fibroblasts by suppression of early growth response-1 expression through upregulation of miR-543 expression. Am J Cancer Res 6: 1358-1370.

6. Salamone S, Colin C, Grillier-Vuissoz I, Kuntz S, Mazerbourg S, et al. (2012) Synthesis of new troglitazone derivatives: anti-proliferative activity in breast cancer cell lines and preliminary toxicological study. Eur J Med Chem 51: 206-215.

7. Wei J, Zhu H, Komura K, Lord G, Tomcik M, et al. (2014) A synthetic PPAR-Î³ agonist triterpenoid ameliorates experimental fibrosis: PPAR-Î³-independent suppression of fibrotic responses. Ann Rheum Dis 73: 446-454.

8. Jeon KI, Phipps RP, Sime PJ, Huxlin KR (2015) Inhibitory effects of PPARÎ³ ligands on TGF-Î²1-induced CTGF expression in cat corneal fibroblasts. Exp Eye Res 138: 52-58.

9. Marra F, DeFranco R, Robino G, Novo E, Efsen E, et al. (2005) Thiazolidinedione treatment inhibits bile duct proliferation and fibrosis in a rat model of chronic cholestasis. World J Gastroenterol 11: 4931-4938.

10. Zhang GY, Yi CG, Li X, Ma B, Li ZJ, et al. (2009) Troglitazone suppresses transforming growth factor-beta1-induced collagen type I expression in keloid fibroblasts. Br J Dermatol 160: 762-770.

11. Zhang GY, Cheng T, Zheng MH, Yi CG, Pan H, et al. (2010) Peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonist inhibits

transforming growth factor-beta1 and matrix production in human dermal fibroblasts. J Plast Reconstr Aesthet Surg 63: 1209-1216.

12. Mendell JT (2005) MicroRNAs: critical regulators of development, cellular physiology and malignancy. Cell Cycle 4: 1179-1184.

13. O'Reilly S (2016) MicroRNAs in fibrosis: opportunities and challenges. Arthritis Res Ther 18: 11.

14. Ji X, Wu B, Fan J, Han R, Luo C, et al. (2015) The Anti-fibrotic Effects and Mechanisms of MicroRNA-486-5p in Pulmonary Fibrosis. Sci Rep 5: 14131.

15. Zhu HY, Li C, Zheng Z, Zhou Q, Guan H, et al. (2015) Peroxisome proliferator-activated receptor-Î³ (PPAR-Î³) agonist inhibits collagen synthesis in human hypertrophic scar fibroblasts by targeting Smad3 via miR-145. Biochem Biophys Res Commun 459: 49-53.

16. Deng YL, Xiong XZ, Cheng NS (2012) Organ fibrosis inhibited by blocking transforming growth factor-ß signaling via peroxisome proliferator-activated receptor ? agonists. Hepatobiliary Pancreat Dis Int 11: 467-478.