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Acetyl CoA carboxylase: Role in NAFLD, NASH, and HCC

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ABSTRACT

Although cancer is the second leading cause of death worldwide, it owns the first place regarding the burden on health management systems involving men and women. Acetyl-CoA carboxylase (ACC) is a key rate-limiting enzyme in the de novo fatty acid (FA) synthesis pathway, and alterations in its expression are seen in cancer cells. Non-alcoholic steatohepatitis (NASH) is the fastest developing cause of hepatocellular carcinoma (HCC). Higher levels of de novo lipogenesis inside hepatic cells are essential in the progression of HCC. Here, we aimed to review the roles and function of ACC in developing non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and, more importantly, HCC. We also reviewed the structure and biological activity of this enzyme in de novo lipogenesis and small-molecule ACC inhibitors designed to target the conditions mentioned above.

In conclusion, ACC is a promising target in the treatment of liver fat-related conditions and HCC.

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Abbreviations

ACC: Acetyl-CoA Carboxylase
HCC: Hepatocellular Carcinoma
NAFLD: Non-alcoholic Fatty Liver Disease
NASH: Non-alcoholic Steatohepatitis
AMPK: AMP-activated Protein Kinase
PO3: Phosphite Ion
SREBP1: Sterol Regulatory-Element Binding Protein-1
DNL: De novo Lipogenesis
FA: Fatty Acid
FASN: FA synthase

Introduction

Acetyl-CoA carboxylase (ACC) is a key rate-limiting enzyme in the de novo fatty acid (FA) synthesis pathway, and alterations in its expression are seen in cancer cells. Considering the importance of FAs in the cellular membrane structure and energy metabolism, FA synthesis is vital for cancer cells. In the physiologic environment, FAs are supplied via exogenous fat intake. However, cancer cells provide their required FAs from intracellular pyruvate through de novo FA synthesis [1].

De novo FA synthesis is considered a metabolic reprogramming in tumorigenesis, allowing cancer cells to become independent of extracellular lipids. Identification of FA synthase (FASN) in 1994 contributed to understanding the importance of the de novo FA synthesis in cancer cell growth and survival [2,3].

During the de novo pathway, glucose carbons get converted to acetyl-CoA. ACC uses acetyl-CoA molecules to synthesize malonyl-CoA, which is essential for this pathway and in determining the activity of the carnitine palmitoyl-transferases (CPTs). CPTs are involved in transporting acyl chains-carnitine couples to the mitochondrial matrix and β-oxidation [4].

According to the world health organization (WHO), although cancer is the second leading cause of death worldwide, it owns the first place regarding the burden on health management systems involving men and women [5]. Hepatocellular carcinoma (HCC) is one of the leading cancers with an increasing incidence rate. HCC is closely associated with liver conditions such as cirrhosis, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) [5].

This review aimed to discuss ACC structure and its role in the physiologic environment, the importance of its action in the development of NAFLD, NASH, tumor growth, and metastasis of HCC, and its utility as a target for further treatments. Further understanding of the above subjects may contribute to the evolution of more efficient drugs.

Biological structure

Chromosome 17q12 harbors the ACC gene, coding a 265 kDa protein. ACC expression gets initiated from at least three promotors, specified to the tissue type [6]. Studies of ACC cDNA coding sequences show minor differences between tissues [7,8]. However, in some tissues, including the liver, adipose tissue, brain, and lactating mammary glands, increased ACC expression has been observed.

According to Abu et al., in ACC production, an open reading frame of 7038 nt in the nucleotide sequence encodes 2346 amino acids with a calculated molecular weight of 264,737 in the HepG2 cells [7]. They found that the cDNA sequence of ACC in the abdominal fat differs from 4410 nt at the 3' to the end of the sequence. Furthermore, the high similarity of HepG2 cDNA sequence with those of rats, chicken, and yeast was reported. Tables 1 and 2 present alignment and conserved sequences of ACC1 and 2 in Homo sapiens, Mus musculus, and Rattus norvegicus.

Tables and Table legends

Table 1: Alignment and Conserved Sequences of ACC1.

Specie Accession number
Homo Sapiens Q13085.2
Mus Musculus NP_579938.2
Rattus Norvegicus NP_071529.1

Specie	Alignment and Conserved Sequences of ACC1
Homo Sapiens	1 MDEPSPLAQPLELNQHSRFIIGSVSEDNSEDEISNLVKLDLIEEKEGSLSPASVGSDTLSDLGISSLQDGLALHIRSSMS 80
Mus Musculus	1 MDEPSPLAKTLELNQHSRFIIGSVSEDNSEDEISNLVKLDL-EEKEGSLSPASVSSDTLSDLGISGLQDGLAFHMRSSMS 79
Rattus Norvegicus	1 MDEPSPLAKTLELNQHSRFIIGSVSEDNSEDEISNLVKLDL-EEKEGSLSPASVSSDTLSDLGISALQDGLAFHMRSSMS 79
Homo Sapiens	81 GLHLVKQGRDRKKIDSQRDFTVASPAEFVTRFGGNKVIEKVLIANNGIAAVKCMRSIRRWSYEMFRNERAIRFV VMVTPE 160
Mus Musculus	80 GLHLVKQGRDRKKIDSQRDFTVASPAEFVTRFGGNKVIEKVLIANNGIAAVKCMRSIRRWSYEMFRNERAIRFVVM VTPE 159
Rattus Norvegicus	80 GLHLVKQGRDRKKIDSQRDFTVASPAEFVTRFGGNKVIEKVLIANNGIAAVKCMRSIRRWSYEMFRNERAIRFVVM VTPE 159
Homo Sapiens	161 DLKANAEYIKMADHYVPVPGGPNNNNYANVELILDIAKRIPVQAVWAGWGHASENPKLPELLLKNGIAFMGPPS QAMWAL 240
Mus Musculus	160 DLKANAEYIKMADHYVPVPGGPNNNNYANVELILDIAKRIPVQAVWAGWGHASENPKLPELLLKNGIAFMGPPS QAMWAL 239
Rattus Norvegicus	160 DLKANAEYIKMADHYVPVPGGANNNNYANVELILDIAKRIPVQAVWAGWGHASENPKLPELLLKNGIAFMGPPS QAMWAL 239
Homo Sapiens	241 GDKIASSIVAQTAGIPTLPWSGSGLRVDWQENDFSKRILNVPQELYEKGYVKDVDDGLQAAEEVGYPVMIKASE GGGGKG 320
Mus Musculus	240 GDKIASSIVAQTAGIPTLPWSGSGLRVDWQENDFSKRILNVPQDLYEKGYVKDVDDGLKAAEEVGYPVMIKASE GGGGKG 319
Rattus Norvegicus	240 GDKIASSIVAQTAGIPTLPWSGSGLRVDWQENDFSKRILNVPQDLYEKGYVKDVDDGLKAAEEVGYPVMIKASEGG GGKG 319
Homo Sapiens	321 IRKVNNADDFPNLFRQVQAEVPGSPIFVMRLAKQSRHLEVQILADQYGNAISLFGRDCSVQRRHQKIIEEAPATIATPAV 400
Mus Musculus	320 IRKVNNADDFPNLFRQVQAEVPGSPIFVMRLAKQSRHLEVQILADQYGNAISLFGRDCSVQRRHQKIIEEAPAAIATPAV 399
Rattus Norvegicus	320 IRKVNNADDFPNLFRQVQAEVPGSPIFVMRLAKQSRHLEVQILADQYGNAISLFGRDCSVQRRHQKIIEEAPAAIATPAV 399
Homo Sapiens	401 FEHMEQCAVKLAKMVGYVSAGTVEYLYSQDGSFYFLELNPRLQVEHPCTEMVADVNLPAAQLQIAMGIPLYRIKDIRMMY 480
Mus Musculus	400 FEHMEQCAVKLAKMVGYVSAGTVEYLYSQDGSFYFLELNPRLQVEHPCTEMVADVNLPAAQLQIAMGIPLFRIKDIRMMY 479
Rattus Norvegicus	400 FEHMEQCAVKLAKMVGYVSAGTVEYLYSQDGSFYFLELNPRLQVEHPCTEMVADVNLPAAQLQIAMGIPLFRIKDIRMMY 479
Homo Sapiens	481 GVSPWGDSPIDFEDSAHVPCPRGHVIAARITSENPDEGFKPSSGTVQELNFRSNKNVWGYFSVAAAGGLHEFADSQFGHC 560
Mus Musculus	480 GVSPWGDAPIDFENSAHVPCPRGHVIAARITSENPDEGFKPSSGTVQELNFRSNKNVWGYFSVAAAGGLHEFADSQFGHC 559
Rattus Norvegicus	480 GVSPWGDAPIDFENSAHVPCPRGHVIAARITSENPDEGFKPSSGTVQELNFRSNKNVWGYFSVAAAGGLHEFADSQFGHC 559
Homo Sapiens	561 FSWGENREEAISNMVVALKELSIRGDFRTTVEYLIKLLETESFQMNRIDTGWLDRLIAEKVQAERPDTMLGVVCGALHVA 640
Mus Musculus	560 FSWGENREEAISNMVVALKELSIRGDFRTTVEYLIKLLETESFQLNRIDTGWLDRLIAEKVQAERPDTMLGVVCGALHVA 639
Rattus Norvegicus	560 FSWGENREEAISNMVVALKELSIRGDFRTTVEYLIKLLETESFQLNRIDTGWLDRLIAEKVQAERPDTMLGVVCGALHVA 639

