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Hepatic growth hormone - JAK2 - STAT5 signalling: Metabolic function, non-alcoholic fatty liver disease and hepatocellular carcinoma progression

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ABSTRACT

The rising prevalence of obesity came along with an increase in associated metabolic disorders in Western countries. Non-alcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of the metabolic syndrome and is linked to primary stages of liver cancer development. Growth hormone (GH) regulates various vital processes such as energy supply and cellular regeneration. In addition, GH regulates various aspects of liver physiology through activating the Janus kinase (JAK) 2- signal transducer and activator of transcription (STAT) 5 pathway. Consequently, disrupted GH - JAK2 - STAT5 signaling in the liver alters hepatic lipid metabolism and is associated with NAFLD development in humans and mouse models. Interestingly, while STAT5 as well as JAK2 deficiency correlates with hepatic lipid accumulation, recent studies suggest that these proteins have unique ambivalent functions in chronic liver disease progression and tumorigenesis. In this review, we focus on the consequences of altered GH - JAK2 - STAT5 signaling for hepatic lipid metabolism and liver cancer development with an emphasis on lessons learned from genetic knockout models.

Abbreviations: ACC, Acetyl-CoA carboxylase; Akt, v-Akt murine thymoma viral oncogene homolog; ALS, Acid labile subunit; ATP, Adenosin triphosphate; CCL_4, Tetrachloride; CDK, Cyclin-dependent kinase; cJun, Cellular Jun; DEN, Diethylnitrosamine; EGF, Epidermal growth factor; ERK, Extracellular signal-regulated kinase; FA, Fatty Acid; FAS/Fasn, Fatty acid synthase; Fatp1, Fatty acid transport protein 1; FGF, Fibroblast growth factor; GC, Glucocorticoids; GH, Growth Hormone; GHR, Growth hormone receptor; GR, Glucocorticoid receptor; GST, Glutathione S-transferase; HBV, Hepatitis B virus; HCV, Hepatitis C virus; HGF, Hepatocyte growth factor; HCC, Hepatocellular carcinoma; IGF, Insulin-like growth factor; JAK, Janus kinase; JNK, c-Jun N-terminal kinase; MAPK, Mitogen-activated protein kinase; mTOR, Mammalian target of rapamycin; NAFL, Non-alcoholic fatty liver; NAFLD, Non-alcoholic fatty liver disease; NASH, Non-alcoholic steatohepatitis; NOX, NADPH-Oxidase; PI3K, Phosphoinositide 3-kinase; PDGF, Platelet-derived growth factor; PPARγ, Peroxisome proliferator-activated receptor gamma; SCD, Stearoyl-CoA desaturase; RAS, Rat sarcoma; RB, Retinoblastoma protein; SOCS, Cytokine signalling; ROS, Reactive oxygen species; SH2, Src homology 2; SREBP, sterol regulatory element-binding protein; STAT, Signal transducer and activator of transcription; T2D, Type 2 diabetes; TGF-β, Transforming growth factor beta; VEGF, Vascular endothelial growth factor; WAT, White adipose tissue; WNT, Wingless/Integrated

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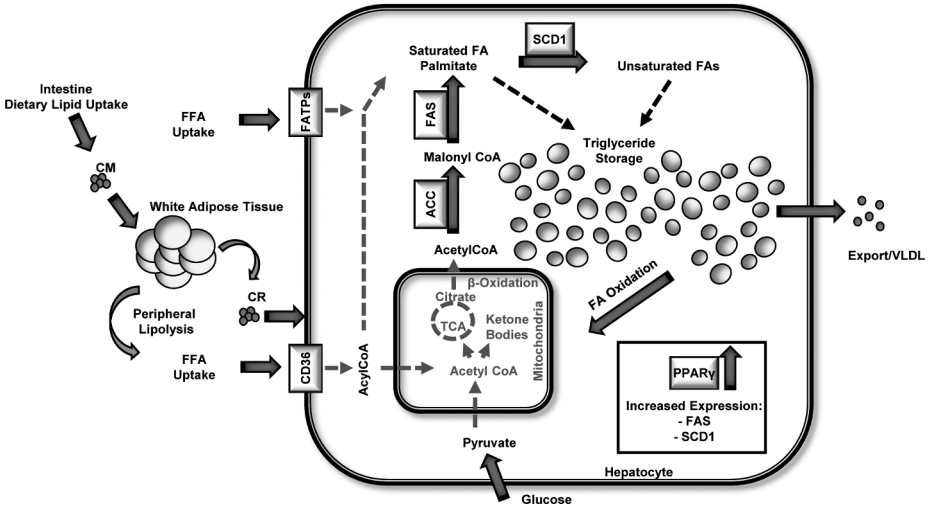

