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?

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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 original wound site [1]. The etiology of keloids is not defined, but ethnic 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, CO2 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-
Trotolitazone 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


