

## Review Article

# Non-alcoholic fatty liver disease associated molecular mechanisms of hepatocarcinogenesis

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**Abstract:** With the prevalence of obesity and insulin resistance, nonalcoholic fatty liver disease (NAFLD) has become one of the most common chronic liver diseases worldwide. As NAFLD can progress to non-alcoholic steatohepatitis (NASH), liver fibrosis and cirrhosis with higher frequency of hepatocellular carcinoma (HCC). Meanwhile, some studies have demonstrated that HCC may also develop in the context of NAFLD without association with advanced fibrosis and cirrhosis, just from simple steatosis. Growing evidence supports that NAFLD is associated with HCC. The mechanism of NAFLD-related HCC involves genetics, metabolic, immunologic, intestinal microbiota and so on. A better understanding of the pathogenesis is conducive to the prevention and individualized treatment of disease. This review summarizes the molecular mechanism of NAFLD-related HCC in recent couple of years.

**Keywords:** Non-alcoholic fatty liver disease, hepatocellular carcinoma, molecular mechanism

## Introduction

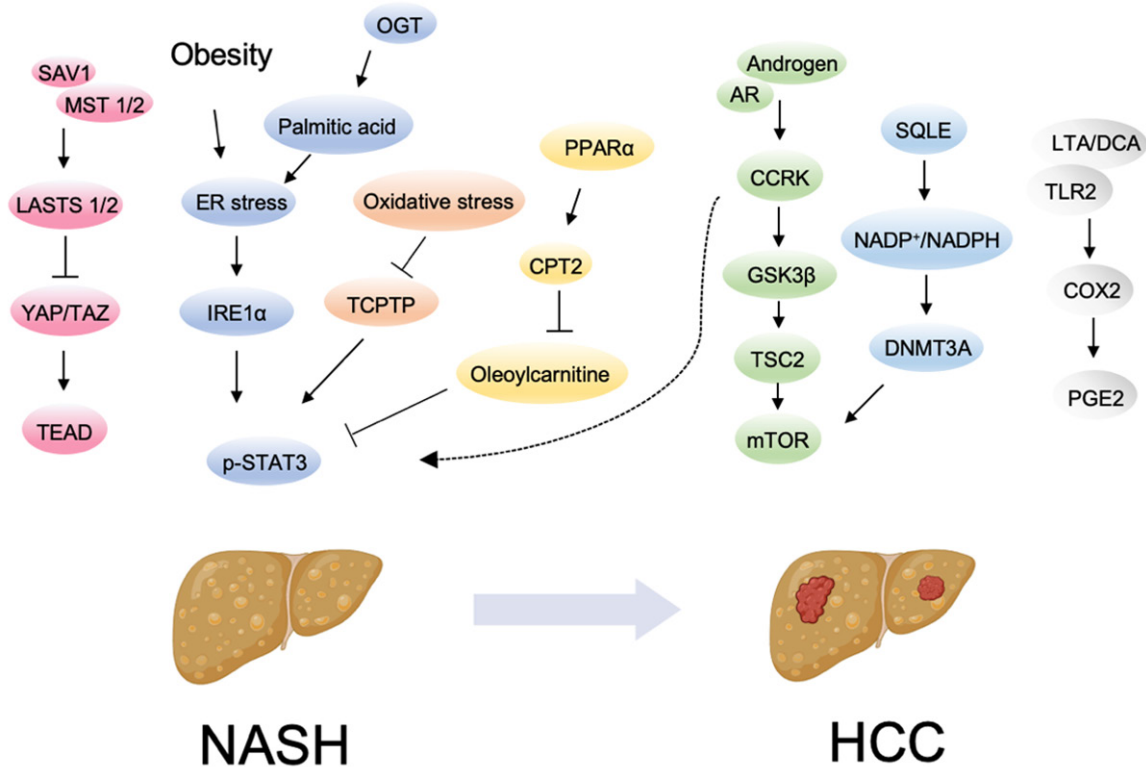
Hepatocellular carcinoma (HCC) is the fifth most common cancer and the second leading cause of cancer-related death all over the world [1, 2]. HCC is identified as a typical inflammation-associated neoplasm, usually occurs in patients with potential chronic liver disease, including infection of hepatitis B virus (HBV) [3], hepatitis C virus (HCV) [4], and alcoholic liver disease [5]. In recent years, nonalcoholic fatty liver disease (NAFLD) becomes the most common chronic liver disease in developed countries and increases exponentially in developing countries, and has become one of the leading causes of HCC [6, 7]. NAFLD comprises a wide histological spectrum, ranging from simple steatosis to liver injury and inflammation-non-alcoholic steatohepatitis (NASH) [8]. NASH is more serious phase of NAFLD which is defined by the presence of lobular inflammation and hepatocyte ballooning histologically [9]. Several studies have demonstrated that NASH patients are more likely to develop advanced fibrosis and cirrhosis, and therefore at a higher risk of HCC [10-12]. However, in the absence of cirrhosis, NAFLD can also progress

to HCC [13, 14]. The mechanism of NAFLD-related HCC is still unclear. It may involve genetic, immunologic, metabolic and gut microbiota pathways. This review attempts to summarize the pathogenesis of NAFLD-related HCC in recent couple of years (**Figure 1**).

## Epidemiology

NAFLD is associated with obesity, insulin resistance, diabetes, known as metabolic syndrome [15-17]. It is reported that NAFLD affects up to 25% adult population in the worldwide [18], about 20% individuals with NAFLD develop NASH [19]. With the prevalence of obesity, NAFLD population will rapidly increase. A meta-analysis shown that the prevalence of NAFLD is estimated at 33.5% in adult population by 2030 [20]. Meanwhile, several studies have shown that the morbidity of NAFLD-related HCC is increasing exponentially [21-23]. In the first large population-based study on NAFLD-related liver cancer registered with the United States Surveillance, Epidemiology and Results (SEER), the proportion of NAFLD-related HCC increased by 9% annually between 2004 and 2009 [24]. Another study used data from the United States

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**Figure 1.** Interaction influence diagrams of NASH associated HCC molecular mechanisms.

Organ Sharing Network (UNO), the researchers noted that the number of NASH-related HCC increased nearly 4-fold from 2002 to 2012 [25]. In the British, the proportion of NAFLD-related HCC increased tenfold from 2000 to 2010 [26]. In Japan, a multi-center retrospective study found that the proportion of patients with non-viral HCC increased from 10.0% to 24.1% in 1991-2010 [27]. They attributed the findings to the growing obesity population and the rising morbidity of diabetes caused by dietary changes [27]. Accordingly, the number of NASH-related HCC patients receiving liver transplantation is also increasing [25].

