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REVIEW

Obesity, Metabolic Dysfunction-Associated Steatotic Liver Disease and Hepatocellular Carcinoma: How Molecular Changes Impact Cellular Functions

Ralf Weiskirchen[1] and Amedeo Lonardo[2,*]

[1]Institute of Molecular Pathobiochemistry, Experimental Gene Therapy, and Clinical Chemistry (IFMPEGKC), RWTH University Hospital Aachen, Pauwelsstr. 30, Aachen, D-52074, Germany
[2]AOU Modena, Department of Internal Medicine, Ospedale Civile di Baggiovara (-2023), Modena, Italy
*Corresponding Author: Amedeo Lonardo. Email: a.lonardo@libero.it

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ABSTRACT: Obesity is a complex chronic condition characterized by an excess of body fat that manifests in various clinical pathophenotypes, each affecting liver health differently. One significant cause of chronic liver diseases among those living with obesity is metabolic dysfunction-associated steatotic liver disease (MASLD), which is linked to one or more cardiometabolic risk factors in individuals who do not engage in harmful alcohol consumption. Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and is increasingly being associated with MASLD through intricate immunological, cellular, proinflammatory, molecular, and genetic mechanisms. In this review, we examine the molecular changes and altered functions of hepatocytes related to lipid accumulation, oxidative stress, inflammatory responses, and the regulation of signaling pathways such as mechanistic target of rapamycin (mTOR), AMP-activated protein kinase (AMPK), and nuclear factor kappa B (NF-κB). We also explore how these processes impact cell proliferation, apoptosis, autophagy, migration, the immunological environment, angiogenesis, and cell differentiation. Finally, we discuss the challenges posed by MASLD-HCC and how these may be effectively managed by promoting effective risk stratification, early diagnosis, and innovative treatment schedules for this numerically growing category of patients.

KEYWORDS: Angiogenesis; apoptosis; autophagy; cell differentiation; migration; proliferation; immunometabolism; inflammatory response; lipid accumulation; oxidative stress

1 Background, Definitions, and Aims

1.1 Obesity

Obesity is a complex chronic condition characterized by the excessive accumulation of adipose tissue, presenting significant challenges to both individual health and public health systems globally [1]. This disease encompasses various pathophenotypes, such as android, gynoid, sarcopenic, metabolically healthy, and unhealthy obesity, each with different associations with liver health in the spectrum of chronic liver disease (CLD). This spectrum includes alcohol-related CLD, viral hepatitis B and C, and metabolic dysfunction-associated steatotic liver disease (MASLD), which is considered the primary manifestation of obesity-related CLD [2]. Body mass index (BMI) has its limitations, as it may misclassify obesity in individuals with well-developed muscle mass or fluid retention [3]. Visceral adiposity is a better indicator of metabolic dysfunction than BMI, making waist circumference a useful sex- and ethnic-specific

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anthropometric measurement [4]. Recognizing the constraints of BMI, experts have introduced the concept of "clinical obesity", which identifies a chronic, systemic illness characterized by excess adiposity leading to impaired bodily functions [5].

1.2 Metabolic Dysfunction-Associated Steatotic Liver Disease

MASLD encompasses simple steatosis, metabolic dysfunction-associated steatohepatitis [MASH, previously known as nonalcoholic steatohepatitis (NASH)], fibrosis, cirrhosis, and MASLD-hepatocellular carcinoma (HCC). MASLD is the type of steatotic liver disease (SLD) associated with one or more cardiometabolic risk factors in individuals who do not consume excessive alcohol [6]. MASLD is the most recent term used to describe the accumulation of fatty substances in the liver along with systemic metabolic dysfunction, replacing previous terms like nonalcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated fatty liver disease (MAFLD) [7].

1.3 Hepatocellular Carcinoma

HCC, the most common histological subtype of primary liver cancer (PLC), develops in the context of CLD from various causes. It has a high mortality rate, and its epidemiological, clinical, and financial burden is expected to increase [8]. While viral CLD has declined in recent years, MASLD has been on the rise, with metabolic comorbidities identified as risk factors and co-factors for HCC through complex genetic, immunological, cellular, proinflammatory, and molecular processes [9]. Understanding these mechanisms necessitates close surveillance and early diagnosis of at-risk patients to pave the way for personalized medicine, chemoprevention, and innovative management of MASLD-HCC [10].

1.4 Aims

Given the rapidly evolving clinical and epidemiological landscape, our aim is to highlight how molecular changes impact cellular functions in the context of obesity-related MASLD-HCC.

2 Criteria of Bibliographic Research

This narrative review explores the molecular mechanisms connecting obesity with MASLD and HCC. To set up this article, we conducted research on PubMed/MEDLINE and the Web of Science Core Collection for relevant articles. In our search strategy we combined Medical Subject Headings and free-text terms related to "obesity", "body mass index", "adiposity", "MASLD", "MAFLD", "NAFL", "NAFLD", "MASH", "NASH", "hepatocellular carcinoma", "liver cancer", "pathogenesis", "immunometabolism", "oxidative stress", "mTOR", "AMPK", "NF-κB", "angiogenesis", "diagnosis", "surveillance", and "therapy". We focused on studies that reported findings in humans and studies published in the English language. The identified sources included peer-reviewed original investigations, systematic reviews, meta-analyses, clinical guidelines, and high-impact narrative reviews that addressed epidemiology, molecular mechanisms, risk stratification, diagnostics, or therapeutic interventions relevant to the obesity/MASLD/HCC axis.

3 Burden and Risk Factors for Obesity, MASLD, and HCC

3.1 Obesity

Affecting more than 1 billion individuals, approximately 13% of the population as of 2022, obesity represents a significant global health concern. The prevalence of obesity has tripled since 1975 and is projected to impact 1.9 billion adults (25%) by 2035 and 3.8 billion, surpassing half of the worldwide adult population, by 2050 [11]. Historically more prevalent in high-income nations, obesity rates are now

increasing most rapidly in low- and middle-income nations, with over 70% of obese individuals living in developing countries [12]. This escalating burden contributes to over 5 million annual deaths related to conditions such as type 2 diabetes, cardiovascular diseases, and various cancers, notably including HCC [11,13]. Consequently, the economic impact of obesity is substantial, with estimates indicating that it may account for more than 3% of global Gross Domestic Product expenditures worldwide by 2060 [14]. As for the causes, obesity involves multiple interactions between genetic, hormonal, behavioral, environmental, and socio-economic determinants, with urbanization dynamics and globalization attitudes facilitating sedentary lifestyles and promoting consumption of calorie-dense, ultra-processed, and insecure foodstuffs [11,15,16].

3.2 Metabolic Dysfunction-Associated Steatotic Liver Disease

An accurate understanding of MASLD epidemiology is essential for planning healthcare resource allocation and health policy decisions [17]. The prevalence of MASLD, MASLD-cirrhosis, MASLD-related end-stage liver disease awaiting liver transplantation, and MASLD-HCC is increasing globally, driven by factors such as an aging general population and rising rates of diabesity [17]. Using data from the 2017 to 2023 edition of the National Health and Nutrition Examination Survey (NHANES), Paik et al. [18] found that the age-standardized prevalence of MASLD was 32.42% with clear sex disparities and ethnic gradients: men had a significantly higher prevalence than women, and Mexicans had the highest burden, followed by Whites, Hispanics, Asians, and Blacks. A meta-analytic review of 35 published studies totaling 513,742 individuals [19] found that the pooled global prevalence of cirrhosis among patients with MASLD was estimated at 3.26% (95% CI: 2.47%–4.31%) in general practice settings and 14.51% (95% CI: 11.22%–18.57%) among individuals in inpatient settings or those referred to liver biopsy. Regionally, higher prevalence rates in high-risk settings were observed in North America and Australia (18.38%; 95% CI: 9.06%–33.75%), followed by Europe (10.16%; 95% CI: 5.71%–17.44%) and Asia (9.12%; 95% CI: 6.11%–13.40%) ($p = 0.007$). Additionally, diagnoses based on ICD coding indicated a significantly greater prevalence of cirrhosis (27.43%) compared to cases confirmed by liver biopsy (13.24%; $p < 0.001$). The estimated pooled all-cause mortality rate for patients with MASLD-related cirrhosis was 7.91 per 100 person-years (95% CI: 4.44–13.71), as reported across nine studies [19].

