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S100A11: A promising biomarker for next-gen treatment of liver disease?

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Chronic liver disease is one of the most prevalent causes of morbidity and mortality worldwide. It has been closely associated with various types of metabolic diseases such as diabetes, obesity, and cardiovascular disease [1,2]. Many different types of factors including viral infections, alcohol abuse, nonalcoholic steatohepatitis (NASH), autoimmune disorders, and metabolic diseases can promote the development of chronic liver disease. The potential involvement of these variable factors results in the complexity and diversity of liver disease [3,4]. Chronic liver disease can progress from nonalcoholic fatty liver disease (NAFLD) to NASH, eventually leading to fibrosis and cirrhosis and ultimately, in some cases, hepatocellular cancer (HCC) [5]. The molecular basis of the development and progression of chronic liver disease are still very poorly understood. When taken altogether, these facts reveal an urgent and unmet need for extensive research efforts into the mechanisms for how chronic liver disease develops and progresses.

The widespread use of animal models has helped us uncover the molecular basis of the development and progression of many human diseases. As an example, the db/db mouse model was used in our recent study to uncover that functionalized gadofullerene ameliorates impaired glycolipid metabolism in type 2 diabetes [6]. Choosing a suitable animal model is critical for the capacity to perform more accurate disease research. Unfortunately, there are very limited numbers of animal model systems for human-related disease research, and the present systems are not enough to deeply and completely reveal these disease-related molecular processes. Based on practical problems and theoretical foundations, developing, and establishing new animal models to screen for potential key pathogenic factors for specific diseases is indeed needed. To solve these limitations, we first worked with other teams to annotate the genome sequence of the Chinese tree shrew (Tupaia belangeri chinensis), a close relative of primates, to provide a genetic basis for the use of this animal as a model for biomedical research [7,8]. Using this resource and Next-Generation sequencing transcriptome profiles we further created a tree shrew diabetes model [9]. Most importantly, our data revealed that the tree shrew may be useful as a novel animal model for the research of human non-obese NAFLD [10,11]. Collectively, these works suggest a novel and important role for the tree shrew as an animal model system.

The latest study in our laboratory [12] established a tree shrew model of the different stages of liver disease to uncover the pathogenic factors involved during chronic liver disease progression. Tree shews fed with a high-fat high-cholesterol (HFHC) diet progressively developed a steatosis, NASH, and fibrosis phenotype. Using an unbiased comparative proteomic analysis of the normal liver compared to different stages of liver disease, the calcium binding protein A11 (S100A11) was markedly induced in liver disease progression. This protein is a member of the S100 family containing two EF-hands (for more detailed information please see our previous review [13]). Experimentally, the overexpression of S100A11 accelerated the deposition of lipids both in hepatic cell lines and in the mouse liver. Mechanistically, high levels of the S100A11 protein competitively interacts with HDAC6 (histone deacetylase 6) to block the binding between HDAC6 and FOXO1 (forkhead box O1 in NAFLD). Blocking/sequestering of the deacetylase promotes the accumulation of the acetylated transcription factor FOXO1 consequently activating autophagy and lipogenesis pathways to accelerate lipid accumulation in the liver. Our result implies that S100A11 may promote the progression from NAFLD to the more severe nonalcoholic steatohepatitis. Consistent with our research, an increasing number of studies show the important role of S100A11 in the onset and progression of human disease, including inflammation [14-16], tumors [17-21] and fibrosis [22-24].

NAFLD and NASH

NAFLD and NASH are the most reported causes of liver disease, which present a worldwide epidemiology and demographic characteristics and will probably emerge as the leading cause of end-stage liver disease in the coming decades [25]. As aforementioned, our latest study identified S100A11 as a key pathogenic factor during chronic liver disease progression by establishing the tree shrew model for the different stages of liver disease and through using an unbiased comparative proteomic analysis [12]. Both in vitro and in vivo studies indicated the potential role of S100A11 in NAFLD and NASH for both diagnosis and treatment. Additionally, Oh *et al.* [26] conducted time course microarrays (2, 4, 6, 8, 12, 16, 20, 24 weeks) on the liver from long-term, high fat diet fed C57BL/6J mice and revealed that S100A11 showed a time-dependent expression pattern underlying the development of diet-induced obesity and non-alcoholic steatohepatitis. Also, in agreement with our findings, Teng *et al.* [27] demonstrated that S100A11 can promote the progression of NAFLD, in which, S100A11 acted as a positive regulator of AKT/mTOR signaling to induce lipid synthesis and increase lipid deposition. In a methionine choline deficiency diet (MCD) -induced model, S100A11 overexpression increased the lipid accumulation and inflammation in mouse liver [28]. Similar to S100A11 in NAFLD and NASH, other

S100 family members (eg, S100A4, S100A8, and S100A9) have been shown to exert a key role in NAFLD [29-31].

