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FGF-10 and FGF-21 mediated inflammation through LDLR in psoriasis plaques

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Abstract

In psoriasis, growth factors may also play a role in inflammation enhancement. Fibroblast growth factor (FGF)-10 and FGF21 are overexpressed and implicated in psoriasis pathogenesis. To postulate the association of FGF10 and FGF21 and transcripts expressed in psoriasis plaques, we analyzed RNA-seq from biopsied Uninvolved skin (UN skin) and center of plaque skin (CE skin) of patients with moderate to severe psoriasis vulgaris and showed different expression of genes (DEGs). *FGF10* and *FGF21* were the upstream regulators with positive activity z-score. Their shared downstream target gene in psoriasis plaques is *LDLR*. Upregulation of *LDLR* may eventually result in inflammatory response exacerbation. *FGF21* regulator was involved in the upregulation of *SOD2* in psoriatic plaques. Although SOD2 activity inhibited ROS production, SOD2 in psoriasis was dysfunctional, which might increase mtROS and progress in inflammation. Treatment that targets FGF10 and FGF21 might provide good outcomes in psoriatic patients.

Keywords: Psoriasis, Inflammation, Fibroblast growth factor 10, Fibroblast growth factor 21

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1. Introduction

Chronic inflammatory diseases are relatively common in the population. With the increasing incidence and recurrence of the diseases, they significantly affect the physical and mental conditions of the patients [1]. Psoriasis is a common chronic inflammatory skin disease that presents thick red plaques of skin and swollen painful joints in psoriatic arthritis [2]. In addition to the skin and joint lesions that cause physical burdens, psoriasis is associated with more significant comorbidities through systemic inflammation [3]. The pathogenesis of psoriasis is still complex and not fully understood. Several growth factors and their signals are involved in the pathogenesis of the disease, and some growth factors are overproduced, leading to dysregulation of keratinocyte proliferation [4]. The Fibroblast Growth Factor family, or FGFs, have addressed the role of cellular biological functions and developmental processes, including the repair and regeneration of tissue. Evidence from *FGFR1* and *FGFR2* knockout keratinocyte mice studies showed a longer time in skin healing after injury [5]. In psoriasis, FGF10 expression was increased in psoriatic plaque skin, which correlated with a high percentage of Ki-67 expression [6], which may imply that FGF10 is involved in psoriatic lesional keratinocyte hyperproliferation. In the serum of psoriatic patients, the FGF21 level was higher than in healthy individuals [7]. Cellular and metabolic stress-induced FGF21 release plays a role in metabolic disorders initiation through enhancing glucose uptake and lipolysis [8, 9]. So, the serum level of FGF21 in psoriatic patients might help predict metabolic risk parameters in psoriasis.

Transcriptomic studies were increasingly popular. High throughput RNA sequencing analysis is developed and is found to be superior to microarray in terms of higher rate of DEG detection and ability to detect novel transcripts [10, 11]. We performed RNA-seq transcriptome analysis between UN skin and CE skin. We aim to reveal novel aspects of growth factor role in psoriatic pathogenesis, especially FGF10 and FGF21. Results may help develop a novel therapeutic modality in the future.

2. Research Methodology

2.1 Patient enrollment

Three samples seem to be adequate regarding human tissue RNA-seq in psoriasis. [12-14]. Three eligible patients with moderate to severe psoriasis (Psoriasis area severity index or PASI ≥10) were recruited. They were over 18 years old and had not received any topical treatment (topical steroid, topical vitamin D analog) at least two weeks, phototherapy and any systemic medication (Prednisolone, Methotrexate, Biologics therapy) at least 4 weeks before the biopsy procedure. This study was designed to correspond to the Declaration of Helsinki's principles and was approved by the ethics committee of Thammasat University (No. MTU-EC-OO-6-188/65).

2.2 Tissue sampling

Classic featured plaques were selected. Uninvolved skin (UN skin) was identified as the normal-appearing skin 10 cm away from the edge of the plaques. The center of lesional skin (CE skin) and UN skin were biopsied using 6-mm punch biopsy equipment. Two % lidocaine with adrenaline was used for pain control. RNA later (ThermoFisher, AMBION, USA) was immediately used to preserve the biopsies at -80° C before the RNA-seq study.

2.3 RNA sequencing (RNA-seq)

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Total RNAs were extracted from each skin biopsy (CE skin, n = 3; UN skin, n = 2). The next-generation sequencing (NGS) was performed with NovaSeq 6000 S4 Reagent Kit with 100 bp paired-end reads. The raw data of this study has been deposited in the NCBI Gene Expression Omnibus (GEO; http://www.ncbi. nlm.nih.gov/geo) and is accessible through GEO Series accession number GSE186117.

2.4 RNA-seq analysis

A commercial company (Macrogen, Seoul, Korea) conducted the basic data analysis.

2.5 DEG analysis

Use QIAGEN's ingenuity pathway analysis (IPA) software (www.qiagen.com/ingenuity). DEGs with p-value < 0.01 and $|\log2FC| \geq 1.5$ were analyzed for their downstream functions and upstream regulators.