Homo Sapiens	641 DVSLRNSVSNFLHSLERGQVLPAHTLLNTVDVELIYEGVKYVLKVTRQSPNSYVVIMNGSCVEVDVHRLSDGGLLLSYDG 720
Mus Musculus	640 DVSLRNSISNFLHSLERGQVLPAHTLLNTVDVELIYEGIKYVLKVTRQSPNSYVVIMNGSCVEVDVHRLSDGGLLLSYDG 719
Rattus Norvegicus	640 DVNLRNSISNFLHSLERGQVLPAHTLLNTVDVELIYEGIKYVLKVTRQSPNSYVVIMNGSCVEVDVHRLSDGGLLLSYDG 719
Homo Sapiens	721 SSYTTYMKEEVDRYRITIGNKTCVFEKENDPSVMRSPSAGKLIQYIVEDGGHVFAGQCYAEIEVMKMVMTLTAVESGCIH 800
Mus Musculus	720 SSYTTYMKEEVDRYRITIGNKTCVFEKENDPSVMRSPSAGKLIQYIVEDGGHVFAGQCYAEIEVMKMVMTLTAVESGCIH 799
Rattus Norvegicus	720 SSYTTYMKEEVDRYRITIGNKTCVFEKENDPSVMRSPSAGKLIQYIVEDGGHVFAGQCYAEIEVMKMVMTLTAVESGCIH 799
Homo Sapiens	801 YVKRPGAALDPGCVLAKMQLDNPSKVQQAELHTGSLPRIQSTALRGEKLHRVFHYVLDNLVNVMNGYCLPDPFFSSKVKD 880
Mus Musculus	800 YVKRPGAALDPGCVIAKMQLDNPSKVQQAELHTGSLPQIQSTALRGEKLHRVFHYVLDNLVNVMNGYCLPDPFFSSRVKD 879
Rattus Norvegicus	800 YVKRPGAALDPGCVIAKMQLDNPSKVQQAELHTGSLPQIQSTALRGEKLHRVFHYVLDNLVNVMNGYCLPDPFFSSKVKD 879
Homo Sapiens	881 WVERLMKTLRDPSLPLLELQDIMTSVSGRIPPNVEKSIKKEMAQYASNITSVLCQFPSQQIANILDSHAATLNRKSEREV 960
Mus Musculus	880 WVERLMKTLRDPSLPLLELQDIMTSVSGRIPLNVEKSIKKEMAQYASNITSVLCQFPSQQIANILDSHAATLNRKSEREV 959
Rattus Norvegicus	880 WVERLMKTLRDPSLPLLELQDIMTSVSGRIPLNVEKSIKKEMAQYASNITSVLCQFPSQQIANILDSHAATLNRKSEREV 959
Homo Sapiens	961 FFMNTQSIVQLVQRYRSGIRGHMKAVVMDLLRQYLRVETQFQNGHYDKCVFALREENKSDMNTVLNYIFSHAQVTKKNLL 1040
Mus Musculus	960 FFMNTQSIVQLVQRYRSGIRGHMKAVVMDLLRQYLRVETQFQNGHYDKCVFALREENKSDMNTVLNYIFSHAQVTKKNLL 1039
Rattus Norvegicus	960 FFMNTQSIVQLVQRYRSGIRGHMKAVVMDLLRQYLRVETQFQNGHYDKCVFALREENKSDMNTVLNYIFSHAQVTKKNLL 1039
Homo Sapiens	1041 VTMLIDQLCGRDPTLTDELLNILTELTQLSKTTNAKVALRARQVLIASHLPSYELRHNQVESIFLSAIDMYGHQFCIENL 1120
Mus Musculus	1040 VTMLIDQLCGRDPTLTDELLNILTELTQLSKTTNAKVALRARQVLIASHLPSYELRHNQVESIFLSAIDMYGHQFCIENL 1119
Rattus Norvegicus	1040 VTMLIDQLCGRDPTLTDELLNILTELTQLSKTTNAKVALRARQVLIASHLPSYDVRHNQVESIFLSAIDMYGHQFCIENL 1119
Homo Sapiens	1121 QKLILSETSIFDVLPNFFYHSNQVVRMAALEVYVRRAYIAYELNSVQHRQLKDNTCVVEFQFMLPTSHPNRGNIPTLNRM 1200
Mus Musculus	1120 QKLILSETSIFDVLPNFFYHSNQVVRMAALEVYVRRAYIAYELNSVQHRQLKDNTCVVEFQFMLPTSHPNRGNIPTLNRM 1199
Rattus Norvegicus	1120 QKLILSETSIFDVLPNFFYHSNQVVRMAALEVYVRRAYIAYELNSVQHRQLKDNTCVVEFQFMLPTSHPNRGNIPTLNRM 1199
Homo Sapiens	1201 SFSSNLNHYGMTHVASVSDVLLDNSFTPPCQRMGGMVSFRTFEDFVRIFDEVMGCFSDSPPQSPTFPEAGHTSLYDEDKV 1280
Mus Musculus	1200 SFASNLNHYGMTHVASVSDVLLDNAFTPPCQRMGGMVSFRTFEDFVRIFDEIMGCFCDSPPQSPTFPESGHTSLYDEDKV 1279
Rattus Norvegicus	1200 SFASNLNHYGMTHVASVSDVLLDNAFTPPCQRMGGMVSFRTFEDFVRIFDEVMGCFCDSPPQSPTFPESGHTSLYDEDKV 1279
Homo Sapiens	1281 PRDEPIHILNVAIKTDCDIEDDRLAAMFREFTQQNKATLVDHGIRRLTFLVAQKDFRKQVNYEVDRRFHREFPKFFTFRA 1360
Mus Musculus	1280 PRDEPIHILNVAIKTDGDIEDDRLAAMFREFTQQNKATLVEHGIRRLTFLVAQKDFRKQVNCEVDQRFHREFPKFFTFRA 1359
Rattus Norvegicus	1280 PRDEPIHILNVAIKTDGDIEDDRLAAMFREFTQQNKATLVEHGIRRLTFLVAQKDFRKQVNCEVDQRFHREFPKFFTFRA 1359
Homo Sapiens	1361 RDKFEEDRIYRHLEPALAFQLELNRMRNFDLTAIPCANHKMHLYLGAAKVEVGTEVTDYRFFVRAIIRHSDLVTKEASFE 1440
Mus Musculus	1360 RDKFEEDRIYRHLEPALAFQLELNRMRNFDLTAIPCANHKMHLYLGAAKVEVGTEVTDYRFFVRAIIRHSDLVTKEASFE 1439
Rattus Norvegicus	1360 RDKFEEDRIYRHLEPALAFQLELNRMRNFDLTAIPCANHKMHLYLGAAKVEVGTEVTDYRFFVRAIIRHSDLVTKEASFE 1439
Homo Sapiens	1441 YLQNEGERLLLEAMDELEVAFNNTNVRTDCNHIFLNFVPTVIMDPSKIEESVRSMVMRYGSRLWKLRVLQAELKINIRLT 1520
Mus Musculus	1440 YLQNEGERLLLEAMDELEVAFNNTNVRTDCNHIFLNFVPTVIMDPSKIEESVRSMVMRYGSRLWKLRVLQAELKINIRLT 1519
Rattus Norvegicus	1440 YLQNEGERLLLEAMDELEVAFNNTNVRTDCNHIFLNFVPTVIMDPSKIEESVRSMVMRYGSRLWKLRVLQAELKINIRLT 1519
Homo Sapiens	1601 IPEMFRQSLIKLWESMSTQAFLPSPPLPSDMLTYTELVLDDQGQLVHMNRLPGGNEIGMVAWKMTFKSPEYPEGRDIIVI 1680
Mus Musculus	1600 IPEMFRQSLIKLWESMSTQAFLPSPPLPSDILTYTELVLDDQGQLVHMNRLPGGNEIGMVAWKMSLKSPEYPDGRDIIVI 1679
Rattus Norvegicus	1600 IPEMFRQSLIKLWESMSTQAFLPSPPLPSDILTYTELVLDDQGQLVHMNRLPGGNEIGMVAWKMSLKSPEYPDGRDVIVI 1679
Homo Sapiens	1681 GNDITYRIGSFGPQEDLLFLRASELARAEGIPRIYVSANSGARIGLAEEIRHMFHVAWVDPEDPYKGYRYLYLTPQDYKR 1760
Mus Musculus	1680 GNDITYRIGSFGPQEDLLFLRASELARAEGIPRIYVAANSGARIGLAEEIRHMFHVAWVDPEDPYKGYKYLYLTPQDYKR 1759

Rattus Norvegicus	1680 GNDITYRIGSFGPQEDLLFLRASELARAEGIPRIYVAANSGARIGLAEEIRHMFHVAWVDSEDPYKGYKYLYLTPQDYKR 1759
Homo Sapiens	1761 VSALNSVHCEHVEDEGESRYKITDIIGKEEGIGPENLRGSGMIAGESSLAYNEIITISLVTCRAIGIGAYLVRLGQRTIQ 1840
Mus Musculus	1760 VSALNSVHCEHVEDEGESRYKITDIIGKEEGLGAENLRGSGMIAGESSLAYDEVITISLVTCRAIGIGAYLVRLGQRTI Q 1839
Rattus Norvegicus	1760 VSALNSVHCEHVEDEGESRYKITDIIGKEEGLGAENLRGSGMIAGESSLAYDEIITISLVTCRAIGIGAYLVRLGQRTI Q 1839
Homo Sapiens	1841 VENSHLILTGAGALNKVLGREVYTSNNQLGGIQIMHNNGVTHCTVCDDFEGVFTVLHWLSYMPKSVHSSVPLLNSKDPID 1920
Mus Musculus	1840 VENSHLILTGAGALNKVLGREVYTSNNQLGGIQIMHNNGVTHSTVCDDFEGVFTVLHWLSYMPKSVHSSVPLLNSKDPID 1919
Rattus Norvegicus	1840 VENSHLILTGAGALNKVLGREVYTSNNQLGGIQIMHNNGVTHCTVCDDFEGVFTVLHWLSYMPKNVHSSVPLLNSKDPID 1919
Homo Sapiens	1921 RIIEFVPTKTPYDPRWMLAGRPHPTQKGQWLSGFFDYGSFSEIMQPWAQTVVVGRARLGGIPVGVVAVETRTVELSIPAD 2000
Mus Musculus	1920 RIIEFVPTKAPYDPRWMLAGRPHPTQKGQWLSGFFDYGSFSEIMQPWAQTVVVGRARLGGIPVGVVAVETRTVELSIPAD 1999
Rattus Norvegicus	1920 RIIEFVPTKAPYDPRWMLAGRPHPTQKGQWLSGFFDYGSFSEIMQPWAQTVVVGRARLGGIPVGVVAVETRTVELSVPAD 1999
Homo Sapiens	2001 PANLDSEAKIIQQAGQVWFPDSAFKTYQAIKDFNREGLPLMVFANWRGFSGGMKDMYDQVLKFGAYIVDGLRECC QPVLV 2080
Mus Musculus	2000 PANLDSEAKIIQQAGQVWFPDSAFKTYQAIKDFNREGLPLMVFANWRGFSGGMKDMYDQVLKFGAYIVDGLRECS QPVMV 2079
Rattus Norvegicus	2000 PANLDSEAKIIQQAGQVWFPDSAFKTYQAIKDFNREGLPLMVFANWRGFSGGMKDMYDQVLKFGAYIVDGLRECS QPVMV 2079
Homo Sapiens	2081 YIPPQAELRGGSWVVIDSSINPRHMEMYADRESRGSVLEPEGTVEIKFRRKDLVKTMRRVDPVYIHLAERLGTPELSTAE 2160
Mus Musculus	2080 YIPPQAELRGGSWVVIDPTINPRHMEMYADRESRGSVLEPEGTVEIKFRKKDLVKTMRRVDPVYIRLAERLGTPELSPTE 2159
Rattus Norvegicus	2080 YIPPQAELRGGSWVVIDPTINPRHMEMYADRESRGSVLEPEGTVEIKFRKKDLVKTMRRVDPVYIRLAERLGTPELSPTE 2159
Homo Sapiens	2161 RKELENKLKEREEFLIPIYHQVAVQFADLHDTPGRMQEKGVISDILDWKTSRTFFYWRLRRLLLEDLVKKKIHNANPELT 2240
Mus Musculus	2160 RKELESKLKEREEFLIPIYHQVAVQFADLHDTPGRMQEKGVINDILDWKTSRTFFYWRLRRLLLEDLVKKKIHNANPELT 2239
Rattus Norvegicus	2160 RKELESKLKEREEFLIPIYHQVAVQFADLHDTPGRMQEKGVINDILDWKTSRTFFYWRLRRLLLEDLVKKKIHSANPELT 2239
Homo Sapiens	2241 DGQIQAMLRRWFVEVEGTVKAYVWDNNKDLAEWLEKQLTEEDGVHSVIEENIKCISRDYVLKQIRSLV QANPEVAMDSII 2320
Mus Musculus	2240 DGQIQAMLRRWFVEVEGTVKAYVWDNNKDLVEWLEKQLTEEDGVRSVIEENIKYISRDYVLKQIRSLV QANPEVAMDSIV 2319
Rattus Norvegicus	2240 DGQIQAMLRRWFVEVEGTVKAYVWDNNKDLVEWLEKQLTEEDGVRSVIEENIKYISRDYVLKQIRSLV QANPEVAMDSIV 2319
Homo Sapiens	2321 HMTQHISPTQRAEVIRILSTMDSPST 2346
Mus Musculus	2320 HMTQHISPTQRAEVVRILSTMDSPST 2345
	2320 HMTQHISPTQRAEVVRILSTMDSPST 2345