Fig. 1. Overview on Hepatic Lipid Metabolism. Dietary lipids are ingested within the intestine to form chylomicron (CM) lipoproteins. CMs are released into the bloodstream to deliver triglycerides to extrahepatic tissues such as adipose tissue. CM remnants (CR) are taken up by the liver. Under fasting conditions, lipolysis is induced in adipose tissue resulting in free fatty acid (FFA) release. FFAs are absorbed by the liver through fatty acid (FA) transporters such as FATP and CD36. Absorbed FAs are converted into acyl- CoA, which is transported into mitochondria and oxidized to form acetyl-CoA, which can be used in the TCA cycle or for β-ketone synthesis. Under fed conditions, *de novo* lipogenesis takes place. Palmitate is newly synthesised from glucose-derived acetyl-CoA by ACC and FAS. Desaturation of FAs is performed by SCD1. Newly formed FAs are further esterified to triglycerides. Triglycerides are either stored in lipid droplets within hepatocytes or loaded into very low density lipoproteins (VLDL), which are released into the bloodstream. TCA: Citric acid cycle; ACC: Acetyl-CoA carboxylase; FAS: Fatty acid synthase; SCD1: Stearoyl-CoA desaturase 1; CD36: Fatty acid transporter; FATP: Fatty acid transport proteins; PPAR: peroxisome proliferator-activated receptor.

1. Introduction

Metabolic homeostasis is vital for organisms to satisfy energy demands and to maintain overall physiologic stability. The liver is one of the body's key detoxifying and metabolic organs, which has the ability to control protein, lipid and carbohydrate metabolism via the absorption, conversion, storage and release of various substrates and metabolites [1–3]. Disturbances in this control unit can lead to the development of various liver diseases stretching from hepatic steatosis to more malignant liver pathologies such as hepatocellular carcinoma (HCC) [4].

Growth hormone (GH) is an important modulator of energy metabolism and continuously regulates several vital processes such as regeneration, cell proliferation and substrate utilisation [5–7]. GH mainly signals via the Janus kinase (JAK) 2 and signal transducer and activator of transcription (STAT) 5 pathway and regulates various features of liver physiology including regulation of somatic growth and maturation associated genes [4]. Cytokine signalling through the JAK-STAT signalling pathway is centrally involved, both for cancer initiation, progression, but also for immune cell escape, immune cell recognition and metabolic control. As such, defining these core cancer pathways and gaining an understanding of their multifaceted interconnections has helped to simplify the complex genetics of cancer. This influenced significantly the approach taken by cancer biologists in studying these diseases, as well as the approach of pharmaceutical development of inhibitors targeting these pathways. Whole body *Jak2* or *Stat5* knockout mice are not viable, demonstrating these proteins are essential for development and survival [8,9]. Thus, conditional knockout models were instrumental to explore functions of these genes in liver physiology.

In this review, we will cover various aspects of liver physiology and liver disease with a special emphasis on lessons learned from animal models that have altered hepatic JAK2-STAT5 signalling.

2. Liver physiology and pathology

The liver performs critical opposite metabolic processes to meet the body's energy demand in response to nutritional and endocrine stimuli such as insulin, glucagon and catecholamines. To maintain metabolic homeostasis, the liver communicates with various metabolically active tissues, including skeletal muscle and adipose tissue [3]. Hepatic protein metabolism encompasses the synthesis and breakdown of different proteins. Albumin, for instance, is exclusively produced by the liver. It is important for the maintenance of colloid osmotic pressure and functions as a carrier protein that transports hormones, fatty acids and metal ions in the bloodstream [10]. Moreover, the liver produces diverse coagulation factors, anticoagulants [11], hormones (e.g. insulin-like growth factor 1 (IGF1)), carrier proteins (e.g. insulin-like growth factor-binding protein), and an inflammatory biomarker, c-reactive protein [12]. Depending on whether blood glucose levels are rising or falling, the liver rapidly employs different metabolic pathways to preserve blood glucose concentrations. In the post-prandial phase, the liver removes excess glucose from blood. It either converts it into glycogen or feeds it into oxidative pathways to generate energy and lipogenic substrates. Conversely, in the post-absorptive phase, when blood glucose levels decrease, glycogen stores are mobilised for glucose production. This is important to provide energy for the brain and other glucose-requiring tissues. When glycogen stores are exhausted, hepatic gluconeogenesis from glucogenic precursors ensures continuous glucose supply [13,14].