The age-standardized incidence rate (ASIR) increased from 475.54 to 593.28 per 100,000 (AAPC 0.71). MASLD was responsible for 138,328 deaths, with a higher mortality rate observed among females (52.18%). The regions of East Asia, South Asia, and North Africa/Middle East reported the highest prevalence and incidence rates, while Western Europe experienced the most rapid growth. Projections indicate that by 2045, the ASIR will reach 928.10 per 100,000, resulting in an estimated 667.58 million new cases, predominantly affecting males [20]. Various explanations may clarify the reasons behind the significant differences in cirrhosis prevalence estimates in published studies [21]. Patient selection varies by study type, such as population-based samples, referral centers, or patients with advanced disease or comorbidities. Diagnostic approaches also differ, ranging from non-invasive scores and imaging to liver biopsy, with varying cirrhosis cut-offs. Additionally, geographical and healthcare system differences can introduce selection bias that affects referrals to specialized care.

Without interventions, the clinical, economic, and quality-of-life burden of MASH from 2021 to 2040 is projected to increase across the United States, Western Europe, the United Kingdom, Japan, Brazil, and Saudi Arabia, highlighting the urgent need for both national and global strategies to reduce the negative impact of MASH on individuals and society [22]. By very definition, MASLD is intricately linked with systemic metabolic dysfunction, and therefore this disorder progresses in parallel with the individual features of the

metabolic syndrome, comprising, further to obesity, altered glucose metabolism, atherogenic dyslipidemia, and arterial hypertension. In MASLD, the risks of fibrotic progression and MASLD-related mortality are directly proportional to the number of individual components of the metabolic syndrome [23].

3.3 Hepatocellular Carcinoma

Wu et al. reported that in 2021, PLC attributed to elevated BMI and/or high fasting plasma glucose (FPG) resulted in 59,970 deaths globally and accounted for 1,540,437 disability-adjusted life years [13]. Additionally, from 1990 to 2021, there has been a consistent global increase in liver cancer due to metabolic risks, with high BMI identified as the predominant risk factor. The highest mortality and Disability-Adjusted Life Year (DALY) burdens were observed in countries with high Socio-Demographic Index (SDI), while the most rapid increase occurred in low-middle SDI countries. The burdens associated with elevated BMI and FPG were greater among men compared to women [13]. Another study has indicated reductions in PLC related to chronic viral hepatitis, contrasted with increased rates of PLC associated with MASLD, particularly in high-SDI regions and among those aged over 75 [24]. There is a global male-to-female ratio of 2.19, though sex differences vary on a regional basis. Finally, the incidence rate is projected to persistently rise from 2021 to 2050 [24].

Elevated FPG indicates systemic insulin resistance and hyperinsulinemia, which activate insulin/IGF-1 pathways. This activation promotes cell proliferation, inhibits apoptosis, and increases oxidative stress and DNA damage in hepatocytes [25]. It should be emphasized that the BMI/FPG attributable fraction of PLC predominantly influences MASLD and MASLD-cirrhosis as intermediate phenotypes [13].

4 Molecular and Cellular Pathogenesis of Obesity-Associated Hepatocellular Carcinoma

4.1 Lipid Accumulation

The earliest morphological feature of MASLD is lipid accumulation in hepatocytes, which represents the biochemical basis for progressive liver injury and hepatocarcinogenesis. In MASLD, excessive storage of triglycerides is closely linked to disruptions in systemic energy balance related to obesity and concurrent cardiometabolic risk factors, independent of harmful alcohol consumption. Moreover, hepatocyte steatosis triggers oxidative stress, inflammatory responses, and abnormal signaling through nutrient-sensing pathways such as mechanistic target of rapamycin complex 1 (mTORC1), AMP-activated protein kinase (AMPK), and nuclear factor kappa B (NF-κB) [26–28]. Mechanistically, cellular hepatic lipid overload originates from three main sources: increased delivery of dietary fatty acids and chylomicron remnants, increased adipose tissue lipolysis releasing non-esterified fatty acids into the portal circulation, and augmented *de novo* lipogenesis (DNL) due to hyperinsulinemia and glucose influx (Fig. 1) [29].

Insulin resistance, a hallmark of obesity, impairs the antilipolytic effect of insulin in peripheral adipose tissue while enhancing its lipogenic effect in the liver through sterol regulatory element-binding protein-1c (SREBP-1c) [30]. Additionally, carbohydrate-responsive element-binding protein (ChREBP), which responds to fructose and glucose signals, has been considered a driving factor in DNL [30]. The excess of saturated long-chain fatty acids like palmitate is converted to triglycerides and stored in dynamic, endoplasmic reticulum (ER)-derived lipid droplets, initially considered harmless but now recognized as lipotoxic when protective mechanisms are overwhelmed [31].

While the majority of MASLD cases still arise from environmental or metabolic drivers in genetically "average" individuals, genetic factors also play a key pathogenic role in MASLD. In humans, gene variants such as *PNPLA3* I148M, *TM6SF2* E167K, *MBOAT7* rs641738, and Glucokinase Regulatory Protein (GCKR)

highlight the importance of lipid droplet biology, VLDL secretion, and phospholipid remodeling in MASLD [32].

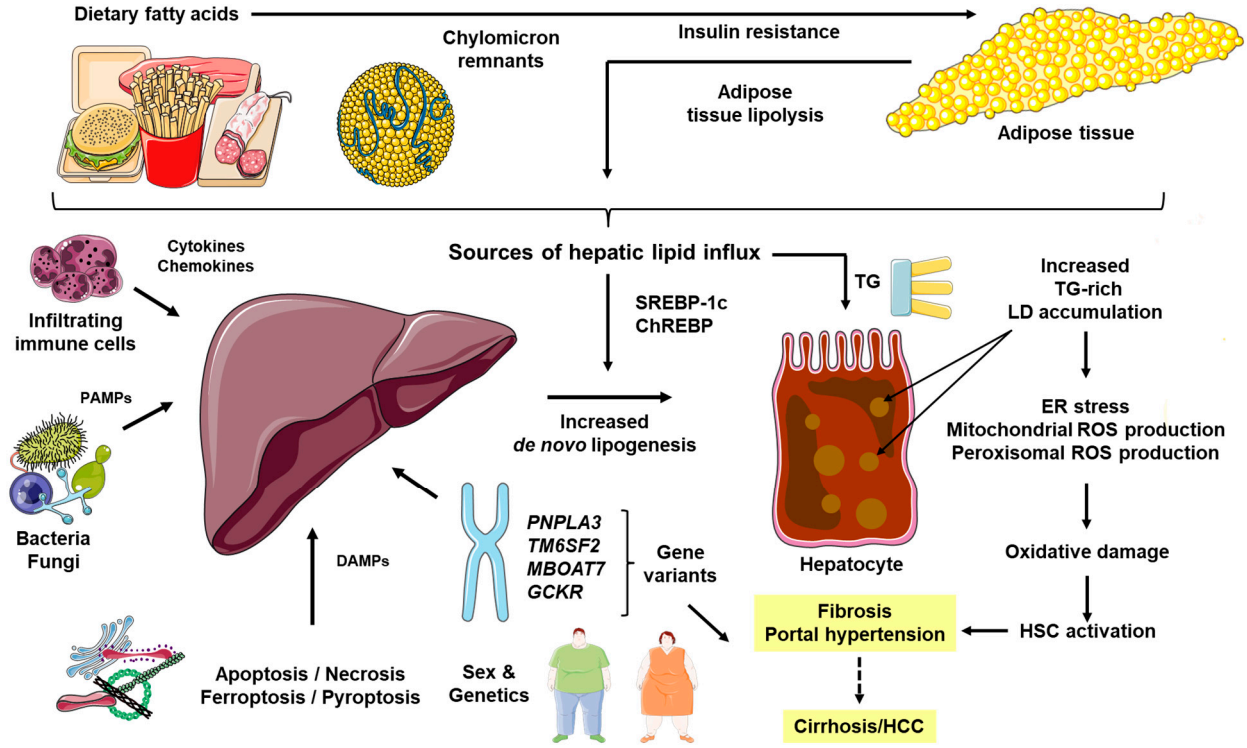

Figure 1: Hepatic lipid overload and its consequences in obesity-related MASLD. Three major sources of hepatic lipid influx, including dietary fatty acids and chylomicron remnants, adipose tissue lipolysis due to insulin resistance, and increased *de novo* lipogenesis driven by SREBP-1c and ChREBP, converge to promote triglyceride-rich lipid droplet accumulation in hepatocytes. This process is modulated by genetic variants in genes encoding *PNPLA3*, *TM6SF2*, *MBOAT7*, and *GCKR*. Excess saturated fatty acids and lipotoxic intermediates induce endoplasmic reticulum (ER) stress, mitochondrial and peroxisomal reactive oxygen species (ROS) production, and oxidative damage. These factors, combined with damage-associated molecular patterns (DAMPs), pathogen-associated molecular patterns (PAMPs), and cytokine release, fuel inflammation, activate hepatic stellate cells (HSCs), and drive fibrogenesis, portal hypertension, and might lead to cirrhosis and hepatocellular carcinoma (HCC). This lowers the threshold for hepatocarcinogenesis. This original illustration was created using Servier Medical ART (SMART) and is licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

The *PNPLA3* I148M gene variant in humans reduces lipase activity at the lipid droplet surface, leading to the retention of triglyceride-rich droplets enriched in polyunsaturated fatty acids and promotes steatogenesis through the development of macrovesicular steatosis [33]. These droplets are more susceptible to lipid peroxidation, which amplifies oxidative and inflammatory signaling.