Table 2: Alignment and Conserved Sequences of ACC2

Specie Accession Number
Homo Sapiens AAR37018.1
Mus Musculus NP_001390456.1
Rattus Norvegicus NP_446374.2

Specie	Alignment and Conserved Sequences of ACC2
Homo Sapiens	1 MVLLLCLSCLIFSCLTFSWLKIWGKMTDSKPITKSKSEANLIPS-QEPFPASDNSGETPQRNGEGHTLPKTPSQAEPASH 79
Mus Musculus	1 MVLLLFLTCLVFSCLTFSWLKIWGKMTDSKPLTNSKVEANLLSS-EESLSASELSGEQLQEHGDHSC----------LSY 69
Rattus Norvegicus	1 MVLLLFLTCLVFSCLTISWLKIWGKMTDSKPLSNSKVDASLLSSkEESFSASD----QSEEHGDCSCPLTTPDQEELASH 76
Homo Sapiens	80 KGPKDAGRRRNSLPPSHQKPPRNPLSSSDAAPSPELQANGIGTQGLEATDTNGLSSSARPQGQQAGSPSKEDKKQANIKR 159
Mus Musculus	70 RGPRDASQQRNSLPSSCQRPPRNPLSSNDTWPSPELQTNWTAAPGPEVPDANGLSFPARPPSQRTVSPSREDRKQAHIKR 149
Rattus Norvegicus	77 GGPVDASQQRNSVPSSHQKPPRNPLSSNDTCSSPELQTNRVAAPGSEVPEANGLPFPARPQTQRTGSPTREDKKQAHIKR 156
Homo Sapiens	160 QLMTNFILGSFDDYSSDEDSVAGSSRESTRKGSRASLGALSLEAYLTTGEAETRVPTMRPSMSGLHLVKRGREHKKLDLH 239
Mus Musculus	150 QLMTSFILGSLDDNSSDEDPSAGSFQNSSRKSSRASLGTLSQEAALNTSDPESHAPTMRPSMSGLHLVKRGREHKKLDLH 229
Rattus Norvegicus	157 QLMTSFILGSLDDNSSDEDPSASSFQTSSRKGSRASLGTLSQEAALNTADPESHTPTMRPSMSGLHLVKRGREHKKLDLH 236
Homo Sapiens	240 RDFTVASPAEFVTRFGGDRVIEKVLIANNGIAAVKCMRSIRRWAYEMFRNERAIRFVVMVTPEDLKANAEYIKMADHYVP 319

Mus Musculus	230 RDFTVASPAEFVTRFGGNRVIEKVLIANNGIAAVKCMRSIRRWAYEMFRNERAIRFVVMVTPEDLKANAEYIKMADQYVP 309
Rattus Norvegicus	237 RDFTVASPAEFVTRFGGNRVIETVLIANNGIAAVKCMRSIRRWAYEMFRNERAIRFVVMVTPEDLKANAEYIKMADQYVP 316
Homo Sapiens	320 VPGGPNNNNYANVELIVDIAKRIPVQAVWAGWGHASENPKLPELLCKNGVAFLGPPSEAMWALGDKIASTVVAQTLQVPT 399
Mus Musculus	310 VPGGPNNNNYANVELIIDIAKRIPVQAVWAGWGHASENPKLPELLCKHEIAFLGPPSEAMWALGDKIASTIVAQTLQIPT 389
Rattus Norvegicus	317 VPGGPNNNNYANVELIIDIAKRIPVQAVWAGWGHASENPKLPELLCKHEIAFLGPPSEAMWALGDKISSTIVAQTLQIPT 396
Homo Sapiens	400 LPWSGSGLTVEWTEDDLQQGKRTSVPEDVYDKGCVKDVDEGLEAAERIGFPLMIKASEGGGGKGIRKAESAEDFPILFRQ 479
Mus Musculus	390 LPWSGSGLTVEWTEDSRHQGKCISVPEDVYEQGCVKDVDEGLQAAEKIGFPLMIKASEGGGGKGIRKAESAEDFPMLFRQ 469
Rattus Norvegicus	397 LPWSGSGLTVEWTEDSQHQGKCISVPEDVYEQGCVRDVDEGLQAAEKVGFPLMIKASEGGGGKGIRRAESAEDFPMLFRQ 476
Homo Sapiens	480 VQSEIPGSPIFLMKLAQHARHLEVQILADQYGNAVSLFGRDCSIQRRHQKIVEEAPATIAPLAIFEFMEQCAIRLAKTVG 559
Mus Musculus	470 VQSEIPGSPIFLMKLAQNARHLEVQVLADQYGNAVSLFGRDCSIQRRHQKIIEEAPATIAAPAVFEFMEQCAVLLAKMVG 549
Rattus Norvegicus	477 VQSEIPGSPIFLMKLAQNARHLEVQVLADQYGNAVSLFGRDCSIQRRHQKIIEEAPATIAAPAVFEFMEQCAVLLAKTVG 556
Homo Sapiens	560 YVSAGTVEYLYSQDGSFHFLELNPRLQVEHPCTEMIADVNLPAAQLQIAMGVPLHRLKDIRLLYGESPWGVTPISFETPS 639
Mus Musculus	550 YVSAGTVEYLYSQDGSFHFLELNPRLQVEHPCTEMIADVNLPAAQLQIAMGVPLHRLKDIRLLYGESPWGVTPIPFETPL 629
Rattus Norvegicus	557 YVSAGTVEYLYSQDGSFHFLELNPRLQVEHPCTEMIADVNLPAAQLQIAMGVPLHRLKDIRLLYGESPWGVTPVSFETPL 636
Homo Sapiens	640 NPPLARGHVIAARITSENPDEGFKPSSGTVQELNFRSSKNVWGYFSVAATGGLHEFADSQFGHCFSWGENREEAISNMVV 719
Mus Musculus	630 SPPIARGHVIAARITSENPDEGFKPSSGTVQELNFRSNKNVWGYFSVAAAGGLHEFADSQFGHCFSWGENREEAISNMVV 709
Rattus Norvegicus	637 SPPIARGHVIAARITSENPDEGFKPSSGTVQELNFRSNKNVWGYFSVAAAGGLHEFADSQFGHCFSWGENREEAISNMVV 716
Homo Sapiens	720 ALKELSIRGDFRTTVEYLINLLETESFQNNDIDTGWLDYLIAEKVQAEKPDIMLGVVCGALNVADAMFRTCMTDFLHSLE 799
Mus Musculus	710 ALKELSIRGDFRTTVEYLVNLLETESFQNNDIDTGWLDHLIAQRVQAEKPDIMLGVVCGALNVADAMFRTCMTEFLHSLE 789
Rattus Norvegicus	717 ALKELSIRGDFRTTVEYLVNLLETESFQNNDIDTGWLDHLIAQRVQAEKPDIMLGVVCGALNVADAMFRTCMTEFLHSLE 796
Homo Sapiens	800 RGQVLPADSLLNLVDVELIYGGVKYILKVARQSLTMFVLIMNGCHIEIDAHRLNDGGLLLSYNGNSYTTYMKEEVDSYRI 879
Mus Musculus	790 RGQVLPADSLLNIVDVELIYGGIKYALKVARQSLTMFVLIMNGCHIEIDAHRLNDGGLLLSYNGSSYTTYMKEEVDSYRI 869
Rattus Norvegicus	797 RGQVLPADSLLNIVDVELIYGGIKYVLKVARQSLTMFVLIMNGCHIEIDAHRLNDGGLLLSYNGSSYTTYMKEEVDSYRI 876
Homo Sapiens	880 TIGNKTCVFEKENDPTVLRSPSAGKLTQYTVEDGGHVEAGSSYAEMEVMKMIMTLNVQERGRVKYIKRPGAVLEAGCVVA 959
Mus Musculus	870 TIGNKTCVFEKENDPTVLRSPSAGKLMQYTVEDGDHVEAGSSYAEMEVMKMIMTLNVQESGRVKYIKRPGVILEAGCVVA 949
Rattus Norvegicus	877 TIGNKTCVFEKENDPTVLRSPSAGKLMQYTVEDGQHVEVGSSYAEMEVMKMIMTLNVQESGRVKYIKRPGAVLEAGCVVA 956
Homo Sapiens	960 RLELDDPSKVHPAEPFTGELPAQQTLPILGEKLHQVFHSVLENLTNVMSGFCLPEPVFSIKLKEWVQKLMMTLRHPSLPL 1039
Mus Musculus	950 RLELDDPSKVHAAQPFTGELPAQQTLPILGEKLHQVFHGVLENLTNVMSGYCLPEPFFSMKLKDWVQKLMMTLRHPSLPL 1029
Rattus Norvegicus	957 KLELDDPSKVHAAQPFTGELPAQQTLPILGERLHQVFHSVLENLTNVMNGYCLPEPFFSMKLKDWVEKLMMTLRHPSLPL 1036
Homo Sapiens	1040 LELQEIMTSVAGRIPAPVEKSVRRVMAQYASNITSVLCQFPSQQ IATILDCHAATLQRKADREVFFINTQSIVQLV 1115
Mus Musculus	1030 LELQEIMTSVAGRIPAPVEKAVRRVMAQYASNITSVLCQFPSQQ [21]IATILDCHAATLQRKADREVFFMNTQSIVQLV 1126
Rattus Norvegicus	1037 LELQEIMTSVAGRIPVPVEKAVRRVMAQYASNITSVLCQFPSQQ IATILDCHAATLQRKVDREAFFMNTQSIVQLI 1112
Homo Sapiens	1116 QRYRSGIRGYMKTVVLDLLRRYLRVEHHFQQAHYDKCVINLREQFKPDMSQVLDCIFSHAQVAKKNQLVIMLIDELCGPD 1195
Mus Musculus	1127 QRYRSGTRGYMKAVVLDLLRKYLNVEHHFQQAHYDKCVINLREQFKPDMTQVLDCIFSHSQVAKKNQLVTMLIDELCGPD 1206
Rattus Norvegicus	1113 QRYRSGTRGYMKAVVLDLLRRYLNVEHHFQQAHYDKCVINLREQFKPDMTRVLDCIFSHSQVAKKNQLVTMLIDELCGPD 1192
Homo Sapiens	1196 PSLSDELISILNELTQLSKSEHCKVALRARQILIASHLPSYELRHNQVESIFLSAIDMYGHQFCPENLKKLILSETTIFD 1275
Mus Musculus	1207 PTLSDELTSILCELTQLSRSEHCKVALRARQVLIASHLPSYELRHNQVESIFLSAIDMYGHQFCPENLKKLILSETTIFD 1286
Rattus Norvegicus	1193 PTLSEELTSILKELTQLSRSEHCKVALRARQVLIASHLPSYELRHNQVESIFLSAIDMYGHQFCPENLKKLILSETTIFD 1272
Homo Sapiens	1276 VLPTFFYHANKVVCMASLEVYVRRGYIAYELNSLQHRQLPDGTCVVEFQFMLPSSHPNRMTVPISITNPDLLRHSTELFM 1355
Mus Musculus	1287 VLPTFFYHENKVVCMASLEVYVRRGYIAYELNSLQHRELPDGTCVVEFQFMLPSSHPNRMAVPISVSNPDLLRHSTELFM 1366
Rattus Norvegicus	1273 VLPTFFYHANKVVCMASLEVYVRRGYIAYELNSLQHRELPDGTCVVEFQFMLPSSHPNRMAMPINVSDPDLLRHSKELFM 1352