### Molecular mechanism of NAFLD-induced HCC

#### Genetic mechanism

With the development of genetic technology, researchers are allowed to obtain comprehensive data on genetic changes associated with NAFLD-related HCC. The differential expression of some genes caused by gene mutation and epigenetic changes is closely related to NAFLD-related HCC.

Hundreds of NAFLD-HCC candidate oncogenes were identified by mutation of “Sleeping Beauty” transposon in NAFLD-HCC mice model (PTEN-KO mice and HFD-fed mice) [28, 29]. Among them, 10 genes were identified as trunk drivers and Sav1 is the only gene identified as specific to NAFLD-HCC [30]. SAV1 is a vital component of hippo signal pathway and is involved in the regulation of organ size, Cell Fate, and Carcinogenesis [31-33]. In mammals, the Hippo signaling pathway consists of macrophage stimulating protein (MST), SAV, large tumor suppressor kinase (LATS) MOB1A and MOB1B, yes-associated protein (YAP), transcription regulator (TAZ), and TEAD [34]. MST negatively regulate transcriptional co-activators YAP and TAZ, which co-regulate gene expression that controls proliferation and differentiation [35]. Activation of YAP and TAZ is associated with liver development, regeneration and tumorigenesis [36]. Kodama T et al. [30] reported that SAV1 attenuates liver injury and apoptosis by reducing hepatic lipid accumulation. Furthermore, SAV1 can inhibit the activation of M1 macrophages and alleviate liver inflammation and fibrosis. Such pathologi-

cal injuries are important factors in NAFLD-HCC transformation.

The mechanism is that SAV may affect the differentiation of hepatic progenitor cells by inhibiting YAP activity [37]. Akashi M et al. found that junctional protein associated with coronary artery disease (JCAD), coronary artery disease-associated gene product, was located at the cell-cell junction of endothelial cells [38]. Continuous studies have found that JCAD is closely related to apoptosis and proliferation, monocyte adhesion, migration and angiogenesis [39, 40]. Recent studies have found that JCAD mRNA is significantly increased in human and mouse NASH-HCC specimens. Overexpression of JCAD in HCC cell lines induced hepatoma cell free fatty acid overload. Moreover, overexpression of JCAD not only promotes the proliferation of HCC cell lines in vitro, but also promotes the growth of subcutaneous xenotransplanted tumor in vivo [41]. The main reason is that JCAD can bind to the kinase domain of LATS2 and inhibit the kinase activity of LATS2, which induces dephosphorylation and nuclear localization of YAP in the Hippo signaling pathway that plays a key role in tumor growth [42, 43]. Endoplasmic reticulum (ER) stress can activate unfolded protein response (UPR) and has been involved in the development of HCC [44]. Inositol-requiring enzyme 1 (IRE1), PKR-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6) are three transmembrane signal transducers mediating UPR on endoplasmic reticulum [45]. Continuous activation of these transducers is associated with increased tumorigenicity [46, 47]. Previous studies have confirmed that IRE1 $\alpha$  is hyperactivated in obesity mice model and is closely associated with liver repair and regeneration [48]. Wu et al. found that the ablation of hepatocyte IRE1 $\alpha$  not only significantly reduced the incidence of diethylnitrosamine-induced HCC in IRE1 $\alpha$ -KO mice fed a normal diet, but also prevented the HCC progression during high-fat diet [49]. IRE1 $\alpha$  induces the phosphorylation of STAT3 and promote the HCC development by interacting with STAT3 in a positive feedback loop [50]. Pogribny IP et al. investigated hepatic transcriptomic and histone modification profiles using Stelic Animal Model (STAM) mice, an animal model of NASH-related liver carcinogenesis resembling disease development in humans [51]. Gene enrichment

analysis shows that many pathways have changed significantly in STAM model [52]. The most significant changes in NASH-fibrotic and HCC stages are inhibition of apoptosis and activation of hepatic stellate cells [51]. Further mechanism studies showed that these changes were caused by gene-specific deacetylation of histone H4 lysine 16 (H4K16) [53]. Fraga MF et al. found that the loss of histone H4K16 is a common epigenetic feature of human cancer [54]. In NASH-HCC, NUPR1 promotes the continuous deacetylation of H4K16 by inhibiting the activity of lysine acetyltransferase KAT8, which eventually leads to HCC [51]. Aberrant activation of the Hedgehog (Hh) pathway is associated with malignant tumors, such as medulloblastoma and basal cell carcinoma, and can mediate fibrotic response to chronic liver injury [55-57]. Indian Hedgehog (Ihh) was up-regulated in NAFLD-HCC and correlated with the volume and number of tumors [58]. Ihh regulates the transdifferentiation of quiescent hepatic stellate cells into proliferative myofibroblasts and the proliferation of EpCAM+ ductal cells to promote fibrosis [59, 60]. More importantly, Ihh can up-regulate the expression of Wnt protein in HSCs and promote the progression of poorly differentiated HCC [61].

### *Metabolic pathways*

Abnormal energy metabolism is considered to be a key factor in the natural course of NAFLD/NASH-induced HCC. Like other cancers, changes in cell metabolism promote malignant transformation of hepatocytes. O-GlcNAc transferase (OGT) is a glycosyltransferase that catalyzes the post-translational modification of a single N-acetylglucosamine from UDP-GlcNAc to a serine or threonine residue in nuclear, mitochondrial and cytoplasmic proteins via a beta-linked N-acetylglucosamine (O-GlcNAc) [62]. It was also found that OGT was overexpressed in several cancers and involved in the metabolic changes of cancer cells [63, 64]. Recent studies have found that OGT is up-regulated in human NAFLD-HCC patients and HCC cell lines and promotes invasion and migration of NAFLD-HCC cell lines [65]. Further studies showed that OGT could induce elevation of palmitic acid in NAFLD-HCC cell lines, and palmitic acid could facilitate the proliferation of NAFLD-HCC cell lines [65]. The specific mechanism is that OGT can activate endoplasmic reticulum (ER) stress

