



Published in final edited form as:

Nucl Receptor Res. 2017 ; 4: . doi:10.11131/2017/101312.

Nuclear Receptor SHP: A Critical Regulator of miRNA and lncRNA Expression and Function

Yongfeng Song^{1,2}, Shan Lu³, Jiajun Zhao¹, and Li Wang^{1,2,4,5,6}

¹Department of Endocrinology and Metabolism, Shandong Provincial Hospital affiliated to Shandong University, Jinan, Shandong, 250021, China

²Department of Physiology and Neurobiology, and the Institute for Systems Genomics, University of Connecticut, Storrs, CT 06269, USA

³Genesis Biotechnology, Trenton, NJ 08619, USA

⁴Veterans Affairs Connecticut Healthcare System, West Haven, CT 06516, USA

⁵Department of Internal Medicine, Section of Digestive Diseases, Yale University, New Haven, CT 06520, USA

⁶School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou, Zhejiang 325035, China

Abstract

Small heterodimer partner (SHP, NR0B2) is identified as a unique orphan nuclear receptor that acts as a transcriptional repressor. SHP plays a crucial role in the control of various physiological processes and in several diseases by regulating the expression of disease-specific genes. Non-coding RNAs (ncRNAs), including long noncoding RNAs (lncRNAs) and microRNAs (miRNAs), are encoded of RNAs that are transcribed but not translated into proteins, which are involved in diverse developmental and cellular processes in eukaryotic organisms. Research during the past decade has identified factors participating in the regulation of ncRNAs biogenesis and function. In this review, we summarize recent findings demonstrating a critical role of SHP as a transcriptional regulator of ncRNAs expression and function.

Keywords

Nuclear receptors; Small heterodimer partner; non-coding RNAs

This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Corresponding Author: Li Wang li.wang@uconn.edu.

Competing Interests

The authors declare no competing interests.

Author Contributions

All authors contributed to the writing of the manuscript.

1. Introduction

Small heterodimer partner (SHP, NR0B2) is a unique member of the nuclear receptor (NRs) superfamily [1]. It generally acts as a transcriptional repressor through interaction with other nuclear receptors or transcription factors (TFs) to inhibit function of these NRs or TFs on specific gene transcription, which contributes to its roles in diverse signaling pathways including metabolism and inflammation, and cell cycle [2]. Non-protein-coding RNAs (ncRNAs) account for more than 98% of the human genome, which play crucial roles in normal development and physiology [3]. ncRNAs are classified as long non-coding RNAs and small non-coding RNAs respectively based on the size of ncRNAs. Long non-coding RNAs are defined as ncRNAs that are longer than 200 nucleotides, while the length of small non-coding RNAs ranges from few to 200 nucleotides [4]. In the past, most studies were focused on elucidating the function and mechanism of ncRNAs, however, relatively little is known about the regulation of ncRNAs by NRs and TFs [5]. Growing evidence suggests that ncRNAs can be regulated at different levels, including promoter transcription, methylation, chromatin state regulation, and post-transcriptional regulation [6, 7]. In this mini-review, we will discuss the regulation of ncRNAs expression by SHP and to elaborate on their possible regulatory mechanisms.

2. The Basic Function of SHP

The most well established function of SHP in hepatic bile acid (BA) biosynthesis was demonstrated more than a decade ago using SHP knockout mice [8,9]. The increased BA levels in Shp-deficient mice could be in part associated with the increased energy metabolism and insulin sensitivity in other metabolic tissues including brown fat [10] and pancreas [11]. Interestingly, loss of SHP in leptin-deficient mice increased insulin sensitivity and diminished the severity of fatty liver [12], whereas overexpression of SHP in adipose tissue exacerbated high-fat diet-induced obesity [13]. In addition to inhibiting the rhythmic expression of BA synthetic enzymes Cyp7a1 and Cyp8b1 [14], SHP also directly represses the cholesterol biosynthesis enzyme, namely 3-hydroxy-3-methylglutaryl coenzyme A reductase [15]. On the other hand, SHP regulates hepatic glucose metabolism by disrupting AMPK-dependent repression of gluconeogenesis [16].