TM6SF2 E167K impairs VLDL secretion, resulting in intrahepatic triglyceride accumulation and altered lipid composition that enhances lipotoxic stress despite lower circulating lipids [34]. Unlike typical cases of obese or metabolic MASLD, individuals with this variant do not present with hypertriglyceridemia [35,36] and have a reduced risk of cardiovascular disease, supporting the notion that “not all fat is alike in MASLD” [37,38].

MBOAT7 rs641738 disrupts phosphatidylinositol remodeling, shifting membrane phospholipid composition toward arachidonic-acid-poor species. This influences membrane fluidity, receptor clustering, and the generation of pro-inflammatory eicosanoids [39,40].

The *GCKR* gene is also implicated in susceptibility to MASLD. The rs1260326 C > T variant enhances hepatic glucose uptake and *de novo* lipogenesis, resulting in increased storage of intrahepatic lipids [32].

Several of these polymorphisms not only increase the severity of steatosis but also enhance oxidative stress and fibrogenic signaling, lowering the threshold for carcinogenesis. At the cellular level, excess saturated fatty acids alter membrane composition, induce ER stress, and activate unfolded protein response pathways mediated by the eIF2 kinase PERKα, ATF6, and IRE1 [41,42]. This in turn triggers c-Jun N-terminal kinase (JNK) and nuclear factor-κB (NF-κB) cascades. Reactive oxygen species (ROS) from overloaded mitochondrial and peroxisomal oxidation damage DNA, disrupt electron transport chain integrity, and initiate lipid peroxidation, amplifying mutagenic and pro-oncogenic signals [42].

Moreover, hepatic steatosis disrupts the sinusoidal microenvironment at the organ level. In particular, lipid-laden hepatocytes release danger-associated molecular patterns (DAMPs) and several metabolites like ceramides and diacylglycerols, which recruit and activate immune cells like Kupffer cells and macrophages [43]. These cells produce inflammatory cytokines, including tumor-necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), promoting insulin resistance, enhancing lipogenesis, and creating a pro-inflammatory environment, setting the soil for cancer development [35]. Simultaneously, lipotoxic intermediates activate hepatic stellate cells, promoting their transdifferentiation to contractile myofibroblasts, thereby driving liver fibrosis that hinders nutrient and oxygen diffusion, maintaining hypoxia-inducible factor-1α (HIF-1α) and facilitating angiogenesis, creating favorable conditions for the development of portal hypertension, and the proliferation of dysplastic hepatocyte nodules [36].

Nutrient-sensing pathways are closely linked to steatosis. Excess caloric intake activates the mechanistic target of rapamycin complex 1 (mTORC1), promoting DNL and inhibiting autophagy, including lipophagy, which, in turn, limits the ability of the liver to mobilize stored triglycerides [44]. Conversely, in MASLD, increased AMP-activated protein kinase (AMPK) activity can inhibit the synthesis of fatty acids and cholesterol by downregulating the expression of genes involved in steatogenesis, such as fatty acid synthase, SREBP-1c, acetyl-CoA carboxylase, and HMG-CoA reductase [45]. Therapeutic interventions that restore AMPK activity, such as the administration of metformin or increasing physical activity, or inhibition of the mTORC1 pathway by rapamycin analogs (i.e., rapalogs), have been shown to reverse steatosis and reduce HCC risk in preclinical models [46].

The distribution of lipid droplets also impacts oncogenic signaling. Particularly, macrosteatosis, characterized by large, macrovesicular cellular fat droplets, can displace the nucleus, provoking gene expression differences, while microvesicular steatosis is associated with mitochondrial dysfunction and increased ROS [47–49]. Advanced imaging and single-cell transcriptomics have revealed diversity in lipid droplet size and properties, suggesting that specific lipid signatures may confer carcinogenic potential. Therefore, lipid accumulation in MASLD is not just a simple, passive storage process but an active driver of hepatocyte damage, fibrosis, portal hypertension, and tumorigenesis through interconnected metabolic, oxidative, inflammatory, and signaling pathways.

4.2 Oxidative Stress

The transition from simple steatosis in MASLD to progressive liver injury that can ultimately lead to HCC is critically driven by sustained oxidative stress, which acts in concert with lipid accumulation, inflammation, and dysregulated signaling pathways to damage hepatocytes and remodel the hepatic

microenvironment [50]. As highlighted above, steatotic hepatocytes experience heightened ROS generation that can contribute to mutagenesis, fibrogenesis, and oncogenesis, thereby forming a central pathobiological link between obesity, MASLD, and HCC.

Sources of ROS generation in MASLD are multifactorial. Caloric excess increases the flux of free fatty acids and fructose into hepatocytes, leading to excessive β-oxidation and tricarboxylic acid cycle overload. This saturates the mitochondrial electron transport chain, leading to abnormally high concentrations of nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH) that create a "traffic jam", causing a partial reversal and leakage of the electron flow at complexes I and III with subsequent formation of superoxide anions and hydrogen peroxide [51]. Apart from ROS generation in mitochondria, enzymes such as NADPH oxidase (NOX), xanthine oxidase (XO), cytochrome P450 2E1 (CYP2E1), cyclooxygenases, and lipoxygenases in the cytosol and plasma membranes also produce ROS, especially hydrogen peroxide [52]. In parallel, increased ER stress triggered by lipoprotein synthesis and by lipid-induced membrane perturbation activates the unfolded protein response (UPR), which elevates ROS through disulfide-bond formation and calcium leakage from the ER, thereby further leading to disease progression by progressing to cell death and dynamic pathophysiological changes [53]. Together, these "multiple hits" overwhelm cellular antioxidant defense mechanisms, shifting the redox balance toward sustained oxidative injury.

Beyond mitochondria, fatty acid-induced oxidative stress in MASLD is also fueled by peroxisomes and by the oxidative protein-folding machinery of the ER [54]. In steatotic hepatocytes, very-long-chain and branched-chain fatty acids that cannot be efficiently oxidized in mitochondria are shunted to peroxisomes. There, acyl-CoA oxidases catalyze the first step of β-oxidation and transfer electrons directly to molecular oxygen, generating stoichiometric amounts of hydrogen peroxide. Under chronic lipotoxic conditions, this peroxisomal flux can exceed the detoxifying capacity of catalase, allowing hydrogen peroxide to diffuse into the cytosol and neighboring organelles. This amplifies redox stress and sustains lipid peroxidation. In parallel, the ER lumen is intrinsically oxidizing to permit correct disulfide-bond formation during protein folding. Thiol-disulfide exchange reactions mediated by protein disulfide isomerase and ER oxidoreductin 1 (Ero1) couple oxidative folding of nascent secretory and membrane proteins to the reduction of oxygen, producing hydrogen peroxide as a by-product [55]. The increased demand for lipoprotein assembly, cytokine and hormone receptors, and acute-phase proteins in MASLD augments this oxidative folding load [56,57]. This, together with lipid-induced membrane perturbation, promotes the accumulation of misfolded proteins, activation of the unfolded protein response, and further reactive species generation. Thus, peroxisomal β-oxidation and ER oxidative protein folding cooperate with mitochondrial dysfunction to maintain a self-perpetuating cycle of oxidative stress that drives hepatocyte injury, fibrogenesis, and, eventually, hepatocarcinogenesis [56].

At the molecular level, ROS induces direct damage to lipids, proteins, and nucleic acids [47]. Lipid peroxidation generates highly reactive aldehydes such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA), which form adducts with DNA and histones, fostering mutagenic lesions that predispose to malignant transformation [58,59]. Oxidative DNA damage, exemplified by 8-oxo-2′-deoxyguanosine formation, representing the most common form of oxidatively damaged DNA, *TP53* and telomerase reverse transcriptase gene mutations, genomic instability, and chromosomal rearrangements, are hallmarks of HCC [60,61]. At the same time, ROS oxidize protein thiols, disrupting enzymatic activity and favoring protein misfolding, which further perpetuates ER stress and activates JNK, NF-κB, and mitogen-activated protein kinase (MAPK) pathways [62]. These signaling cascades promote hepatocyte apoptosis or, paradoxically, survival and proliferation in precancerous clones, depending on the redox threshold and cellular context.