Fibrosis and cirrhosis

Fibrosis and cirrhosis often occur in many kinds of chronic liver disease, then hepatic stellate cell was activated and secrete extracellular matrix proteins that generate the fibrous scar [32]. Previous studies reported that patients with non-cirrhotic chronic liver disease may have an increased mortality rate when compared to controls, which are closely with mortality and morbidity [33]. Interestingly, our tree shrew model proteomic analysis [12], and the time-dependent expression microarrays analysis [26] suggested a pro-fibrotic role of S100A11 in liver fibrosis. Another study in our lab (unpublished) found that S100A11 is activated in mice, rat, tree shrew, and humans with liver fibrosis. Both in vivo and in vitro overexpression of S100A11displayed an ability to exacerbate liver fibrosis; in contrast, inhibition of S100A11 improved liver fibrosis. In agreement with these results, Sobolewski et al. also showed that S100A11 upregulation significantly contributes to inflammation and fibrosis development, which are key drivers of hepatocarcinogenesis [28]. Furthermore, a recent study shown that overexpression of S100A11 reversed the inhibition of Tranilast on AngII-induced over-proliferation, migration, and fibrosis in human cardiac fibroblasts, accompanied by an activation of the TGF-β/Smad pathway [34]. Furthermore, S100A11 expression is increased during lung fibrosis and adenocarcinoma progression [23]. Finally, proteomic analyses identified S100A11 as a new regulator of Aldo-induced collagen production in human cardiac fibroblasts [22].

Hepatocellular cancer (HCC)

HCC is one of the main cancers leading to cancer-related death worldwide. It was ranked sixth in incidence and fourth in mortality, having approximately 840,000 new cases and causing over 780,000 deaths per year according to the World Health Organization's statistics in 2018 [35,36]. Analysis of the proteome of steatotic liver tissues from mice spontaneously developing HCC identified S100A11 as playing a key role in this process. The inflammatory, pro-fibrotic, and oncogenic role of S100A11 in vivo, in vitro, and ex-vivo analyses, strongly indicated a main driver role of S100A11 in hepatocarcinogenesis [28]. Additionally, high levels of RNA expression of S100A11 in human HCC tumors in TCGA (the Cancer Genome Atlas), along with high levels of protein detected by immunohistochemistry, are associated with poor survival of HCC patients [37,38]. S100A11 also has a role in the epithelial-mesenchymal transition (EMT) during HCC metastasis. S100A11 contributes to a higher liver matrix stiffness-induced EMT, with S100A11 translocating through the cell membrane during higher stiffness-induced EMT in HCC metastasis [39]. Related to the EMT, Luo et al. demonstrated epidermal growth factor receptor variant III (EGFRvIII) mediates hepatocellular carcinoma cell invasion by promoting S100A11 expression [40]. In a study of the role of S100A11 in intrahepatic cholangiocarcinoma (ICC), it was shown that S100A11 was increased in ICC tumor tissues, promotes the TGF-β-induced EMT through the SMAD2/3 signaling pathway, and further findings suggested that the S100A11/P38/MAPK signaling pathway may be a potential therapeutic target for ICC patients [41,42].

Liver diseases, including NAFLD, NASH, alcoholic liver disease (ALD), fibrosis, cirrhosis, and HCC are major causes of illness and death worldwide. Liver disease causes serious public health problems because of its high prevalence and the limited effective diagnosis and treatment targets. As a disease having a poor long-term clinical outcome, the complex diversity of pathogenic factors and different molecular events in the liver pathological process urgently require new diagnostic markers and therapeutic targets. By establishing and utilizing a new animal model, the Chinese tree shrew, we identified S100A11, which plays an important role in different pathological processes in the liver. Our research results combined with other teams suggest that S100A11 can promote the occurrence and development of NAFLD, NASH, liver fibrosis, and liver cancer (Figure 1). Altogether, these exciting findings reveal the potential value of S100A11 as a target for diagnosis and treatment of liver diseases in the future.