2.1. Hepatic lipid metabolism and non-alcoholic fatty liver disease

Hepatic lipid metabolism is the body's central source for synthesis and distribution of fatty acids (FA), triglycerides and cholesterol. Under normal conditions, the liver does not function as a lipid storage depot. The fat content in hepatocytes is relatively low. This is accomplished by a delicate balance of FA/triglyceride synthesis and breakdown as well as by distributing lipids to peripheral tissues (Fig. 1). Persistent dysfunctions in liver metabolism, which might result from dietary insults, obesity and/or genetic mutations, are major contributors to the development of a progressive fatty degeneration of hepatocytes [1,15]. This pathologic triglyceride accumulation in hepatocytes, termed hepatic steatosis, is a general characteristic of liver pathologies. It is summarised under the term non-alcoholic fatty liver disease (NAFLD). NAFLD is the most common cause of chronic liver disease worldwide and represents a major public health problem. Sedentary lifestyle and globalization of unhealthy diets have driven an epidemic increase in developing NAFLD over the past several decades [16–18]. Of note, NAFLD is not associated with alcohol consumption or the use of steatogenic medication [19]. It is considered to be the hepatic manifestation of the metabolic syndrome, which is a cluster of pathologies that increase the risk for developing coronary heart disease and type 2 diabetes (T2D) including obesity, hyperlipidemia, hyperglycemia, insulin resistance, mitochondrial damage, oxidative stress response, and inflammatory cytokines [17,20]. In most studies, it is estimated that the prevalence of NAFLD ranges from 25% to 45% in the Western

population [21,22]. About 60% of NAFLD-bearing individuals are considered to be obese and 88% to exhibit features of the metabolic syndrome [17]. Alarmingly, obese individuals are at a significantly higher risk to develop cancer and at least 3.6% of all new cancer cases in adults are obesity-related [23]. In addition, evidence are accumulating that epigenetic changes also play an important role in NAFLD progression [24].

In order to assess the severity of NAFLD, the disease is subdivided into two categories: non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH) [17,19]. Approximately 30% of NAFLD-bearing individuals have NASH, which is the progressive form of NAFLD and it is histologically different from simple steatosis. It encompasses hepatic inflammation (steatohepatitis) and fibrosis that may further progress to cirrhosis [25,26]. FA-induced hepatic lipotoxicity is a key pathogenic event in NASH development, secondary to increased FA oxidation and formation of reactive oxygen species (ROS). Hepatic lipotoxicity is the consequence of limited hepatic capacity to oxidize, store and to export FAs as triglycerides, while at the same time FA-influx from the periphery is aggregating. In NASH, lipotoxicity promotes liver injury and cell death by increasing oxidative stress (mitochondrial dysfunction) and hepatic inflammation (steatohepatitis), which can be accompanied by variable degrees of hepatic fibrosis [17,25,27,28]. While simple steatosis is linked to a relatively positive clinical outcome, its progression to NASH severely increases the risk of developing progressive fibrosis, cirrhosis and eventually HCC [29–31].

In NAFLD, key enzymes involved in hepatic *de novo* lipogenesis are upregulated, e.g. acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) and stearoyl-CoA desaturase (SCD) 1 [32]. Additionally, hepatic expression of the FA transporter CD36 positively correlates with NAFLD in patients, emphasizing its importance in NAFLD. In addition, increased liver triglyceride content was linked to overexpression of hepatic CD36 in mice [33–37]. Moreover, increased expression of the lipogenic transcription factor peroxisome proliferator-activated receptor gamma (PPARγ) is associated with augmented triglyceride accumulation in hepatocytes. While healthy livers express low levels of PPARγ [38], steatotic livers from patients and murine models exhibit increased PPARγ expression and activity [39–43]. Likewise, amplified levels of PPARγ are associated with the upregulation of proteins involved in FA uptake, such as CD36 [42], but also overlap with the induction of lipogenic genes such as *Acc*, *Fasn* (FAS) and *Scd1* [40,44].