Importantly, ROS themselves are harmful epigenetic regulators that interfere with DNA methylation, histone-modifying enzymes, and RNA modification, accelerating epigenomic re-programming toward oncogenic phenotypes, serving as an exemplar of "mutagenic oxidative stress" [63].

Oxidative stress also orchestrates crosstalk between parenchymal and non-parenchymal cells. Damaged hepatocytes release DAMPs such as mitochondrial DNA and oxidized phospholipids, which engage toll-like receptors (TLRs) on Kupffer cells and recruit infiltrating monocyte-derived macrophages [64]. The resulting production of TNF-α, IL-1β, and IL-6 amplifies ROS generation through NOXs, establishing a vicious circle of oxidative injury and inflammation. In parallel, hydrogen peroxide and 4-HNE activate hepatic stellate cells, triggering the transition to a myofibroblast cell phenotype (i.e., the myofibroblast), capable of producing and secreting large quantities of extracellular matrix compounds, triggering hepatic fibrosis [58,65]. The fibrotic milieu impairs sinusoidal perfusion, resulting in portal hypertension, and exacerbates local hypoxia. It induces HIF-1α, which further stimulates angiogenesis and glycolytic re-programming, additional factors driving HCC growth and metastasis [36].

Furthermore, several gene variants trigger the cellular oxidative stress landscape. Defined variants such as *PNPLA3* I148M, *TM6SF2* E167K, and *MBOAT7* rs641738 aggravate steatosis and mitochondrial dysfunction, enhancing ROS output and diminishing antioxidant capacity [33,40]. Epigenetic alterations, including microRNA dysregulation, further compromise mitochondrial biogenesis and augment oxidative injury [66].

Concurrently, antioxidant defense mechanisms are blunted in the pathogenesis of MASLD. Nuclear factor erythroid 2-related factor 2 (*NRF2*), representing one of the master regulators of redox homeostasis, is functionally repressed by hyper nutrition, leading to insufficient transcription of detoxifying enzymes such as superoxide dismutase 2 (SOD2), catalase (CAT), and glutathione peroxidase (GPX4) [59]. Additionally, glutathione stores are depleted by chronic oxidative challenge, and the failure in the cellular antioxidant defense systems provokes ferroptosis, an iron-dependent, peroxidation-driven cell death. This leads to a rapid decline in hepatocyte function, hepatocyte loss, and compensatory proliferation [59].

In physiological conditions, NRF2 orchestrates a tiered antioxidant defense network that counterbalances the distinct ROS generated in hepatocytes [67]. Superoxide anion, produced by the mitochondrial electron transport chain, NADPH oxidases, and other oxidases, is rapidly dismutated to hydrogen peroxide by cytosolic and mitochondrial superoxide dismutases. Additionally, catalase, glutathione peroxidases, and peroxiredoxins further reduce hydrogen peroxide and lipid hydroperoxides, using glutathione or thioredoxin as electron donors. In MASLD, chronic nutrient excess, insulin resistance, and lipotoxicity increase the generation of superoxide, hydrogen peroxide, and hydroxyl radicals beyond this buffering capacity [68]. Hyper nutrition-associated repression or maladaptive activation of NRF2 leads to inadequate induction of these detoxifying enzymes and phase II antioxidant genes. Concomitant depletion of reduced glutathione and impaired NADPH regeneration compromise the recycling of glutathione peroxidases and peroxiredoxins, thereby favoring lipid peroxidation, protein oxidation, and conditions prone to ferroptosis [69]. Antioxidant vitamins play a crucial role in these pathways. Specifically, vitamin E and other lipophilic antioxidants terminate lipid peroxyl radical chain reactions within membranes and lipid droplets, while vitamin C and other water-soluble vitamins regenerate oxidized vitamin E and support maintenance of the glutathione pool. Consequently, the antioxidant activities of vitamin C and E effectively mitigate hepatocyte injury [70].

Patients with obesity and MASLD often consume energy-dense, micronutrient-poor diets and may exhibit suboptimal circulating levels of vitamins [70]. This further weakens endogenous antioxidant defenses and promotes disease progression. Conversely, nutrient stress states such as fasting or caloric restriction transiently enhance mitochondrial ROS but concomitantly activate NRF2, AMPK, and sirtuin pathways in

mice [71]. This leads to the upregulation of antioxidant and cytoprotective genes, improving redox resilience in an adaptive hormetic response that appears blunted in chronic overnutrition. Understanding how ROS species, enzymatic and non-enzymatic antioxidants, *NRF2* signaling, and vitamin status interact in MASLD is crucial for the rational design of antioxidant- and nutrition-based preventive and therapeutic strategies.

Therapeutic strategies targeting oxidative stress thus constitute an attractive avenue for MASLD-HCC prevention. Lifestyle interventions, bariatric surgery, and insulin-sensitizing agents alleviate lipotoxic substrates and restore mitochondrial function [72]. Fasting-mimicking drugs, such as metformin, activate AMPK and not only reduce DNL but also enhance antioxidant defenses and increasing glucose uptake [73], whereas depletion of *NRF2* or *CYP2E1* protects against steatohepatitis and HCC in preclinical models [74,75]. However, these findings are still under debate, and NRF2 seems to have a dual role in HCC development [76]. Additionally, novel agents such as ferroptosis inhibitors [77], mitochondrial-targeted antioxidants such as the synthetic analogue of coenzyme Q10 known as MitoQ [78], and peroxisome proliferator-activated receptor (PPAR) agonists [79] are under investigation, aiming to interrupt the cycle of ROS-mediated injury that is a driving force of MASLD toward malignancy. Given the uncertainties surrounding our complete understanding of the molecular pathogenesis of disease modulation, the ROS-driven cycle remains pivotal in driving the increasing number of obesity-related MASLD-HCC worldwide. Innovative approaches are crucial in this regard.

4.3 Inflammatory Responses

Chronic, low-grade inflammation is another defining hallmark that drives the progression from lipid-laden hepatocytes in MASLD towards liver fibrosis, its hemodynamic complications, and HCC. As discussed above, steatotic hepatocytes act as both initiators and amplifiers of this inflammatory cascade by releasing DAMPs, saturated fatty acid metabolites, and triggering oxidative stress. DAMPs are recognized by pattern-recognition receptors (PRRs) such as TLR4 and nucleotide-binding oligomerization domain-like receptor family pyrin domain containing-3 (NLRP3) located on resident Kupffer cells and recruited monocyte-derived macrophages [43]. The activation of these receptors triggers downstream signaling through NF-κB and MAPKs, leading to the transcription of pro-inflammatory cytokines, reinforcing insulin resistance, stimulating the activation of hepatic stellate cells, and perpetuating hepatocellular injury.

The gut-liver axis further enhances hepatic inflammation during MASLD. High-fat, low-fiber diets promote gut dysbiosis and increased intestinal permeability, facilitating the translocation of lipopolysaccharide (LPS) into the portal circulation [80]. LPS acts as an endotoxin that binds to TLR4 on Kupffer cells and sinusoidal endothelial cells, intensifying cytokine release and ROS production [80]. Simultaneously, adipose-tissue macrophages in obese individuals secrete TNF-α and IL-6 that reach the liver via the systemic circulation, highlighting the complexity of a metabolic low-grade, chronic, subclinical systemic inflammatory state (metaflammation).

Inflammasome activation is a crucial amplifier of sterile inflammation in MASLD. Excess saturated fatty acids, cholesterol crystals, and ROS prime and activate NLRP3, leading to caspase-1-mediated cleavage of pro-IL-1β into its mature, bioactive forms [81]. These cytokines drive leukocyte recruitment to the liver and promote hepatocyte pyroptosis, releasing additional DAMPs and reinforcing the inflammatory circuit [82,83]. *NLRP3*-deficient mouse models exhibit attenuation of steatohepatitis and reduced HCC burden, highlighting the translational relevance of inflammasome blockade [84].

