Targeting super enhancers for liver disease: A review

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Background: Super enhancers (SEs) refer to the ultralong regions of a gene accompanied by multiple transcription factors and cofactors and strongly drive the expression of cell-type-related genes. Recent studies have demonstrated that SEs play crucial roles in regulating gene expression related to cell cycle progression and transcription. Aberrant activation of SEs is closely related to the occurrence and development of liver disease. Liver disease, especially liver failure and hepatocellular carcinoma (HCC), constitutes a major class of diseases that seriously endanger human health. Currently, therapeutic strategies targeting SEs can dramatically prevent disease progression and improve the prognosis of animal models. The associated new approaches to the treatment of related liver disease are relatively new and need systematic elaboration. **Objectives:** In this review, we elaborate on the features of SEs and discuss their function in liver disease. Additionally, we review their application prospects in clinical practice in the future. The article would be of interest to hepatologists, molecular biologists, clinicians, and all those concerned with targeted therapy and prognosis of liver disease. **Methodology:** We searched three bibliographic databases (Web of Science Core Collection, Embase, PubMed) from 01/1981 to 06/2022 for peer-reviewed scientific publications focused on (1) gene treatment of liver disease; (2) current status of SE research; and (3) targeting SEs for liver disease. We included English language original studies only. **Results:** The number of published studies considering the role of enhancers in liver disease is considerable. Since SEs were just defined in 2013, the corresponding data on SEs are scarce: approximately 50 papers found in bibliographic databases on the correlation between enhancers (or SEs) and liver disease. Remarkably, half of these papers were published in the past three years, indicating the growing interest of the scientific community in this issue. Studies have shown that treatments targeting components of SEs can improve outcomes in liver disease in animal and clinical trials. **Conclusions:** The treatment of liver disease is facing a bottleneck, and new treatments are needed. Therapeutic regimens targeting SEs have an important role in the treatment of liver disease. However, given the off-target effect of gene therapy and the lack of clinical trials, the available experimental data are still

fragmented and controversial.

1 **Title page**

2 **Targeting super enhancers for liver disease: A review**

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31 **Abstract**

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36 closely related to the occurrence and development of liver disease. Liver disease, especially liver

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60   available experimental data are still fragmented and controversial.

61

62   **Keywords** Gene expression, Liver disease, Prognosis, Super enhancer, Therapeutic strategy

63

64   **INTRODUCTION**

65   Enhancers that were initially identified and characterized in simian virus 40 (SV40) are referred

66   to as a short DNA sequence in the genome (*Banerji et al., 1981*). As a cis-acting regulatory

67   element, enhancers can activate gene transcription by combining with transcription factors,

68   enhancer-binding proteins or activators (*Kadonaga, 1998; Ong and Corces, 2011; Plank and*

69   *Dean, 2014*). Based on high-throughput sequencing technology, for example, chromatin

70   immunoprecipitation sequencing (ChIP-Seq), an increasing number of enhancers have been

71   identified. Each enhancer is critical for a subset of all the genes expressed within a specific

72   tissue or cell type (*Levine and Tjian, 2003; Plank and Dean, 2014*). In recent years, a new

73   concept has been established to define super enhancers (SEs). Several enhancers are stitched

74   together and bound by a high number of transcription factors and cofactors (*Hnisz et al., 2013;*

75   *Whyte et al., 2013*). SEs can activate the expression of identity-determining genes in stem cells,

76   thereby playing a pivotal role in regulating cell fate. In addition, subsequent studies have shown

77   that SEs are closely related to tumors, inflammation, Alzheimer's disease, atherosclerosis and

78   autoimmune diseases (*Blinka et al., 2016; Brown et al., 2014; Chapuis et al., 2013; Costa-Reis*

79   *and Sullivan, 2013; Duan et al., 2016; Hnisz et al., 2013; Hnisz et al., 2015; Loven et al., 2013*).

80   To date, more effective treatment strategies in clinical practice are lacking for certain liver

81   diseases, such as liver failure and hepatocellular carcinoma (HCC); thus, these diseases cause

82 high mortality(*Fattovich et al., 2004; Moreau et al., 2013; Sarin et al., 2019*). There are many

83 traditional treatments for liver disease. In recent years, due to optimized medical drug treatment,

84 liver interventional therapy and artificial liver treatment, the quality of life and survival rate of viral

85 hepatitis, liver cirrhosis, liver failure, liver cancer and other liver diseases have improved. It is

86 difficult to further improve the survival rate. Liver transplantation is difficult to carry out due to the

87 shortage of liver resources and high cost. In view of the occurrence of liver fibrosis, liver cancer

88 and other liver diseases related to gene expression, targeted therapy for related genes is the

89 current research focus. From the perspective of epigenetics, treating the root causes of these

90 diseases has great prospects. Epigenetic studies have shown that SE-targeted therapy

91 contributes to disease prognosis. Components of SEs, such as bromodomain-containing protein

92 4 (BRD4) and CCAAT/enhancer-binding proteins (C/EBPs), have been subjected to extensive

93 and in-depth research. Serving as a coactivator for gene transcription, BRD4 has been found to

94 be related to liver fibrosis, HCC and hepatitis B virus infection (*Francisco et al., 2017; Zhang et

95 al., 2015; Zhubanchaliyev et al., 2016*). C/EBPα, an important member of the transcription factor

96 C/EBP family, is closely associated with the aforementioned liver diseases (*Chen et al., 2000;

97 Tao et al., 2012; Weymann et al., 2009*). Notably, pharmacologic inhibition of BRD4 or

98 transfection of the C/EBPα gene has produced promising therapeutic effects in animal models

99 (*Mei et al., 2007; Singh et al., 2016; Wang et al., 2009; Wang et al., 2015*). SEs appear to be

100 promising candidates for effective therapeutic strategies against liver disease. In this article, we

101 review a comprehensive description of SEs and recent studies that have targeted transcription

102 factors and cofactors of SEs in liver disease and propose strategies from clinical treatment

103 perspectives based on SEs.

104

105 **SURVEY METHODOLOGY**

106 We searched the Web of Science Core Collection, Embase and PubMed for peer-reviewed

107 articles focused on (1) gene treatment of liver disease; (2) current status of SE research; and (3)

108 targeting SEs for liver disease published from 01/1981 to 06/2022.

109 1. "Liver disease" was used as a basic query, and "super enhancer" or "enhancer" was added for

110 detailed query.

111 2. "Liver disease" and "gene therapy" queries were used to search for information about targeted

112 gene therapy for liver disease.

113 A large variety of original research articles and reviews were searched. Of the 6783 publications

114 retrieved from bibliographic databases for "enhancer and liver disease", 1631 articles were

115 classified as clinical trials or randomized controlled trials. The "gene therapy and liver disease"

116 query returned 6894 publications, 824 of which were clinical trials or randomized controlled trials.

117 At the time of writing this article, we focused on the SE components in the treatment of liver

118 disease. Therefore, we tended to include the "super enhancer" item. A total of 121 articles

119 describing the relationship between SE components and liver disease were investigated.

120 Inclusion criteria: experimental studies involving mice, rats or humans, published in English and

121 listed in Web of Science Core Collection, Embase and PubMed starting from 01 January 1981;

122 original experimental in vivo or in vitro studies featuring liver disease gene therapy on enhancers

123 or SEs.

124 Exclusion criteria: publications before January 1st, 1981; unobtainable English version of the

125 article. We also excluded books and documents, commentaries, summaries, editorials, and

126 duplicate studies.

127 The earliest article that included SEs was published in 2015. From 2015 to 2022, a total of 50

128 articles met this requirement. We classified and summarized the parameters of SE exposure

129 (structural features, biological effects) and their impact on liver disease.