and trigger the progress of NAFLD-HCC by phosphorylating JNK and NF- $\kappa$ B subunits [66, 67]. Squalene epoxidase (SQLE) is the second key regulatory enzyme in cholesterol biosynthesis [68], and involved in NAFLD-HCC progression [69]. SQLE implements its carcinogenic role through its metabolites-cholesterol ester and nicotinamide adenine dinucleotide phosphate (NADP<sup>+</sup>) [70]. SQLE overexpressed promotes accumulation of liver free cholesterol and cholesteryl ester, which is lipotoxic and can lead to NASH [71], which is highly susceptible to HCC [11]. Increased NADP<sup>+</sup>/NADPH ratios triggered a series of events, including oxidative stress-induced DNA methyltransferase 3a (DNMT3A) expression [72], DNMT3A-mediated epigenetic silencing of phosphatase and tensin homolog (PTEN) and activation of Akt-mTOR (rapamycin mammalian target) [73, 74]. Acylcarnitines is a compound of acyl-coenzyme A and carnitine catalyzed by carnitine palmitoyl-transferase (CPT) located on mitochondrial membrane. Acylcarnitine metabolism is a key factor in regulating the balance of intracellular glucose and lipid metabolism and involved in many metabolic diseases [75]. Fujiwara N et al. reported that acylcarnitine species accumulated in NASH-driven HCC due to the down-regulation of CPT2 and its transcriptional regulators peroxisome proliferator-activated receptor  $\alpha$  (PPAR $\alpha$ ) [76]. On the one hand, decreased expression of CPT2 alleviates lipotoxicity by restraining Src-mediated JNK activation, on the other hand, oleoylcarnitine accumulation induced by CPT2 down-regulation can activate STAT3 and its downstream signaling molecules and induce self-renewal of HCC cells [76]. Sun H et al. demonstrated that androgen receptor (AR)-driven oncogene, cell cycle-related kinase (CCRK), cooperates with obesity-induced proinflammatory signaling to promote NASH-related hepatocarcinogenesis [77]. CCRK, as a member of cell cycle-dependent kinase, has been confirmed as a direct AR-regulated oncogene in hepatocellular carcinogenesis by activating GSK3 $\beta$ / $\beta$ -catenin and AKT/EZH2 signaling pathways [78, 79]. In mice, CCRK liver specific ablation not only eliminates obesity-related lipid accumulation, glucose intolerance and insulin resistance, but also eliminates the development of HCC. Mechanistically, CCRK accelerates feedforward loop by inducing co-occupancy and transcriptional up-regulation of STAT3-AR promoter, which activates mTORC1/

4E-BP1/S6K/SREBP1 cascade through GSK3 $\beta$  phosphorylation. In addition, CCRK induces mTORC1-dependent G-csf expression to enhance the recruitment and tumorigenicity of polymorphonuclear bone marrow-derived suppressor cells [77]. These findings reveal the dual role of inflammation-CCRK in promoting metabolism and immunosuppressive reprogramming through mTORC1 activation, thus establishing a tumorigenic microenvironment for the development of NASH-HCC.

### *Immunologic pathways*

Shalapour S et al. reported that the accumulation of liver resident IgA<sup>+</sup> cell in human and mice with NASH-induced HCC. These inflammation-induced IgA<sup>+</sup> cells expressed programmed death ligand 1 (PD-L1) and interleukin-10 [80]. Further studies demonstrated that these IgA<sup>+</sup> cells had immunosuppressive effect and could directly inhibit liver cytotoxic CD8<sup>+</sup> T lymphocytes [81]. CD8<sup>+</sup> T lymphocytes deficiency can accelerate HCC development [82]. Neutrophil extracellular traps (NETs) are large reticular structures consisting of decondensed chromatin, neutrophil-derived nuclear, cytoplasmic and granular proteins, which can capture and kill pathogens [83]. NETs are considered to be a significant apparatus of innate immune system against pathogens, but also related to autoimmunity, chronic inflammation and cancer pathophysiology [84]. Tsung A et al. reported that NETs formation increases in NASH-related HCC. Inhibiting the NETs formation through deoxyribonuclease (DNase), the subsequent inflammation pattern of the liver was changed, resulting in a decrease in the number and volume of tumors [85]. In viral hepatitis models, activated platelets contribute to hepatic injury mediated by cytotoxic T lymphocyte (CTL) [86]. In addition, blocking platelet activation and aggregation eliminates the influx of hepatic T cells and subsequent liver injury and tumorigenesis, without affecting the function of peripheral T cells in viral hepatitis [86]. Heikenwalder M et al. reported that the number of platelets and platelet aggregates in the liver of mice fed with high fat diet and NAFLD/NASH patients increased significantly [87]. Aspirin-clopidogrel (Asp-Clo) therapy can inhibit the infiltration of immune cells in the liver and further inhibit NASH and NASH-induced HCC [88]. Kupffer cells, a special macrophage of the liver,

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**Table 1.** Application of gene knockout mouse model in NASH associated HCC

Authors	Model	Comments/Outcomes
Kodama T et al., 2018	Liver specific PTEN-KO	↑ Lipid accumulation, apoptosis, fibrogenesis and hepatocarcinogenesis vs WT mice
Wu Y et al., 2018	liver-specific IRE1 $\alpha$ KO	↓ Hepatocyte proliferation, ↑ Hepatic apoptosis, TNF and IL-6 vs WT mice
Chong YC et al., 2019	liver-specific IHH-KO	↓ Stellate cells activation, Epcam <sup>+</sup> ductal cells proliferation and fibrosis vs WT mice
Sun H et al., 2018	liver-specific CCRK-KO	↑ Lipid accumulation, glucose intolerance and insulin resistance vs WT mice
Tsung A et al., 2018	Whole body PAD4 KO	↓ Neutrophil extracellular traps formation, liver inflammation, tumor growth vs WT mice
Weber A et al., 2019	Whole body GPIb $\alpha$ KO	↓ Platelet cargo, platelet adhesion and platelet activation vs WT mice
Tiganis T et al., 2018	liver-specific PTPN2-KO	↑ T cell recruitment, fibrosis and tumor formation vs WT mice
Loo TM et al., 2017	Whole body TLR2 KO	↓ Secretory phenotype of hepatic stellate cells and tumor formation vs WT mice

↑ Increased; ↓ decreased; KO knockout; PTEN phosphatase and tensin homolog; IRE1 $\alpha$  inositol-requiring enzyme 1; IHH Indian hedgehog; CCRK cell cycle-related kinase; PAD4 peptidyl arginine deaminase type 4; GPIb $\alpha$  platelet membrane glycoprotein 1b- $\alpha$ ; PTPN2; TLR2 toll-like receptor 2.