Homo Sapiens	1356 DSGFSPLCQRMGAMVAFRRFEDFTRNFDEVISCFANVPKDTPLFSEARTSLYSEDDCKSLREEPIHILNVSIQCADHLED 1435
Mus Musculus	1367 DSGFSPLCQRMGAMVAFRRFEEFTRNFDEVISCFANVQTDTLLFSKACTSLYSEEDSKSLREEPIHILNVAIQCADHMED 1446
Rattus Norvegicus	1353 DSGFSPLCQRMGAMVAFRRFEEFTRNFDEVISCFANVPTDTPLFSKACTSLYSEEDSKSLQEEPIHILNVAIQCADHMED 1432
Homo Sapiens	1436 EALVPILRTFVQSKKNILVDYGLRRITFLIAQEKEFPKFFTFRARDEFAEDRIYRHLEPALAFQLELNRMRNFDLTAVPC 1515
Mus Musculus	1447 EALVPVFRAFVQSKKHILVDYGLRRITFLVAQEREFPKFFTFRARDEFAEDRIYRHLEPALAFQLELSRMRNFDLTAVPC 1526
Rattus Norvegicus	1433 ERLVPVFRAFVQSKKHILVDYGLRRITFLIAQEREFPKFFTFRARDEFAEDRIYRHLEPALAFQLELSRMRNFDLTAVPC 1512
Homo Sapiens	1516 ANHKMHLYLGAAKVKEGVEVTDHRFFIRAIIRHSDLITKEASFEYLQNEGERLLLEAMDELEVAFNNTSVRTDCNHIFLN 1595
Mus Musculus	1527 ANHKMHLYLGAAKVKEGLEVTDHRFFIRAIIRHSDLITKEASFEYLQNEGERLLLEAMDELEVAFNNTSVRTDCNHIFLN 1606
Rattus Norvegicus	1513 ANHKMHLYLGAAKVKEGLEVTDHRFFIRAIIRHSDLITKEASFEYLQNEGERLLLEAMDELEVAFNNTSVRTDCNHIFLN 1592
Homo Sapiens	1596 FVPTVIMDPFKIEESVRYMVMRYGSRLWKLRVLQAEVKINIRQTTTGSAVPIRLFITNESGYYLDISLYKEVTDSRSGNI 1675
Mus Musculus	1607 FVPTVIMDPLKIEESVRDMVMRYGSRLWKLRVLQAEVKINIRQTTSDSAIPIRLFITNESGYYLDISLYREVTDSRSGNI 1686
Rattus Norvegicus	1593 FVPTVIMDPLKIEESVRAMVMRYGSRLWKLRVLQAEVKINIRQTTSDCAVPIRLFITNESGYYLDISLYKEVTDSRSGNI 1672
Homo Sapiens	1676 MFHSFGNKQGPQHGMLINTPYVTKDLLQAKRFQAQTLGTTYIYDFPEMFRQALFKLWGSPDKYPKDILTYTELVLDSQGQ 1755
Mus Musculus	1687 MFHSFGNKQGSLHGMLINTPYVTKDLLQAKRFQAQSLGTTYVYDFPEMFRQALFKLWGSPEKYPKDILTYTELVLDSQGQ 1766
Rattus Norvegicus	1673 MFHSFGNKQGSLHGMLINTPYVTKDLLQAKRFQAQSLGTTYVYDFPEMFRQALFKLWGSPEKYPKDILTYTELVLDSQGQ 1752
Homo Sapiens	1756 LVEMNRLPGGNEVGMVAFKMRFKTQEYPEGRDVIVIGNDITFRIGSFGPGEDLLYLRASEMARAEGIPKIYVAANSGARI 1835
Mus Musculus	1767 LVEMNRLPGCNEVGMVAFKMRFKTPEYPEGRDAVVIGNDITFQIGSFGIGEDFLYLRASEMARTEGIPQIYLAANSGARM 1846
Rattus Norvegicus	1753 LVEMNRLPGCNEVGMVVFKMRFKTPEYPEGRDTIVIGNDITFQIGSFGIGEDFLYLRASEMARTEGIPQIYLAANSGARM 1832
Homo Sapiens	1836 GMAEEIKHMFHVAWVDPEDPHKGFKYLYLTPQDYTRISSLNSVHCKHIEEGGESRYMITDIIGKDDGLGVENLRGSGMIA 1915
Mus Musculus	1847 GLAEEIKQIFQVAWVDPEDPHKGFRYLYLTPQDYTQISSQNSVHCKHIEDEGESRYVIVDVIGKDANLGVENLRGSGMIA 1926
Rattus Norvegicus	1833 GLSEEIKQIFQVAWVDPEDPYKGFRYLYLTPQDYTQISSQNSVHCKHIEDEGESRYVIVDVIGKDSSLGVENLRGSGMIA 1912
Homo Sapiens	1916 GESSLAYEEIVTISLVTCRAIGIGAYLVRLGQRVIQVENSHIILTGASALNKVLGREVYTSNNQLGGVQIMHYNGVSHIT 1995
Mus Musculus	1927 GEASLAYEKTVTISMVTCRALGIGAYLVRLGQRVIQVENSHIILTGAGALNKVLGREVYTSNNQLGGVQIMHTNGVSHVT 2006
Rattus Norvegicus	1913 GEASLAYEKNVTISMVTCRAIGIGAYLVRLGQRVIQVENSHIILTGAGALNKVLGREVYTSNNQLGGVQIMHTNGVSHVT 1992
Homo Sapiens	1996 VPDDFEGVYTILEWLSYMPKDNHSPVPIITPTDPIDREIEFLPSRAPYDPRWMLAGRPHPTLKGTWQSGFFDHGSFKEIM 2075
Mus Musculus	2007 VPDDFEGVCTILEWLSFIPKDNRSPVPITTPSDPIDREIEFTPTKAPYDPRWMLAGRPHPTLKGTWQSGFFDHGSFKEIM 2086
Rattus Norvegicus	1993 VPDDFEGVCTILEWLSYIPKDNQSPVPIITPSDPIDREIEFTPTKAPYDPRWLLAGRPHPTLKGTWQSGFFDHGSFKEIM 2072
Homo Sapiens	2076 APWAQTVVTGRARLGGIPVGVIAVETRTVEVAVPADPANLDSEAKIIQQAGQVWFPDSAYKTAQAVKDFNREKLPLMIFA 2155
Mus Musculus	2087 APWAQTVVTGRARLGGIPVGVIAVETRTVEVAVPADPANLDSEAKIIQQAGQVWFPDSAYKTAQVIRDFNKERLPLMIFA 2166
Rattus Norvegicus	2073 APWAQTVVTGRARLGGIPVGVIAVETRSVEVAVPADPANLDSEAKIIQQAGQVWFPDSAFKTAQVIRDFNQEHLPLMIFA 2152
Homo Sapiens	2156 NWRGFSGGMKDMYDQVLKFGAYIVDGLRQYKQPILIYIPPYAELRGGSWVVIDATINPLCIEMYADKESRGGVLEPEGTV 2235
Mus Musculus	2167 NWRGFSGGMKDMYEQMLKFGAYIVDGLRLYEQPILIYIPPCAELRGGSWVVLDSTINPLCIEMYADKESRGGVLEPEGTV 2246
Rattus Norvegicus	2153 NWRGFSGGMKDMYEQMLKFGAYIVDSLRLFKQPVLIYIPPGAELRGGAWVVLDSSINPLCIEMYADKESRGGVLEPEGTV 2232
Homo Sapiens	2236 EIKFRKKDLIKSMRRIDPAYKKLMEQLGEPDLSDKDRKDLEGRLKAREDLLLPIYHQVAVQFADFHDTPGRMLEKGVISD 2315
Mus Musculus	2247 EIKFRKKDLVKTIRRIDPVCKKLVGQLGKAQLPDKDRKELEGQLKAREELLLPIYHQVAVQFADLHDTPGHMLEKGIISD 2326
Rattus Norvegicus	2233 EIKFRKKDLVKTIRRIDPVCKKLLGQLGTAQLPDKDRKELESQLKAREDLLLPIYHQVAVQFADLHDTPGHMLEKGIISD 2312
Homo Sapiens	2316 ILEWKTARTFLYWRLRRLLLEDQVKQEILQASGELSHVHIQSMLRRWFVETEGAVKAYLWDNNQVVVQWLEQHWQAGDGP 2395
Mus Musculus	2327 VLEWKTARTFFYWRLRRLLLEAQVKQEILRASPELNHEHTQSMLRRWFVETEGAVKAYLWDSNQVVVQWLEQHWSAKDGL 2406
Rattus Norvegicus	2313 VLEWKTTRTYFYWRLRRLLLEAQVKQEILRASPELSHEHTQSMLRRWFVETEGAVKAYLWDSNQVVVQWLEQHWSARDNL 2392
Homo Sapiens	2396 RSTIRENITYLKHDSVLKTIRGLVEENPEVAVDCVIYLSQHISPAERAQVVHLLSTMDSPAST 2458
Mus Musculus	2407 RSTIRENINYLKRDSVLKTIQSLVQEHPEVIMDCVAYLSQHLTPAERIQVAQLLSTTESPASS 2469
Rattus Norvegicus	2393 RSTIRENINYLKRDSVLKTIQSLVQEHPEATMDCVAYLSQHLTPAEQMQVVQLLSTTESPASH 2455

ACCs are found in both prokaryotes and eukaryotes and are categorized in the same manner. Prokaryotic ACC is a heterogeneous enzyme in archaea, bacteria, dicotyledonous, and non-gramineous monocotyledonous plants (9). Holoenzyme of prokaryotic ACC is composed of three subunits, including biotin carboxylase (BC), biotin carboxyl carrier protein (BCCP), and carboxyltransferases (CT, subdivided as CT-α and CT-β). These subunits can be readily detached from each other due to the instability of the holoenzyme [9].