As the liver is rich in mitochondria, they play an important role in the removal of hepatic FAs to produce energy in form of adenosin triphosphate (ATP). However, during NAFLD progression, the liver attempts to compensate for the increased fat deposition by increasing the rate of FA oxidation, which results in enhanced ROS production [45]. Yet, the mitochondrial antioxidant defence system is not potent enough to control constant oxidative stress. At some point, mitochondria are not able to cope with hepatic lipid overload, which leads eventually to decreased ATP production and mitochondrial dysfunction [46,47]. To counteract mitochondrial dysfunction, peroxisomes are additionally activated, thereby accelerating the formation of ROS [45]. Of note, mitochondrial dysfunction and increased ROS production have been linked to patients with NAFLD/NASH, which raises the possibility that NAFLD is a mitochondrial disease [48–53]. Moreover, electron microscopy imaging of liver tissue of patients with NAFLD revealed big and swollen mitochondria indicating mitochondrial dysfunction [53]. Since oxidative stress/damage is linked to NAFLD/NASH progression [52,54], several therapeutic strategies have been proposed to target oxidative stress in patients with NAFLD. However, many antioxidant therapies in patients have failed to improve disease progression [47,52]. Vitamin E supplementation, for example, has been proposed as a potential treatment approach to improve NASH, but concerns about its safety emerged, since it increased insulin resistance, triglyceride levels and the risk of developing hemorrhagic stroke [52,55–59]. Consequently, the safest treatment strategies to counteract NAFLD progression are to improve nutrition by caloric restriction, to increase physical activity, and to reduce weight.

2.2. Hepatocellular carcinoma

HCC is the fifth most common cancer and the third most frequent cause of cancer-related deaths worldwide [60–62]. HCC accounts for 85%–90% of primary liver cancers and worldwide HCC emerges mainly from chronic viral infections (hepatitis C virus (HCV) and hepatitis B virus (HBV)) and alcohol-induced liver injury [29,63,64]. Yet, obesity- and T2D-related NAFLD and its more aggressive manifestation, NASH, evolve as a driving force and are likely to become the leading risk factor in the near future [63–67]. Even though HCC emergence is higher among patients with a fibrotic/cirrhotic background, HCC has recently been reported to occur in presence of NASH without cirrhosis [29,31,62,68,69]. Remarkably, HCC occurrence was reported in patients who show NAFLD along with features of the metabolic syndrome, but no obvious signs of NASH and fibrosis were observed [70–72]. Of note, NAFLD-related HCCs emerging from non-cirrhotic/fibrotic livers are poorly understood and need to be investigated in more detail. Typically, HCC progression is a stepwise process, which might take decades to evolve. It usually emerges from cirrhosis, which over time will develop dysplastic lesions that can transform, under the influence of clonal selection, into HCC (Fig. 2) [73–75]. During this stepwise process, the liver is constantly exposed to liver injury, which leads to compensatory proliferation, metabolic and oxidative stress, and inflammation. Long-lasting liver injury eventually leads to the accumulation of genetic and epigenetic alterations that will evolve slowly to pre-malignant hepatocytes and ultimately to complex and heterogeneous liver tumours [76]. Various signalling pathways are de-regulated in HCC including growth factors (e.g. family members of IGF, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), hepatocyte growth factor (HGF)), developmental pathways (e.g. Wingless/Integrated (WNT), Hedgehog, Notch), and angiogenesis (vascular endothelial growth factor (VEGF)). Further, proliferative/survival signalling cascades (e.g. rat sarcoma (RAS), v-Akt murine thymoma viral oncogene homolog/mammalian target of rapamycin (Akt/mTOR)) and the suppression of cell cycle regulators and tumour suppressors (e.g., p53, retinoblastoma protein (RB) and D type cyclins plus cyclin-dependent kinases (CDK)) are involved in malignant transformation [77,78,76,79,80]. HCC is an aggressive tumour type and is often diagnosed at a late stage, when there is limited prospect of cure. Many clinical studies have failed to improve the survival of HCC-patients due to the heterogeneity and complexity of HCC [81,82].

3. Overview on the hepatic GH-JAK2-STAT5 pathway

The cytokine GH, a 22 kDa single chain polypeptide, is the main promoter of postnatal body growth and plays a significant role in substrate metabolism throughout life. It has several target tissues including the liver, muscle, bone and adipose tissue. GH fulfils its function either directly or indirectly via its effectors, most notably IGF-1 [83]. GH secretion from somatotrophs in the anterior pituitary gland is regulated by hypothalamic hormones: growth hormone releasing hormone induces pulsatile GH secretion, while somatostatin exerts inhibitory effects on GH release. Intestinal-derived ghrelin also exhibits stimulatory effects on GH secretion [84]. In addition, physiologic stimuli such as fasting, exercise and acute stress positively act on GH secretion, whereas obesity and excess of fuels such as glucose inhibit it [4,85]. The metabolic effects of GH are diverse and partly depend on substrate availability [86]. GH's metabolic functions include optimisation of body composition and adaptation to energy shortage; enhancing white adipose tissue (WAT) lipolysis and overall FA oxidation, while promoting protein synthesis or decreasing protein breakdown depending on the actual energy status [83,85]. Further, GH influences systemic glucose metabolism both directly and by antagonising insulin