Adaptive immune responses become dysregulated as MASLD progresses. Lipid antigens presented by thymocyte antigen CD1d molecules activate hepatic invariant natural killer T (iNKT) cells, initially having protective effects through IL-4 and IL-10 secretion but later adopting a pro-fibrogenic phenotype

characterized by interferon-γ (IFN-γ) and TNF-α production [85]. Th17 cell expansion and elevated IL-17 levels correlate with liver fibrosis stages and tumor growth, while cytotoxic $CD8^+$ T cells undergo exhaustion due to persistent antigenic stimulation, up-regulation of programmed cell-death-1 (PD-1), and an immunosuppressive cytokine milieu [86]. Regulatory T cells (Tregs) accumulate in the steato-fibrotic liver, secreting transforming growth factor-β (TGF-β) and IL-10, thereby dampening anti-tumor immunity and facilitating oncogenesis [87]. This evolving immunological landscape supports the concept of "immune senescence" in MASLD-HCC, which might explain the reduced efficacy of immune-checkpoint inhibitors in this numerically increasing patient population [88].

Cytokine-driven cross talks between parenchymal and non-parenchymal cells accelerate fibrogenesis and angiogenesis. IL-6 and TNF-α activate Janus kinase (JAK)-Signal transducer and activator of transcription (STAT) pathways in hepatocytes, promoting compensatory proliferation and survival of dysplastic cell clones [89]. At the same time, TGF-β released by Kupffer cells and platelets stimulates hepatic stellate cell transdifferentiation into myofibroblasts, depositing extracellular matrix that remodels the sinusoidal architecture and promotes HIF-1α-mediated vascular endothelial growth factor (VEGF) expression. The resulting neo-vasculature supplies nutrients to emerging tumor nodules while enabling immune-cell trafficking that is skewed toward tumor-promoting subsets.

Similar to the generation of ROS, genetic factors in humans can predispose to inflammation. The *PNPLA3* I148M variant hampers lipid-droplet remodeling, leading to increased lipotoxic stress and heightened cytokine production. *TM6SF2* and *MBOAT7* polymorphisms also exacerbate steatohepatitis through dysfunctional lipid handling and altered membrane composition [33,40]. Epigenetic modifications, including DNA methylation of anti-inflammatory genes and microRNA dysregulation such as miR-155 and miR-34a, further perpetuate a pro-inflammatory state in hepatocytes [90]. The multitude of factors impacting the inflammatory responses in MASLD illustrates the notion that this disease is triggered by a dynamic, multi-cellular network that links metabolic dysfunction, lipotoxicity, fibrogenic remodeling, and immune evasion, ultimately creating an environment conducive to hepatocarcinogenesis.

These pathogenic models pave the way for active investigation of therapeutic approaches targeting inflammatory pathways. Lifestyle modification and bariatric surgery reduce adipose-derived cytokines and improve gut barrier function. Several pharmacologic agents such as glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., exenatide, dulaglutide, liraglutide, and semaglutide), PPAR agonists (e.g., clofibrate, gemfibrozil, and fenofibrate), and statins, exhibit anti-inflammatory properties alongside metabolic benefits. Specific inhibitors of NLRP3, TLR4 antagonists, and monoclonal antibodies against IL-1β or IL-17 are being explored in early-phase trials [79,91]. Notably, the dual GLP-1/GIP agonist tirzepatide and the FXR agonist obeticholic acid have demonstrated histologic improvements that correlate with reduced inflammatory markers, offering hope for disease modification [92,93].

4.4 Immunological Milieu and Immunometabolism

Obesity-associated MASLD creates a chronically inflamed, immunosuppressed hepatic microenvironment, in which innate immune cells undergo profound metabolic rewiring. Activated Kupffer cells and infiltrating monocyte-derived macrophages shift toward an M1-like, glycolysis-dominated phenotype that promotes production of TNF-α, IL-1β and IL-6, further promoting insulin resistance and hepatocyte injury [43]. However, under conditions of chronic obesity-related metabolic dysfunction, these macrophages acquire lipid droplets, upregulate PPAR-γ, and transition to an M2-like state that secretes TGF-β and VEGF, promoting hepatic fibrogenesis and neoangiogenesis [94]. Neutrophils, mobilized by chemokines such as C-X-C motif chemokine ligand-1 (CXCL1) and -2 (CXCL2), generate myeloperoxidase-derived oxidants and

neutrophil extracellular traps, but prolonged exposure to lipotoxic mediators induces immunosuppressive granulocytic myeloid-derived suppressor cells that dampen anti-tumor T-cell responses [95].

Natural killer (NK) cells and invariant natural killer T (iNKT) cells play pivotal roles in tumor surveillance, mediating antitumor functions through cytotoxicity and cytokine secretion. NK cells can prevent the development of liver fibrosis by exerting cytolytic activity against hepatic stellate cells [96]. However, in experimental models of SLD, NK cells are activated and trigger a pro-inflammatory cytokine milieu, thereby promoting MASLD development [97]. Moreover, excess free fatty acids downregulate activating receptors, such as natural cytotoxicity triggering receptor (NKp46) and natural killer group 2 member D (NKG2D) and force a metabolic switch from oxidative phosphorylation to aerobic glycolysis, limiting cytolytic capacity [78]. Concurrently, increased expression of PD-1 and the T-cell immunoreceptor with immunoglobulin and ITIM domains (TIGIT) drives an exhausted phenotype that permits clonal expansion of dysplastic hepatocytes [98].

Adaptive immunity is equally reshaped by metabolic cues. Steatotic antigen-presenting cells favor differentiation of naïve $CD4^+$ T cells toward pro-inflammatory Th17 cells via IL-6 and IL-23. Chronic antigenic load skews $CD8^+$ T cells toward an exhausted, PD-1^+/T-cell immunoglobulin and mucin domain-containing 3 (TIM-3)$^+$ state characterized by impaired interferon-γ production and reliance on fatty-acid oxidation for survival [99–101]. Tregs accumulate in advanced MASLD and early HCC, triggered by TGF-β and lipid-mediated activation of the transcription factor FOXP3, consuming local glucose, thereby establishing a metabolically restrictive and immunosuppressive niche [102].

Immunometabolism also influences non-cellular components of the tumor microenvironment. Hypoxia arising from sinusoidal capillarization activates HIF-1α, inducing glycolytic enzymes and lactate transporters in both hepatocytes and immune cells. Extracellular lactate acidifies the milieu, further suppressing effector T-cell function while stimulating increased glycolysis and lactate production, M2 polarization, and angiogenesis [94]. In parallel, cholesterol crystals and oxidized phospholipids accumulate in hepatic stellate cells and dendritic cells, triggering NLRP3 inflammasome activation and perpetuating IL-1β release [103]. Excessive intracellular cholesterol reduces membrane fluidity and blunts antigen presentation, weakening anti-tumor immunity [104]. In addition, several genetic variants discussed above aggravate steatosis and modulate immune infiltration. Specifically, the *PNPLA3* I148M polymorphism promotes lipid droplet retention in hepatocytes and macrophages, increasing lipotoxic stress and cytokine production in humans. On the other hand, *TM6SF2* and *MBOAT7* variants change membrane lipid composition, affecting TLR signaling thresholds and inflammasome sensitivity in humans. These gene polymorphisms could impact the variability in immune responses and cancer risk among the MASLD population [33,40].

The overall impact of these changes is an immune environment characterized by a contradiction, in which increased inflammatory signals exist alongside impaired tumor immunosurveillance. This allows premalignant clones to arise, escape immune detection and thrive. This duality has significant implications, as recent studies indicate that HCC related to MASLD shows a poorer response to immune checkpoint inhibitors [105]. This may be attributed to the high presence of exhausted T cells, immunosuppressive myeloid cell populations, and anergy induced by various metabolites.

Therapeutic strategies aimed at recalibrating immunometabolism are of considerable clinical interest. Lifestyle interventions and metabolic bariatric surgery decrease circulating free fatty acids and restore mitochondrial fitness in immune cells, partially reversing exhaustion signatures. Pharmacologic activators of AMPK (e.g., metformin) and inhibitors of mTOR complex 1 (e.g., rapalogs) can re-establish oxidative metabolism, enhance memory T-cell formation, and reduce M2 macrophage polarization. Similarly, synthetic and semi-synthetic FXR agonists (e.g., obeticholic acid, fexaramine, and chenodeoxycholic acid) and GLP-1

receptor agonists indirectly modulate the immune microenvironment by reducing steatosis and gut-derived endotoxemia due to modification of the gut microbiota [106]. Moreover, novel agents that block IL-17 and TNF-α, which amplify and perpetuate liver damage resulting from NLRP3 activation, or that deplete myeloid-derived suppressor cells, in combination with immune-checkpoint inhibitors, may overcome the metabolic and immunological barriers unique to MASLD-HCC [107]. It is expected that this ever-expanding therapeutic arsenal may contribute to improving our understanding of the complex immunological milieu and immunometabolism in the field of obesity-related MASLD-HCC.