Liver fibrosis occurs due to the excessive accumulation of extracellular matrix proteins from activated hepatic stellate cells (HSCs) in response to liver injury. Loss of SHP sensitized liver to cholestatic liver fibrosis [17], which involved E2F1 and Egr1 transcription factors [18]. In terms of liver cancer, SHP expression was lost in human hepatocellular carcinoma (HCC) [19], which was likely attributed by SHP inhibition of hepatocyte proliferation [20], activation of apoptosis [21] and in the repression of epigenetic modifying enzymes [22, 23]. With regard to breast cancer, numerous studies provided the possibility that estrogen signaling would be specifically inhibited at multiple levels by SHP expression [24,25]. SHP as a tumor suppressor also interacts with other partners for its anti-tumor activity. Indeed, the transcriptional activity of glioma-associated oncogene homologue (Gli) was reported to be inhibited by SHP [26]. Recent studies showed that SHP is an essential negative regulator of the innate immune signaling. SHP repressed the inflammasome activation induced by toll-like receptor (TLR) [27] and NLR Family Pyrin Domain Containing 3 (NLRP3) [28] in

macrophages. A small molecule activator of SHP showed strong effect in inhibiting HCC cell migration by suppressing chemokine (C-C motif) ligand 2 (Ccl2) [29]. Overall, SHP exerts a crucial function to protect liver against various insults and injury and is indispensable to maintain bile acid, lipid and glucose homeostasis.

3. SHP Regulation of ncRNAs

It is well established that ncRNAs exhibit a broad range of functions. However, less is known how ncRNAs gene transcription is controlled by NRs. Recent studies suggest that SHP plays a pivotal role in the regulation of ncRNA expression.

3.1. SHP in microRNA regulation

3.1.1. miR-433 and miR-127—miR-433 and miR-127 are part of a miRNA cluster but are expressed from independent overlapping primary transcripts [30]. The gene structures of the miR-433-127 loci are well conserved among multiple species [31]. Further study demonstrated that the miR-433 and miR-127 promoters were commonly activated by estrogen related receptor gamma ($ERR\gamma$) which was inhibited by SHP [32], providing the 1st evidence for the regulation of miRNA expression by SHP (Figure 1A). Interestingly, miR-433 inhibited liver cancer migration by targeting cAMP response element-binding protein (CREB) [33], whereas miR-127 inhibited HCC cell migration by targeting transforming growth factor- β (TGF- β)-mediated MMP13 [34]. A new study showed that miR-127 repressed high-mobility-group protein 2 (HMGB2) to modulate pluripotency of mouse embryonic stem cells and liver tumor initiating cells [35].

3.1.2. miR-206—MiR-206, a member of the miR-1 family, was initially identified as a skeletal muscle specific miRNA [36] that played an important function in muscle development. For the regulation of miR-206 expression, TGF- β has been reported to inhibit miR-206 expression to regulate muscle differentiation [37]. We revealed a cascade “dual inhibitory” mechanism governing miR-206 gene transcription by SHP [38]. Specifically, $ERR\gamma$ transactivated the promoter of YY1 (Ying Yang 1), which repressed the transcription factor AP1 (c-Jun and c-Fos)-induced miR-206 promoter activity. The SHP inhibition of $ERR\gamma$ led to decreased YY1 expression and the derepression of YY1 on AP1 activity, ultimately leading to the activation of miR-206 (Figure 1B).

3.1.3. miR-34a—Farnesoid X Receptor (FXR), the nuclear bile acid receptor, plays a pivotal role in maintaining bile acid homeostasis [39]. The miR-34a levels were elevated in FXR null mice but decreased in obese mice when FXR signaling was activated by FXR agonist GW4064 or FXR overexpression [40]. The expression of miR-34a was downregulated by FXR involving SHP. p53 is a key activator of miR-34a [41], which is destabilized by SHP [42] and Mdm2 [43]. When FXR is activated, SHP is recruited to the miR-34a promoter to inhibit p53 occupancy in the miR-34a promoter, thereby causing repression of miR-34a gene transcription in liver [40] (Figure 1C). Under normal conditions, miR-34a levels are down-regulated by the FXR/SHP cascade pathway. However, in the livers of obese mice, the FXR/SHP pathway is dysregulated and miR-34a levels are highly

elevated, resulting in the reduced expression of its target gene SIRT1; an important regulator in the pathogenesis of metabolic disease [40].