130

131 **STRUCTURAL AND FUNCTIONAL CHARACTERISTICS OF ENHANCERS AND SUPER**

132 **ENHANCERS**

133 In contrast to promoters, enhancers are characterized by enrichment with RNA polymerase,

134 transcription factors and coactivators (*Levine and Tjian, 2003*). Enhancers are indispensable in

135 gene transcription. Gene transcription dramatically declines in the absence of enhancers (*Banerji*

136 *et al., 1981; Shin et al., 2016*). Interestingly, enhancer-related transcription does not depend on

137 the direction or position of the enhancer. The distance of enhancers from the target genes is

138 variable. They can be located in the 5′ or 3′ regulatory regions, as well as within introns, and can

139 even be located on different chromosomes (*Lomvardas et al., 2006; Spilianakis et al., 2005*).

140 BRD4, C/EBPα, P300, H3K27ac, MED1, MyoD, T-bet, Oct4 + Sox2 + Nanog and Pu.1 have

141 been used to detect the existence of typical enhancers, while some of them, such as BRD4,

142 C/EBPα, P300, H3K27ac, MED1, MyoD and T-bet, have been used to identify SEs (*Brown et al.,*

143 *2014; Pott and Lieb, 2015; Witte et al., 2015*). Currently, more than one indicator is

144 simultaneously employed to obtain a robust set of SEs that are highly associated with cell type-

145 specific genes(*Shin et al., 2016*). SEs with unusually high enrichment with the aforementioned

146 transcription factors and coactivators, compared to those with typical enhancers, are identified

147 based on the development and maturation of high-throughput chromatin conformation-capturing

148 technology. SEs can induce higher levels of target gene expression than enhancers (*Pott and*

149 *Lieb, 2015*). **(Figure 1)**

150 A three-step approach was adopted to identify the SEs (*Pott and Lieb, 2015; Whyte et al., 2013*).

151 (1) Enhancers are identified according to ChIP-seq data for cell type-specific master transcription

152 factors. (2) Constituent enhancers within 12.5 kb are stitched together to form a single large

153 sequence. (3) The total background-normalized ChIP-seq signal for BRD4, C/EBPα, MED1,

154 H3K27ac or other transcription factors for the stitched enhancers and the remaining individual

155 enhancers are ranked to generate a curve, at which the slope of the plot is 1 as a cutoff to

156 separate SEs and typical enhancers. SEs are defined as regions above the point of the curve,

157 and the remaining enhancer regions are considered typical enhancers. (**Figure 2**)

158 SEs participate in gene transcription and determine cell fate in vitro and in vivo. In early fat

159 synthesis in preadipocytes, hotspots that are integrated with many and various important

160 transcription factors, such as MED1, usually constitute the core component of an SE. The

161 differentiation of preadipocytes can be regulated by interfering with the binding of transcription

162 factors in the hotspot region and SEs (*Siersbæk et al., 2014*). Wap, which is regulated by an SE

163 constituted of three individual enhancers, regulates milk production in mice. Using CRISPR/Cas9

164 gene-editing technology, interfering with the constituent enhancers of Wap SE in the mouse

165 genome leads to dramatically reduced expression levels of Wap genes by ~99%, indicating the

166 important role of SE in regulating gene expression in vivo (*Shin et al., 2016*).

167 Disease-associated single-nucleotide polymorphisms (SNPs) are more common within SEs than

168 typical enhancers in disease-related cells. Since it has been suggested that altered expression of

169 cell identity genes might contribute to some diseases, intervention SEs to regulate gene

170 expression that control and define cell identity will acquire the purpose of curing disease (*Hnisz

171 et al., 2013*). In recent years, SEs have been found to be related to various diseases(*Shin, 2018*).

172 Theoretically, using the SE complex as a target is more effective in patients who overexpress

173 components of an SE complex. Based on the profound gene-regulating ability of SEs,

174 transcription factors and cofactors have been used as novel targets in clinical research on

175 disease therapy and show broad application prospects (*Ding et al., 2015; Fedorov et al., 2014;*

176 *Tao et al., 2012; Zhubanchaliyev et al., 2016*).

177

178 **SUPER ENHANCERS IN LIVER DISEASE**

179 **Super enhancers in hepatocellular carcinoma**

180 HCC cells exploit an aberrant transcriptional program to sustain their infinite growth and

181 progression. Recent evidence has indicated that the continuous and robust transcription of

182 oncogenes in cancer cells is often driven by SEs (*Loven et al., 2013; Sengupta and George,*

183 *2017*). SEs are also involved in driving diversified oncogenes in HCC cells. SE landscapes differ

184 between HCC and normal liver cells, with the former being extensively reprogrammed during

185 liver carcinogenesis. Critical components of the SE complex, namely, BRD4, cyclin-dependent

186 kinase 7 (CDK7) and MED1, are frequently overexpressed in HCC patients and are closely

187 associated with a poor prognosis(*Tsang et al., 2019*).

188 Oncogenic SEs were first identified in multiple myeloma cells, with a high assembly of BRD4 and

189 MED1 (*Loven et al., 2013*). BRD4 is a member of the bromodomain and extra terminal domain

190   (BET) family of proteins, which includes BRD2, BRD3, BRD4 and BRDT (*Bisgrove et al., 2007;*

191   *Florence and Faller, 2001; Noguchi-Yachide, 2016*). As an important epigenetic reader, BRD4 is

192   the crucial component of an SE. In general, BRD4 recruits different transcriptional regulators,

193   such as MED1 and positive transcription elongation factor b (P-TEFb), to regulate the expression

194   of target genes (*Jang et al., 2005; Schnepp and Maris, 2013; Yang et al., 2005*). To interact with

195   RNA polymerase II (RNAP II), P-TEFb must be recruited to transcriptional units (*Marshall et al.,*

196   *1996; Marshall and Price, 1995; Peterlin and Price, 2006*). Interestingly, BRD4 is a specific

197   activator that is known to recruit P-TEFb to transcription units (*Jang et al., 2005; Yang et al.,*

198   *2005*). Moreover, through nonacetylated histones, such as the gamma herpesvirus f73 protein

199   and the NF-κB subunit RELA, BRD4 can also regulate DNA replication, the cell cycle, gene

200   transcription and other cellular activities (*Tang et al., 2013*).

201   In HCC patients, de novo SE formation is accompanied by BRD4 redistribution (*Tsang et al.,*

202   *2019*). BRD4 is significantly upregulated in HCC patients and in liver cancer cell lines, and the

203   overexpression of BRD4 in cancer tissues is correlated with poor prognosis in HCC patients

204   (*Tsang et al., 2019; Zhang et al., 2015*). In HCC patients, E2F2 was identified as the first

205   downstream direct target of BRD4. Further experiments confirmed E2F2 as a key player in BRD4

206   inhibition (*Hong et al., 2016*). Another downstream target of BRD4 is Pescadillo homolog 1

207   (PES1), and BRD4 regulates PES1, revealing the antitumor effect of BET inhibitors in HCC (*Fan*

208   *et al., 2018*). Taken together, these results shed new light on the regulation of BRD4 in HCC.

209   C/EBPα is an important member of the C/EBP family that contains a highly conserved leucine

210   zipper domain in the C-terminus related to dimerization and DNA binding (*Osada et al., 1996;*

211   *Ramji and Foka, 2002; Takiguchi, 1998*). It is known as one of the most abundant transcription

212   factors in the liver(*Ramji and Foka, 2002*). C/EBPα plays a pivotal role in the control of cell

213   proliferation and differentiation, the metabolism of phospholipids and carbohydrates, and

214   inflammation involving hepatocytes, adipocytes and hematopoietic cells (*House et al., 2010;*

215   *Johansen et al., 2001; Lekstrom-Himes and Xanthopoulos, 1998; Loomis et al., 2007; Zhao et al.,*

216   *2007*). Notably, transfection of C/EBPα small interfering RNA (siRNA) into mice results in a 70%

217   to 80% reduction in endogenous C/EBPα protein and a decrease in glycogen synthesis in the

218   liver (*Qiao et al., 2006; Wang et al., 1995*). C/EBPα$^{-/-}$ mice exhibit cell proliferation defects in the

219   liver and lung (*Gery et al., 2005*). These studies show that C/EBPα deficiency can lead to liver

220   metabolic disorders.