play a key role in platelet aggregation in the liver [89]. Kupffer cells can “dock” with GPIb $\alpha$ , a glycoprotein on the surface of platelet membrane [90]. When GPIb $\alpha$  was blocked, liver inflammation was improved. It is inferred that blocking GPIb $\alpha$  can reduce NASH-reduced HCC [87]. Previous studies have confirmed that protein tyrosine phosphatase (PTP) is extensively oxidized and inactivated in obese mice with NAFLD [89]. T cell protein tyrosine phosphatase (TCPTP) plays a key role in the immune system and is considered as a negative regulator of inflammation [91]. TCPTP is a negative regulator of STAT family proteins, the oxidation of TCPTP promotes the phosphorylation of signal transducer and activator of transcription (STAT) family proteins, including STAT-1, STAT-3, and STAT-5 [92, 93]. Gurzov et al. found that TCPTP oxidized significantly in the liver of NAFLD patients and obese mice [89]. Further study demonstrated that TCPTP inactive results the recruitment of immune cells (especially CD4<sup>+</sup> and CD8<sup>+</sup> T cell) in the liver and promotes the expression of fibrosis genes (encoding  $\alpha$ -smooth muscle actin (ACTA2) and transforming growth factor  $\beta$  (TGFB)) [94]. These pathological changes contribute progression from NAFL to NASH and eventually lead to liver fibrosis and even cirrhosis. This fibrosis/cirrhosis liver may contain HCC progenitor cells, which can suffer malignant transformation and progress to HCC.

### Gut microbiota

Intestinal barrier consists of intact epithelial lining, mucus layer, Paneth and goblet cells, mucosa-associated lymphoid tissue and a number of secreted factors, and is a highly dynamic system. It is well known that gut microbiota plays a critical role in health maintenance

and disease progression [95]. Liver is directly exposed to intestinal microbial components and metabolites through portal vein (the gut-liver axis), which are known closely related to HCC [96]. Analysis of the gut microbial profiles of DMBA-treated mice show that HFD-fed mice exhibited a prominent increase in Gram-positive gut microbiota in their feces [97]. lipoteichoic acid (LTA), a major cell wall component in Gram-positive gut microbial component, translocates to the liver to form a carcinogenic microenvironment and promote obesity-induced HCC. LTA cooperates with the gut microbial metabolite deoxycholic acid (DCA) to enhance the senescence hepatic stellate cells (HSC) and increase the expression of senescence-associated secretory phenotype (SASP) and cyclooxygenase-2 (COX-2) through Toll-like receptor 2 (TLR2). COX-2 induces the elevation of prostaglandin E2 (PGE2), which binds to PTEP4 receptor to inhibit the anti-tumor immunity and promote the development of obesity-associated HCC [98].

### Conclusion

NAFLD is common global epidemic and is associated with a variety of health-related complications, one of which is elevated frequency of cancer. Increasing evidence suggests that NAFLD, especially NASH, contributes to the HCC development in recent years (Table 1). Although the new cellular and molecular mechanisms leading to NAFLD-related HCC have been revealed in recent studies. No effective target has yet been found to control the transition from NAFLD to HCC. More importantly, we should pay more attention to whether there are “multiple types” of NAFLD, one or several of which are more likely to be converted to HCC and whether there are sensitive and specific

biomarker to predict the transition. In addition, we also need to pay attention to the disease course and treatment response of “different types” of NAFLD-related HCC. Resolving these problems will not only reduce the incidence of NAFLD-related HCC, but also help clinicians to personalize the treatment of NAFLD-related HCC patient.

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### Disclosure of conflict of interest

None.

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### References

- [1] Siegel RL, Miller KD and Jemal A. Cancer statistics, 2017. *CA Cancer J Clin* 2017; 67: 7-30.
- [2] Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M and Gores G. Hepatocellular carcinoma. *Nat Rev Dis Primers* 2016; 2: 16018.
- [3] Levrero M and Zucman-Rossi J. Mechanisms of HBV-induced hepatocellular carcinoma. *J Hepatol* 2016; 64: S84-S101.
- [4] Carrat F, Fontaine H, Dorival C, Simony M, Di-allo A, Hezode C, De Ledinghen V, Larrey D, Haour G, Bronowicki JP, Zoulim F, Asselah T, Marcellin P, Thabut D, Leroy V, Tran A, Habersetzer F, Samuel D, Guyader D, Chazouilleres O, Mathurin P, Metivier S, Alric L, Riachi G, Gournay J, Abergel A, Cales P, Ganne N, Loustaud-Ratti V, D'Alteroche L, Causse X, Geist C, Minello A, Rosa I, Gelu-Simeon M, Portal I, Raffi F, Bourliere M and Pol S. Clinical outcomes in patients with chronic hepatitis C after direct-acting antiviral treatment: a prospective cohort study. *Lancet* 2019; 393: 1453-1464.
- [5] Lee BP, Vittinghoff E, Dodge JL, Cullaro G and Terrault NA. National trends and long-term outcomes of liver transplant for alcohol-associated liver disease in the United States. *JAMA Intern Med* 2019; 179: 340-348.
- [6] Alexander M, Loomis AK, van der Lei J, Duarte-Salles T, Prieto-Alhambra D, Ansell D, Pasqua A, Lapi F, Rijnbeek P, Mosseveld M, Waterworth DM, Kendrick S, Sattar N and Alazawi W. Risks and clinical predictors of cirrhosis and hepatocellular carcinoma diagnoses in adults with diagnosed NAFLD: real-world study of 18 million patients in four European cohorts. *BMC Med* 2019; 17: 95.
- [7] Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L and Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; 64: 73-84.
- [8] Buzzetti E, Pinzani M and Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metab Clin Exp* 2016; 65: 1038-1048.
- [9] Schuster S, Cabrera D, Arrese M and Feldstein AE. Triggering and resolution of inflammation in NASH. *Nat Rev Gastroenterol Hepatol* 2018; 15: 349-364.
- [10] Marengo A, Rosso C and Bugianesi E. Liver cancer: connections with obesity, fatty liver, and cirrhosis. *Annu Rev Med* 2016; 67: 103-117.
- [11] Suzuki A and Diehl AM. Nonalcoholic steatohepatitis. *Annu Rev Med* 2017; 68: 85-98.
- [12] Sircana A, Paschetta E, Saba F, Molinaro F and Musso G. Recent insight into the role of fibrosis in nonalcoholic steatohepatitis-related hepatocellular carcinoma. *Int J Mol Sci* 2019; 20: 1745.
- [13] Bengtsson B, Stål P, Wahlin S, Björkström NK and Hagström H. Characteristics and outcome of hepatocellular carcinoma in patients with NAFLD without cirrhosis. *Liver Int* 2019; 39: 1098-1108.
- [14] Mohamad B, Shah V, Onyshchenko M, Elshamy M, Aucejo F, Lopez R, Hanouneh IA, Alhaddad R and Alkhoury N. Characterization of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD) patients without cirrhosis. *Hepatol Int* 2016; 10: 632-639.
- [15] Tilg H, Moschen AR and Roden M. NAFLD and diabetes mellitus. *Nat Rev Gastroenterol Hepatol* 2017; 14: 32-42.
- [16] Yki-Järvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. *Lancet Diabetes Endocrinol* 2014; 2: 901-910.
- [17] Fan JG, Kim SU and Wong VW. New trends on obesity and NAFLD in Asia. *J Hepatol* 2017; 67: 862-873.
- [18] Yu Y, Cai J, She Z and Li H. Insights into the epidemiology, pathogenesis, and therapeutics of nonalcoholic fatty liver diseases. *Adv Sci (Weinh)* 2019; 6: 1801585.