3.1.4. miR-200c—The miR-200c was initially identified to be distinctively expressed in the lung [44], which has been demonstrated to regulate key processes in tumorigenesis, including epithelial-mesenchymal transition (EMT), migration, invasion, stem cell maintenance, stromal remodeling and oxidative stress response [45]. Transcriptional regulation is the primary level of control for miR-200c expression. Zinc finger E-box-binding protein homeobox 1 (ZEB1), which was identified as a miR-200c target [46], was shown to repress miR-200c expression in a negative feedback loop [47]. The expression of miR-200c was activated by peroxisome proliferator activated receptor alpha (PPAR α) and liver receptor homolog-1 (LRH-1) but inhibited by SHP. Knockdown of SHP dramatically enhanced the ability of the LRH-1 agonist RJW100 to induce miR-200c. Furthermore, co-expression of PPAR α and LRH-1 transactivated the miR-200c promoter, which was repressed by SHP co-expression, suggesting that SHP represses miR-200c expression by inhibiting the activity of PPAR α and LRH-1 [48] (Figure 1D).

3.2. SHP as a target of miRNAs

In spite of its critical role in the regulation of miRNA expression, SHP can also be a target of miRNAs. It was found that SHP was downregulated in multiple prostate cancer cell lines. The mature form of miR-141 was upregulated in prostate cancer cells. miR-141 can bind to SHP 3' UTR resulting in translational suppression and RNA degradation, which modulates androgen receptor transcriptional activity [49].

4. SHP in LncRNA Regulation

Despite intensive efforts aimed at understanding the function of lncRNAs, little is known about how lncRNAs are regulated transcriptionally. Several recent studies shed lights on the role of SHP in lncRNAs expression regulation.

4.1. H19

H19 is imprinted and almost exclusively expressed from the maternally inherited allele [50]. The activation of H19 in various cancers including HCC and bladder carcinoma [51] has a significant influence on tumor growth. H19 expression is low in adult human liver but is highly induced in livers with cholestatic fibrosis and cirrhosis, indicating that H19 may be involved in the pathogenesis of liver fibrosis [52]. Hepatic overexpression of the anti-apoptotic protein Bcl2 caused SHP protein degradation. SHP inhibited *H19* RNA expression. Therefore, in Bcl2 over-expressed mice, H19 was markedly induced due to loss of SHP repression [52]. Further detailed studies showed that bile acid accumulation induced by bile duct ligation (BDL) increased hepatic *H19* RNA expression. The up-regulation of *H19* RNA enhanced immuno-cell infiltration, activated hepatic stellate cells, and promoted cholangiocyte proliferation, which facilitated the development of cholestatic liver fibrosis [53]. A most recent study identified a novel function of H19 in non-alcoholic fatty liver disease (NAFLD) by interaction with RNA binding protein polypyrimidine tract-binding protein 1 (PTBP1) to modulate hepatic lipogenesis and glucose metabolism [54]. In

particular, *H19*RNA facilitated PTBP1's association with SREBP1c mRNA and protein, leading to increased stability and nuclear transcriptional activity. Ectopic expression of H19 induced steatosis and pushed the liver into a "pseudo fed" state in response to fasting by promoting PTBP1-mediated SREBP1c protein cleavage and nuclear translocation. Deletion of H19 or knockdown of PTBP1 abolished high-fat and high-sucrose (HFHS) diet-induced steatosis.

