A Novel Therapeutic Strategy for Antifibrotic Based on a New Gene NS5ATP9

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Abstract

In this article, we introduced a screening of anti-fibrotic drugs focused on new genes. More precisely, we screened and cloned 127 new genes, reporting on a potential target gene and two promising drugs for fibrosis. Among 127 genes, hepatitis C virus nonstructural protein 5A transactivated protein 9 (NS5ATP9), which expression is significantly upregulated by tenofovir disoproxil fumarate (TDF)/tenofovir alafenamide fumarate (TAF), suppresses hepatic stellate cells (HSCs) and HFL1 cells (lung fibroblasts) activation. Therefore, we reported NS5ATP9 as a potential therapeutic target, and TDF/TAF as a new promising therapeutic strategy in fibrosis. These results elucidate mechanisms of disease and translate molecular techniques into clinical treatment.

Discovery of 127 New Genes and the Main Achievements

By the suppression of subtractive hybridization (SSH) and yeast-two hybrid system, 127 new genes were screened, cloned, and registered at GenBank (Table 1) [1,2]. These new genes which were found in the liver have been demonstrated to be closely related to liver diseases such as viral hepatitis, liver fibrosis, fatty liver, and hepatocellular carcinoma (HCC) (Figure 1).

For several decades, our group was committed to studying of these 127 new genes, providing a new research perspective for liver diseases. Hepatitis C virus core protein-binding protein 6 (HCBP6) upregulates sterol regulatory element-binding protein 1c (SREBP1c) expression by binding to the C/EBPβ-binding site in the SREBP1c promoter [3] and then modulating intracellular triglyceride homeostasis [4]. Hepatitis C virus nonstructural protein 5A trans-activated protein 6 (NS5ATP6) regulates the intracellular triglyceride level via fibroblast growth factor 21 (FGF21), and independently of sirtuin1 (SIRT1) and SREBP1 [5]. HCV promotes the profibrogenic effect of HCV NS5A-transactivated protein 13 (NS5ATP13), by transforming growth factor β1/Sekelso mothers against decapentaplegic homolog 3 (TGFβ1/Smad3) and nuclear factor κB (NF-κB) signal pathways. Moreover, as a pro-fibrogenic factor, NS5ATP13 expression is down-regulated by CX-4945, a CK2 specific inhibitor [6]. Besides, NS5ATP13 promotes the proliferation and migration of HepG2 cells (human hepatoblastoma HepG2 cell line). Also, oxymatrine (OMT) may inhibit liver cancer progression by down-regulating NS5ATP13 expression [7]. Hepatitis C virus nonstructural protein 5A-associated binding protein 37 (NS5ABP37) inhibits cancer cell proliferation and promotes its apoptosis, by altering SREBP-dependent lipogenesis and cholesterogenesis and inducing oxidative stress and endoplasmic reticulum stress [8]. In HCC, hepatitis B virus X Ag-transactivated protein 8 (XTP8) acts as a valuable prognostic predictor by forming a positive feedback loop with FOXM1 oncogene [9]. Hepatitis C virus p7 trans-regulated protein 3 (p7TP3), the direct target gene of miR-182-5p, inhibits HCC by...
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Figure 1. Main achievements of new genes
suppressing migration, invasion, adhesion, proliferation and cell cycle progression of liver cancer cell via Wnt/β-catenin signaling pathway, which suggests that p7TP3 might be a new promising tumor suppressor [10]. HBX protein trans-activate gene (XTP4) suppresses apoptosis of HepG2 by up-regulating Bcl-2 and Bax expression [11], and promotes the migration and invasion of HepG2 via regulation of epithelial-mesenchymal transition (EMT) related molecules E-cadherin and N-cadherin [12]. HBV PS1 trans-activator protein 2 (PS1TP2) inhibits apoptosis of HepG2 via the mitochondrial pathway, and promotes proliferation via adenosine 5-monophosphate-activated protein kinase (AMPK) pathway [13]. Besides, NS5ATP9 is a new gene that has been widely recognized in various fields over recent years.