4.5 Regulation of Signaling Pathways Such as mTOR, AMPK, and NF-κB, and How They Influence Processes Like Cell Proliferation, Apoptosis, Autophagy, Migration, and Differentiation

As discussed, metabolic overload in obesity-associated MASLD disrupts nutrient-sensing and stress-response signaling networks. AMPK, mTOR, and NF-κB pathways are key regulators that integrate metabolic processes with cellular fate decisions [26–28]. Based on this important functionality, it is evident that these pathways can accelerate hepatocarcinogenesis when chronically dysregulated.

The multi-protein complex mTORC1, which includes the kinase mTOR, is consistently activated in steatotic hepatocytes due to excess amino acids, insulin, and growth factors [108]. This leads to the phosphorylation of S6 kinase and the eukaryotic translation initiation factor 4E-binding protein (4E-BP1), promoting cap-dependent translation of cyclin D1, c-Myc, and other drivers of G1/S progression, resulting in uncontrolled cell proliferation [108]. Persistent mTORC1 signaling also suppresses autophagy, including lipophagy, by phosphorylating UNC51-like autophagy-activating kinase 1 (ULK1) [108]. This limits the ability of the cell to clear damaged mitochondria and excess lipid droplets, leading to increased oxidative stress and genomic instability. Additionally, mTORC1 crosstalk with HIF-1α promotes glycolytic flux and VEGF expression, enhancing angiogenesis and migration of premalignant hepatocytes [109].

On the other hand, AMPK acts as an energy sensor that is typically activated by rising AMP/ATP ratios. In MASLD, lipotoxicity and insulin resistance reduce its activity, removing a critical restraint on mTORC1 and on DNL via SREBP-1c. Reduced AMPK signaling leads to diminished fatty acid oxidation and autophagic flux, allowing for triglyceride accumulation and ER stress. This weakens p53-mediated checkpoints that would otherwise induce apoptosis in damaged cells [110,111]. In line with these findings, therapeutic reactivation of AMPK through caloric restriction, exercise, or metformin restores mitochondrial biogenesis and rescues autophagy, reducing ROS, limiting mutation burden, and repressing tumor initiation in preclinical MASLD-HCC models [46]. In all these processes, NF-κB serves as a central hub linking metabolic stress to inflammatory and survival pathways [94]. DAMPs, LPS, and saturated fatty acids engage TLR4 and IL-1 receptor signaling, leading to the induction of TNF-α, IL-6, and anti-apoptotic proteins, such as B-cell lymphoma-extra-large (Bcl-xL) and cellular FLICE-inhibitory protein (c-FLIP), protecting injured hepatocytes from apoptosis, promoting survival, and sustaining compensatory proliferation and fibrosis. NF-κB also up-regulates matrix metalloproteinases (MMPs) and chemokines that facilitate extracellular matrix remodeling, cell migration, tumor invasion, and metastasis [112].

It should be noted that these pathways interact bidirectionally. mTORC1 activation inhibits autophagy, increasing ROS, which activates NF-κB, supporting survival and inflammation. Conversely, AMPK phosphorylation of TSC complex subunit 2 (TSC2 or tuberin) and regulatory associated protein of mTOR (RAPTOR) restrains mTORC1, while AMPK-mediated phosphorylation of p65 dampens NF-κB transcriptional activity, highlighting the tumor-suppressive role of AMPK [113]. Dysregulated lipid species such as diacylglycerols and ceramides modulate these crosstalk nodes by activating protein kinase C or by

inhibiting AKT, tipping the balance toward either unchecked proliferation or lipotoxic apoptosis depending on the cellular context [114].

Studies in zebrafish have shown that cell differentiation is also influenced by these pathways. mTORC1 is involved in hepatocyte-to-cholangiocyte transdifferentiation and cholangiocyte-to-hepatocyte transdifferentiation [115]. It is most likely that this reprogramming during tissue injury is mediated through Notch and Wnt/β-catenin pathways, contributing to the emergence of progenitor-like HCC subtypes with aggressive behavior [116]. On the other hand, AMPK impacts histone deacetylation and gene expression, thereby contributing to the global regulation of protein acetylation and connecting epigenetic chromatin modifications with the cellular metabolic state [117]. All these processes interfere with NF-κB signaling that up-regulates epithelial-mesenchymal transition (EMT) transcription factors, such as Snail and Twist, driving loss of epithelial polarity, and further driving cell migration and invasion, thereby promoting the acquisition of invasive traits [118].

Collectively, the aberrant activation of mTOR and NF-κB coupled with AMPK deficiency orchestrates a molecular environment that promotes hepatocyte proliferation, suppresses apoptosis and autophagy, enhances migration and dedifferentiation, and drives the progression from MASLD to HCC. Consequently, the rebalancing of this signaling triad is crucial for reducing the increasing burden of obesity-related HCC and pharmacological modulation of these axes is a rational strategy for MASLD-HCC prevention and therapy. mTOR inhibitors like everolimus show anti-proliferative effects but are limited by feedback activation of AKT. Dual PI3K/mTOR or mTORC1/2 inhibitors, and intermittent dosing schedules, are being explored to mitigate resistance [119]. AMPK activators, including metformin and the mitochondrial complex I inhibitor Imeglimin, are consolidated approaches or emerging therapies for the management of diabetes [120,121]. It is logical to speculate that the combination of these drugs with immune checkpoint inhibitors (ICIs) will be potentially effective in counteracting hepatic carcinogenesis, especially of MASLD-related HCC. Moreover, NF-κB blockade through IKKβ inhibitors or proteasome inhibitors can restore apoptotic sensitivity. However, systemic immunosuppression remains a concern [122]. Precision approaches that target liver-specific NF-κB components or upstream sensors, such as TLR4 antagonists and NLRP3 inhibitors, may offer safer alternatives.

4.6 Angiogenesis

As discussed earlier, the metabolic dysfunction associated with obesity-associated MASLD requires that hepatocytes and non-parenchymal cells persistently experience lipotoxicity and oxidative stress. Physiologically, the metabolic zonation of the liver is an important feature that helps maintain whole body homeostasis [123]. However, during progressive MASLD zonation is disturbed, leading to zones of micro-hypoxia that act as powerful inducers of intra- and extrahepatic neoangiogenesis [124]. Accumulated fat droplets enlarge hepatocytes, compress sinusoidal spaces, and disrupt liver perfusion, stabilizing transcription factors HIF-1α and HIF-2α, which up-regulate vascular endothelial growth factor-A (VEGF-A), angiopoietin-2, and platelet-derived growth factor-BB (PDGF-BB). These mediators promote the sprouting of aberrant neovessels that, while initially compensating for oxygen deprivation, will ultimately provide a vascular scaffold supporting the clonal expansion of dysplastic hepatocytes [125]. Kupffer cells and infiltrating monocyte-derived macrophages amplify this response by producing TNF-α and IL-6, cytokines that further enhance HIF-1α activity and stimulate VEGF secretion. Meanwhile, ROS generated by dysfunctional mitochondria oxidize lipids and activate NF-κB, further driving proangiogenic gene expression. Activated hepatic stellate cells triggered by TGF-β and lipotoxic aldehydes, transdifferentiate to myofibroblasts and secrete type I collagen and laminin, promote the capillarization of sinusoids, narrowing

the fenestrations of liver sinusoidal endothelial cells (LSECs), and promoting hypoxia, establishing a self-perpetuating loop of liver fibrosis and neoangiogenesis [65,126]. Under these conditions, lipid-laden LSECs lose their anti-angiogenic phenotype and express adhesion molecules like vascular cell adhesion molecule 1 (VCAM-1) and intracellular adhesion molecule 1 (ICAM-1), facilitating recruitment of proangiogenic neutrophils and myeloid-derived suppressor cells (Fig. 2) [127].