4.2. MEG3

Maternally expressed gene 3 (MEG3) is an imprinted gene and plays an important role in development and growth [55]. MEG3 RNA was dramatically elevated in the liver of *Shp*^{-/-} mice compared with wild type mice, which was revealed by RNA-seq [56]. The MEG3 promoter was activated by ectopic expression of cAMP response element-binding protein (CREB), which was inhibited by SHP overexpression. Therefore, SHP inhibited MEG3 gene transcription by repressing transactivation of the MEG3 promoter [56, 57] (Figure 2). Interestingly, MEG3 interacted with RNA binding protein PTBP1 to cause SHP mRNA decay, thus providing a feedback mechanism to control SHP expression.

5. Conclusion

The diversity of ncRNAs shows a new level of the complexity of nature and makes ncRNA research relatively complex. However, due to the cell-specific expression pattern of ncRNAs, this new area gives us great opportunities to develop more personalized approaches for clinical applications and diagnosis. New lncRNAs related to human liver diseases are frequently identified which may serve as serum biomarkers [58]. More importantly, the pivotal role of SHP in the control of miRNAs and lncRNAs expression will enable new discoveries for future therapeutic intervention.

Acknowledgments

L.W. is supported by NIH R01DK104656, R01DK080440, R01ES025909, R21AA022482, R21AA024935, R01AA026322, VA Merit Award 1I01BX002634, P30 DK34989 (Yale Liver Center) and the National Natural Scientific Foundation of China (Grant No. 81572443).

References

1. Rudraiah S, Zhang X, Wang L. Nuclear Receptors as Therapeutic Targets in Liver Disease: Are We There Yet? *Annual Review of Pharmacology and Toxicology*. 2016; 56:605–626.
2. Zhang Y, Hagedorn CH, Wang L. Role of nuclear receptor SHP in metabolism and cancer. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*. 2011; 1812(8):893–908. [PubMed: 20970497]
3. Esteller M. Non-coding RNAs in human disease. *Nature Reviews Genetics*. 2011; 12(12):861–874.
4. Beermann J, Piccoli M-T, Viereck J, Thum T. Non-coding rnas in development and disease: background, mechanisms, and therapeutic approaches. *Physiological Reviews*. 2016; 96(4):1297–1325. [PubMed: 27535639]
5. Yang Z, Wang L. Regulation of microRNA expression and function by nuclear receptor signaling. *Cell & Bioscience*. 2011; 1(1) article 31.
6. Breving K, Esquela-Kerscher A. The complexities of microRNA regulation: mirandering around the rules. *The International Journal of Biochemistry & Cell Biology*. 2010; 42(8):1316–1329. [PubMed: 19800023]