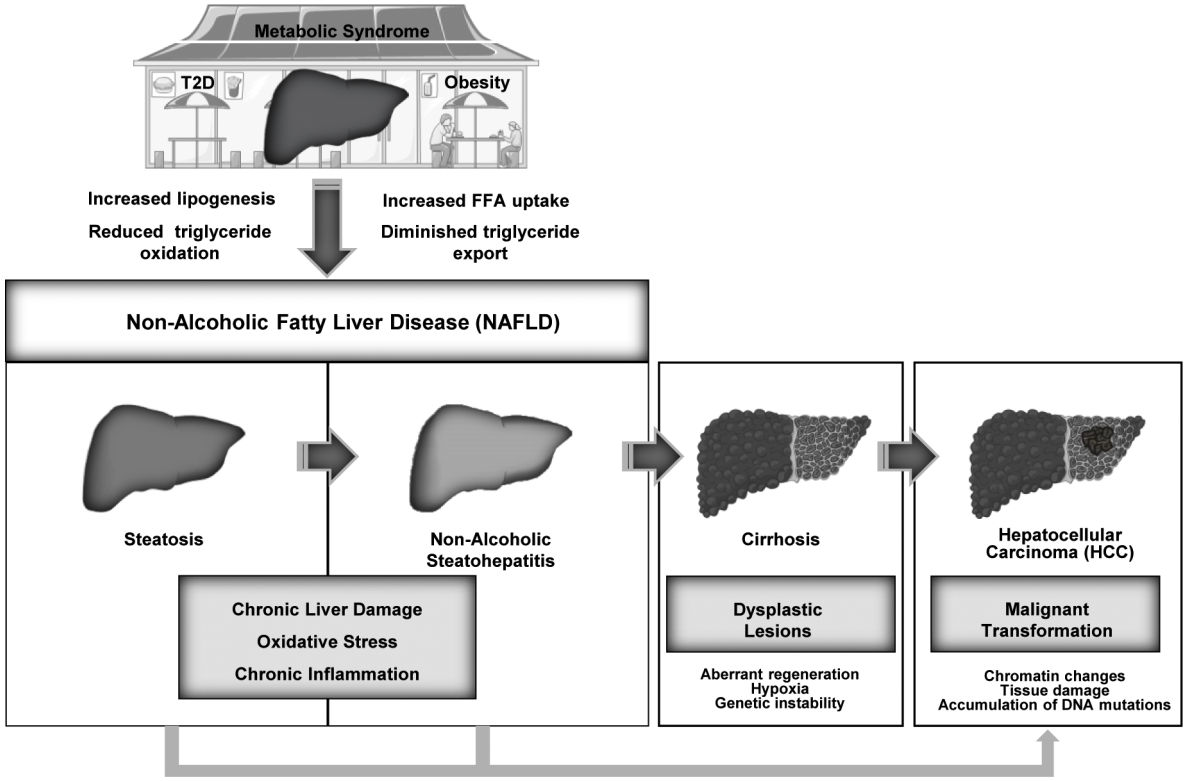

Fig. 2. Tumorigenesis from Non-alcoholic Fatty Liver Disease. The progression of NAFLD is tightly associated with metabolic risk factors such as obesity, type 2 diabetes (T2D) and the metabolic syndrome. The pathogenesis of HCC in NAFLD classically follows a sequential process: from steatosis to NASH (fibrotic; non-fibrotic), to cirrhosis which may further progress to HCC. HCC may also emerge from any stage of non-cirrhotic or non-fibrotic NAFLD.

function. This leads to the inhibition of glucose oxidation and to the induction of hepatic gluconeogenesis [83,85].