On the other hand, eukaryotic ACC is a homogeneous enzyme in yeasts, algae, plants, and animals and comprises three sections. These sections include BC, BC–CT interaction, BCCP domain in the N-terminal, and the CT domain in the C-terminal. It also owns a central domain that is not catalytic [10-12].

X-ray crystal structure of yeast CT domain showed a shape similar to a quarter disk. The interface of a dimer of the ACC is the location of the enzyme's active site [13]. The enzyme activity can be inhibited by locating the inhibitors at this site, making it unable to bind to substrates (malonyl CoA and acetyl CoA) [14].

Three segments have been found in the structure of the BC domain; A, B, and C. The active site comprises A and C segments, and the B domain is responsible for closing the active site during catalysis by undergoing a significant conformational alteration. Studies suggest that the larger size of the eukaryotic ACC in comparison to bacterial ACC (550 residues vs. 450 residues, respectively) is due to the numerous inserted segments between A and B domains (the AB linker) at the N-terminus [15].

E. coli ACC shows a symmetrical structure in the C-terminus of the BCCP domain in the form of a flattened β-barrel composed of two sets of four antiparallel β strands [16]. A tight β-turn of this structure consisting of the Ala-Met-Lys-Met biotinylation motif is the place of the biotin part. BCCP owns an eight-residue protruding segment called 'thumb,' which interacts with biotin and makes it easier for the biotin moiety to access the active components of the enzyme [17]. Human ACC does not own the 'thumb,' making the covalent biotin attachment in the BCCP flexible.

The BT domain's structure shows a long helix surrounded by an eight-stranded anti-parallel β-barrel (β22–β29) and a 'hook' connecting the terminal of the helix to the first strand of β-barrel (β22). Considering the lack of direct contact between BC and CT domains, the BT domain facilitates the interactions between these parts [17]. Central fields are specific to the eukaryotic ACCs and are responsible for holding the BC and CT domains in the correct positions during catalysis.

Furthermore, the CT domain comprises two subdomains called N and C domains, both of which own a crotonase fold (a β-β-α superhelix), and their equivalents in bacterial CT are called β and α. A 'canyon' is placed in the interface of a dimer of the CT that is the active site of the domain, making it necessary for the CT domain to dimerize for catalysis [18].

Biological activity

ACC is a biotin-dependent catalyzer that contributes to the production of malonyl-CoA by catalyzing carboxylation of acetyl-CoA through biotin carboxylation and carboxyl transference [9,19,20]. The catalysis process by ACC is a two-step process involving three domains. In the first step, the BCCP domain makes a covalent link with biotin, leading to its carboxylation by the BC domain. Carboxyl groups and energy needed for the first step are derived from bicarbonate and ATP phosphates. Coordination of the ATP phosphates is achieved by divalent cations, including Mg^{2+} and Mn^{2+}. In the second step, malonyl-CoA gets produced by transference of biotin's activated carboxyl group to acetyl-CoA embedded in the CT domain [21].

ACC has two tissue-specific isoforms, ACC1 and 2, and both have specific activity and site of action. Liver and adipose tissue express ACC1, while ACC2 is mainly expressed in oxidative tissues, including cardiac and skeletal muscles. ACC1 is a cytosolic rate-limiting enzyme involved in the long-chain fatty acid synthesis by catalyzation of the first committed step of this pathway. The resultant malonyl-CoA with the catalysis of fatty acid synthase (FASN) adds two carbons to the fatty acid chain leading to its expansion [10].

However, ACC2 leads to allosteric inhibition of carnitine palmitoyl-transferase by malonyl-CoA in the mitochondrial outer membrane and regulates FAOxn and fatty acid transfer within mitochondria for β-oxidation [21]. Although ACC1 and 2 have an amino acid sequence equal to 73%, ACC2 owns a 140-residue part at the N-terminus with highly hydrophobic first 20 residues, which causes its association with the mitochondrial membrane; human white adipose tissue shows an increased expression of a type of ACC2 which doesn't have an N-terminal mitochondrial targeting segment [22,23].

According to literature, citrate stimulates mammalian ACC1 and 2, whereas long-chain saturated acyl-CoA inhibits their actions. Citrate has a 1000-fold effect on ACC2 compared to its 4-fold impact on ACC. Furthermore, they get inactivated through phosphorylation by AMP-activated protein kinase (AMPK, at Ser80 in ACC1, Ser222 in ACC2) and cAMP-dependent protein kinase (protein kinase A, at Ser1201 in ACC1 [24,25]. ACCs have two binding sites for citrate; 1. An activating site with higher affinity (Kd ~1 mM) and 2. An inhibitory site with a lower affinity (Ki ~30 mM). MIG12, a cytosolic protein, promotes the stimulatory impact of citrate on the ACC1 and is embedded in the ACC1 polymer structure. On the other hand, forming a complex with other proteins leads to the downregulation of MIG12 (spot 14 (~17 kD)) [15,26].

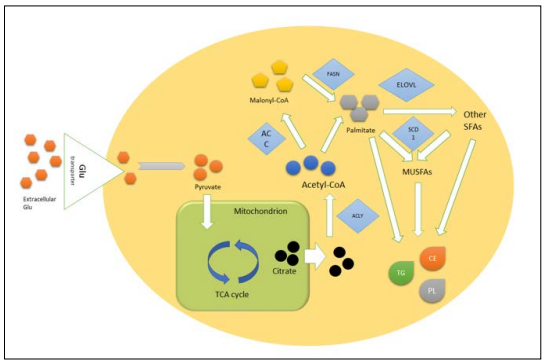

Figure 1. de novo lipogenesis and role of ACC

ACC signaling in cancer

Regulators involved in the signaling of lipid biosynthesis are noteworthy targets for tumor suppressors and oncogenes to cause alterations in de novo fatty acid synthesis [27]. By rewiring their energy production from a glycolysis-dependent pathway to a lipogenesis-dependent pathway, cancer cells enhance their survival against stress [28].

Considering the rapid cell division of cancer cells, it seems that manipulation of lipid synthesis is a way of meeting the need for significant amounts of the cell membrane, which is mainly made of phospholipids. Interestingly, studies have shown that a substantial part of the newly synthesized lipids in cancer cells are phospholipids (figure 1) [29-31]. Moreover, studies report a high percentage of saturated and monounsaturated FAs among recently produced lipids that will be embedded in the detergent-resistant microdomains or rafts, mediating signal transduction, intracellular

trafficking, and signal transduction [32].

On the other hand, studies confirm an increased expression level of ACC in multiple cancers such as breast, prostate, liver, etc. Various studies have shown that silencing ACC1 using RNAi strategies results in decreased synthesis of FAs and impairment of mitochondrial potentials, leading to oxidative stress and subsequent apoptotic cell death. Moreover, the apoptosis caused by ACC1 inhibition can be reversed by adding palmitic acid (16:0) to the medium, an end product of the FA synthesis pathway. These results confirm the importance of ACC's role in the survival and growth of cancer cells [33-35].

ACC's Role in NAFLD, NASH, and HCC

Non-alcoholic steatohepatitis (NASH) is now the fastest developing cause of hepatocellular carcinoma (HCC), and patients with NASH cirrhosis show a higher HCC incidence rate (0.5 to 2.6%) [36].

Higher levels of de novo lipogenesis inside hepatic cells are essential in the progression of non-alcoholic fatty liver disease (NAFLD) and HCC [37,38]. Primarily, NAFLD results from consuming diets full of refined carbohydrates [39].

As discussed, ACC causes malonyl-CoA formation from acetyl-CoA, providing the substrate for de novo lipogenesis and inhibiting fatty acid oxidation. Thus, ACC plays a vital role in controlling the flux of carbon intermediates between carbohydrate and fatty acid metabolism (40).

Phosphorylation of ACC decreases malonyl-CoA within cells, suppressing fatty acid synthesis and inhibiting the development of early signs of NAFLD and fibrosis (41). In the meantime, endoplasmic reticulum stress (ERS) exists in non-alcoholic fatty liver cells. As a simulation, the induction of ERS in HepG2 cell lines contributed to the destruction of ER structure and elevation of lipid deposition through increasing ACC1 expression (42).

Multiple pathways have been suggested by literature for ACC1 engaged paths leading to HCC progression;

a higher rate of liver cancer cell proliferation is seen in mice with ACC1 gene mutations that lead to elevated de novo lipogenesis. This phenomenon happens due to inhibiting phosphorylation of ACC1 & 2 inside liver lesions via inducing loss of function mutations in AMPK expressing genes, contributing to an increase in de novo lipogenesis [42,43]. Also, non-tumorous liver cells in the tumor margin induce de novo lipogenesis in the tumor cells upon the HCC progression (figure 2).

HCC cells up-regulate gene expression of a transmembrane glycoprotein called CD147. CD147 plays a vital role in the proliferation and metastasis of HCC cells. One of the CD147 mechanisms of function is through activating Akt/mTOR signaling pathway to up-regulate the expression of sterol regulatory element-binding protein 1c (SREBP1c). These steps lead to activation of the transcription process of central lipogenic genes such as FASN and ACC1, leading to increased de novo lipogenesis (figure 2) [37,44].