7. Wu Z, Liu X, Liu L, et al. Regulation of lncRNA expression. *Cellular & Molecular Biology Letters*. 2014; 19(4):561–575. [PubMed: 25311814]
8. Wang L, Lee Y-K, Bundman D, et al. Redundant pathways for negative feedback regulation of bile acid production. *Developmental Cell*. 2002; 2(6):721–731. [PubMed: 12062085]
9. Wang L, Han Y, Kim C-S, Lee Y-K, Moore DD. Resistance of SHP-null Mice to Bile Acid-induced Liver Damage. *The Journal of Biological Chemistry*. 2003; 278(45):44475–44481. [PubMed: 12933814]
10. Wang L, Liu J, Saha P, et al. The orphan nuclear receptor SHP regulates PGC-1 α expression and energy production in brown adipocytes. *Cell Metabolism*. 2005; 2(4):227–238. [PubMed: 16213225]
11. Wang L, Huang J, Saha P, et al. Orphan Receptor Small Heterodimer Partner Is an Important Mediator of Glucose Homeostasis. *Molecular Endocrinology*. 2006; 20(11):2671–2681. [PubMed: 16803864]
12. Huang J, Iqbal J, Saha PK, et al. Molecular characterization of the role of orphan receptor small heterodimer partner in development of fatty liver. *Hepatology*. 2007; 46(1):147–157. [PubMed: 17526026]
13. Tabbi-Anneni I, Cooksey R, Gunda V, et al. Overexpression of nuclear receptor SHP in adipose tissues affects diet-induced obesity and adaptive thermogenesis. *American Journal of Physiology-Endocrinology and Metabolism*. 2010; 298(5):E961–E970. [PubMed: 20124506]
14. Lee SM, Zhang Y, Tsuchiya H, Smalling R, Jetten AM, Wang L. Small heterodimer partner/neuronal PAS domain protein 2 axis regulates the oscillation of liver lipid metabolism. *Hepatology*. 2015; 61(2):497–505. [PubMed: 25212631]
15. Datta S, Wang L, Moore DD, Osborne TF. Regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase promoter by nuclear receptors liver receptor homologue-1 and small heterodimer partner: A mechanism for differential regulation of cholesterol synthesis and uptake. *The Journal of Biological Chemistry*. 2006; 281(2):807–812. [PubMed: 16282330]
16. Chanda D, Li T, Song K-H, et al. Hepatocyte growth factor family negatively regulates hepatic gluconeogenesis via induction of orphan nuclear receptors small heterodimer partner in primary hepatocytes. *The Journal of Biological Chemistry*. 2009; 284(42):28510–28521. [PubMed: 19720831]
17. Young JP, Qatanani M, Chua SS, et al. Loss of orphan receptor small heterodimer partner sensitizes mice to liver injury from obstructive cholestasis. *Hepatology*. 2008; 47(5):1578–1586. [PubMed: 18393320]
18. Zhang Y, Xu N, Xu J, et al. E2F1 is a novel fibrogenic gene that regulates cholestatic liver fibrosis through the Egr-1/SHP/EID1 network. *Hepatology*. 2014; 60(3):919–930. [PubMed: 24619556]
19. He N, Park K, Zhang Y, Huang J, Lu S, Wang L. Epigenetic inhibition of nuclear receptor small heterodimer partner is associated with and regulates hepatocellular carcinoma growth. *Gastroenterology*. 2008; 134(3):793–802. [PubMed: 18325392]
20. Zhang Y, Xu P, Park K, Choi Y, Moore DD, Wang L. Orphan receptor small heterodimer partner suppresses tumorigenesis by modulating cyclin D1 expression and cellular proliferation. *Hepatology*. 2008; 48(1):289–298. [PubMed: 18537191]
21. Zhang Y, Soto J, Park K, et al. Nuclear receptor SHP, a death receptor that targets mitochondria, induces apoptosis and inhibits tumor growth. *Molecular and Cellular Biology*. 2010; 30(6):1341–1356. [PubMed: 20065042]
22. Zhang Y, Wang L. Nuclear receptor SHP inhibition of Dnmt1 expression via ERR γ . *FEBS Letters*. 2011; 585(9):1269–1275. [PubMed: 21459093]
23. Zhang Y, Andrews GK, Wang L. Zinc-induced Dnmt1 expression involves antagonism between MTF-1 and nuclear receptor SHP. *Nucleic Acids Research*. 2012; 40(11):4850–4860. [PubMed: 22362755]
24. Johansson L, Thomsen JS, Damdimopoulos AE, Spyrou G, Gustafsson J-A, Treuter E. The orphan nuclear receptor SHP inhibits agonist-dependent transcriptional activity of estrogen receptors ER α and ER β . *The Journal of Biological Chemistry*. 1999; 274(1):345–353. [PubMed: 9867849]