| Serial number | Gene name | Registration number (GenBank) |
|---------------|-----------|-----------------------------|
| 19            | XTP4      | AF490253                    |
| 20            | XTP5      | AF490254                    |
| 21            | XTP6      | AF490255                    |
| 22            | XTP7      | AF490256                    |
| 23            | XTP8      | AF490257                    |
| 24            | XTP9      | AF490258                    |
| 25            | XTP10     | NM_001326303                |
| 26            | X-30      | AY280722                    |
| 27            | C1        | AY555145                    |
| 28            | C2        | AF530058                    |
| 29            | C12       | AF529371                    |
| 30            | E2BP1     | AY459290                    |
| 31            | E2BP2     | AF529373                    |
| 32            | E2BP3     | DQ294736                    |
| 33            | E2BP4     | AF189768                    |
| 34            | EBP1      | AF529372                    |
| 35            | EBP2      | AF529373                    |
| 36            | EBP3      | AF530058                    |
| 37            | EBP4      | AY134474                    |
| 38            | EBP19     | AF529373                    |
| 39            | EBP36     | AY189820                    |
| 40            | HCBP1     | AF359506                    |
| 41            | HCBP6     | AY032594                    |
| 42            | HCBP12    | AF395068                    |
| 43            | HCTP4     | AY734680                    |
| 44            | NS3BP     | AF435951                    |
| 45            | NS3TP1    | AY116969                    |
| 46            | NS3TP2    | AY116970                    |
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| 47 | NS3TP6 | XM_017004595 |
|----|--------|-------------|
| 48 | PreS1BP1 | AY535000 |
| 49 | PS2BP1 | AF497566 |
| 50 | SBP1 | AY281252 |
| 51 | TAHCCP1 | AY038359 |
| 52 | TAHCCP2 | AY039043 |
| 53 | TTP1 | AF407672 |
| 54 | XBP-1 | AF529374 |
| 55 | LRRP1 | AY358788 |
| 56 | PS1TP1 | AY646229 |
| 57 | PS1TP2 | AY426673 |
| 58 | PS1TP3 | AY426674 |
| 59 | PS1TP4 | AY427952 |
| 60 | PS1TP5TP1 | AY861801 |
| 61 | PS1TP6 | AY444749 |
| 62 | PS2TP1 | AY561706 |
| 63 | PS2TP2 | AY561707 |
| 64 | PS2TP3 | AY561704 |
| 65 | PS2TP4 | AY561705 |
| 66 | CSTP1 | AY553877 |
| 67 | PS1TP3BP1 | DQ910907 |
| 68 | NS5ATP13TP1 | AY459295 |
| 69 | NS5ATP13TP2 | AY459296 |
| 70 | HBeAgTP | AY423624 |
| 71 | PFAAP1 | AF530059 |
| 72 | PFAAP2 | AF530060 |
| 73 | PFAAP3 | AF530061 |
| 74 | PFAAP4 | AF530062 |
| 75 | PFAAP5 | AF530063 |
| 76 | FBP2 | AY553876 |
| 77 | FBP1 | AY553875 |
| 78 | NS5ATP5BP1 | AY459291 |
| 79 | HCTP4BP | AY390431 |
| 80 | NS5ATP1BP16 | AY390430 |
| 81 | NS5ABP37 | AY543840 |
| 82 | XTP3TPB | AY453410 |
| 83 | XTP3TPA | AY453409 |
| 84 | DNAPTP1 | AY450389 |
| 85 | DNAPTP2 | AY450390 |
| 86 | DNAPTP3 | AY450391 |