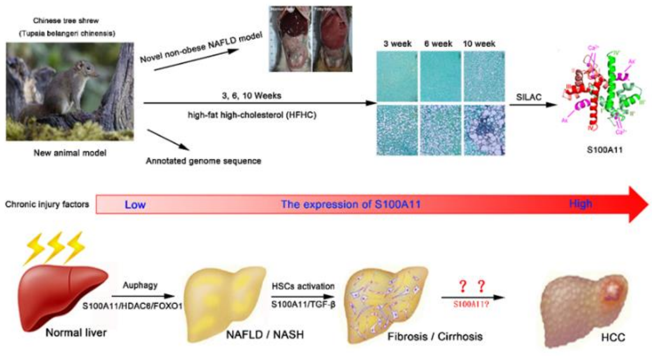

Figure 1: S100A11 in liver diseases

Annotating the genome sequence and establishing non-obese NAFLD of Chinese tree shrew (*Tupaia belangeri chinensis*) as novel animal model. Tree shews fed with a HFHC diet progressively developed the different stages of liver disease (steatosis, NASH, and fibrosis). Using an unbiased comparative proteomic analysis of the normal liver compared to different stages of liver disease, the calcium binding protein A11 (S100A11) was markedly induced in liver disease progression. In NAFLD/NASH, high level of the S100A11 protein competitively interacts with HDAC6 to block the binding between HDAC6 and FOXO1. Blocking/sequestering of the deacetylase promotes the accumulation of the acetylated transcription factor FOXO1 consequently activating autophagy and lipogenesis pathways to accelerate lipid accumulation in the liver. Meanwhile, the S100A11 could promote liver fibrosis through activating the hepatic stellate cells by mediating the TGF-β pathway.

So far, the current research on S100A11 in liver disease is very limited, and there are still many challenges to be overcome in the future. First, the specific mechanism of action of S100A11 at specific stages of liver disease, and the relationship with other S100 proteins of this family needs to be studied further. Secondly, the specific molecular function, mechanism(s), and crosstalk of S100A11 in different types of liver cells at different stages of liver disease require a large number of animal and human clinical studies because of the multiple types of cells found in the liver. Thirdly, in view of the potential application of S100A11 in the diagnosis and treatment of liver diseases, large-scale clinical blood verification and detection kits, monoclonal antibodies, ELISA conditions, etc. need to be further strengthened. Based on the current understanding of S100A11 in the pathogenesis of chronic liver diseases, we believe that S100A11 may facilitate the earlier diagnosis and generation of new treatments for liver disease in the future.

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References

1. Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, et al. Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. *J Hepatol.* 2018; 69: 718-735.
2. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol.* 2019; 70: 151-171.