25. Kovacic A, Speed CJ, Simpson ER, Clyne CD. Inhibition of aromatase transcription via promoter II by short heterodimer partner in human preadipocytes. *Molecular Endocrinology*. 2004; 18(1): 252–259. [PubMed: 14593077]
26. Kim K, Kim KH, Cho HK, Kim HY, Kim HH, Cheong J. SHP (small heterodimer partner) suppresses the transcriptional activity and nuclear localization of Hedgehog signalling protein Gli1. *Biochemical Journal*. 2010; 427(3):413–422. [PubMed: 20175750]
27. Yuk J-M, Shin D-M, Lee H-M, et al. The orphan nuclear receptor SHP acts as a negative regulator in inflammatory signaling triggered by Toll-like receptors. *Nature Immunology*. 2011; 12(8):742–751. [PubMed: 21725320]
28. Yang C-S, Kim J-J, Kim TS, et al. Small heterodimer partner interacts with NLRP3 and negatively regulates activation of the NLRP3 inflammasome. *Nature Communications*. 2015; 6 article no. 6115.
29. Yang Z, Koehler AN, Wang L. A novel small molecule activator of nuclear receptor SHP inhibits HCC cell migration via suppressing Ccl2. *Molecular Cancer Therapeutics*. 2016; 15(10):2294–2301. [PubMed: 27486225]
30. Song G, Wang L. MiR-433 and miR-127 arise from independent overlapping primary transcripts encoded by the miR-433-127 locus. *PLoS ONE*. 2008; 3(10) Article ID e3574.
31. Song G, Wang L. A conserved gene structure and expression regulation of miR-433 and miR-127 in mammals. *PLoS ONE*. 2009; 4(11) Article ID e7829.
32. Song G, Wang L. Transcriptional mechanism for the paired miR-433 and miR-127 genes by nuclear receptors SHP and ERR γ . *Nucleic Acids Research*. 2008; 36(18):5727–5735. [PubMed: 18776219]
33. Yang Z, Tsuchiya H, Zhang Y, Hartnett ME, Wang L. MicroRNA-433 inhibits liver cancer cell migration by repressing the protein expression and function of cAMP response element-binding protein. *The Journal of Biological Chemistry*. 2013; 288(40):28893–28899. [PubMed: 23979134]
34. Yang Z, Zhang Y, Wang L. A feedback inhibition between miRNA-127 and TGF β /c-Jun cascade in HCC cell migration via MMP13. *PLoS ONE*. 2013; 8(6) Article ID e65256.
35. Zhao Y, Yang Z, Wu J, et al. High-mobility-group protein 2 regulated by microRNA-127 and small heterodimer partner modulates pluripotency of mouse embryonic stem cells and liver tumor initiating cells. *Hepatology Communications*. 2017; 1(8):816–830. [PubMed: 29218329]
36. McCarthy JJ. MicroRNA-206: the skeletal muscle-specific myomiR. *Biochimica et Biophysica Acta (BBA)—Gene Regulatory Mechanisms*. 2008; 1779(11):682–691. [PubMed: 18381085]
37. Winbanks CE, Wang B, Beyer C, et al. TGF- β regulates miR-206 and miR-29 to control myogenic differentiation through regulation of HDAC4. *The Journal of Biological Chemistry*. 2011; 286(16): 13805–13814. [PubMed: 21324893]
38. Song G, Wang L. Nuclear receptor SHP activates miR-206 expression via a cascade dual inhibitory mechanism. *PLoS ONE*. 2009; 4(9) Article ID e6880.
39. Kong B, Wang L, Chiang JYL, Zhang Y, Klaassen CD, Guo GL. Mechanism of tissue-specific farnesoid X receptor in suppressing the expression of genes in bile-acid synthesis in mice. *Hepatology*. 2012; 56(3):1034–1043. [PubMed: 22467244]
40. Lee J, Padhye A, Sharma A, et al. A pathway involving farnesoid X receptor and small heterodimer partner positively regulates hepatic sirtuin 1 levels via MicroRNA-34a inhibition. *The Journal of Biological Chemistry*. 2010; 285(17):12604–12611. [PubMed: 20185821]
41. Chang T-C, Wentzel EA, Kent OA, et al. Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. *Molecular Cell*. 2007; 26(5):745–752. [PubMed: 17540599]
42. Yang Z, Zhang Y, Kemper JK, Wang L. Cross-regulation of protein stability by p53 and nuclear receptor SHP. *PLoS ONE*. 2012; 7(6) Article ID e39789.
43. Yang Z, Wang L. An autoregulatory feedback loop between Mdm2 and SHP that fine tunes Mdm2 and SHP stability. *FEBS Letters*. 2012; 586(8):1135–1140. [PubMed: 22575647]
44. Wang Y, Weng T, Gou D, Chen Z, Chintagari NR, Liu L. Identification of rat lung-specific microRNAs by microRNA microarray: Valuable discoveries for the facilitation of lung research. *BMC Genomics*. 2007; 8 article no. 29.