GH signalling is mediated via the GH receptor (GHR, Fig. 3). The GHR is a homodimeric cytokine receptor (similar to the prolactin, erythropoietin and thrombopoietin receptor) [87]. Binding of GH to the GHR causes a structural change in the GHR transmembrane domain that leads to movement of intracellular domains, which allows transphosphorylation of two receptor-associated JAK2 kinases [88]. Activated JAK2 phosphorylates the intracellular domain of the GHR and further tyrosine phosphorylates recruited STAT5A and STAT5B transcription factors (collectively referred to as STAT5). Activated STAT5 forms parallel homo- or heterodimers and translocates into the nucleus, where it binds to specific inverted repeat DNA response elements, typically a consensus sequence of $TTCN_3GAA$. STAT5 DNA binding together with the recruitment of cofactors or binding of synergistic acting transcription factors initiates target gene transcription [4,89]. Although STAT1 and STAT3 can be activated by GH, STAT5 is considered to be the major mediator of GH signalling [4,87]. In addition to the JAK-STAT pathway, binding of GH to the GHR induces phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) signalling pathways. STAT5 can facilitate chromatin remodelling functions; most importantly it can promote DNA loop formation via oligomerization through its N-terminus found at enhancer and promoter sites [90,91].

STAT5A and STAT5B are highly conserved and show an amino acid sequence similarity of 98% [89]. The highest degree of divergence between the two proteins is found in the C-terminal transactivation domain, in the Src homology 2 (SH2) domain required for parallel dimerization after tyrosine phosphorylation and in the N-domain required for receptor docking and oligomerization. The genes encoding STAT5A and STAT5B have a size of 30 and 54 kb, respectively, and lie head to head on chromosome 17q11.2 in humans and on chromosome 11 in mice [8,90,92]. Both proteins are broadly expressed and can be activated by different cytokines [89,93]. Interestingly, it was shown that STAT5A is prevalently expressed in the mammary gland regulating lactation via prolactin, while STAT5Bs expression is higher in hepatocytes, thereby exhibiting cell preferential transcriptional patterns [89,94–96]. Hepatic STAT5B mainly confers the expression of GH-induced genes, of which some are found to be sexually dimorphic in mice and rats [97–100]. This might also apply to humans [101,102], as GH secretion, albeit to a lesser extent than observed in rodents, shows differences in the secretion pattern between males and females [103,104]. Hepatic STAT5 drives the transcription of suppressor of cytokine signalling 2 (*Socs2*), *Igf1*, acid labile subunit (*Als*) and components of the cytochrome p450 detoxifying system [105–108]. Moreover, hepatic STAT5 controls systemic GH levels and limits GH-induced gene expression through negative regulators IGF-1 and SOCS2 [109,110]. Hepatic IGF-1 is a vital factor in controlling postnatal body growth upon GH stimulation [5–7,89,111]. Impaired secretion of GH or non-activation of STAT5 due to mutations of the GHR leads to dwarfism secondary to reduced levels of IGF-1 [9,112]. Murine knockout studies have confirmed the role of STAT5B in postnatal body growth. Mice with impaired STAT5 function show significantly reduced postnatal body growth upon reduced IGF-1 serum levels [99]. These findings are in line with reports on human patients who harbour a STAT5B missense mutation and show severe growth failure [113–116].

3.1. The glucocorticoid receptor as cofactor for STAT5

STAT5 transcription factors usually operate in concert with co-activator or co-repressor molecules to regulate transcription [91]. One important general cofactor that acts in synergy with STAT5 is the glucocorticoid receptor (GR; reviewed in [4]). Glucocorticoids (GC) are steroid hormones which are produced and secreted by the adrenal cortex as important integrators in the body's adaptation to stress and the maintenance of metabolic homeostasis [117,118]. Hepatic STAT5

