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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/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

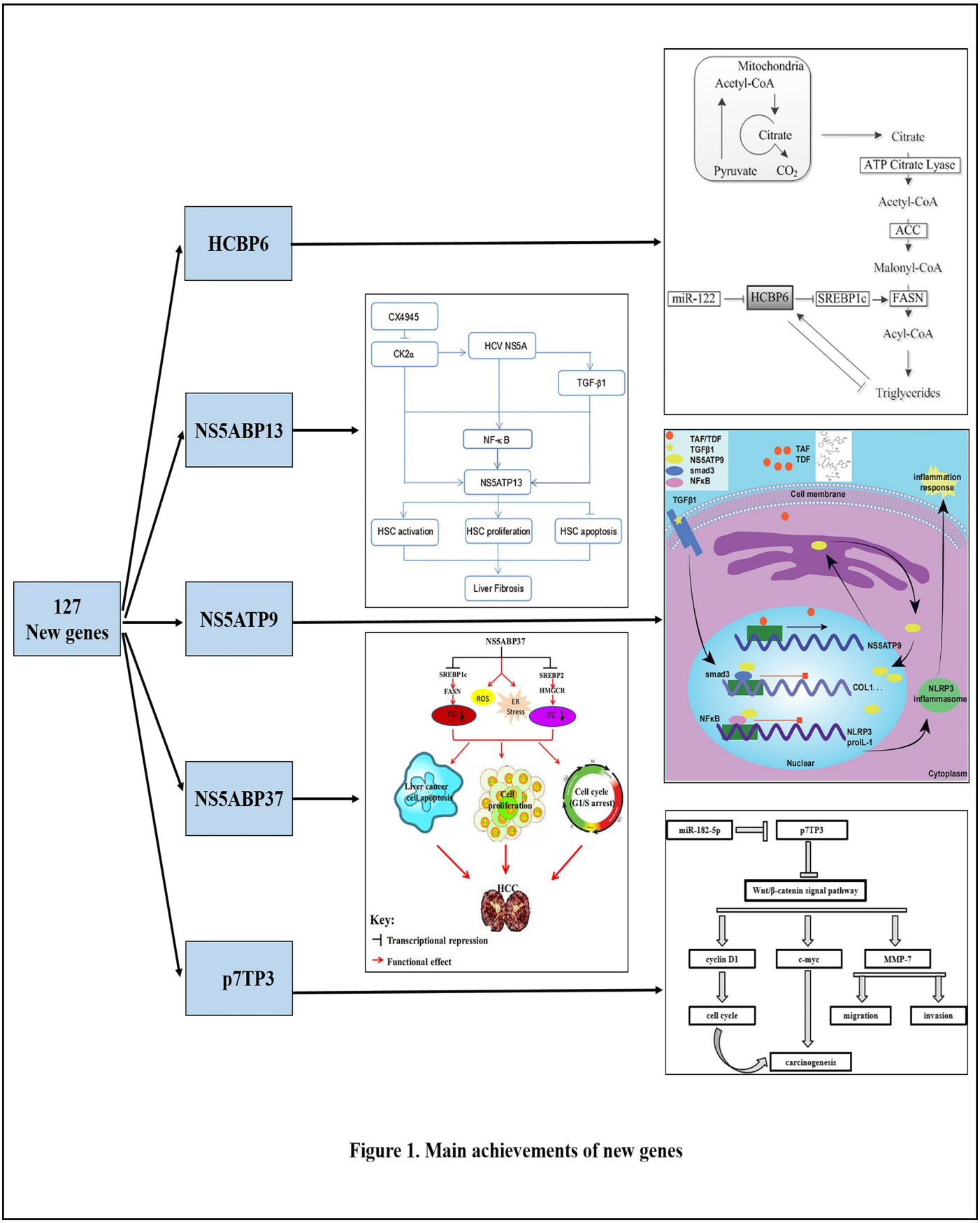

Figure 1. Main achievements of new genes

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)
1	NS5ATP1	AF529362
2	NS5ATP2	AF529363
3	NS5ATP3	AF529364
4	NS5ATP4	AF529365
5	NS5ATP5	AF529366
6	NS5ATP6	AF529367
7	NS5ATP7	AF529368
8	NS5ATP8	AF529369
9	NS5ATP9	AF529370
10	NS5ATP10	AK000514
11	NS5ATP11	AK091427
12	DNAPTP1TPA	DQ414820
13	NS5ATP13	AY820769
14	NS5BBP1	BC020596
15	MBP1	DQ307498
16	XTP1	AF488828
17	XTP2	AF488829
18	XTP3	AF490252
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

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	ABF61801
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	AF543840
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

103	NS5ATP4A	DQ908899
104	NS5ATP4ABP1	DQ630520
105	PS1TP5	AY427953
106	XTP3TPATP1	DQ457058
107	FTP1	AY605045
108	XTP12	AY598792
109	PS1TP5BP1	DQ471327
110	P7TP1	AY596776
111	NS3TP6BP2	AC097504
112	NS3TP6BP3	AC023785
113	TTG1	DQ323046
114	XTP11	AY740520
115	DNAPTP1BP1	DQ414819
116	DNAPTP1TP	DQ451688
117	HBEBP2BPA	DQ499597
118	HBEBP2BPB	DQ499598
119	HBEBP2BPC	DQ499599
120	NS2TP	AY605046
121	NS4ATP1	AY740521
122	NS4ATP2	AY846876
123	TTG1A	DQ529299
124	PS1TP2BP1	DQ787424
125	HCBP12BPA	DQ499468
126	XTP3TPATP2	DQ457059
127	NS3TP6BP1	AC124014

Table 1: 127 new genes.

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/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

development of hematopoietic stem/progenitor cells [18], and so on. In addition, different kinds of tumor development are associated with uncontrolled expression of NS5ATP9, including HCC [19], breast cancer [20], thyroid carcinoma [21], and non-small cell lung cancer [22].

Endogenous NS5ATP9 expression is overexpressed in CCl_4-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 CCl_4-induced liver fibrosis and bleomycin-induced pulmonary fibrosis, while TAF 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 lipoid-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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