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- [19] Spengler EK and Loomba R. Recommendations for diagnosis, referral for liver biopsy, and treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Mayo Clin Proc* 2015; 90: 1233-1246.
- [20] Estes C, Razavi H, Loomba R, Younossi Z and Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. *Hepatology* 2018; 67: 123-133.
- [21] Wong CR, Nguyen MH and Lim JK. Hepatocellular carcinoma in patients with non-alcoholic fatty liver disease. *World J Gastroenterol* 2016; 22: 8294-8303.
- [22] Petrick JL, Braunlin M, Laversanne M, Valery PC, Bray F and McGlynn KA. International trends in liver cancer incidence, overall and by histologic subtype, 1978-2007. *Int J Cancer* 2016; 139: 1534-1545.
- [23] Pais R, Fartoux L, Goumard C, Scatton O, Wendum D, Rosmorduc O and Ratziu V. Temporal trends, clinical patterns and outcomes of NAFLD-related HCC in patients undergoing liver resection over a 20-year period. *Aliment Pharmacol Ther* 2017; 46: 856-863.
- [24] Younossi ZM, Otgonsuren M, Henry L, Venkatesan C, Mishra A, Erario M and Hunt S. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. *Hepatology* 2015; 62: 1723-1730.
- [25] Wong RJ, Cheung R and Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. *Hepatology* 2014; 59: 2188-2195.
- [26] Dyson J, Jaques B, Chattopadhyay D, Lochan R, Graham J, Das D, Aslam T, Patanwala I, Gaggari S, Cole M, Sumpter K, Stewart S, Rose J, Hudson M, Manas D and Reeves HL. Hepatocellular cancer: the impact of obesity, type 2 diabetes and a multidisciplinary team. *J Hepatol* 2014; 60: 110-117.
- [27] Tateishi R, Okanoue T, Fujiwara N, Okita K, Kiyosawa K, Omata M, Kumada H, Hayashi N and Koike K. Clinical characteristics, treatment, and prognosis of non-B, non-C hepatocellular carcinoma: a large retrospective multicenter cohort study. *J Gastroenterol* 2015; 50: 350-360.
- [28] Watanabe S, Horie Y, Kataoka E, Sato W, Dohmen T, Ohshima S, Goto T and Suzuki A. Non-alcoholic steatohepatitis and hepatocellular carcinoma: lessons from hepatocyte-specific phosphatase and tensin homolog (PTEN)-deficient mice. *J Gastroenterol Hepatol* 2007; 22 Suppl 1: S96-S100.
- [29] Nakagawa H. Recent advances in mouse models of obesity- and nonalcoholic steatohepatitis-associated hepatocarcinogenesis. *World J Hepatol* 2015; 7: 2110-2118.
- [30] Kodama T, Yi J, Newberg JY, Tien JC, Wu H, Finegold MJ, Kodama M, Wei Z, Tamura T, Takehara T, Johnson RL, Jenkins NA and Copeland NG. Molecular profiling of nonalcoholic fatty liver disease-associated hepatocellular carcinoma using SB transposon mutagenesis. *Proc Natl Acad Sci U S A* 2018; 115: E10417-E10426.
- [31] Halder G and Johnson RL. Hippo signaling: growth control and beyond. *Development* 2011; 138: 9-22.
- [32] Patel SH, Camargo FD and Yimlamai D. Hippo signaling in the liver regulates organ size, cell fate, and carcinogenesis. *Gastroenterology* 2017; 152: 533-545.
- [33] Yimlamai D, Christodoulou C, Galli GG, Yanger K, Pepe-Mooney B, Gurung B, Shrestha K, Cahhan P, Stanger BZ and Camargo FD. Hippo pathway activity influences liver cell fate. *Cell* 2014; 157: 1324-1338.
- [34] Meng Z, Moroishi T and Guan KL. Mechanisms of Hippo pathway regulation. *Genes Dev* 2016; 30: 1-17.
- [35] Lu L, Finegold MJ and Johnson RL. Hippo pathway coactivators Yap and Taz are required to coordinate mammalian liver regeneration. *Exp Mol Med* 2018; 50: e423.
- [36] Kim W, Khan SK, Gvozdenovic-Jeremic J, Kim Y, Dahlman J, Kim H, Park O, Ishitani T, Jho EH, Gao B and Yang Y. Hippo signaling interactions with Wnt/ $\beta$ -catenin and Notch signaling repress liver tumorigenesis. *J Clin Invest* 2017; 127: 137-152.
- [37] Liu H, Jiang D, Chi F and Zhao B. The Hippo pathway regulates stem cell proliferation, self-renewal, and differentiation. *Protein Cell* 2012; 3: 291-304.
- [38] Akashi M, Higashi T, Masuda S, Komori T and Furuse M. A coronary artery disease-associated gene product, JCAD/KIAA1462, is a novel component of endothelial cell-cell junctions. *Biochem Biophys Res Commun* 2011; 413: 224-229.
- [39] Hara T, Monguchi T, Iwamoto N, Akashi M, Mori K, Oshita T, Okano M, Toh R, Irino Y, Shinohara M, Yamashita Y, Shioi G, Furuse M, Ishida T and Hirata KI. Targeted disruption of JCAD (Junctional Protein Associated with coronary artery Disease)/KIAA1462, a coronary artery disease-associated gene product, inhibits angiogenic processes in vitro and in vivo. *Arterioscler Thromb Vasc Biol* 2017; 37: 1667-1673.
- [40] Jones PD, Kaiser MA, Ghaderi Najafabadi M, Koplev S, Zhao Y, Douglas G, Kyriakou T, Andrews S, Rajmohan R, Watkins H, Channon KM, Ye S, Yang X, Björkegren JLM, Samani NJ and Webb TR. JCAD, a gene at the 10p11 coro-