221   A recent study demonstrated that the SE landscape in HCC involves extensive reprogramming

222   (*Tsang et al., 2019*). C/EBPα is a component in the SE complex (*Hah et al., 2015; Pott and Lieb,*

223   *2015*). Numerous studies have shown that C/EBPα is a tumor suppressor, and the expression

224   levels of the C/EBPα gene and protein in normal tissues and adjacent tissues are significantly

225   higher those that in liver cancer tissues (*Tan et al., 2005; Tseng et al., 2009*). Small activating

226   RNAs (saRNAs) can upregulate CEBPA mRNA in human HCC cells and inhibit the growth of

227   liver cancer (*Voutila et al., 2017*). The proliferation time of C/EBPα-knockout hepatocyte cells is

228   reduced, and atypia and tumorigenicity are increased, suggesting that C/EBPα promotes

229   hepatocyte differentiation and tumor formation (*Wang et al., 2010*). In addition, downregulation of

230   C/EBPα expression in hepatocellular carcinoma is significantly associated with tumor stage and

231   shorter survival and may be used as an important marker for prognosis (*Tseng et al., 2009*). As a

232   target of C/EBPα, miR-134 is downregulated in HCC cells and inhibits HCC cell invasion and

233   metastasis (*Faraji et al., 2014*). Notably, activation of the PI3K/AKT signaling pathway in

234   hepatoma cells blocks C/EBPα-mediated inhibition of mitosis and proliferation, revealing that

235   hepatoma cells might escape C/EBPα-mediated inhibition of tumor cell proliferation via activation

236   of the PI3K/AKT pathway (*Datta et al., 2007*). TNF-α inhibits the activity of the proximal promoter

237   of C/EBPα genes, thereby decreasing the expression of C/EBPα mRNA and protein in the

238   Hep3B human cell line (*Foka et al., 2009*).

239   Ubiquitin-proteasome system (UPS)-mediated C/EBPα elimination accelerates the growth of

240   liver cancer in mice (*Wang et al., 2010*). The mechanism of C/EBPα elimination during

241   carcinogenesis may be associated with elevation of gankyrin, a protein interacting with the serine

242   193 isoform of C/EBPα. Metallothionein (MT) has been closely related to liver cancer (*Datta et al.,*

243   *2007*). The expression of MT-1 and MT-2A in HCC is obviously decreased. Phosphorylation of

244   the T222 and T226 sites of the C/EBPα gene by GSK-3 (glycogen synthase kinase 3) increases

245   MT expression. If the downstream target gene of GSK-3 is blocked, the expression of the MT

246   gene is significantly reduced.

247   CDK7 is a key gene that maintains the normal cell cycle and plays an important role in RNA

248   transcription (*Fisher, 2005*). Previous studies have illustrated that CDK7 is highly expressed in a

249   variety of tumors and is closely related to the progression and prognosis of these tumors. CDK7

250   has emerged as a therapeutic target in the treatment of tumors and inflammatory diseases

251   (*Fisher, 2019*). As a component of the SE complex, CDK7 is frequently amplified in HCC patients

252   (*Tsang et al., 2019*). Inhibition of CDK7-mediated expression of CDK1 or p34 Cdc2 (Cdc2) can

253   lead to G0/G1 cell cycle arrest to exert an antitumor effect (*Bi et al., 2019*).

254   MED1 is a subunit of the mediator complex, a coactivator involved in regulating the transcription

255   of RNAP II-dependent genes. It functions as a bridge to transmit information from gene-

256   regulating proteins to RNAP II transcription machinery, serving as a scaffold for the assembly of

257   a functional preinitiation complex with RNAP II and transcription factors (*Allen and Taatjes, 2015;*

258   *Malik and Roeder, 2010; Whyte et al., 2013*). MED1 was initially used to identify SEs (*Whyte et*

259   *al., 2013*). Many studies have shown that MED1 is closely related to various cancers, including

260   HCC (*Cai et al., 2019; Jia et al., 2014; Leonard and Zhang, 2019; Tsang et al., 2019*). Liver-

261   specific MED1 null mice do not develop liver tumors, as MED1-deficient hepatocytes do not

262   show increased proliferation or progress to liver cancer (*Jia et al., 2014; Matsumoto et al., 2010*).

263   Notably, nonalcoholic fatty liver disease (NAFLD)-associated HCC shows activation of Sirtuin 7

264   SE (SIRT7) (*Wu et al., 2022*). In hepatoma cells, depletion of SIRT7 SE induces H3K18

265   acetylation and reactivation of key metabolic and immune regulators, leading to significant

266   suppression of tumorigenicity in vitro and in vivo. Long noncoding RNA (lncRNA)-DAW is driven

267   by a liver-specific SE and is transcriptionally activated by HNF4G, promoting liver cancer cell

268   proliferation through activation of the Wnt/b-catenin pathway (*Liang et al., 2021*). Ajuba LIM

269   protein (AJUBA) is an SE-associated gene regulated by transcription factor 4 (TCF4) in HCC

270   cells (*Zhang et al., 2020*). High AJUBA expression in HCC patients is associated with an invasive

271   phenotype and unfavorable result. Otherwise, depletion of the AJUBA gene markedly decreases

272   cell migration and invasion both in vitro and in vivo.

273

274   **Super enhancers in liver fibrosis**

275   Liver fibrosis is a kind of chronic liver disease that endangers human health and is a risk factor

276   for progression into liver cirrhosis, liver cancer and liver failure. Therefore, timely and effective

277   treatment of liver fibrosis is very important. Recent studies have demonstrated that SEs can

278   regulate the progression of lung and cardiac fibrosis (*Horie et al., 2018; Micheletti et al., 2017*).

279   Components of an SE complex, such as BRD4, C/EBPα, CDK7 and MED1, have been subjected

280   to in-depth research and found to be associated with liver fibrosis.

281   Hepatic stellate cell (HSC) proliferation and extracellular matrix secretion are the core links in

282   liver fibrosis. As a genomic regulator,BRD4 plays a role in the response to stimulation of HSCs

283   and directs the fibrotic response through its interaction with myofibroblast transcription (*Ding et*

284   *al., 2015; Zhubanchaliyev et al., 2016*). The CXC chemokine CXCL6 (GCP-2) enhances the

285   SMAD3-BRD4 interaction and directly promotes BRD4 binding to the C-MYC promoter and

286   CMY-C binding to the EZH2 promoter via the SMAD2/BRD4/C-MYC/EZH2 pathway, thereby

287   inducing the expression of profibrogenic genes in HSCs (*Cai et al., 2018*).