3. Results and Discussion

We found that FGF-10 and FGF-21 were the upstream regulators with positive activity z-score. Their predicted activity and downstream target genes in psoriasis plaques are shown in **Figure 1.**

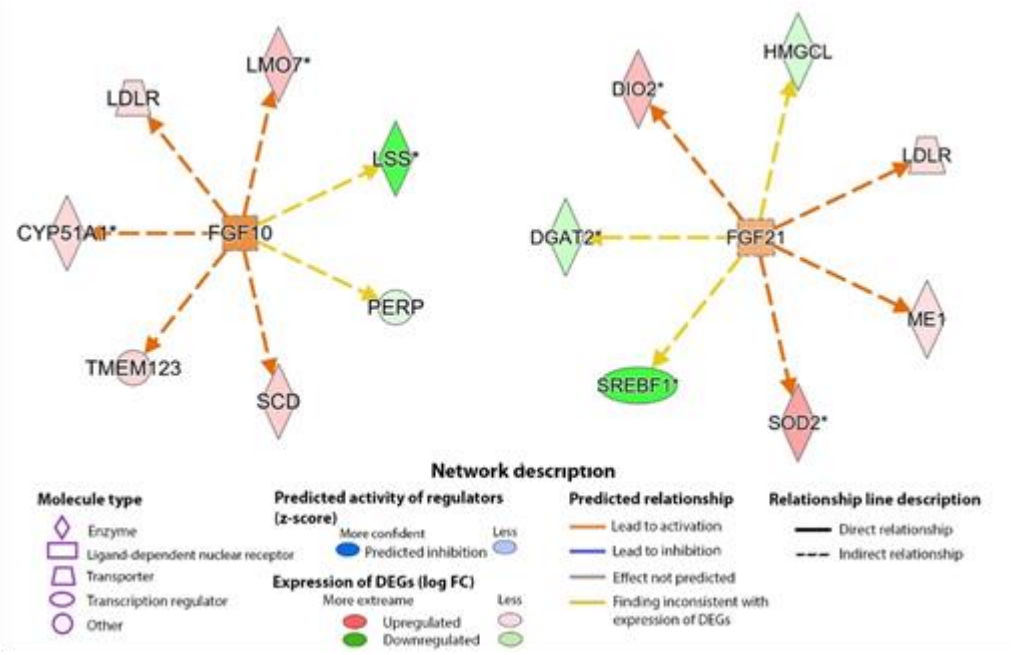

Figure 1 Regulatory function of FGF-10 and FGF-21 over DEGs in psoriatic plaques

Our results showed that *FGF-10* and *FGF-21* were predicted to be the regulators with positive activity z-score regulated over several DEGs of psoriasis plaques. *FGF10* encoded FGF10, which was found to be upregulated in the upper psoriatic dermis. It stimulates keratinocyte growth and maintains an epidermal hyperproliferation state in psoriasis, proved by a high level of Ki-67 proliferation marker **[6]**. In psoriasis, a study showed that *FGF2* was significantly upregulated in imiquimod-treated human IL-26 transgenic mice and psoriasis patients **[15]**. Moreover, the serum level of FGF2 was

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reduced in psoriatic patients treated with Goeckerman's therapy and correlated to PASI score **[16]**. Its receptor was upregulated in lesional psoriatic skin**[17]**. The common downstream target of these two FGFs was *LDLR*, which encodes low-density lipoprotein receptors (LDLRs). *LDLR*, a lipid metabolism-related gene, is induced by FGF10 *in vitro* lung epithelium [18]. FGF21 can also increase LDLR levels through Cnpy2/Msap enhancement [19]. LDL-c binds to LDLR to uptake cholesterol to cells. When LDLR expression increases, it decreases LDL-C levels, leading to intracellular cholesterol accumulation, which can exacerbate the inflammatory response **[20]** by induction of epidermal cells to release pro-inflammatory cytokines and reactive oxygen species [21]. In addition, the results also showed that *FGF-21* was involved in upregulation of *SOD2* in psoriatic plaques. The manganese superoxide dismutase, which is a mitochondrial protein that is encoded by the *SOD2* gene, also known as MnSOD, is a key player in the detoxification of mitochondrial ROS (mtROS) [22]. mRNA level of SOD2 in lesional psoriatic skin was higher than in the normal population [23]. Like the SOD2 protein, it was overexpressed in lesional psoriatic skin [24]. FGF21 stimulated SOD2 activity and inhibited ROS production, suppressing oxidative stress [25]. However, several studies revealed an association between metabolic and atherosclerotic risk in psoriasis[26-28]. A study showed downregulation of *SOD2* gene in human psoriatic macrophage which might be inferred that SOD2 function in psoriatic macrophage was impaired. Psoriasis induced SOD2 dysfunction resulting in mtROS enhancement and progression of inflammation [29].

4. Conclusion

Our result suggested that FGF-10 and FGF-21 could mediate inflammation via upregulation of LDLR in psoriasis plaques. The upregulation of FGF-21-mediated SOD2 may also intensify the inflammation. Dysfunction of SOD2 might increase mtROS and induce inflammation in psoriatic patients. Modalities that block FGF-10 and FGF-21 could provide a new promising outcome to patients with psoriasis.

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