3. Hernandez-Gea V, Friedman SL. Pathogenesis of liver fibrosis. *Annu Rev Pathol.* 2011; 6: 425-456.
4. Bataller R, Brenner DA. Liver fibrosis. *The Journal of clinical investigation.* 2005; 115: 209-218.
5. Tanwar S, Rhodes F, Srivastava A, Trembling PM, Rosenberg WM. Inflammation and fibrosis in chronic liver diseases including non-alcoholic fatty liver disease and hepatitis C. *World J Gastroenterol.* 2020; 26: 109-133.
6. Wu J, Chen Y, Li X, Ran L, Liu X, et al. Functionalized Gadofullerene Ameliorates Impaired Glycolipid Metabolism in Type 2 Diabetic Mice. *J Genet Genomics.* 2021; S1673-8527(21)00319-2
7. Fan Y, Huang ZY, Cao CC, Chen CS, Chen YX, et al. Genome of the Chinese tree shrew. *Nat Commun.* 2013; 4: 1426.
8. Xu L, Zhang Y, Liang B, Lü LB, Chen CS, et al. [Tree shrews under the spotlight: emerging model of human diseases]. *Dongwuxue Yanjiu.* 2013; 34: 59-69.
9. Wu X, Xu H, Zhang Z, Chang Q, Liao S, et al. Transcriptome Profiles Using Next-Generation Sequencing Reveal Liver Changes in the Early Stage of Diabetes in Tree Shrew (Tupaia belangeri chinensis). *J Diabetes Res.* 2016; 2016: 6238526.
10. Zhang L, Wu X, Liao S, Li Y, Zhang Z, et al. Tree shrew (Tupaia belangeri chinensis), a novel non-obese animal model of non-alcoholic fatty liver disease. *Biol Open.* 2016; 5: 1545-1552.
11. Zhang L, Zhang Z, Li Y, Liao S, Wu X, et al. Cholesterol induces lipoprotein lipase expression in a tree shrew (Tupaia belangeri chinensis) model of non-alcoholic fatty liver disease. *Scientific reports.* 2015; 5: 15970.
12. Zhang L, Zhang Z, Li C, Zhu T, Gao J, et al. S100A11 Promotes Liver Steatosis via FOXO1-Mediated Autophagy and Lipogenesis. *Cell Mol Gastroenterol Hepatol.* 2021; 11: 697-724.
13. Zhang L, Zhu T, Miao H, Liang B. The Calcium Binding Protein S100A11 and Its Roles in Diseases. *Front Cell Dev Biol.* 2021; 9: 693262.
14. Safronova A, Araujo A, Camanzo ET, Moon TJ, Elliott MR, et al. Alarmin S100A11 initiates a chemokine response to the human pathogen Toxoplasma gondii. *Nat Immunol.* 2019; 20: 64-72.
15. Zhang Y, Yang X, Zhu XL, Bai H, Wang ZZ, et al. S100A gene family: immune-related prognostic biomarkers and therapeutic targets for low-grade glioma. *Aging (Albany NY).* 2021; 13: 15459-15478.
16. Bin L, Howell MD, Kim BE, Hall CF, Streib JE, et al. Inhibition of S100A11 gene expression impairs keratinocyte response against vaccinia virus through downregulation of the IL-10 receptor 2 chain. *J Allergy Clin Immunol.* 2009; 124: 270-277, 277.e1.
17. Tu Y, Xie P, Du X, Fan L, Bao Z, et al. S100A11 functions as novel oncogene in glioblastoma via S100A11/ANXA2/NF-κB positive feedback loop. *J Cell Mol Med.* 2019; 23: 6907-6918.
18. Xiao M, Li T, Ji Y, Jiang F, Ni W, et al. S100A11 promotes human pancreatic cancer PANC-1 cell proliferation and is involved in the PI3K/AKT signaling pathway. *Oncol Lett.* 2018; 15: 175-182.
19. Sato H, Sakaguchi M, Yamamoto H. Therapeutic potential of targeting S100A11 in malignant pleural mesothelioma. 2018; 7: 11.
20. Xie P, Du X, Fan L, Bao Z, Sun G, et al. LASP1-S100A11 axis promotes colorectal cancer aggressiveness by modulating TGFβ/Smad signaling. *Journal of cellular and molecular medicine.* 2016; 6: 26112.
21. Sato H, Sakaguchi M, Yamamoto H, Tomida S, Aoe K, et al. Therapeutic potential of targeting S100A11 in malignant pleural mesothelioma. *Oncogenesis.* 2018; 7:11.
22. Martínez-Martínez E, Ibarrola J, Lachén-Montes M, Fernández-Celis A, Jaisser F, et al. Differential proteomics reveals S100-A11 as a key factor in aldosterone-induced collagen expression in human cardiac fibroblasts. *J Proteomics.* 2017; 166: 93-100.
23. Gocheva V, Naba A, Bhutkar A, Guardia T, Miller KM, et al. Quantitative proteomics identify Tenascin-C as a promoter of lung cancer progression and contributor to a signature prognostic of patient survival. *Proc Natl Acad Sci U S A.* 2017; 114: E5625-E5634.