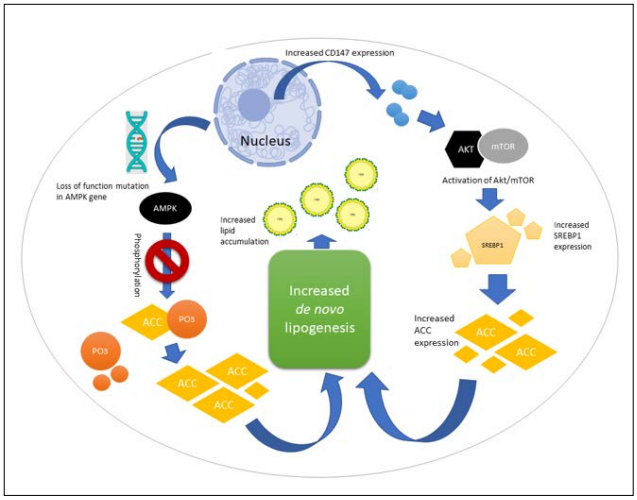

Figure 2: ACC-Related Pathways in the Development of HCC

In accordance, ACC activation by inhibiting 6-phosphogluconate dehydrogenase (6PGD) -an upregulated enzyme in HCC- reduces NADPH/NAD+ and NADH concentrations within cells, leading to increased HCC cell oxidative stress and lower survival [45].

dysregulation of the FA oxidative decomposition due to enzyme impairment has also been reported. ACC attaches to the carnitine palmitoyl-transferase 1 (CPT1), which is placed in the outer mitochondrial membrane and transfers long-chain fatty acyl-CoA to carnitine for oxidation inside mitochondria. The complex of ACC/CPT1 coordinates β-oxidation and formation of FAs, and in this way, ACC prevents mitochondrial distribution of CPT1 under satisfactory glucose circumstances. In glucose starvation conditions within HCC cells, ACC detaches from CPT1. The released free CPT1 molecules relocate within the mitochondrial membrane, enhancing β-oxidation and protecting HCC cells during metabolic stress [41,46].

Thus, ACC1-mediated FA synthesis controls the intracellular lipid content needed for energy homeostasis during metabolic stress, preventing cell death due to FA oxidation [46]. ACC1 plays two essential roles in HCC survival, providing substrate and enzyme for FA oxidation in glucose deficiency conditions [46,47].

Overall, higher de novo lipogenesis is correlated with tumor development and higher recurrence rates, and more aggressive HCC cells [37]. Suppression of lipogenic enzymes, including ACC1, inhibits proliferation in HepG2 hepatoma cells [37,47].

However, Che et al. evaluated the effects of de novo lipogenesis on tumorigenesis in various mouse models of hepatic cancer. Interestingly, they resulted that depending on the active oncogenes involved in HCC development, different types of dependency on lipogenesis are seen[48]. The HCC cells might be dependent on or independent of de novo lipogenesis. Accordingly, ACC inhibition in an HCC mouse model treated with diethylnitrosamine resulted in a two-fold higher tumor incidence than the controls [49].

ACC silencing also significantly suppressed cell viability in human HepG2 cells and rat liver cell line BRL 3A [47].

On this matter, two ACC polymorphisms were significantly associated with various effects on the overall survival; the homozygous variant genotype in rs7211875 and rs11871275 significantly increased and decreased mortality rate in HCC patients, respectively, confirming the two sides of ACC's effect on the HCC tumorigenesis [50].

ACC Role in chemo-resistance

Resistance to chemotherapy in HCC cells rises from the cancer stem cells. HepG2SF1 and Huh7SF1 are the two cell lines showing stem-like characteristics. The evaluation of these cell lines revealed increased expression of the enzymes involved in de novo lipogenesis, including ACC [51].

Chen et al. suggested 6-phosphogluconate dehydrogenase (6GPD) as a promising therapeutic target against HCC cell resistance. 6GPD acts through the inactivation of ACC and AMPK enzymes, and protects the HCC cells from oxidative stress, confirming the role of ACC in chemoresistance induction [45].

Similar results have been obtained from animal studies. Rat HCC models have revealed higher de novo lipogenesis following mutation of AMPK phosphorylation sites inside the ACC1 structure, which have been associated with sorafenib resistance as the first-generation targeted therapy agent in late-stage HCC. More importantly, ACC1 inhibition has led to higher sorafenib efficacy and improved HCC cell survival due to reduced AMPK-mediated ACC1 phosphorylation [42].

ACC Inhibitors

ACC inhibitors have long been developed and used in agriculture as herbicides. Moreover, regarding ACC's critical role in the development of various conditions, ACC inhibitors have been considered potential therapeutic targets during the past decades [52]. ACC is mainly involved in de novo lipogenesis (DNL). Its inhibition decreases hepatic lipid synthesis and increases fatty acid oxidation, making it an exciting target in treating NAFLD, NASH, and even HCC. Multiple studies have shown that genetic impairment of ACC in mice models also decreases DNL, thus improving hepatic cell health [53].

In recent decades, small molecules have shown significant progress in treating multiple conditions. Small molecules are designed to bind to the allosteric or orthosteric sites of the specific targets, thus inhibiting or impairing their function. Many characteristics of these molecules make them the best choice for therapeutic investigations in modern-day medicine, including aqueous solubility, tissue distribution, and cellular permeability, making them effective on the surface and intracellular proteins. However, a short half-life is one limitation of this technology, and frequent dosing is required to achieve the target levels [54].

Table 3. ACC small-molecule inhibitors used for HCC, NAFLD, and NASH treatment.

Inhibitors	Mechanism of Action	IC50	Disease	Study Population	Dosing	Study Result	Side Effects	Reference
PF-05221304 (Clesacostat)	Liver-targeted reversible ACC1/2 inhibitor	61 nmol/L	NAFLD	Phase IIa trial	2, 10, 25, and 50 mg once daily (QD)	50-65% reduction in liver fat with doses ≥10 mg QD	A dose-dependent elevation in serum triglycerides (TG) in 23/305 (8%)	[55]
GS-0976 (Firsocostat)	Liver-targeted ACC1/2 Inhibitor Binds to the BC Domain	N/A	NASH	Phase II trial	20 mg daily	A relative reduction in liver fat by 29%	Elevation in TG of 16 patients (>500 mg/dL)	[53]
ND-654	Liver-Targeted ACC1/2 Allosteric Inhibitor Binds to the BC Domain	Inhibits ACC1 with 3 nM, and ACC2 with 8 nM	HCC	Tumor-bearing rats	10 mg/kg daily	55% reduction in tumor burden and 40% in mortality	None	[42]
IMA-1	ACC1 inhibitor, Inhibits Interaction with arachidonate 12-Lipoxygenase (ALOX12)	N/A	NASH	Male mice and Cynomolgus macaque therapeutic models	N/A	Significantly blocked NASH progression	Did not elicit hyperlipidemia	[60]

Compound 1-1	Liver-Targeted ACC1/2 Allosteric Inhibitor Binds to the BC Domain	N/A	NAFLD	Rodent models of NAFLD	10 mg/kg	23-36% reduction in hepatic DNL and 43-61% in TG content	30-130% elevation in plasma TG	[61]
NDI-010976	Liver-Targeted ACC1/2 Allosteric Inhibito	N/A	Hepatic de novo lipogenesis (DNL)	A randomized, double-blind, placebo-controlled, crossover trial	A single oral dose of 20, 50, or 200 mg	70-104% inhibition of DNL	Diarrhea in 38%	[62]
WZ66	Liver-targeted ACC1/2 Inhibitor Binds to the CT Domain	435.9 and 141.3 nM	NASH	Mice models	50 mg/kg	Efficiently attenuated hepatic steatosis and inhibited macrophage and hepatic stellate cell activation.	Moderate elevation in plasma TG	[63]
Compound 1-2	Selective ACC1 Inhibitor	0.58 nM and >10,000 nM	NAFLD/ NASH	Mice models	once daily at doses of 3, 10, and 30 mg/kg	62% reduction in hepatic steatosis and fibrosis	None	[64]
ND-630	Liver-Targeted ACC1/2 Inhibitor, Binds to the BC Domain	3.9 μM and 6.6 μM	Hepatic steatosis	Rat models	N/A	Reduces hepatic steatosis, improves insulin sensitivity, reduces weight gain without affecting food intake, and favorably affects dyslipidemia	None	[65]
MK-4074	Liver-Targeted ACC1/2 Inhibitor	3 nM	Hepatic steatosis	Phase I trial	a single dose of 140 mg, or as a divided dose (70 mg b.i.d.)	It might be beneficial for the treatment of NAFLD, Reduced liver triglyceride by 36%	200% elevation in plasma TG	[66]

In table 3, we discuss the suggested ACC1 small-molecular inhibitors in treating NAFLD, NASH, and HCC. Most of these inhibitors are dual inhibitors of ACC1 and 2 except for the IMA-1 and compound-1, which are selective ACC1 inhibitors. Although multiple mechanisms of action have been suggested for these inhibitors, they mainly inhibit ACC by binding to the BC domain. The BC domain is a great pharmaceutical target due to its shallow and hydrophilic pocket structure with excellent physiochemical characteristics [53]. By binding to the BC domain, they inhibit the dimerization of ACC and impair its enzymatic function.

All presented inhibitors are substrates for organic anion-transporting polypeptide (OATP) transporters and hence are liver-directed due to this property. As a result, the tissue distribution of these molecules is asymmetrical to ensure adequate liver concentrations and liver-directed therapeutic effect and low plasma concentrations to minimize the side effects [55].

ACC miRNA-Mediated Regulation

MicroRNAs (miRNAs) are essential endogenous, tissue-specific, small non-protein-coding RNAs involved in the cellular homeostasis of animals and plants by gene regulation. MiRNAs are structured from 22 nucleotides, and pair with the mRNAs resulting from protein-coding genes and regulate their expression after transcription [56].

Regarding the fact that miRNAs affect almost all the genetic pathways within cells, including cell proliferation and cellular death, their normal function is of importance, and their dysregulated expression is usually associated with cancer development. miRNAs are differentially expressed in various cancers so their down-regulation increases oncogene expression, and their up-regulation suppresses tumor-suppressor genes. Thus, miRNAs may act as both tumor suppressors and oncogenes [57,58].

According to the literature, 400 miRNAs have been discovered in humans, and the list is yet to extend [59]. Here, we summarized the miRNAs involved in hepatic lipogenesis by affecting ACC expression (table 4).