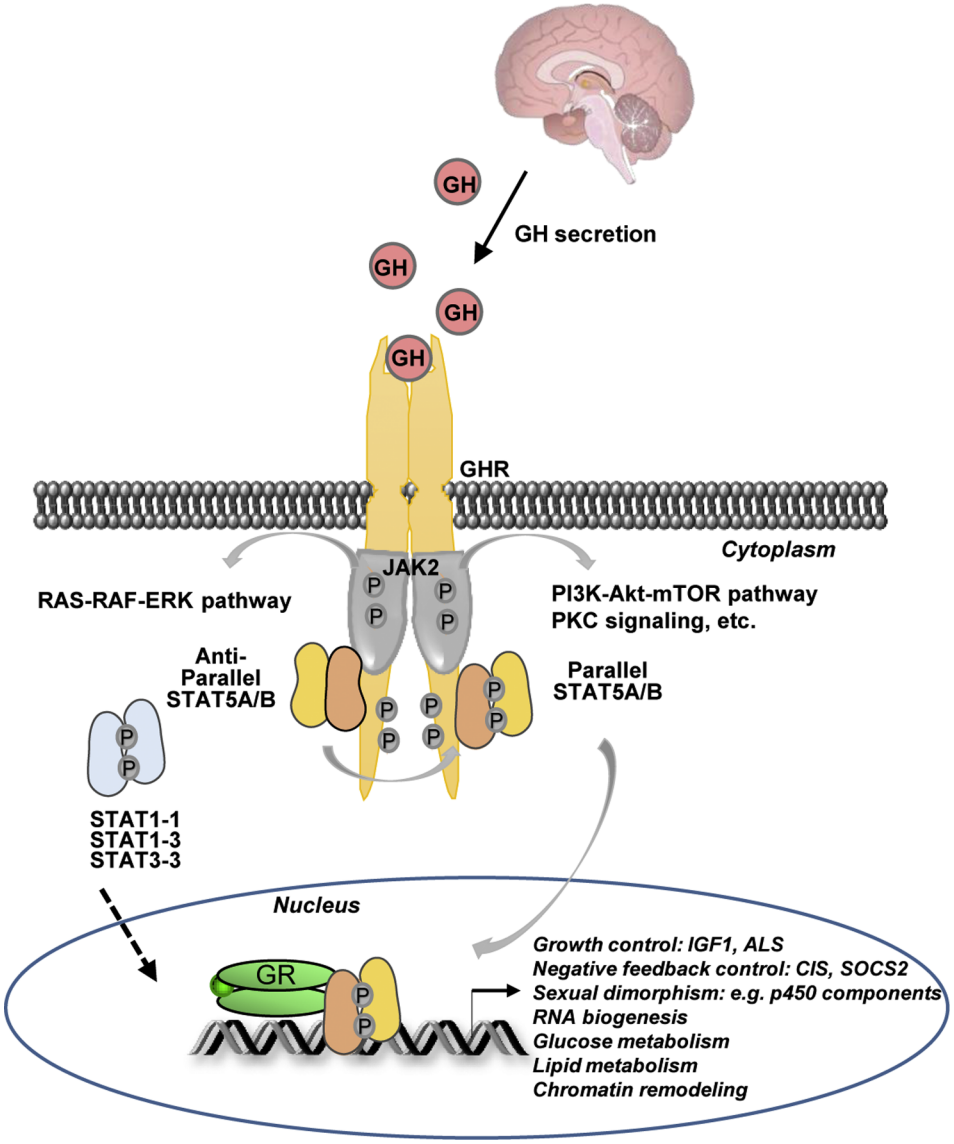

Fig. 3. JAK2-STAT5 signalling induced by GH action. GH is secreted by somatotrophs in the pituitary gland and binds to a GHR dimer, which induces a conformational change of the GHR that activates JAK2. Subsequently, JAK2 phosphorylates multiple tyrosine residues in the cytoplasmic domain of the GHR. The activated GHR-JAK2 complex enables binding and tyrosine phosphorylation of STAT5 proteins. Activated STAT5 translocates to the nucleus and modulates gene expression. Additionally, GH-activated JAK2 can activate multiple signalling proteins and pathways including STAT1/STAT3 (in particular upon low or absent expression of STAT5), MAPK and PI3K signalling. Transcription of *Socs2*, *Igf1*, *Als*, and many metabolic genes affecting glucose and lipid metabolism are induced by activated STAT5. ALS, Acid-labile subunit; CIS, Cytokine inducible SH2 containing protein; GH, Growth hormone; GHR, GH receptor; GR, Glucocorticoid receptor; IGF1, Insulin-like growth factor 1; JAK2, Janus kinase 2; STAT, Signal transducer and activator of transcription; SOCS2, Suppressor of cytokine signalling 2.

or GR deficiency results in retardation of postnatal body growth in a similar manner [111,119]. The close interaction between the GR and STAT5 involves binding of the AF1 region of the GR to the N-terminus of STAT5 [111,119]. The STAT5-GR interaction is essential for gene regulation by GH and it is also important for prolactin-mediated gene regulation where it can accelerate transcription of STAT5 target-genes [119,120]. Thus, the induction of full transcriptional activation of STAT5 can require docking of a nuclear hormone receptor (such as the GR). STAT5-GR regulated gene sets are involved in somatic growth and sexual maturation. In addition, the STAT5-GR interaction controls ribosomal protein genes [119]. Both STAT5 and GR transcription factors are important for the maintenance of energy homeostasis, but mouse phenotypes upon conditional deletion of either gene were distinct in respect to lipid and glucose metabolism. Interference with hepatic GC-GR signalling was associated with defects in gluconeogenesis leading to fasting hypoglycaemia. However, there was no significant impact on hepatic lipid homeostasis under basal conditions [121,122]. In contrast, impairment of hepatic GH-STAT5 signalling is associated with aberrant glucose metabolism, fatty liver disease and the sensitization of hepatocytes to injury and tumorigenic transformation [9,122–125].