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- nary artery disease locus, regulates hippo signaling in endothelial cells. *Arterioscler Thromb Vasc Biol* 2018; 38: 1711-1722.
- [41] Ye J, Li TS, Xu G, Zhao YM, Zhang NP, Fan J and Wu J. JCAD promotes progression of nonalcoholic steatohepatitis to liver cancer by inhibiting LATS2 kinase activity. *Cancer Res* 2017; 77: 5287-5300.
- [42] Paramasivam M, Sarkeshik A, Yates JR, Fernandes MJ and McCollum D. Angiotensin family proteins are novel activators of the LATS2 kinase tumor suppressor. *Mol Biol Cell* 2011; 22: 3725-3733.
- [43] Guo C, Wang X and Liang L. LATS2-mediated YAP1 phosphorylation is involved in HCC tumorigenesis. *Int J Clin Exp Pathol* 2015; 8: 1690-1697.
- [44] Corazzari M, Gagliardi M, Fimia GM and Piacentini M. Endoplasmic reticulum stress, unfolded protein response, and cancer cell fate. *Front Oncol* 2017; 7: 78.
- [45] Chen Y and Brandizzi F. IRE1: ER stress sensor and cell fate executor. *Trends Cell Biol* 2013; 23: 547-555.
- [46] Cubillos-Ruiz JR, Bettigole SE and Glimcher LH. Tumorigenic and immunosuppressive effects of endoplasmic reticulum stress in cancer. *Cell* 2017; 168: 692-706.
- [47] Papaioannou A and Chevet E. Driving cancer tumorigenesis and metastasis through UPR signaling. *Curr Top Microbiol Immunol* 2018; 414: 159-192.
- [48] Jiang S, Yan C, Fang QC, Shao ML, Zhang YL, Liu Y, Deng YP, Shan B, Liu JQ, Li HT, Yang L, Zhou J, Dai Z, Liu Y and Jia WP. Fibroblast growth factor 21 is regulated by the IRE1 $\alpha$ -XBP1 branch of the unfolded protein response and counteracts endoplasmic reticulum stress-induced hepatic steatosis. *J Biol Chem* 2014; 289: 29751-29765.
- [49] Wu Y, Shan B, Dai J, Xia Z, Cai J, Chen T, Lv S, Feng Y, Zheng L, Wang Y, Liu J, Fang J, Xie D, Rui L, Liu J and Liu Y. Dual role for inositol-requiring enzyme 1 $\alpha$  in promoting the development of hepatocellular carcinoma during diet-induced obesity in mice. *Hepatology* 2018; 68: 533-546.
- [50] Fang P, Xiang L, Huang S, Jin L, Zhou G, Zhuge L, Li J, Fan H, Zhou L, Pan C and Zheng Y. IRE1 $\alpha$ -XBP1 signaling pathway regulates IL-6 expression and promotes progression of hepatocellular carcinoma. *Oncol Lett* 2018; 16: 4729-4736.
- [51] de Conti A, Dreval K, Tryndyak V, Orisakwe OE, Ross SA, Beland FA and Pogribny IP. Inhibition of the cell death pathway in nonalcoholic steatohepatitis (NASH)-related hepatocarcinogenesis is associated with histone H4 lysine 16 deacetylation. *Mol Cancer Res* 2017; 15: 1163-1172.
- [52] Dow M, Pyke RM, Tsui BY, Alexandrov LB, Nakagawa H, Taniguchi K, Seki E, Harismendy O, Shalpour S, Karin M, Carter H and Font-Burgada J. Integrative genomic analysis of mouse and human hepatocellular carcinoma. *Proc Natl Acad Sci U S A* 2018; 115: E9879-E9888.
- [53] Zhang R, Erler J and Langowski J. Histone acetylation regulates chromatin accessibility: role of H4K16 in inter-nucleosome interaction. *Biophys J* 2017; 112: 450-459.
- [54] Audia JE and Campbell RM. Histone modifications and cancer. *Cold Spring Harb Perspect Biol* 2016; 8: a019521.
- [55] Hanna A and Shevde LA. Hedgehog signaling: modulation of cancer properties and tumor microenvironment. *Mol Cancer* 2016; 15: 24.
- [56] Shen X, Peng Y and Li H. The injury-related activation of hedgehog signaling pathway modulates the repair-associated inflammation in liver fibrosis. *Front Immunol* 2017; 8: 1450.
- [57] Yang JJ, Tao H and Li J. Hedgehog signaling pathway as key player in liver fibrosis: new insights and perspectives. *Expert Opin Ther Targets* 2014; 18: 1011-1021.
- [58] Chong YC, Lim TE, Fu Y, Shin EM, Tergaonkar V and Han W. Indian Hedgehog links obesity to development of hepatocellular carcinoma. *Oncogene* 2019; 38: 2206-2222.
- [59] Matsumoto T, Takai A, Eso Y, Kinoshita K, Manabe T, Seno H, Chiba T and Marusawa H. Proliferating EpCAM-positive ductal cells in the inflamed liver give rise to hepatocellular carcinoma. *Cancer Res* 2017; 77: 6131-6143.
- [60] Higashi T, Friedman SL and Hoshida Y. Hepatic stellate cells as key target in liver fibrosis. *Adv Drug Deliv Rev* 2017; 121: 27-42.
- [61] Yang K, Wang X, Zhang H, Wang Z, Nan G, Li Y, Zhang F, Mohammed MK, Haydon RC, Luu HH, Bi Y and He TC. The evolving roles of canonical WNT signaling in stem cells and tumorigenesis: implications in targeted cancer therapies. *Lab Invest* 2016; 96: 116-136.
- [62] Hart GW, Housley MP and Slawson C. Cycling of O-linked beta-N-acetylglucosamine on nucleocytoplasmic proteins. *Nature* 2007; 446: 1017-1022.
- [63] Yang X, Ongusaha PP, Miles PD, Havstad JC, Zhang F, So WV, Kudlow JE, Michell RH, Olefsky JM, Field SJ and Evans RM. Phosphoinositide signalling links O-GlcNAc transferase to insulin resistance. *Nature* 2008; 451: 964-969.
- [64] Jóźwiak P, Forma E, Bryś M and Krześlak A. O-GlcNAcylation and metabolic reprogramming in cancer. *Front Endocrinol (Lausanne)* 2014; 5: 145.
- [65] Xu W, Zhang X, Wu JL, Fu L, Liu K, Liu D, Chen GG, Lai PB, Wong N and Yu J. O-GlcNAc trans-