Table 4: miRNAs Associated with ACC Expression in Lipogenesis

miRNA	Effect on ACC Expression	References
miR-33	Downregulation of ACC and FAS in Mice Liver Leading to Lipid Accumulation	[67]
miR-182	Down-Regulation of ACC and FAS in the Liver of Mice	[68]
miR-291b-3p	Significant Decrease in Phosphorylated ACC and ACC1 Levels by Reducing Phosphorylated AMPK	[69]
miR-122	Overexpression of ACC Genes, Particularly ACC2, Leads to Reduced Liver Steatosis in Mice.	[70]
miR-195	Suppression of ACC and FAS mRNA levels	[71]
miR-370	Stimulates Expression of ACC1 and FAS Via Expression of SREBP-1c in HepG2 cells	[72]
miR-1/miR-206	Suppresses Lipogenic Genes Including FASN and ACC1 by Downregulation of LXRα in HepG2 Cells	[73]
miR-613	Same as miR-1/miR-206. Causes Lipid Accumulation in HepG2 Cells	[73]
miR-378	Down-Regulation of ACC1, FASN, and SCD1 Via Direct Targeting of p110α in Mice	[74]
miR-130a	Down-Regulates Genes Related to NAFLD (ACC1, SCD1, FASN, etc.), Leading to Lower Lipid Accumulation.	[75]
miR-21	Regulation of Lipid-Associated Genes such as ACC1 in HepG2 cells by Regulating LRP6 and up-Regulation of ACC in Human Prostate Cancer Cells	[75,76]
miR-1224-5p	Indirectly Deactivates ACC via Inhibition of AMPKα1	[77]
miR-451	Decreases hosphorylation of ACC in ser79	[78]
miR-155	Reduces ACC1 Expression in NAFLD Patients	[79]
miR-613	Suppresses LXRα and its Target Genes, Including ACC	[80]
miR-204	Decreases Posphorylation of AMPK and ACC	[81]
miR-212-5p	Suppresses both mRNA and Protein Levels of ACC and FASN	[82]

Conclusion

Here, we reviewed the structure and function of the ACC enzyme in the biological environment and its role in the development and progression of NAFLD, NASH, and HCC as the most common vital conditions of the liver. We further assessed the ACC's role in the survival and prognosis of the HCC, especially as a therapeutic target. We concluded ACC is an integral part of de novo lipogenesis and de novo lipogenesis is an important part of the accumulation of fat in the liver tissue and the development of HCC. Reported data regarding its function in HCC are different, and there is a controversy. Multiple ACC inhibitors have been structured targeting this enzyme in controlling the mentioned conditions, and promising results have been reported regarding Clesacostat and Firsocostat in phase II clinical trials. However, further investigation of the other inhibitors is required.

In conclusion, ACC is a promising target for treating liver fat-related conditions and HCC.

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Conflicts of interest

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AA gathered the data and wrote the manuscript.

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References

1. Wang C, Ma J, Zhang N, Yang Q, Jin Y, et al. (2015) The acetyl-CoA carboxylase enzyme: a target for cancer therapy? Expert review of anticancer therapy 15: 667-676.
2. Garcia MR, Steinbauer B, Srivastava K, Singhal M, Mattijssen F, et al. (2017) Acetyl-CoA carboxylase 1-dependent protein acetylation controls breast cancer metastasis and recurrence. Cell metabolism 26: 842-855.
3. Kuhajda FP, Jenner K, Wood FD, Hennigar RA, Jacobs LB, et al. (1994) Fatty acid synthesis: a potential selective target for antineoplastic therapy. Proceedings of the National Academy of Sciences 91: 6379-6383.
4. Brownsey R, Boone A, Elliott J, Kulpa J, Lee W (2006) Regulation of acetyl-CoA carboxylase. Biochemical Society Transactions 34: 223-227.
5. Hartke J, Johnson M, Ghabril M (2017) The diagnosis and treatment of hepatocellular carcinoma. Semin Diagn Pathol 34: 153-159.
6. Sinilnikova OM, Ginolhac SM, Magnard C, Leone M, Anczukow O, et al. (2004) Acetyl-CoA carboxylase α gene and breast cancer susceptibility. Carcinogenesis 25: 2417-2424.
7. Abu-Elheiga L, Jayakumar A, Baldini A, Chirala SS, Wakil SJ (1995) Human acetyl-CoA carboxylase: characterization, molecular cloning, and evidence for two isoforms. Proceedings of the National Academy of Sciences 92: 4011-4015.
8. Ha J, Daniel S, Kong IS, Park CK, Tae HJ, et al. (1994) Cloning of human acetyl-CoA carboxylase cDNA. European journal of biochemistry 219: 297-306.
9. Cronan Jr JE, Waldrop GL (2002) Multi-subunit acetyl-CoA carboxylases. Progress in lipid research 41: 407-435.
10. Wei J, Tong L (2015) Crystal structure of the 500-kDa yeast acetyl-CoA carboxylase holoenzyme dimer. Nature 526: 723-727.
11. Hunkeler M, Hagmann A, Stuttfeld E, Chami M, Guri Y, et al. (2018) Structural basis for regulation of human acetyl-CoA carboxylase. Nature 558: 470-474.
12. Wei J, Tong L (2018) How Does Polymerization Regulate Human Acetyl-CoA Carboxylase 1? : ACS Publications 5495-5496.
13. Zhang H, Yang Z, Shen Y, Tong L (2003) Crystal structure of the carboxyltransferase domain of acetyl-coenzyme A carboxylase. Science 299: 2064-2067.
14. Zhang H, Tweel B, Li J, Tong L (2004) Crystal structure of the carboxyltransferase domain of acetyl-coenzyme A carboxylase in complex with CP-640186. Structure 12: 1683-1691.
15. Yao X, Soden C, Summers MF, Beckett D (1999) Comparison of the backbone dynamics of the apo-and holo-carboxy-terminal domain of the biotin carboxyl carrier subunit of Escherichia coli acetyl-CoA carboxylase. Protein science 8: 307-317.
16. Solbiati J, Chapman-Smith A, Cronan JE (2002) Stabilization of the biotinoyl domain of Escherichia coli acetyl-CoA carboxylase by interactions between the attached biotin and the protruding "thumb" structure. Journal of Biological Chemistry 277: 21604-21609.
17. Wu X, Huang T (2019) Recent development in acetyl-CoA carboxylase inhibitors and their potential as novel drugs. Future Medicinal Chemistry 12: 533-561.
18. Tong L (2013) Structure and function of biotin-dependent carboxylases. Cellular and Molecular Life Sciences 70: 863-891.
19. Wakil SJ, Stoops JK, Joshi VC (1983) Fatty acid synthesis and its regulation. Annual review of biochemistry 52: 537-579.
20. Ki-Han K (1997) Regulation of mammalian acetyl-coenzyme A carboxylase. Annual review of nutrition 17: 77.
21. Tong L (2005) Acetyl-coenzyme A carboxylase: crucial metabolic enzyme and attractive target for drug discovery. Cellular and Molecular Life Sciences CMLS 62: 1784-1803.
22. Abu-Elheiga L, Brinkley WR, Zhong L, Chirala SS, Woldegiorgis G, et al. (2000) The subcellular localization of acetyl-CoA carboxylase 2. Proceedings of the National Academy of Sciences 97: 1444-1449.
23. Castle JC, Hara Y, Raymond CK, Garrett-Engele P, Ohwaki K, et al. (2009) ACC2 is expressed at high levels human white adipose and has an isoform with a novel N-terminus. PLoS One 4: e4369.
24. Locke GA, Cheng D, Witmer MR, Tamura JK, Haque T, et al. (2008) Differential activation of recombinant human acetyl-CoA carboxylases 1 and 2 by citrate. Archives of biochemistry and biophysics 475: 72-79.
25. Kim C-W, Moon Y-A, Park SW, Cheng D, Kwon HJ, et al. (2010) Induced polymerization of mammalian acetyl-CoA carboxylase by MIG12 provides a tertiary level of regulation of fatty acid synthesis. Proceedings of the National Academy of Sciences 107: 9626-9631.
26. Colbert CL, Kim C-W, Moon Y-A, Henry L, Palnitkar M, et al. (2010) Crystal structure of Spot 14, a modulator of fatty acid synthesis. Proceedings of the National Academy of Sciences 107: 18820-18825.
27. Wang Y, Yu W, Li S, Guo D, He J, et al. (2022) Acetyl-CoA carboxylases and diseases. Frontiers in Oncology 12: 836058.
28. Luo J, Hong Y, Lu Y, Qiu S, Chaganty BK, et al. (2017) Acetyl-CoA carboxylase rewires cancer metabolism to allow cancer cells to survive inhibition of the Warburg effect by cetuximab. Cancer letters 384: 39-49.
29. Alò PL, Visca P, Trombetta G, Mangoni A, Lenti L, et al. (1999) Fatty acid synthase (FAS) predictive strength in poorly differentiated early breast carcinomas. Tumori Journal 85: 35-40.
30. Shurbaji MS, Kalbfleisch JH, Thurmond TS (1996) Immunohistochemical detection of a fatty acid synthase (OA-519) as a predictor of progression of prostate cancer. Human pathology 27: 917-921.
31. Migita T, Ruiz S, Fornari A, Fiorentino M, Priolo C, et al. (2009) Fatty acid synthase: a metabolic enzyme and candidate oncogene in prostate cancer. Journal of the National Cancer Institute 101: 519-532.
32. Wang C, Rajput S, Watabe K, Liao D-F, Cao D (2010) Acetyl-CoA carboxylase-α as a novel target for cancer therapy. Frontiers in Bioscience-Scholar 2: 515-526.
33. Chajes V, Cambot M, Moreau K, Lenoir GM, Joulin V (2006) Acetyl-CoA carboxylase α is essential to breast cancer cell survival. Cancer research 66: 5287-5294.