| 87 | DNAPTP4 | AY450392 |
| 88 | DNAPTP5 | AY450393 |
| 89 | DNAPTP6 | AY450394 |
| 90 | PPS22-1 | AY498718 |
| 91 | NS3TP2TP | AY425618 |
| 92 | NS5ATP6TP1 | AY339614 |
| 93 | NS5ATP6TP2 | AY339615 |
| 94 | HuALR | AF146394 |
| 95 | P7TP3 | AY820138 |
| 96 | P7TP2 | AY819648 |
| 97 | AsTP3 | AY744367 |
| 98 | AsTP2 | AY744366 |
| 99 | FTP2 | AY740522 |
| 100 | AsTP | AY720898 |
| 101 | AsTP1 | AY605064 |
| 102 | XTP13 | AY631401 |
For several decades, our group was committed to studying these 127 new genes, providing a new research perspective for liver diseases. Hepatitis C virus core protein-binding protein 6 (HCBP6) upregulates sterol regulatory element-binding protein 1c (SREBP1c) expression by binding to the C/EBPβ-binding site in the SREBP1c promoter [3] and then modulating intracellular triglyceride homeostasis [4]. Hepatitis C virus nonstructural protein 5A trans-activated protein 6 (NS5ATP6) regulates the intracellular triglyceride level via fibroblast growth factor 21 (FGF21), and independently of sirtuin 1 (SIRT1) and SREBP1 [5]. HCV promotes the profibrogenic effect of HCV NS5A-transactivated protein 13 (NS5ATP13), by transforming growth factor β1/Sekelsky mothers against decapentaplegic homolog 3 (TGFβ1/Smad3) and nuclear factor κB (NF-κB) signal pathways. Moreover, as a pro-fibrogenic factor, NS5ATP13 expression is down-regulated by CX-4945, a CK2 specific inhibitor [6]. Besides, NS5ATP13 promotes the proliferation and migration of HepG2 cells (human hepatoblastoma HepG2 cell line). Also, oxymatrine (OMT) may inhibit liver cancer progression by down-regulating NS5ATP13 expression [7]. Hepatitis C virus nonstructural protein 5A-associated binding protein 37 (NS5ABP37) inhibits cancer cell proliferation and promotes its apoptosis, by altering SREBP-dependent lipogenesis and cholesterogenesis and inducing oxidative stress and endoplasmic reticulum stress [8]. In HCC, hepatitis B virus X Ag-transactivated protein 8 (XTP8) acts as a valuable prognostic predictor by forming a positive feedback loop with FOXM1 oncogene [9]. Hepatitis C virus p7 trans-regulated protein 3 (p7TP3), the direct target gene of miR-182-5p, inhibits HCC by suppressing migration, invasion, adhesion, proliferation and cell cycle progression of liver cancer cell via Wnt/β-catenin signaling pathway, which suggests that p7TP3 might be a new promising tumor suppressor [10]. HBX protein trans-activate gene (XTP4) suppresses apoptosis of HepG2 by up-regulating Bcl-2 and Bax expression [11], and promotes the migration and invasion of HepG2 via regulation of epithelial-mesenchymal transition (EMT) related molecules E-cadherin and N-cadherin [12]. HBV PS1 trans-activator protein 2 (PS1TP2) inhibits apoptosis of HepG2 via the mitochondrial pathway, and promotes proliferation via adenosine 5-monophosphate-activated protein kinase (AMPK) pathway [13]. Besides, NS5ATP9 is a new gene that has been widely recognized in various fields over recent years.