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- ferase promotes fatty liver-associated liver cancer through inducing palmitic acid and activating endoplasmic reticulum stress. *J Hepatol* 2017; 67: 310-320.
- [66] Ma Z, Chalkley RJ and Vosseller K. Hyper-GlcNAcylation activates nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells (NF- $\kappa$ B) signaling through interplay with phosphorylation and acetylation. *J Biol Chem* 2017; 292: 9150-9163.
- [67] Martinez MR, Dias TB, Natov PS and Zachara NE. Stress-induced O-GlcNAcylation: an adaptive process of injured cells. *Biochem Soc Trans* 2017; 45: 237-249.
- [68] Gill S, Stevenson J, Kristiana I and Brown AJ. Cholesterol-dependent degradation of squalene monooxygenase, a control point in cholesterol synthesis beyond HMG-CoA reductase. *Cell Metab* 2011; 13: 260-273.
- [69] Liang JQ, Teoh N, Xu L, Pok S, Li X, Chu ESH, Chiu J, Dong L, Arfianti E, Haigh WG, Yeh MM, Ioannou GN, Sung JY, Farrell G and Yu J. Dietary cholesterol promotes steatohepatitis related hepatocellular carcinoma through dysregulated metabolism and calcium signaling. *Nat Commun* 2018; 9: 4490.
- [70] Liu D, Wong CC, Fu L, Chen H, Zhao L, Li C, Zhou Y, Zhang Y, Xu W, Yang Y, Wu B, Cheng G, Lai PB, Wong N, Sung JY and Yu J. Squalene epoxidase drives NAFLD-induced hepatocellular carcinoma and is a pharmaceutical target. *Sci Transl Med* 2018; 10: eaap9840.
- [71] Ioannou GN. The role of cholesterol in the pathogenesis of NASH. *Trends Endocrinol Metab* 2016; 27: 84-95.
- [72] Sharpe LJ and Brown AJ. Controlling cholesterol synthesis beyond 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR). *J Biol Chem* 2013; 288: 18707-18715.
- [73] Zhao Z, Wu Q, Cheng J, Qiu X, Zhang J and Fan H. Depletion of DNMT3A suppressed cell proliferation and restored PTEN in hepatocellular carcinoma cell. *J Biomed Biotechnol* 2010; 2010: 737535.
- [74] Dai YJ, Wang YY, Huang JY, Xia L, Shi XD, Xu J, Lu J, Su XB, Yang Y, Zhang WN, Wang PP, Wu SF, Huang T, Mi JQ, Han ZG, Chen Z and Chen SJ. Conditional knockin of Dnmt3a R878H initiates acute myeloid leukemia with mTOR pathway involvement. *Proc Natl Acad Sci U S A* 2017; 114: 5237-5242.
- [75] McCoin CS, Knotts TA and Adams SH. Acylcarnitines—old actors auditioning for new roles in metabolic physiology. *Nat Rev Endocrinol* 2015; 11: 617-625.
- [76] Fujiwara N, Nakagawa H, Enooku K, Kudo Y, Hayata Y, Nakatsuka T, Tanaka Y, Tateishi R, Hikiba Y, Misumi K, Tanaka M, Hayashi A, Shibahara J, Fukayama M, Arita J, Hasegawa K, Hirschfield H, Hoshida Y, Hirata Y, Otsuka M, Tateishi K and Koike K. CPT2 downregulation adapts HCC to lipid-rich environment and promotes carcinogenesis via acylcarnitine accumulation in obesity. *Gut* 2018; 67: 1493-1504.
- [77] Sun H, Yang W, Tian Y, Zeng X, Zhou J, Mok MTS, Tang W, Feng Y, Xu L, Chan AWH, Tong JH, Cheung YS, Lai PBS, Wang HKS, Tsang SW, Chow KL, Hu M, Liu R, Huang L, Yang B, Yang P, To KF, Sung JY, Wong GLH, Wong VWS and Cheng ASL. An inflammatory-CCRK circuitry drives mTORC1-dependent metabolic and immunosuppressive reprogramming in obesity-associated hepatocellular carcinoma. *Nat Commun* 2018; 9: 5214.
- [78] Feng H, Cheng AS, Tsang DP, Li MS, Go MY, Cheung YS, Zhao GJ, Ng SS, Lin MC, Yu J, Lai PB, To KF and Sung JJ. Cell cycle-related kinase is a direct androgen receptor-regulated gene that drives  $\beta$ -catenin/T cell factor-dependent hepatocarcinogenesis. *J Clin Invest* 2011; 121: 3159-3175.
- [79] Feng H, Yu Z, Tian Y, Lee YY, Li MS, Go MY, Cheung YS, Lai PB, Chan AM, To KF, Chan HL, Sung JJ and Cheng AS. A CCRK-EZH2 epigenetic circuitry drives hepatocarcinogenesis and associates with tumor recurrence and poor survival of patients. *J Hepatol* 2015; 62: 1100-1111.
- [80] Shalapour S, Lin XJ, Bastian IN, Brain J, Burt AD, Aksenov AA, Vrbancic AF, Li W, Perkins A, Matsutani T, Zhong Z, Dhar D, Navas-Molina JA, Xu J, Loomba R, Downes M, Yu RT, Evans RM, Dorrestein PC, Knight R, Benner C, Anstee QM and Karin M. Inflammation-induced IgA+ cells dismantle anti-liver cancer immunity. *Nature* 2017; 551: 340-345.
- [81] Chauvin JM, Pagliano O, Fourcade J, Sun Z, Wang H, Sander C, Kirkwood JM, Chen TH, Maurer M, Korman AJ and Zarour HM. TIGIT and PD-1 impair tumor antigen-specific CD8<sup>+</sup> T cells in melanoma patients. *J Clin Invest* 2015; 125: 2046-2058.
- [82] Gabrielson A, Wu Y, Wang H, Jiang J, Kallakury B, Gatalica Z, Reddy S, Kleiner D, Fishbein T, Johnson L, Island E, Satoskar R, Banovac F, Jha R, Kachhela J, Feng P, Zhang T, Tesfaye A, Prins P, Loffredo C, Marshall J, Weiner L, Atkins M and He AR. Intratumoral CD3 and CD8 T-cell densities associated with relapse-free survival in HCC. *Cancer Immunol Res* 2016; 4: 419-430.
- [83] Branzk N, Lubojemska A, Hardison SE, Wang Q, Gutierrez MG, Brown GD and Papayanopoulos V. Neutrophils sense microbe size and selectively release neutrophil extracellular traps in response to large pathogens. *Nat Immunol* 2014; 15: 1017-1025.
- [84] Jorch SK and Kubers P. An emerging role for neutrophil extracellular traps in noninfectious disease. *Nat Med* 2017; 23: 279-287.