34. Brusselmans K, De Schrijver E, Verhoeven G, Swinnen JV (2005) RNA interference–mediated silencing of the acetyl-CoA-carboxylase-α gene induces growth inhibition and apoptosis of prostate cancer cells. Cancer research 65: 6719-6725.
35. Zhan Y, Ginanni N, Tota MR, Wu M, Bays NW, et al. (2008) Control of cell growth and survival by enzymes of the fatty acid synthesis pathway in HCT-116 colon cancer cells. Clinical Cancer Research 14: 5735-5742.
36. Bobkov YV, Walker III WB, Cattaneo AM (2021) Altered functional properties of the codling moth Orco mutagenized in the intracellular loop-3. Scientific reports 11: 1-16.
37. Calvisi DF, Wang C, Ho C, Ladu S, Lee SA, et al. (2011) Increased lipogenesis, induced by AKT-mTORC1-RPS6 signaling, promotes development of human hepatocellular carcinoma. Gastroenterology 140: 1071-1083.
38. Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, et al. (2005) Sources of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty liver disease. The Journal of clinical investigation 115: 1343-1351.
39. Rahman K, Desai C, Iyer SS, Thorn NE, Kumar P, et al. (2016) Loss of junctional adhesion molecule a promotes severe steatohepatitis in mice on a diet high in saturated fat, fructose, and cholesterol. Gastroenterology 151: 733-746.
40. McGarry JD, GF L, DW F (1978) carnitine palmitoyltransferase. I. The site of inhibition of hepatic fatty acid oxidation by malonyl. CoA J Biol Chem 253: 4128-4136.
41. Rigano D, Sirignano C, Taglialatela-Scafati O (2017) The potential of natural products for targeting PPARα. Acta Pharmaceutica Sinica B 7: 427-438.
42. Lally JS, Ghoshal S, DePeralta DK, Moaven O, Wei L, et al. (2019) Inhibition of acetyl-CoA carboxylase by phosphorylation or the inhibitor ND-654 suppresses lipogenesis and hepatocellular carcinoma. Cell metabolism 29: 174-182.
43. Yahagi N, Shimano H, Hasegawa K, Ohashi K, Matsuzaka T, et al. (2005) Co-ordinate activation of lipogenic enzymes in hepatocellular carcinoma. European Journal of Cancer 41: 1316-1322.
44. Li J, Huang Q, Long X, Zhang J, Huang X, et al. (2015) CD147 reprograms fatty acid metabolism in hepatocellular carcinoma cells through Akt/mTOR/SREBP1c and P38/PPARα pathways. Journal of hepatology 63: 1378-1389.
45. Chen H, Wu D, Bao L, Yin T, Lei D, et al. (2019) 6PGD inhibition sensitizes hepatocellular carcinoma to chemotherapy via AMPK activation and metabolic reprogramming. Biomedicine & Pharmacotherapy 111: 1353-13358.
46. Wang MD, Wu H, Fu GB, Zhang HL, Zhou X, et al. (2016) Acetyl-coenzyme A carboxylase alpha promotion of glucose-mediated fatty acid synthesis enhances survival of hepatocellular carcinoma in mice and patients. Hepatology 63: 1272-1286.
47. Ye B, Yin L, Wang Q, Xu C (2019) ACC1 is overexpressed in liver cancers and contributes to the proliferation of human hepatoma Hep G2 cells and the rat liver cell line BRL 3A. Molecular Medicine Reports 19: 3431-3440.
48. Che L, Pilo MG, Cigliano A, Latte G, Simile MM, et al. (2017) Oncogene dependent requirement of fatty acid synthase in hepatocellular carcinoma. Cell cycle 16: 499-507.
49. Nagarajan SR, Paul-Heng M, Krycer JR, Fazakerley DJ, Sharland AF, et al. (2019) Lipid and glucose metabolism in hepatocyte cell lines and primary mouse hepatocytes: a comprehensive resource for in vitro studies of hepatic metabolism. American Journal of Physiology-Endocrinology and Metabolism 316: E578-E89.
50. Chi Y-C, Hsieh D-H, Lin C-Y, Chen H-Y, Huang C-Y, et al. (2015) Phosphorous diffuser diverged blue laser diode for indoor lighting and communication. Scientific reports 5: 1-9.
51. Bort A, Sánchez BG, de Miguel I, Mateos-Gómez PA, Diaz-Laviada I (2020) Dysregulated lipid metabolism in hepatocellular carcinoma cancer stem cells. Molecular biology reports 47: 2635-2647.
52. Luo D-X, Tong D-J, Rajput S, Wang C, Liao D-F, et al. (2012) Targeting acetyl-CoA carboxylases: small molecular inhibitors and their therapeutic potential. Recent patents on anti-cancer drug discovery 7: 168-184.
53. Alkhouri N, Lawitz E, Noureddin M, DeFronzo R, Shulman GI (2020) GS-0976 (Firsocostat): an investigational liver-directed acetyl-CoA carboxylase (ACC) inhibitor for the treatment of non-alcoholic steatohepatitis (NASH). Expert opinion on investigational drugs 29: 135-141.
54. Martín-Acosta P, Xiao X (2021) PROTACs to address the challenges facing small molecule inhibitors. European journal of medicinal chemistry 210: 112993.
55. Calle RA, Amin NB, Carvajal-Gonzalez S, Ross TT, Bergman A, Aggarwal S, et al. ACC inhibitor alone or co-administered with a DGAT2 inhibitor in patients with non-alcoholic fatty liver disease: two parallel, placebo-controlled, randomized phase 2a trials. Nature Medicine. 2021;27(10):1836-48.
56. Bartel DP (2009) MicroRNAs: target recognition and regulatory functions. Cell 36: 215-233.
57. Mishra S, Yadav T, Rani V (2016) Exploring miRNA based approaches in cancer diagnostics and therapeutics. Critical reviews in oncology/hematology 98: 12-23.
58. Ambros V (2001) microRNAs: tiny regulators with great potential. Cell 107: 823-826.
59. Ruby JG, Stark A, Johnston WK, Kellis M, Bartel DP, et al. (2007) Evolution, biogenesis, expression, and target predictions of a substantially expanded set of Drosophila microRNAs. Genome research 17: 1850-1864.
60. Zhang X-J, Ji Y-X, Cheng X, Cheng Y, Yang H, et al. (2021) A small molecule targeting ALOX12-ACC1 ameliorates nonalcoholic steatohepatitis in mice and macaques. Science Translational Medicine 13: 8116.
61. Goedeke L, Bates J, Vatner DF, Perry RJ, Wang T, et al. (2018) Acetyl-C o A Carboxylase Inhibition Reverses NAFLD and Hepatic Insulin Resistance but Promotes Hypertriglyceridemia in Rodents. Hepatology 68: 2197-2211.
62. Stiede K, Miao W, Blanchette HS, Beysen C, Harriman G, et al. (2017) Acetyl-coenzyme A carboxylase inhibition reduces de novo lipogenesis in overweight male subjects: A randomized, double-blind, crossover study. Hepatology 66: 324-334.
63. Gao Y-s, Qian M-y, Wei Q-q, Duan X-b, Wang S-l, et al. (2020) WZ66, a novel acetyl-CoA carboxylase inhibitor, alleviates nonalcoholic steatohepatitis (NASH) in mice. Acta Pharmacologica Sinica 41: 336-347.
64. Tamura YO, Sugama J, Iwasaki S, Sasaki M, Yasuno H, et al. (2021) Selective Acetyl-CoA Carboxylase 1 Inhibitor Improves Hepatic Steatosis and Hepatic Fibrosis in a Preclinical Nonalcoholic Steatohepatitis Model. Journal of Pharmacology and Experimental Therapeutics 379: 280-289.
65. Harriman G, Greenwood J, Bhat S, Huang X, Wang R, et al. (2016) Acetyl-CoA carboxylase inhibition by ND-630 reduces hepatic steatosis, improves insulin sensitivity, and modulates dyslipidemia in rats. Proceedings of the National Academy of Sciences 113: E1796-E805.
66. Kim C-W, Addy C, Kusunoki J, Anderson NN, Deja S, et al. (2017) Acetyl CoA carboxylase inhibition reduces hepatic steatosis but elevates plasma triglycerides in mice and

humans: a bedside to bench investigation. Cell metabolism 26: 394-406.
67. Zhang H, Yang L, Wang Y, Huang W, Li Y, et al. (2020) Oxymatrine alleviated hepatic lipid metabolism via regulating miR-182 in non-alcoholic fatty liver disease. Life Sciences 257: 118090.
68. Goedeke L, Salerno A, Ramírez CM, Guo L, Allen RM, et al. (2014) Long-term therapeutic silencing of miR-33 increases circulating triglyceride levels and hepatic lipid accumulation in mice. EMBO molecular medicine 6: 1133-1141.
69. Meng X, Guo J, Fang W, Dou L, Li M, et al. (2016) Liver microRNA-291b-3p promotes hepatic lipogenesis through negative regulation of adenosine 5′-monophosphate (AMP)-activated protein kinase α1. Journal of Biological Chemistry 291: 10625-10634.
70. Esau C, Davis S, Murray SF, Yu XX, Pandey SK, et al. (2006) miR-122 regulation of lipid metabolism revealed by in vivo antisense targeting. Cell metabolism 3: 87-98.
71. Guo J, Fang W, Sun L, Lu Y, Dou L, et al. (2018) Ultraconserved element uc. 372 drives hepatic lipid accumulation by suppressing miR-195/miR4668 maturation. Nature communications 9: 1-15.
72. Duan Y, Pei K, Cai H, Tu S, Zhang Z, et al. (2016) Bioactivity evaluation-based ultra high-performance liquid chromatography coupled with electrospray ionization tandem quadrupole-time-of-flight mass spectrometry and novel distinction of multi-subchemome compatibility recognition strategy with Astragali Radix-Fructus Corni herb-pair as a case study. Journal of pharmaceutical and biomedical analysis 129: 514-534.
73. Liu W, Cao H, Yan J, Huang R, Ying H (2015) Micro-managers of hepatic lipid metabolism and NAFLD. Wiley Interdisciplinary Reviews RNA 6: 581-593.
74. Watanabe S, Horie Y, Suzuki A (2005) Hepatocyte-specific Pten-deficient mice as a novel model for nonalcoholic steatohepatitis and hepatocellular carcinoma. Hepatology research 33: 161-166.
75. Liu J, Tang T, Wang G-D, Liu B (2019) LncRNA-H19 promotes hepatic lipogenesis by directly regulating miR-130a/PPARγ axis in non-alcoholic fatty liver disease. Bioscience Reports 39.
76. Kanagasabai T, Li G, Shen TH, Gladoun N, Castillo-Martin M, et al. (2022) MicroRNA-21 deficiency suppresses prostate cancer progression through downregulation of the IRS1-SREBP-1 signaling pathway. Cancer letters 525: 46-54.
77. Chen T, Yan D, Cheng X, Ji X, Bian J, et al. (2018) miR-1224-5p Enhances Hepatic Lipogenesis by Targeting Adenosine Monophosphate–Activated Protein Kinase α 1 in Male Mice. Endocrinology 159: 2008-2021.
78. Hur W, Lee JH, Kim SW, Kim J-H, Bae SH, et al. (2015) Downregulation of microRNA-451 in non-alcoholic steatohepatitis inhibits fatty acid-induced proinflammatory cytokine production through the AMPK/AKT pathway. The international journal of biochemistry & cell biology 64: 265-276.
79. Wang L, Zhang N, Wang Z, Ai D-m, Cao Z-y, et al. (2016) Decreased MiR-155 level in the peripheral blood of non-alcoholic fatty liver disease patients may serve as a biomarker and may influence LXR activity. Cellular Physiology and Biochemistry 39: 2239-2248.
80. Zhong D, Zhang Y, Zeng Y-j, Gao M, Wu G-z, et al. (2013) MicroRNA-613 represses lipogenesis in HepG2 cells by downregulating LXRα. Lipids in Health and Disease 12: 1-9.
81. Zhang Y, Ma Y, Gu M, Peng Y (2020) lncRNA TUG1 promotes the brown remodeling of white adipose tissue by regulating miR-204-targeted SIRT1 in diabetic mice. International journal of molecular medicine 46: 2225-2234.
82. Hu M-J, Long M, Dai R-J (2022) Acetylation of H3K27 activated lncRNA NEAT1 and promoted hepatic lipid accumulation in non-alcoholic fatty liver disease via regulating miR-212-5p/GRIA3. Molecular and Cellular Biochemistry 477: 191-203.