288   A significant change in HSC activation leads to the reduction or even disappearance of

289   intracellular lipid droplets (*Kasakura et al., 2014*). C/EBPα gene expression is one of the

290   important regulators of adipocyte differentiation. Its main function is to promote the entry of

291   adipocytes into terminal differentiation, activating HSCs and inducing their apoptosis to inhibit the

292   progression of liver fibrosis. In addition, C/EBPα expression can reduce liver fibrosis in vitro (*Tao*

293   *et al., 2015*). The possible mechanism is that autophagy is involved in the expression of C/EBPα,

294   but this mechanism needs to be further validated. Scientists have found that C/EBPα induced the

295   apoptosis of HSCs in mice but exerted no significant effect on hepatocytes. Overexpression of

296   C/EBPα upregulates p53 gene expression through PPARγ and then upregulates Fas, tumor

297   necrosis-related factor apoptosis-inducing ligand and DR5 expression, thereby inducing the

298   apoptosis of HSCs and inhibiting liver fibrosis (*Wang et al., 2009*). Importantly, transfection of the

299   C/EBPα gene ameliorates CCL4-induced hepatic fibrosis in mice (*Mei et al., 2007*). Therefore,

300   C/EBPα is believed to play an important role in the pathological process of liver fibrosis.

301

302   **Super enhancers in viral hepatitis**

303   Hepatitis B virus (HBV) infection with HBV reactivation has a high incidence and mortality (*Choi*

304   *and Lim, 2017; Garg et al., 2011; Solay et al., 2018*). For example, in patients with B-cell

305   lymphoma receiving obinutuzumab or rituximab immunochemotherapy, 8.2% showed HBV

306   reactivation (*Kusumoto et al., 2018*). Hepatitis B reactivation can lead to more than 39.3% short-

307   term mortality of patients with HBV-ACLF. Therefore, the mechanism underlying HBV

308   reactivation needs to be further clarified. Recent research has shown that treatment with the

309   BRD4 inhibitor JQ1 stimulates HBV transcription and increases the occupancy of BRD4 in the

310   HBV genome in HepG2.2.15 cells (*Francisco et al., 2017*). Moreover, as a catalytic subunit of the

311   NuA4 complex, TIP60 localized to the chromatin complex of HBV cccDNA inhibits HBV

312   replication and catalyzes histone H4 acetylation to recruit BRD4 (*Nishitsuji et al., 2018*). These

313   results suggest that the redistribution of BRD4 is accompanied by de novo SEs and imply that

314   this redistribution plays an important role in the molecular mechanism of HBV replication and

315   reactivation, thus providing evidence for clinical therapy.

316   In HBV, C/EBPα at low concentrations can bind to the hepatitis B core promoter/enhancer to

317   activate hepatitis B virus gene transcription, while C/EBPα at high concentrations can inhibit

318   hepatitis B virus gene transcription (*Lopez-Cabrera et al., 1990*). As a multifunctional protein,

319   p21 not only directly binds to DNA but also binds to the C/EBPα domain, activating the HBV core

320   promoter in the form of the p21/C/EBPα complex and promoting high expression of C/EBPα

321   (*Chen et al., 2015*). Another study finds that hepatitis B virus X protein (HBX) promotes the

322   expression of p21, and HBX also binds to the leucine zipper domain of C/EBPα to activate

323   transcription of the pregenomic promoter of HBV(*Park et al., 2000*). Moreover, IL-4

324   downregulates the expression of C/EBPα and inhibits its binding to the core upstream regulatory

325   sequence/enhancer site, thereby inhibiting HBV DNA expression and replication (*Lin et al., 2003*).

326

327

328   **Super enhancers in fatty liver**

329   An animal study provided a new mechanism for liver fat accumulation and the clinical application

330   of JQ1 in the treatment of fatty liver. It is reported that there are some upregulated genes related

331   to lipid accumulation. Fructose force-feeding enhances histone acetylation and BRD4 binding to

332   the transcription region of fructose-inducible genes, thereby inducing lipid accumulation in the

333   livers of mice. Interestingly, administration of JQ1 inhibits this process (*Yamada et al., 2016*).

334   Moreover, induction of adipogenesis in fibroblasts leads to dynamic BRD4 redistribution to de

335   novo SEs that control adipocyte differentiation. Inhibition of bromodomain-containing proteins of

336   the BET family prevents BRD4 from assembling at these de novo SEs and disrupts related gene

337   transcription, thus blocking adipogenesis (*Brown et al., 2018*).

338   C/EBPα plays a pivotal role in maintaining lipid homeostasis in the liver. Lipogenesis-related

339   genes acetyl-CoA carboxylase, fatty acid synthase and sterol regulatory element-binding protein-

340   1c are robustly suppressed by C/EBPα siRNA in db/db mice (*Qiao et al., 2006*). Expression of

341   C/EBPα mRNA increases significantly in the NAFLD mouse model compared with mice fed a

342   normal diet (*Hossain et al., 2018; Park et al., 2019*). Reduction in the expression of adipogenic

343   protein C/EBPα ameliorates high-fat diet (HFD)-induced obesity and a related metabolic disease,

344   hepatic steatosis (*Hu et al., 2019; Seo et al., 2018*). The transcription factor C/EBPα shows the

345   greatest dominant-repressive effect on small heterodimer partner (SHP) expression in HepG2

346   and human hepatocytes, leading to the progression and severity of NAFLD (*Benet et al., 2015*).

347   MED1 is critical for the development of NAFLD in mice. MED1-knockout mice that receive a HFD

348   for up to 4 months fail to develop fatty liver, whereas mice with MED1 that receive a HFD develop

349   severe hepatic steatosis (*Bai et al., 2011*). MED1 may be considered a potential therapeutic

350   target for NAFLD.

351

Super enhancers in other liver diseases

The mutation in the BRD4 gene in mice produces a null allele. BRD4 heterozygotes exhibit

prenatal and postnatal growth defects related to a decreased proliferation rate. In addition,

mutant mice also display various anatomical abnormalities, including abnormal liver cells

(*Houzelstein et al., 2002*). In alcoholic hepatitis (AH), liver neutrophil infiltration is an important

pathological feature. Chemokine expression significantly increases through activated cytokine

pathways. Additionally, multiple CXCL chemokines are upregulated through RNA-seq and

histone modification ChIP-seq of human liver explants. Epigenome editing (for example, dCas9-

KRAB) or pharmacologic inhibition of BET proteins, which are important to SE function, decrease

chemokine expression in vitro and decrease neutrophil infiltration in murine models of AH (*Liu et

al., 2021*).

363

TARGETING SUPER ENHANCERS FOR LIVER DISEASE TREATMENT

Recently, SEs have emerged as novel therapeutic agents in the epigenetic field (*Shin, 2018*).

Drug development against components of SEs has become a hotspot. Interestingly, BRD4,

C/EBPα, CKD7, MED1 and other factors have been extensively studied and some drugs have

already been tested in clinical trials **(Table 1, Table 2 and Figure 3)**.

Using the CRISPR/Cas9 gene-editing approach, knockout of BRD4, MED1 and CDK7

significantly represses cell proliferation and colony formation in both Huh7 and HepG2 cell lines

in vitro (*Tsang et al., 2019*), suggesting that the components of the SE complex may serve as

therapeutic targets for HCC.

Based on the chemical structure, potent BET inhibitors have been classified into three classes:

isoxazoles, amides/urea and 1'2'4-triazoles (*Fedorov et al., 2014*). IBET-762 and JQ1, common

BRD4 inhibitors, inhibit BRD4 proteins by binding to acetylated histones (*Filippakopoulos et al.,

2010; Wyce et al., 2013*).

The small-molecule inhibitors JQ1 and OTX015 targeting BRD4 in HCC cells substantially

378 suppress the expression of the HCC-SE gene. JQ1 treatment also dramatically inhibits HCC-SE

379 gene expression in HCC cell lines (*Tsang et al., 2019*). In HCC cells, JQ1 exerts an anti-

380 proliferative effect by inducing cell cycle arrest and apoptosis (*Li et al., 2016*). Short hairpin RNA

381 (shRNA) suppresses BRD4 expression, leading to impaired HCC cell proliferation, migration and

382 invasion (*Li et al., 2016; Wang et al., 2015*). Additionally, miR-329 suppresses HCC cell invasion

383 by regulating BRD4 expression. Upregulated expression of miR-329 results in the inhibition of

384 BRD4 mRNA and protein expression (*Zhou et al., 2016*). As the active part in the SF1126

385 prodrug,LY294002 combines with BRD4 and prevents BRD4 from interacting with acetylated

386 histone-H4 proteins on chromatin, thus replacing BRD4 coactivator proteins from the

387 transcriptional start site of MYC in the Huh7 and SK-Hep1 HCC cell lines (*Mahadevan et al.,*

388 *2012; Singh et al., 2016*). As a dual PI3K/BRD4 inhibitor, SF1126 has completed a phase I

389 clinical trial in humans, showing a good safety profile, and it is hoped that it will be applied to

390 patients in the future.