**NS5ATP9**

NS5ATP9 genomic DNA, which is located on human chromosome 15q22.1, encodes a protein with 111 amino acid residues [14]. It is also known as KIAA0101, OEACT-1, P15PAF, L5, PCNA-associated factor (PAF), and is registered in GenBank under the AF529370 registration number. NS5ATP9 participates in many physiological functions, such as cartilage formation [15], DNA damage repair [16], cell cycle regulation [17], the maturation and
Endogenous NS5ATP9 expression is overexpressed in CCl4-induced liver fibrosis mouse models and TGFβ1-treated hepatic stellate cells (HSCs) [23]. In LX2 cells (human HSC cell line), NS5ATP9 directly binds to Smad3 and inhibits its phosphorylation, which induces the suppression of the TGFβ1/Smad3 signal pathway [24]. Besides, compared with wild type mice, NS5ATP9 deficiency results in significantly higher levels of ECM deposition, indicating that NS5ATP9 attenuates liver fibrosis in vivo and in vitro [23]. In lung fibroblasts, NS5ATP9 suppresses its activation via the TGFβ1/Smad3 signal pathway [25]. These studies confirmed that NS5ATP9 inhibits liver fibrosis and lung fibrosis.

**Drugs Screening**

Given that NS5ATP9 is a potential therapeutic target for liver fibrosis and lung fibrosis, drugs or small molecule compounds targeted at NS5ATP9 are expected to treat fibrosis. In primary vaginal epithelial cells, expression of NS5ATP9 in mRNA level is up-regulated after cells are stimulated by TDF for 1 or 7 days [26]. Therefore, we hypothesized that TDF and its pro-drug, TAF, may promote regression of fibrosis via up-regulated NS5ATP9.

In vivo, TAF inhibits both CCl4-induced liver fibrosis and bleomycin-induced pulmonary fibrosis, while inhibits activation of HSCs and lung fibroblasts in vitro [23,25]. Previous studies have also shown that TDF/TAF inhibit liver fibrosis by inhibiting TGFβ1/Smad3 and NF-κB/NLRP3 inflammasome signaling pathways activation and regulating the differentiation, activation, and proliferation of HSCs [23].

Consistent with previous findings [14], TDF/TAF upregulate NS5ATP9 expression both in the liver and in the lung. By using dual-luciferase reporter assays, we showed that NS5ATP9 promoter activity was upregulated by TDF and TAF. Therefore, TDF/TAF could prevent progression and promote the reversion of fibrosis by upregulating the expression of NS5ATP9.

**Conclusions and Perspectives**

In summary, our study proposed a novel role of TDF/TAF in fibrosis progression through assembling TGFβ1/Smad3 and NF-κB/NLRP3 inflammasome signaling pathways via upregulating the expression of NS5ATP9, thus defining NS5ATP9 as a potential therapeutic target and TDF/TAF as novel drugs for fibrosis.

**Challenges**

Fibrosis is defined as the accumulation of extracellular matrix (ECM) in specific organs. TDF/TAF inhibits liver fibrosis and lung fibrosis in mouse models. However, to elucidate the role of TDF/TAF in clinic, we asked the following questions: 1. Do the results from mouse experiments translate to human liver fibrosis and lung fibrosis? So results in a large, prospective, double-blind study are needed [27]. 2. Do TDF and TAF inhibit fibrosis in other organs or fibrosis due to other causes, such as bile duct ligation (BDL)-induced liver fibrosis [28]? 3. When used to treat different organ fibrosis, what is the optimal time and dosages of TDF/TAF? This means that the pharmacokinetics of TDF and TAF in liver fibrosis are indispensable [29]. 4. New insight into liver fibrosis therapy is that the intercellular crosstalk between HSCs and those “responded” cells (such as hepatic macrophages and natural killer/natural killer T cells) has been a critical event involved in HSC activation and fibrogenesis [30]. We propose that TDF and TAF inhibit NF-κB/NLRP3 inflammasome in mice [17]. However, how TDF and TAF affect the inflammation and immune system is not completely solved.

**Opportunities**

Compared with other novel treatment strategies, such as low-energy extracorporeal shock waves [31], hyperbranched lipid-based lipid nanoparticles [32], acetyl-CoA carboxylase [33], as marketed drugs, adverse reactions to TDF/TAF can be effectively followed up with broad physician support, and an adequate number of patients. In addition, the cooperation of multiple clinical departments could fill the gap related to TDF/TAF in the treatment of fibrosis affecting other organs.

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