24. Doubková M, Karpíšek M, Mazoch J, Skřičková J, Doubek M. Prognostic significance of surfactant protein A, surfactant protein D, Clara cell protein 16, S100 protein, trefoil factor 3, and prostatic secretory protein 94 in idiopathic pulmonary fibrosis, sarcoidosis, and chronic pulmonary obstructive disease. *Sarcoidosis Vasc Diffuse Lung Dis.* 2016; 33: 224-234.
25. Younossi Z, Anstee QM, Marietti M, Hardy T, Henry L, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol.* 2018; 15: 11-20.
26. Oh HY, Shin SK, Heo HS, Ahn JS, Kwon EY, et al. Time-dependent network analysis reveals molecular targets underlying the development of diet-induced obesity and non-alcoholic steatohepatitis. *Genes Nutr.* 2013; 8: 301-316.
27. Teng F, Jiang J, Zhang J, Yuan Y, Li K, et al. The S100 calcium-binding protein A11 promotes hepatic steatosis through RAGE-mediated AKT-mTOR signaling. *Metabolism.* 2021; 117: 154725.
28. Sobolewski C, Abegg D, Berthou F, Dolicka D, Calo N, et al. S100A11/ANXA2 belongs to a tumour suppressor/oncogene network deregulated early with steatosis and involved in inflammation and hepatocellular carcinoma development. *Gut.* 2020; 69: 1841-1854.
29. Zhang YH, Ma Q, Ding P, Li J, Chen LL, et al. S100A4 Gene is Crucial for Methionine-Choline-Deficient Diet-Induced Non-Alcoholic Fatty Liver Disease in Mice. *Yonsei Med J.* 2018; 59: 1064-1071.
30. Mukai K, Miyagi T, Nishio K, Yokoyama Y, Yoshioka T, et al. S100A8 Production in CXCR2-Expressing CD11b+Gr-1high Cells Aggravates Hepatitis in Mice Fed a High-Fat and High-Cholesterol Diet. *J Immunol.* 2016; 196: 395-406.
31. Liu YF, Wei JY, Shi MH, Jiang H, Zhou J. Glucocorticoid Induces Hepatic Steatosis by Inhibiting Activating Transcription Factor 3 (ATF3)/S100A9 Protein Signalling in Granulocytic Myeloid-derived Suppressor Cells. *J Biol Chem.* 2016; 291: 21771-21785.
32. Kisseleva T, Brenner D. Molecular and cellular mechanisms of liver fibrosis and its regression. *Nat Rev Gastroenterol Hepatol.* 2021; 18: 151-166.
33. Sharma S, Khalili K, Nguyen GC. Non-invasive diagnosis of advanced fibrosis and cirrhosis. *World J Gastroenterol.* 2014; 20: 16820-30.
34. Chen Y, Huang M, Yan Y, He D. Tranilast inhibits angiotensin II-induced myocardial fibrosis through S100A11/ transforming growth factor-β (TGF-β1)/Smad axis. *Bioengineered.* 2021; 12: 8447-8456.
35. Chen Z, Xie H, Hu M, Huang T, Hu Y, et al. Recent progress in treatment of hepatocellular carcinoma. *Am J Cancer Res.* 2020; 10: 2993-3036.
36. El Jabbour T, Lagana SM, Lee H. Update on hepatocellular carcinoma: Pathologists' review. *World J Gastroenterol.* 2019; 25: 1653-1665.
37. Lee HY, Chen CK, Ho CM, Lee SS, Chang CY, et al. EIF3C-enhanced exosome secretion promotes angiogenesis and tumorigenesis of human hepatocellular carcinoma. *Oncotarget.* 2018; 9: 13193-13205.
38. Melle C, Ernst G, Schimmel B, Bleul A, von Eggeling F. Colon-derived liver metastasis, colorectal carcinoma, and hepatocellular carcinoma can be discriminated by the Ca(2+)-binding proteins S100A6 and S100A11. *PloS one.* 2008; 3: e3767.
39. Dong Y, Zheng Q, Wang Z, Lin X, You Y, et al. Higher matrix stiffness as an independent initiator triggers epithelial-mesenchymal transition and facilitates HCC metastasis. *Journal of hematology & oncology.* 2019; 12: 112.
40. Luo X, Xie H, Long X, Zhou M, Xu Z, et al. EGFRvIII mediates hepatocellular carcinoma cell invasion by promoting S100 calcium binding protein A11 expression. *PloS one.* 2013; 8: e83332.
41. Zhang MX, Gan W, Jing CY, Zheng SS, Yi Y, et al. S100A11 promotes cell proliferation via P38/MAPK signaling pathway in intrahepatic cholangiocarcinoma. *Mol Carcinog.* 2019; 58: 19-30.
42. Zhang M, Zheng S, Jing C, Zhang J, Shen H, et al. S100A11 promotes TGF-β1-induced epithelial-mesenchymal transition through SMAD2/3 signaling pathway in intrahepatic cholangiocarcinoma. *Future Oncol.* 2018; 14: 837-847.

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