391 JQ1 eliminates cytokine production and blunts LPS-induced cytokine storms in mice by reducing

392 inflammation levels, thus rescuing mice from death (*Belkina et al., 2013*). Similarly, JQ1

393 abrogates cytokine-induced HSC activation and BRD4-mediated profibrotic enhancer activity in

394 mice (*Ding et al., 2015; Zhubanchaliyev et al., 2016*). Additionally, JQ1 reduces carbon

395 tetrachloride (CCl4)-induced α-smooth muscle actin (α-SMA) expression (*Hassan et al., 2019*).

396 These studies suggest that BRD4 of the SE complex is a potential therapeutic target for patients

397 with liver inflammatory diseases, such as liver fibrosis and liver failure.

398 In a preclinical trial of liver disease, treatment with C/EBPα small activating RNA (saRNA) has

399 shown significant clinical promise by reducing tumor volume and improving essential biomarkers

400 of liver function, such as alanine transaminase, aspartate aminotransferase, bilirubin and

401 albumin (*Reebye et al., 2014; Zhao et al., 2017*). This is the first saRNA therapy for a

402 cirrhosis/HCC model to be entered in a human clinical trial.

403 In a recent phase I clinical trial, patients included advanced HCC with cirrhosis, resulting from

404 liver metastases or nonalcoholic steatohepatitis. They receive MTL-CEBPA therapy, a small

405   RNA that can upregulate C/EBP-α. MTL-CEBPA is the first saRNA in clinical trials. This study

406   demonstrates that MTL-CEBPA therapy is safe and has potential synergistic efficacy with

407   tyrosine kinase inhibitors (TKIs) in HCC. These data encourage further clinical trials and

408   combination studies of MTL-CEBPA + sorafenib in HCC (*Sarker et al., 2020*).

409   Xylocydine, a novel CDK7 inhibitor, can effectively induce significant cell growth inhibition and

410   apoptosis in vitro and in vivo, making it a good candidate for HCC treatment (*Cho et al., 2010*).

411   THZ1, another recently developed CDK7 inhibitor, can effectively suppress the growth of various

412   cancers. It can significantly reduce liver tumor size by repressing HCC cell proliferation,

413   demonstrating an antitumor effect (*Tsang et al., 2019*). New CDK7 inhibitors targeting the SE

414   complex for HCC patients are worth further research.

415

416   **CONCLUSIONS**

417   Traditional treatment methods for liver disease, including drugs, artificial liver, interventional

418   therapy, and surgery, have made it difficult to further improve the survival rate of patients with

419   liver disease, and liver transplantation is difficult to carry out due to the shortage of liver

420   resources and expensive costs. We need to find new methods to further improve treatment of

421   liver disease patients. In view of the occurrence of liver fibrosis, liver cancer and other liver

422   diseases related to gene expression, targeted therapy for related genes is a current research

423   hotspot. From the perspective of epigenetics, treating these diseases from the root causes has

424   great application prospects.

425   The recent discovery of genome-wide SEs and the identification of their unique features in both

426   normal development and disease progression have become hotspots in clinical and basic

427   research. SE is characterized by a larger gene region with unusually high enrichment of binding

428   sites for transcription factors and cofactors, which controls and defines cell identity (*Pott and Lieb,*

429   *2015*). A number of studies have suggested the key role played by SEs in many diseases and

430   their therapeutic value in clinical applications (*Shin, 2018*). In addition, SEs can be used as

431   promising prognostic markers in predicting disease risk and progression. Notably, we have

432 noticed that an increasing number of studies on liver diseases and SEs are emerging. It is

433 believed that information on SEs as therapeutic targets in liver disease will become more

434 abundant with further research. This treatment method will change the past phenomenon of

435 treating the symptoms but not the root causes of liver disease and solve the clinical problems

436 from the root to achieve the goal of curing liver disease.

437 Super enhancer RNAs (seRNAs) are the products of SEs, which interact with various proteins

438 and possess functional homogeneity with their host SEs (*Xiao et al., 2021*). The mechanism is

439 reflected in three aspects: (1) regulation in cis or trans configurations; (2) promotion of chromatin

440 looping; and (3) localization in the cytoplasm mediating various cell activities. seRNAs are mostly

441 related to autoimmune diseases, cancers, embryonic stem cells, skeletal myoblast differentiation,

442 and so on. Tissue specificity is an outstanding feature of SEs, particularly in the occurrence and

443 development of embryonic stem cells and cancers. Moreover, seRNAs regulate transcription or

444 bind to RNA-binding proteins (RBPs) to facilitate the effect of SEs.

445 seRNAs are involved in almost all tumor processes, including tumor formation, apoptosis,

446 proliferation, adhesion, migration and immune response(*Tan et al., 2020*). Cancer-related

447 seRNAs, such as HCCL5(*Peng et al., 2019*) and LINC01503(*Xie et al., 2018*), play a key role in

448 many aspects of tumor occurrence and development. In theory, SEs can become targets of

449 carcinogenic signals. SEs cause over-transcription of oncogenes, thus contributing to

450 tumorigenesis. As a product of SE activation, ectopic expression of seRNAs promotes the

451 development of cancer(*Mikhaylichenko et al., 2018*). These studies show the potential role of

452 seRNAs as biomarkers in cancer treatment. In addition, SEs have a pivotal role in immune

453 responses. The seRNAs IFNG-r-49 regulates the expression of IL-26 and IL-22 in inflammatory

454 bowel disease (IBD), but does not regulate the expression of IFNG (*Aune et al., 2017*).

455 As a product of SEs, seRNAs may be involved in the origin of various diseases. Blocking

456 seRNAs or SEs may be effective. Nowadays, pioneer works have promoted alternative methods

457 to efficiently manipulate enhancer RNAs (eRNAs) levels. Many methods such as siRNA,

458 antisense oligonucleotide (ASO), CRISPR/Cas9 and BET inhibitors can be selected for

459 manipulating RNAs, including seRNAs. eRNA or seRNA-targeted therapy holds a great potential

460 that is increasingly being considered (*Leveille et al., 2015*).

461 Although there is compelling evidence showing SE functions in regulating cell identity-

462 determining genes, the degree of their involvement remains controversial. An important problem

463 to be solved to enable epigenetic treatment of liver disease is the nonspecific nature of related

464 drugs. For example, although BRD4 inhibitors may have shown high specificity, the BRD4

465 protein is involved in many gene regulatory processes and is tissue specific. Scholars can predict

466 the toxicity of these compounds, but the mechanism of off-target effects has not been elucidated.

467 Moreover, research in the field of liver disease is still relatively limited and mainly focuses on

468 HCC. Hence, we urgently need more basic and clinical research to better understand the

469 mechanisms of SEs and observe their clinical application effect to safely use them as a

470 therapeutic target for the treatment of liver disease.

471 Despite various problems, epigenetic research on SEs has provided us with new therapeutic

472 strategies for clinical practice. The roles played by individual SEs vary with downstream genes,

473 and their overall effect in a particular liver disease, for example HCC, is relatively stable. This

474 provides high confidence for the research of SEs in HCC. We hope more studies will provide

475 novel directions for significant breakthroughs in the near future.