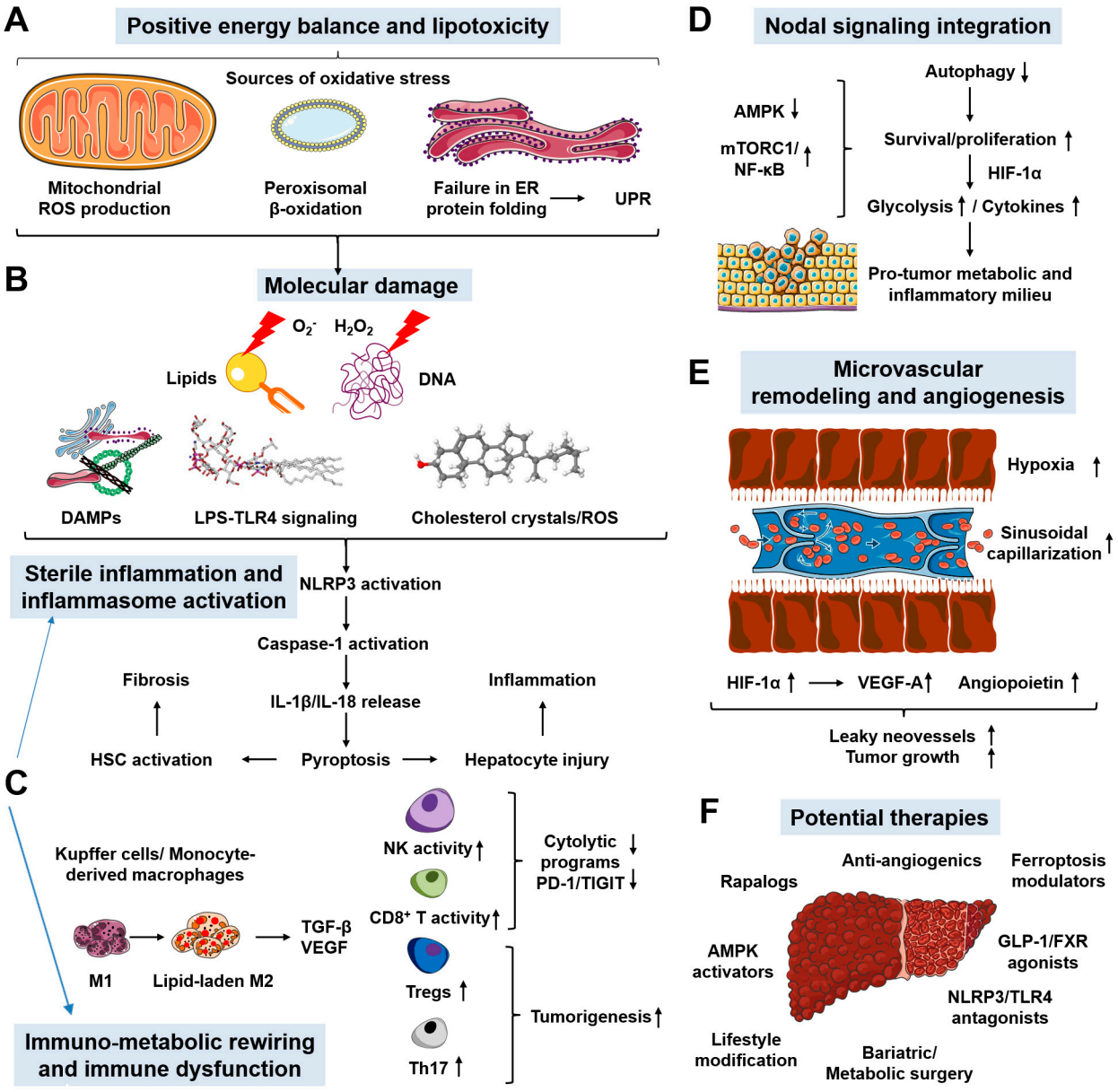

Figure 2: Redox-inflammation-immunometabolism feedback loops that enable fibrogenesis, angiogenesis, and immune escape in obesity-related MASLD-HCC. (**A**) Caloric excess and lipotoxicity increase reactive oxygen species (ROS) production from mitochondria (electron leak at complexes I/III), peroxisomal β-oxidation of very-long-chain fatty acids, and failure in endoplasmic reticulum (ER) protein folding and unfolded protein response (UPR). The resulting superoxide and hydrogen peroxide initiate lipid peroxidation and DNA damage. (**B**) Damage-associated molecular patterns (DAMPs), lipopolysaccharide (LPS)/TLR4 signaling, and cholesterol crystals/ROS prime and activate NLRP3, leading to caspase-1 activation, IL-1β/IL-18 release, and pyroptosis, which

amplify hepatocyte injury and stellate cell activation. (**C**) Kupffer cells/monocyte-derived macrophages shift from glycolytic M1-like activation toward lipid-laden M2-like states that secrete TGF-β/VEGF. NK and $CD8^+$ T cells downregulate cytolytic programs and exhibit PD-1/TIGIT-driven exhaustion. Tregs and Th17 cells accumulate, tipping the balance toward tumor promotion. (**D**) Reduced AMPK activity and sustained mTORC1/NF-κB signaling suppress autophagy, promote survival/proliferation, and upregulate HIF-1α-dependent glycolysis and cytokines, locking tissues into a pro-tumor metabolic and inflammatory state. (**E**) Sinusoidal capillarization and hypoxia stabilize HIF-1α/2α in hepatocytes and non-parenchymal cells, inducing VEGF-A and angiopoietins. The resulting tortuous, leaky neovessels facilitate tumor growth, immune evasion, and heterogeneous drug delivery. (**F**) Lifestyle interventions, bariatric/metabolic surgery, AMPK activators (e.g., metformin), rapalogs, NLRP3/TLR4 antagonists, GLP-1/FXR agonists, ferroptosis modulators, and anti-angiogenics (e.g., anti-VEGF) target different nodes in the loop. Additionally, a rational combination of these strategies may be helpful in some cases in MASLD-HCC therapy. This original illustration was created using Servier Medical ART (SMART) and is licensed under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

Moreover, the newly formed vessels in tumors are structurally and functionally abnormal, being tortuous, poorly covered by pericytes, and hyper-permeable, leading to irregular perfusion and a heterogeneous tumor microenvironment [128]. This "vascular chaos" promotes the selection of aggressive clones, facilitates metastatic dissemination, and hinders drug delivery. The metabolic environment rich in free fatty acids and lactate impairs dendritic cell maturation and promotes immune tolerance. This partially explains why immunotherapy appears to be less effective in MASLD-HCC compared to HCC arising in the context of chronic liver disease due to viral etiology [105].

Nevertheless, angiogenesis in obesity-driven MASLD represents the vascular arm of a broader maladaptive response to lipotoxic hypoxia. It integrates signals from nutrient-sensing pathways, innate immunity, and fibrogenesis to create a pro-tumor niche. Because neovascularization promotes the expansion of malignant hepatocytes and shapes an immune-evasive microenvironment, successful interception of the obesity-MASLD-HCC cascade will require strategies that simultaneously target metabolic dysfunction, suppress inflammation, reduce portal pressure, and remodel aberrant vasculature [129].

Therapeutically, angiogenesis is a prime target in advanced diseases. Bevacizumab, an anti-VEGF monoclonal antibody, combined with the programmed death-ligand-1 inhibitor atezolizumab, is a first-line regimen for the treatment of patients with unresectable HCC [130]. However, the efficacy of this immunotherapy in HCC with non-viral etiologies such as MASLD is less effective, possibly because VEGF blockade does not fully reverse the immune-metabolic suppression characteristic of this etiology [131]. Multi-kinase inhibitors such as sorafenib, lenvatinib, and regorafenib simultaneously inhibit VEGF receptors, PDGF receptors, and RAF kinases. However, their benefits are counterbalanced by significant adverse effects, especially in obese patients with metabolic comorbidities [132]. Combination approaches that associate anti-angiogenic agents with AMPK activators or NLRP3 inflammasome inhibitors might be a rational strategy for simultaneously correcting both vascular and inflammatory derangements, although this needs to be explored experimentally.

5 Implications for Therapy

Treatment options for obesity and MASLD have been extensively discussed elsewhere [11,133]. Here, we will specifically focus on the challenges posed by obesity-related MASLD-HCC. These challenges include delayed diagnosis resulting from insufficient surveillance, limited access to curative interventions such as tumor ablation, surgical resection, and liver transplantation, as well as diminished responsiveness to certain treatments used in advanced disease states. These treatments include locoregional therapies like

transarterial chemoembolization (TACE) and transarterial radioembolization (TARE), as well as systemic therapies like ICIs such as atezolizumab and durvalumab, often used in combination with other drugs like bevacizumab or tremelimumab, and tyrosine kinase inhibitors (TKIs) such as sorafenib and regorafenib.

5.1 Late Diagnosis

MASLD-HCC is often detected at later stages because surveillance programs do not consistently include patients without cirrhosis [134]. Many patients are not included in surveillance programs, leading to diagnosis at more advanced stages (Barcelona Clinic Liver Cancer C or D), which limits options for curative treatment [135].