## Non-alcoholic fatty liver disease and hepatocellular carcinoma

- [85] van der Windt DJ, Sud V, Zhang H, Varley PR, Goswami J, Yazdani HO, Tohme S, Loughran P, O'Doherty RM, Minervini MI, Huang H, Simmons RL and Tsung A. Neutrophil extracellular traps promote inflammation and development of hepatocellular carcinoma in nonalcoholic steatohepatitis. *Hepatology* 2018; 68: 1347-1360.
- [86] Iannacone M, Sitia G, Isogawa M, Marchese P, Castro MG, Lowenstein PR, Chisari FV, Ruggeri ZM and Guidotti LG. Platelets mediate cytotoxic T lymphocyte-induced liver damage. *Nat Med* 2005; 11: 1167-1169.
- [87] Malehmir M, Pfister D, Gallage S, Szydlowska M, Inverso D, Kotsiliti E, Leone V, Peiseler M, Surewaard BGJ, Rath D, Ali A, Wolf MJ, Drescher H, Healy ME, Dauch D, Kroy D, Krenkel O, Kohlhepp M, Engleitner T, Olkus A, Sijmonsma T, Volz J, Deppermann C, Stegner D, Helbling P, Nombela-Arrieta C, Rafiei A, Hinterleitner M, Rall M, Baku F, Borst O, Wilson CL, Leslie J, O'Connor T, Weston CJ, Adams DH, Sheriff L, Teijeiro A, Prinz M, Bogeska R, Anstee N, Bongers MN, Notohamiprodjo M, Geisler T, Withers DJ, Ware J, Mann DA, Augustin HG, Vegiopoulos A, Milsom MD, Rose AJ, Lalor PF, Llovet JM, Pinyol R, Tacke F, Rad R, Matter M, Djouder N, Kubes P, Knolle PA, Unger K, Zender L, Nieswandt B, Gawaz M, Weber A and Heikenwalder M. Platelet GPIIb/IIIa is a mediator and potential interventional target for NASH and subsequent liver cancer. *Nat Med* 2019; 25: 641-655.
- [88] Sitia G, Aiolfi R, Di Lucia P, Mainetti M, Fiocchi A, Mingozzi F, Esposito A, Ruggeri ZM, Chisari FV, Iannacone M and Guidotti LG. Antiplatelet therapy prevents hepatocellular carcinoma and improves survival in a mouse model of chronic hepatitis B. *Proc Natl Acad Sci U S A* 2012; 109: E2165-2172.
- [89] Wong CH, Jenne CN, Petri B, Chrobok NL and Kubes P. Nucleation of platelets with blood-borne pathogens on Kupffer cells precedes other innate immunity and contributes to bacterial clearance. *Nat Immunol* 2013; 14: 785-792.
- [90] Kanaji T, Ware J, Okamura T and Newman PJ. GPIIb/IIIa regulates platelet size by controlling the subcellular localization of filamin. *Blood* 2012; 119: 2906-2913.
- [91] Wiede F, Shields BJ, Chew SH, Kyparissoudis K, van Vliet C, Galic S, Tremblay ML, Russell SM, Godfrey DI and Tiganis T. T cell protein tyrosine phosphatase attenuates T cell signaling to maintain tolerance in mice. *J Clin Invest* 2011; 121: 4758-4774.
- [92] Shields BJ, Wiede F, Gurzov EN, Wee K, Hauser C, Zhu HJ, Molloy TJ, O'Toole SA, Daly RJ, Sutherland RL, Mitchell CA, McLean CA and Tiganis T. TCPTP regulates SFK and STAT3 signaling and is lost in triple-negative breast cancers. *Mol Cell Biol* 2013; 33: 557-570.
- [93] Loh K, Fukushima A, Zhang X, Galic S, Briggs D, Enriori PJ, Simonds S, Wiede F, Reichenbach A, Hauser C, Sims NA, Bence KK, Zhang S, Zhang ZY, Kahn BB, Neel BG, Andrews ZB, Cowley MA and Tiganis T. Elevated hypothalamic TCPTP in obesity contributes to cellular leptin resistance. *Cell Metab* 2011; 14: 684-699.
- [94] Grohmann M, Wiede F, Dodd GT, Gurzov EN, Ooi GJ, Butt T, Rasmiena AA, Kaur S, Gulati T, Goh PK, Treloar AE, Archer S, Brown WA, Muller M, Watt MJ, Ohara O, McLean CA and Tiganis T. Obesity drives STAT-1-dependent NASH and STAT-3-dependent HCC. *Cell* 2018; 175: 1289-1306, e1220.
- [95] Tomás-Barberán FA, Selma MV and Espín JC. Interactions of gut microbiota with dietary polyphenols and consequences to human health. *Curr Opin Clin Nutr Metab Care* 2016; 19: 471-476.
- [96] Yu LX and Schwabe RF. The gut microbiome and liver cancer: mechanisms and clinical translation. *Nat Rev Gastroenterol Hepatol* 2017; 14: 527-539.
- [97] Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, Iwakura Y, Oshima K, Morita H, Hattori M, Hattori M, Honda K, Ishikawa Y, Hara E and Ohtani N. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. *Nature* 2013; 499: 97-101.
- [98] Loo TM, Kamachi F, Watanabe Y, Yoshimoto S, Kanda H, Arai Y, Nakajima-Takagi Y, Iwama A, Koga T, Sugimoto Y, Ozawa T, Nakamura M, Kumagai M, Watashi K, Taketo MM, Aoki T, Narumiya S, Oshima M, Arita M, Hara E and Ohtani N. Gut microbiota promotes obesity-associated liver cancer through PGE-mediated suppression of antitumor immunity. *Cancer Discov* 2017; 7: 522-538.