476

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480

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490

491 **Competing Interests**

492 The authors declare that they have no competing interests.

493

494 **Author Contributions**

495 ● Zhongyuan Yang drafted the manuscript.

496 ● Zhongyuan Yang, Yunhui Liu and Qiuyu Cheng contributed to literature search.

497 ● Tao Chen have contributed to the study conception and design.

498

499 **Data Availability**

500 The following information was supplied regarding data availability: This article is a literature

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502

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880

Figure 1

Figure 1 Characteristics of typical and super enhancers

Compared with typical enhancers, SEs span a larger genomic region, enriching more transcription factors, cofactors, and transcriptional activity-related histone modifications, and showing stronger transcription levels.
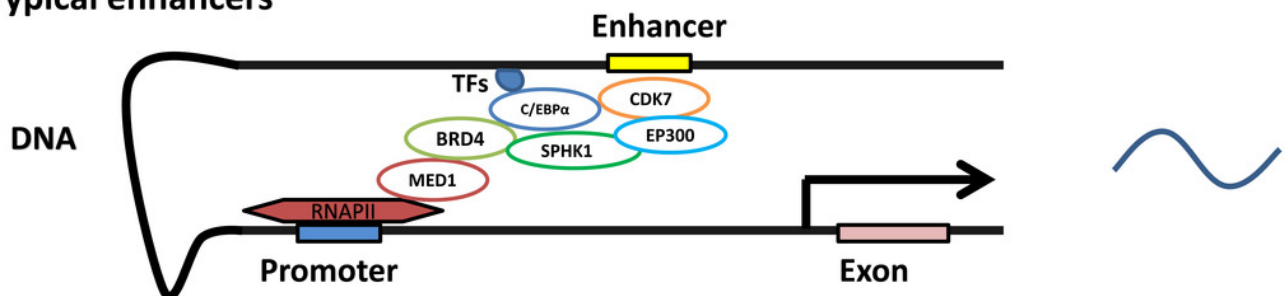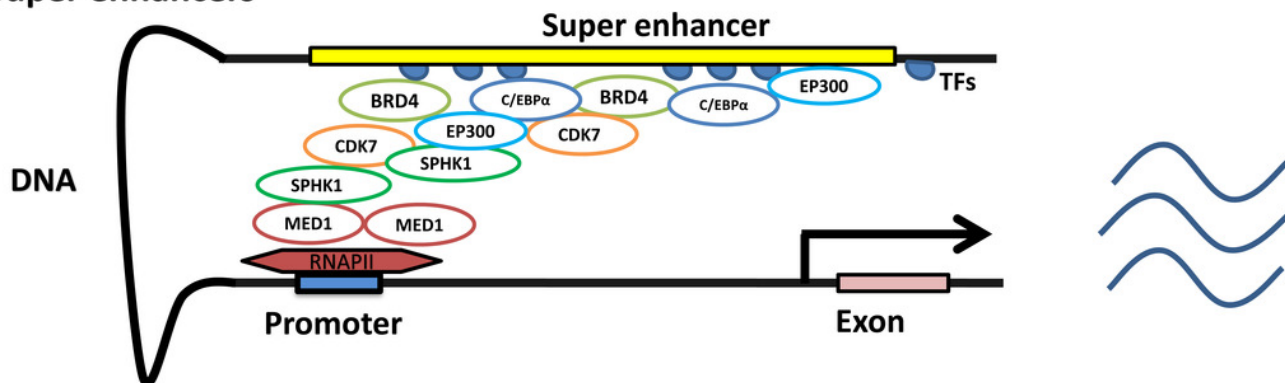
Figure 2

Figure 2 Defining super enhancers

Typical enhancers are defined by calling peaks on ChIP-seq signal levels. All typical enhancers regions are ranked along the x axis on the basis of the BRD4, C/EBPα, MED1 or/and H3K27ac enrichment plotted on the y axis. SEs are defined as regions to the right of the inflection point of the resulting curve where the slope is one.
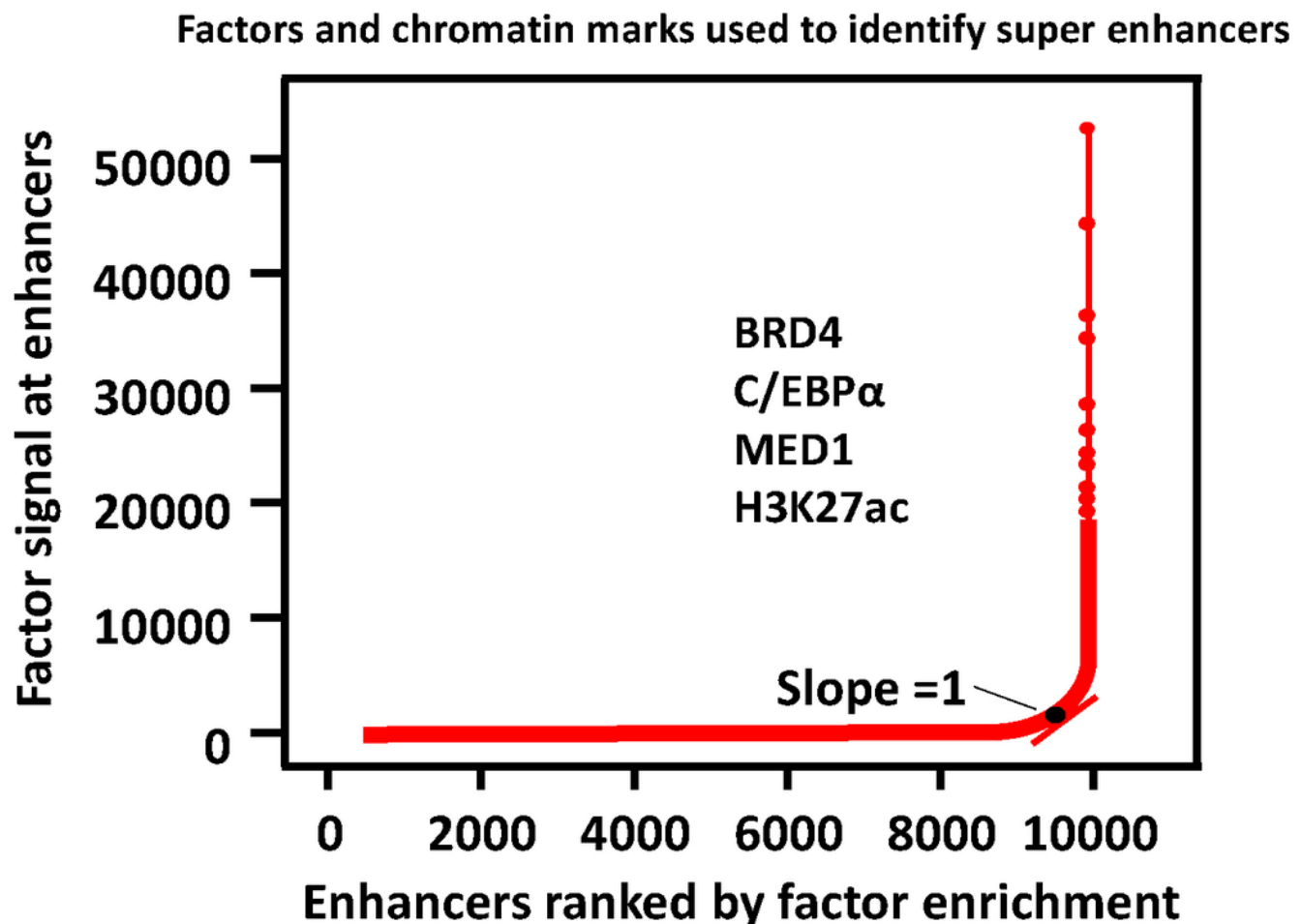
Figure 3