5.2 Limited Access to Curative Treatment

Patients with MASLD-HCC have a higher risk of post-surgical complications, including increased morbidity and mortality, which may limit eligibility for surgical resection [136]. The presence of the full-blown metabolic syndrome negatively impacts post-operative outcomes [137], and malnutrition, commonly observed in this patient population, is a further contributor to increased post-operative risk.

5.3 Nutrition

Nutrition plays a critical yet often overlooked role in the management of MASLD-cirrhosis. Addressing nutritional deficiencies is particularly important for patients with MASLD-HCC who are awaiting interventions to slow disease progression or are being prepared for curative treatments such as surgical resection or liver transplantation [138].

5.4 Metabolic Bariatric Surgery

There are no clear guidelines on the use of metabolic bariatric surgery in patients with MASLD-cirrhosis awaiting liver transplantation. Furthermore, patients with MASLD-HCC have a higher mortality rate on the waiting list [139]. The possible utilization of metabolic bariatric surgery in achieving hepatic recompensation among those with MASLD-cirrhosis is gaining increasing attention [140]. While sleeve gastrectomy can improve candidacy in morbidly obese patients awaiting transplantation [141], it remains to be assessed whether MBS is a reasonable option among well-selected individuals with compensated MASLD-HCC and without significant portal hypertension.

5.5 Immunotherapy

Accumulating evidence indicates that chronic sterile low-grade inflammation of metabolic origin in the context of MASLD serves not only as the primary trigger of malignant transformation of hepatocyte lineage, but also reshapes the immune background. This leads to immune system exhaustion and favors the loss of cancer immune surveillance [142]. These biological phenomena explain why immunotherapy may be less effective in patients with MASLD-related HCC compared to those with HCC due to other etiologies, owing to immune alterations specific to MASLD [105].

In summary, obesity-related MASLD-HCC presents unique clinical challenges. These challenges include frequent late-stage diagnoses and limited availability of curative interventions such as surgical resection or transplantation. Advanced therapeutic modalities, like TACE, transarterial radioembolization (TARE), immune checkpoint inhibitors, and tyrosine kinase inhibitors, often show reduced efficacy in this population. The lack of adequate surveillance, especially in non-cirrhotic individuals, leads to delayed detection and limits treatment options. Metabolic syndrome and malnutrition increase perioperative risk

and hinder postoperative recovery. However, nutritional optimization before major interventions is often overlooked and remains essential. Dietary approaches, such as intermittent fasting, may improve insulin sensitivity and reduce hepatic steatosis, potentially impacting tumor metabolism and immune response, although long-term safety data are scarce. Current guidelines on bariatric surgery in MASLD-cirrhosis transplant candidates are unclear, but sleeve gastrectomy may offer advantages in specific cases. The use of metabolic surgery in compensated MASLD-HCC is still being studied. Furthermore, chronic inflammation from metabolic dysfunction impairs the effectiveness of immunotherapy by promoting immune exhaustion and reducing cancer surveillance.

6 Conclusions and Future Direction

Patients with obesity-related MASLD-HCC often present with advanced-stage disease, multiple comorbidities, and increased risk of post-operative complications. To counteract this unfavorable clinical scenario, the research agenda for MASLD-HCC prioritizes improved risk stratification [143] and early disease detection through the development of enhanced screening and surveillance methods.

In line with emerging expert suggestions, surveillance may be extended—beyond cirrhosis—to a portion of the elderly with MASLD who have non-invasively identified advanced fibrosis [6,144–146]. In this context, integrated risk scores that combine metabolic risk factors, genetic information, and non-invasive fibrosis markers could be implemented to identify high-risk patients who should undergo HCC surveillance with an improved cost-benefit ratio. Blood-based biomarkers, imaging advancements, and artificial intelligence (AI)-assisted risk prediction tools offer the potential to enhance HCC surveillance in MASLD.

Key areas of investigation include understanding the specific molecular mechanisms and tumor microenvironment characteristics of (obesity-related)-MASLD-HCC, refining non-invasive diagnostic techniques, and identifying new therapeutic targets. Advancing innovative therapies like nanotechnologies and personalized medicine, which were not discussed in this review, is crucial, especially considering the limited effectiveness of currently available immune checkpoint inhibitors. Additionally, there are fewer approved pharmacological treatments for MASLD-HCC compared to HCC from other causes, highlighting the significance of supportive management strategies like weight reduction, increased physical activity, improved nutrition, comprehensive management of dysmetabolic conditions (such as type 2 diabetes, dyslipidemia, and arterial hypertension), and portal hypertension in caring for patients with obesity-related MASLD-HCC.

Ongoing clinical trials are anticipated to address the unique pathophysiology of MASLD-related HCC to optimize treatment strategies. Simultaneously, research efforts should concentrate on developing new agents that target MASH/MASLD directly, such as resmetirom and semaglutide [147,148], even though their roles in MASLD-HCC are still unclear.

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List of Abbreviations Used

4E-BP1	Eukaryotic translation initiation factor 4E-binding protein
4-HNE	4-hydroxynonenal
ACC	Acetyl-CoA carboxylase
AKT	Protein kinase B
AMPK	AMP-activated protein kinase
BCLC	Barcelona Classification of Liver Cancer
BMI	Body mass index
CAT	Catalase
ChREBP	Carbohydrate-responsive element-binding protein
CLD	Chronic liver disease
CYP2E1	Cytochrome P450 2E1
CXCL1/2	C-X-C motif chemokine ligand-1/2
DALY	Disability-adjusted life year
DAMP(s)	Danger-associated molecular pattern(s)
DNL	*De novo* lipogenesis
EMT	Epithelial–mesenchymal transition
ER	Endoplasmic reticulum
FOXP3	Forkhead-box-protein 3
FPG	Fasting plasma glucose
FXR	Farnesoid X receptor
GCKR	Glucokinase regulator protein
GPX4	Glutathione peroxidase
HCC	Hepatocellular carcinoma
HIF-1α	Hypoxia-inducible factor-1α
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HSC(s)	hepatic stellate cell(s)
ICAM	Intercellular adhesion molecule 1
ICI(s)	Immune checkpoint inhibitor(s)
iNKT	Invariant natural killer T
IL	Interleukin
IFN-γ	Interferon-γ
JNK	c-Jun N-terminal kinase
LPS	Lipopolysaccharides
LSEC(s)	Liver sinusoidal endothelial cell(s)
MAFLD	Metabolic dysfunction-associated fatty liver disease
MAPK(s)	Mitogen-activated protein kinase(s)
MASH	Metabolic dysfunction-associated steatohepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
MASLD-HCC	Metabolic dysfunction-associated steatotic liver disease-related hepatocellular carcinoma
MBOAT7	Membrane-bound O-acetyltransferase domain-containing protein 7
MBS	Metabolic bariatric surgery
MDA	Malondialdehyde
MDSC(s)	Myeloid-derived suppressor cell(s)
mTOR	Mechanistic target of rapamycin
mTORC1	Mechanistic target of rapamycin complex 1
NAFLD	Nonalcoholic fatty liver disease
NHANES	National Health and Nutrition Examination Survey
NF-κB	Nuclear factor-κB

NLRP3	Nucleotide-binding oligomerization domain-like receptor family pyrin domain containing-3
NOX	NADPH oxidase
NRF2	Nuclear factor erythroid 2-related factor 2
PD-1	Programmed cell-death-1
PD-L1	Programmed death-ligand-1
PDGF-BB	Platelet-derived growth factor-BB
PLC	Primary liver cancer
PNPLA3	Patatin-like phospholipase domain-containing 3
PPAR	Peroxisome proliferator-activated receptor
PRR(s)	Pattern-recognition receptor(s)
RAPTOR	Regulatory-associated protein of mTOR
ROS	Reactive oxygen species
S6K	Ribosomal protein-S6 kinase
SDI	Socio-demographic index
SLD	Steatotic liver disease
SOD2	Superoxide dismutase 2
SREBP-1c	Sterol regulatory element-binding protein-1c
TACE	Transarterial chemoembolization
TARE	Transarterial radioembolization
TGF-β	Transforming growth factor-β
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIM3	T-cell immunoglobulin and mucin-domain containing-3
TKI(s)	Tyrosine kinase inhibitors
TLR(s)	Toll-like receptor(s)
TM6SF2	Transmembrane 6 superfamily, member 2
TNF-α	Tumor necrosis factor-α
Tregs	Regulatory T cells
ULK	UNC-51-like autophagy-activating kinase 1
UPR	Unfolded protein response
VCAM	Vascular cell adhesion molecule 1
VEGF	Vascular endothelial growth factor
XO	Xanthine oxidase

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