45. Batista L, Bourachot B, Mateescu B, Reyat F, Mechta-Grigoriou F. Regulation of miR-200c/141 expression by intergenic DNA-looping and transcriptional read-through. *Nature Communications*. 2016; 7 article no. 8959.
46. Gregory PA, Bert AG, Paterson EL, et al. The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. *Nature Cell Biology*. 2008; 10(5):593–601. [PubMed: 18376396]
47. Brabletz S, Bajdak K, Meidhof S, et al. The ZEB1/miR-200 feedback loop controls Notch signalling in cancer cells. *EMBO Journal*. 2011; 30(4):770–782. [PubMed: 21224848]
48. Zhang Y, Yang Z, Whitby R, Wang L. Regulation of miR-200c by nuclear receptors PPAR α , LXR-1 and SHP. *Biochemical and Biophysical Research Communications*. 2011; 416(1–2):135–139. [PubMed: 22100809]
49. Xiao J, Gong A, Eischeid AN, et al. MiR-141 modulates androgen receptor transcriptional activity in human prostate cancer cells through targeting the small heterodimer partner protein. *The Prostate*. 2012; 72(14):1514–1522. [PubMed: 22314666]
50. Gabory A, Jammes H, Dandolo L. The H19 locus: role of an imprinted non-coding RNA in growth and development. *BioEssays*. 2010; 32(6):473–480. [PubMed: 20486133]
51. Matouk IJ, DeGroot N, Mezan S, et al. The H19 non-coding RNA is essential for human tumor growth. *PLoS ONE*. 2007; 2(9) article e845.
52. Zhang Y, Liu C, Barbier O, et al. Bcl2 is a critical regulator of bile acid homeostasis by dictating Shp and lncRNA H19 function. *Scientific Reports*. 2016; 6 Article ID 20559.
53. Song Y, Liu C, Liu X, et al. H19 promotes cholestatic liver fibrosis by preventing ZEB1-mediated inhibition of epithelial cell adhesion molecule. *Hepatology*. 2017; 66(4):1183–1196. [PubMed: 28407375]
54. Liu C, Yang Z, Wu J, et al. lncRNA H19 interacts with polypyrimidine tract-binding protein 1 to reprogram hepatic lipid homeostasis. *Hepatology*. 2017
55. Zhou Y, Zhang X, Klibanski A. MEG3 noncoding RNA: a tumor suppressor. *Molecular Endocrinology*. 2012; 48(3):R45–R53.
56. Zhang L, Yang Z, Trottier J, Barbier O, Wang L. Long noncoding RNA MEG3 induces cholestatic liver injury by interaction with PTBP1 to facilitate shp mRNA decay. *Hepatology*. 2017; 65(2): 604–615. [PubMed: 27770549]
57. Yu A-M, Ingelman-Sundberg M, Cherrington NJ, et al. Regulation of drug metabolism and toxicity by multiple factors of genetics, epigenetics, lncRNAs, gut microbiota, and diseases: a meeting report of the 21st International Symposium on Microsomes and Drug Oxidations (MDO). *Acta Pharmaceutica Sinica B (APSB)*. 2017; 7(2):241–248.
58. Yang Z, Ross RA, Zhao S, Tu W, Liangpunsakul S, Wang L. lncRNA AK054921 and AK128652 are potential serum biomarkers and predictors of patient survival with alcoholic cirrhosis. *Hepatology Communications*. 2017; 1(6):513–523. [PubMed: 29104954]