Figure 3 The pathways mediated via SEs in each individual liver disease

Treatment and intervention targets of SEs in each individual liver disease such as liver cancer, liver fibrosis, viral hepatitis and fatty liver.
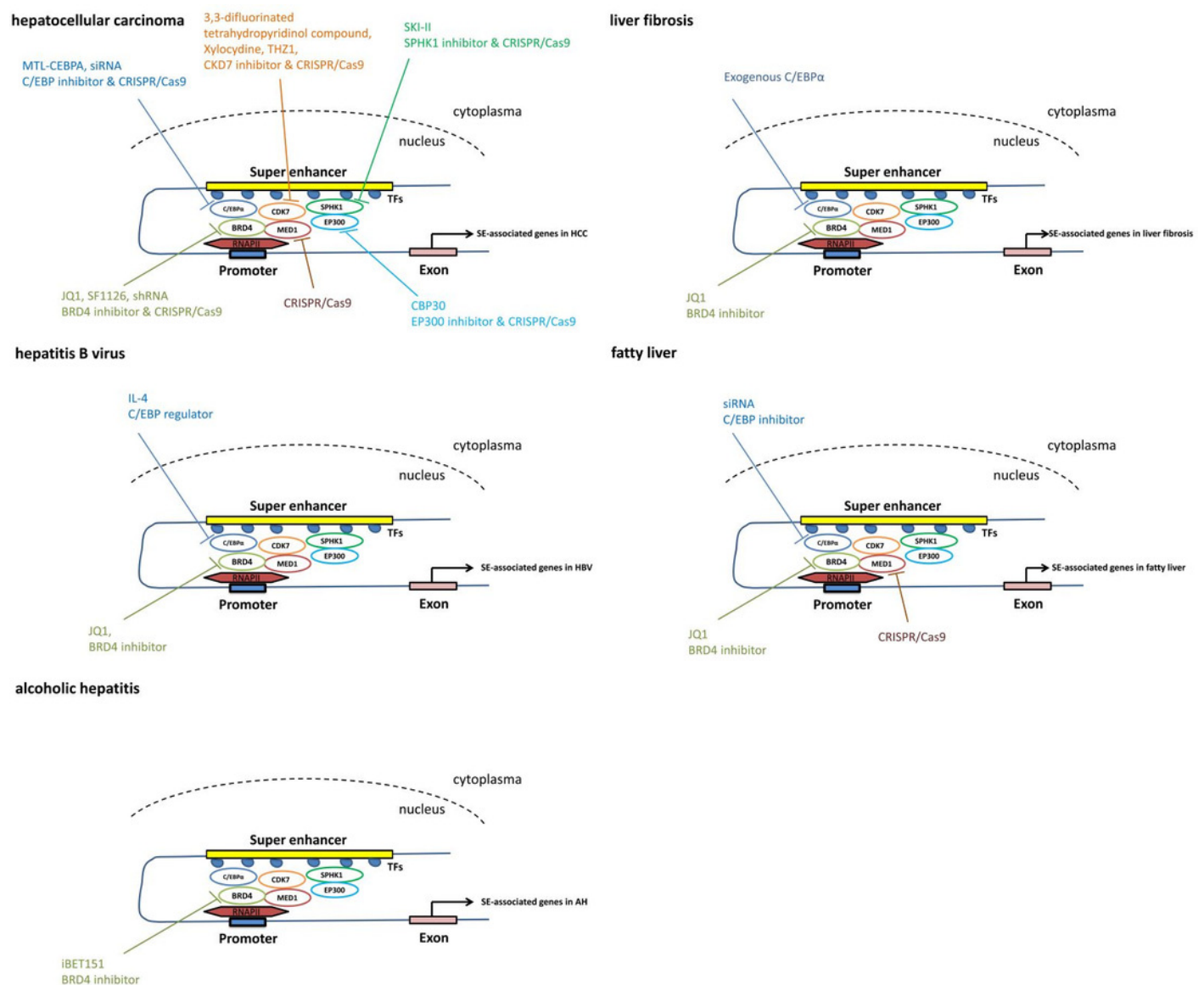
Table 1. Examples of small-molecule inhibitors targeting super enhancers component in liver diseases

Note: The table is sorted by disease type and publication time. BRD4: bromodomain-containing protein 4; C/EBPs: CCAAT/enhancer-binding proteins; CDK7: cyclin-dependent kinase 7

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Small-molecule inhibitor	Target factor	Liver disease	Target model	Clinical phase	Main results	References
Xylocydine	CDK1, CDK2 and CDK7	Hepatocellular Carcinoma	Mouse (SNU-354 cells are injected subcutaneously into male athymic nude mice)	-	Xylocydine inhibits growth of HCC xenografts in Balb/C-nude mice	Cho SJ, et al.2010
SF1126	PI3K/BRD4	Hepatocellular Carcinoma	Mouse (SK-Hep1 cells or Huh-7 cells are injected subcutaneously into the NSG mouse)	Human clinical trial Phase I	Treatment with SF1126 either alone or in combination with sorafenib show significant antitumor activity in HCC	Singh AR, et al.2016; Mahadevan D, et al.2012
JQ1	BRD4	Hepatocellular Carcinoma	SK-Hep1, Huh7 and HepG2 cells	-	BRD4 inhibition causes MYC-independent large-scale gene expression changes in liver cancer cells	Hong SH, et al.2016
JQ1	BRD4	Hepatocellular Carcinoma	Mouse (HCCLM3 and Hep3B HCC xenograft models)	-	JQ1 inhibits tumor growth in HCC mouse model	Li GQ, et al.2016
THZ1	CDK7	Hepatocellular Carcinoma	Mouse (Luciferase-labeled Huh7 cells are injected into the liver of nude mice to establish liver tumor)	-	THZ1 significantly reduces the liver tumor size	Tsang FH, et al.2019
JQ1	BRD4	Hepatocellular Carcinoma	HepG2 and Huh7 cells	-	JQ1 reduces the expression of the HCC-SE genes in HCC cell lines	Tsang FH, et al.2019
THZ1	CDK7	Hepatocellular Carcinoma	HepG2 and Huh7 cells	-	SE-associated genes acquired in HCC cells is substantially reduced	Tsang FH, et al.2019
SKI-II	SPHK1	Hepatocellular Carcinoma	HepG2 and Huh7 cells	-	SKI-II strikingly abolishes the cell proliferation and colony formation of HCC cells	Tsang FH, et al.2019
CBP30	EP300	Hepatocellular Carcinoma	HepG2 and Huh7 cells	-	CBP30 represses the expression of the 13 HCC-SE-genes	Tsang FH, et al.2019
3,3-difluorinated tetrahydropyridinol compound	CDK7	Hepatocellular Carcinoma	Mouse (HepG2 cells are inoculated subcutaneously into the BALB/c male nude mice)	-	3,3-difluorinated tetrahydropyridinol compound suppresses tumor growth of HepG2 cell xenografts in nude mice	Bi W, et al.2019
MTL-CEBPA	C/EBP	Hepatocellular Carcinoma	Human (adults with advanced hepatocellular carcinoma with cirrhosis, or resulting from nonalcoholic steatohepatitis or with liver metastases)	Human clinical trial Phase I (NCT02716012)	MTL-CEBPA is the first saRNA in clinical trials and demonstrates an acceptable safety profile and potential synergistic efficacy with TKIs in HCC	Sarker D, et al.2020
JQ1	BRD4	Hepatocellular Carcinoma	HepG2 and LO2 cells	-	JQ1 significantly reduces SIRT7 mRNA levels	Wu F, et al.2022

JQ1	BRD4	Liver Fibrosis	Mouse (carbon tetrachloride-induced fibrosis in mouse)	-	JQ1 is protective and can reverse the fibrotic response	Ding N, et al.2015
JQ1	BRD4	Liver Fibrosis	Mouse (CCl4 induces liver fibrosis in twenty male Swiss albino mice)	-	A synergistic reduction in α-SMA is observed when cells are co-treated with JQ1 and atorvastatin loaded NPs	Hassan R, et al.2019
JQ1	BRD4	Faty Liver	Mouse (Fructose intake induces hepatic steatosis by activating fat synthesis)	-	JQ1 reduces expressions of fructose-inducible genes, histone acetylation and BRD4 binding around these genes	Yamada A, et al.2016
JQ1	BRD4	Faty Liver	Adipocytes	-	JQ1 can attenuate adipogenesis	Brown JD, et al.2018
iBET151	BRD4	Alcoholic Hepatitis	Mouse (using the NIH/NIAAA 10 days chronic-binge alcohol feeding protocol to mimic the histopathology of human AH in mice)	-	iBET151 reduces Cxcl expression and neutrophilic infiltration in murine model of AH	Liu M, et al.2021
IL-4	C/EBPα	Hepatitis B virus	Hep3B cells	-	IL-4 inhibits C/EBPα binding to hepatitis B core promoter/enhancer, thus inhibiting HBV DNA expression and replications	Lin SJ, et al. 2003
JQ1	BRD4	Hepatitis B virus	HepG2.2.15 cells	-	JQ1 stimulates HBV transcription and increases the occupancy of BRD4 in the HBV genome	Francisco et al. 2017

2 Note: The table is sorted by disease type and publication time.

3 BRD4: bromodomain-containing protein 4; C/EBPs: CCAAT/enhancer-binding proteins; CDK7: cyclin-

4 dependent kinase 7

Table 2. Examples of Interference tools targeting super-enhancers component in liver diseases

Note: The table is sorted by disease type and publication time. BRD4: bromodomain-containing protein 4; C/EBPs: CCAAT/enhancer-binding proteins; CDK7: cyclin-dependent kinase 7

1   Table 2. Examples of Interference tools targeting super-enhancers component in liver diseases

Target model	Factors for SE identification	Target gene	Interference tools	Liver disease	Main results	References
Mouse	C/EBP	SEs component C/EBPα	C/EBP-α gene knock-in	Hepatocellular Carcinoma (using diethylnitrosamine to induce hepatocellular carcinoma in our mice)	The C/EBP-α knock-in mice produce half the number of hepatocellular nodules	Tan EH, et al.2005
Mouse	C/EBP	SEs component C/EBPα	C/EBPα-S193D knock-in	Hepatocellular Carcinoma (C/EBPα-S193D knock-in mice)	S193D mutation mice cause chromatin remodeling leading to histological appearance of 'foci-like' nodules, which are also observed in liver of old mice	Jin J, et al.2010
Mouse	MED1	SEs component MED1	CRISPR/Cas9	Hepatocellular Carcinoma (diethylnitrosamine-induced hepatocarcinogenesis)	No proliferative expansion of PBP/MED1 null hepatocytes is noted in the PBP/MED1(DeltaLiv) mouse liver	Matsumoto K, et al.2010
HepG2, Hep3B, SMMC-7721, Bel-7402 and Huh7 cells	BRD4	SEs component BRD4	shRNA	Hepatocellular Carcinoma(HepG2, Hep3B, SMMC-7721, Bel-7402 and Huh7 cells)	shRNA can suppress BRD4 expression in HCC cells, and result in impaired HCC cell proliferation, migration and invasion	Wang F, et al.2015
Mouse	BRD4	SEs component BRD4	shRNA	Hepatocellular Carcinoma (The tumor cells are inoculated subcutaneously in nude mice to produce the model)	BRD4 shRNA significantly inhibits HCC cell proliferation in vivo	Zhang et al. 2015
HepG2 and Hep3B cells	C/EBPα	SEs component C/EBPα	saRNA	Hepatocellular Carcinoma (HepG2 and Hep3B cells)	saRNA inhibits growth of liver cancer cell lines in vitro	Voutila J, et al.2017
HepG2 and Huh7 cells	BRD4, MED1, EP300, CDK7, SPHK1	SE-complex components	CRISPR/Cas9	Hepatocellular Carcinoma(HepG2 and Huh7 cells)	The inactivation of CDK7, SPHK1, BRD4, EP300, and MED1 attenuates cell proliferation, colony formation and the cell migratory ability	Tsang FH, et al.2019
Mouse	SPHK1	SE-complex components	CRISPR/Cas9	Hepatocellular Carcinoma(Huh7 cells in nude mice)	knockdown of SPHK1 drastically abolishes hepatic tumor growth and pulmonary metastasis	Tsang FH, et al.2019
Mouse	CDK7	SE-complex components	CRISPR/Cas9	Hepatocellular Carcinoma(HepG2 and Huh7 cells in nude mice)	The knockout of CDK7 in HCC cells completely abolishes the incidence of tumor formation in the nude mice	Tsang FH, et al.2019
HepG2 and Huh7 cells	H3K27ac, TCF4	SEs component TCF4	shRNA, CRISPR/Cas9	Hepatocellular Carcinoma (HepG2 and Huh7 cells)	Inhibition TCF4 inhibits HCC cell migration and invasion ability	Zhang C, et al.2020
HepG2 cells	H3K27ac, HNF4G	SEs component HNF4G	shRNA	Hepatocellular Carcinoma (HepG2 cells)	Knockdown of HNF4G suppresses gene transcription of lncRNA-DAW to prevent tumor growth	Liang W, et al.2021

HepG2 and LO2 cells	H3K27ac, BRD4	SEs component SIRT7	CRISPR/Cas9	Hepatocellular Carcinoma (HepG2 and LO2 cells)	Depletion of SIRT7 SE in hepatoma cells induces global H3K18 acetylation and reactivates key metabolic and immune regulators, leading to marked suppression of tumorigenicity in vitro	Wu F, et al.2022
Mouse	H3K27ac, BRD4	SEs component SIRT7	CRISPR/Cas9	Hepatocellular Carcinoma (4-week-old female athymic nude mice are subcutaneously injected with HepG2 WT and SIRT7 SE$^{-/-}$ cells)	SIRT7 SE$^{-/-}$ cells exhibits significant inhibition of tumor growth in a xenograft model when compared with WT cells	Wu F, et al.2022
Mouse	C/EBP	SEs component C/EBPα	C/EBP-α gene	Liver Fibrosis (CCl4-induced liver fibrosis model in mice)	Exogenous C/EBP-alpha gene reduces the content of collagens and the content of hydroxyproline	Mei S, et al.2007
Mouse	C/EBPα	SEs component C/EBPα	C/EBP-α gene	Liver Fibrosis (CCl4-induced liver fibrosis model in mice)	Ad-C/EBP-α decreases extracellular matrix deposition and γ-GT levels	Tao LL, et al.2012
Mouse	C/EBPα	SEs component C/EBPα	siRNA	Faty Liver (8-wk-old wild-type and db/db mice)	Expression of lipogenesis genes is robustly suppressed in the C/EBPα siRNA-treated db/db mice	Qiao L, et al.2006
Mouse (MED1 knockout ED1(ΔLiv) mice)	MED1	SEs component MED1	CRISPR/Cas9	Faty Liver (Mice are fed with a high-fat diet for up to 4 months)	The mice fail to develop fatty liver	Bai L, et al.2011
Mouse	C/EBPα	SEs component C/EBPα	siRNA	Faty Liver (NAFLD)	Hepatic triglyceride content, Kleiner scores and other NAFLD related index are partially reversed by C/EBPα siRNA	Hu S, et al.2019

Note: The table is sorted by disease type and publication time.

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