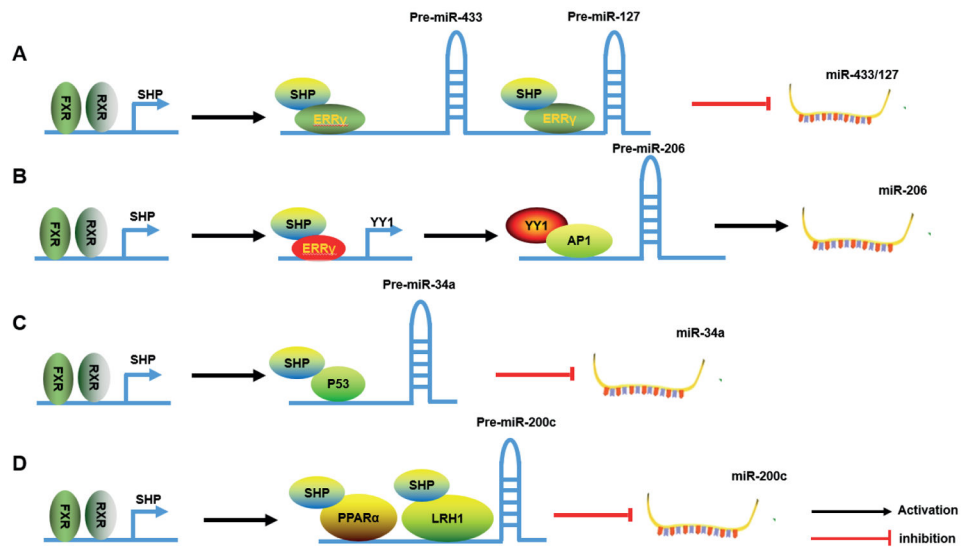


Figure 1. SHP as a transcriptional regulator of miRNA expression

A) SHP inhibits $ERR\gamma$ transactivation of the promoters of miR-433 and miR-127, which results in the repression of these two miRNAs. B) SHP activates miR-206 expression via a cascade dual inhibitory mechanism. The inhibition of $ERR\gamma$ by SHP leads to decreased YY1 expression and the derepression of YY1 on AP1 activity, ultimately leading to the activation of miR-206. C) SHP inhibits p53 transactivation of the miR-34a promoter, resulting in the repression of miR-34a. D) SHP represses miR-200c expression by inhibiting the activity of PPAR α and LRH-1.

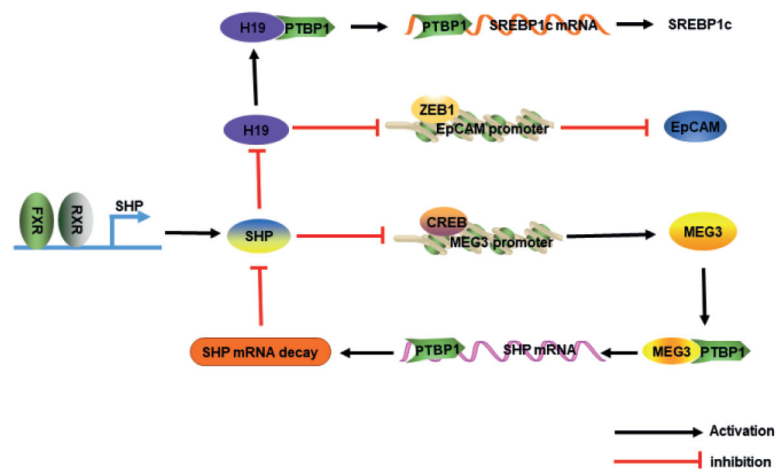


Figure 2. SHP as a transcriptional regulator of lncRNA expression

SHP functions as a transcriptional repressor of both MEG3 and H19 expression. SHP represses CREB transactivation of the MEG3 promoter, resulting in the inhibition of MEG3 expression. In a feedback regulatory loop, MEG3 recruits PTBP1 to Shp mRNA, resulting in Shp mRNA decay. SHP also represses lncRNA H19 expression. H19 in turn inhibits ZEB1 binding to the EpCAM promoter, thus prevents the repressive effect of ZEB1 on EpCAM transcription. H19 also recruits PTBP1 to Srebp1c mRNA to increase its stability, thus enhances lipogenesis.