4. Hepatic STAT5 or JAK2 loss in steatosis and liver cancer

Disruption of hepatic GH-JAK2-STAT5 signalling is associated with liver diseases development in humans and mouse models. Yet, its exact role in liver disease progression remained enigmatic until conditional deletion in liver epithelium were performed using mouse models. In the following paragraphs, we will focus on the *in vivo* consequences of altered hepatic GH-JAK2-STAT5 signalling in lipid metabolism and liver disease.

GH is known to promote lipolysis in WAT thereby liberating free FA that can be used as energy source in peripheral tissues [85]. Excess GH signalling, as observed in acromegaly, is linked to increased lipolysis and reduced fat mass. On the other hand, GH deficiency is linked to fatty liver development [126,127]. In addition, loss of function mutations of the GHR associates with NAFLD in adults [128]. Although these correlations between steatosis and changes in GH action are known, the mechanism of GH-STAT5 signalling in patients' liver metabolism is still incompletely understood. Mouse models with disrupted GH-JAK2-STAT5 signalling allowed the study of underlying molecular changes to provide mechanistic insights (Table 1). Several studies and our data confirmed that loss of hepatic GH-JAK2-STAT5 signalling results in hepatic steatosis [9,122,123,125,129–131]. Disruption of this signalling pathway in hepatocytes is associated with increased deposition of

Table 1
Synopsis of Mouse Models to study GH-JAK2-STAT5 Signalling in Liver disease and Cancer.

System	Mouse Model	Promoter	Body Growth	Fatty Liver	Hepatic Inflammation	Fibrosis	Liver Cancer	References
Conditional KO and compound models	$GHR^{\Delta hep}$	Alb-Cre	Normal[a]/ Reduced[b]	Yes	No	No	NA	[9][a] [20][b]
	$JAK2^{\Delta hep}$	Alb-Cre[c,d], Alfp-Cre[e]	Reduced	Yes	No	No	60[e] weeks of age	[130][c] [129][d] [131][e]
	$JAK2^{\Delta hep}JAK2^{\Delta adipose}$	Alb-Cre, Adipoq-Cre	Reduced	No	No	No	NA	[132,86]
	$JAK2^{\Delta hep}CD36^{\Delta hep}$	Alb-Cre	Reduced	Yes, but improved	No	No	NA	[37]
	$STAT5^{\Delta hep}$	Alb-Cre[f,g,h], Alfp-Cre[i,j,k]	Reduced	Yes	No	No	68[g] weeks of age	[123][f] [169][g] [162][h] [119][l] [122][j] [125][k]
	$STAT5^{\Delta hep}GR^{\Delta hep}$	Alfp-Cre	Reduced	Yes	Minor	Minor	36 weeks of age	[122]
	$STAT5^{\Delta hep}CD36^{-/-}$	Alb-Cre	NA	Yes, but improved	NA	NA	NA	[137]
Conditional KO crossed to GH transgenic mice	GH^{tg}	Metallothionein	Increased	No	Yes	Yes	40–50 weeks of age	[84,181,125]
	$GH^{tg}JAK2^{\Delta hep}$	Metallothionein, Alfp-Cre	Reduced	Yes	Minor	No	60 weeks of age	[131]
	GH^{tg} $STAT5^{\Delta hep}$	Metallothionein, Alfp-Cre	Reduced	Yes	No	No	28 weeks of age	[125,131]
Cholestasis-induced liver fibrosis	$Mdr2^{-/-}GHR^{-/-}$	–	Reduced	No	–	Increased	20% at 48 weeks of age	[182]
	$Mdr2^{-/-}STAT5^{\Delta hep}$	Alfp-Cre	Reduced	Yes	–	Increased	No	[160]
DEN-induced liver tumorigenesis	$JAK2^{\Delta hep}$	Alb-Cre	Reduced	Yes	Reduced	–	~75% at 40 weeks after treatment	[163]
	$STAT5^{\Delta hep}$	Alfp-Cre	Reduced	Yes	Yes, unchanged	–	25% at 32 weeks after treatment	[164]
CCL_4 -induced liver fibrosis	$STAT5^{\Delta hep}$	Alb-Cre	–	Yes	–	Increased	8–12 weeks after treatment	[124,162]
	$STAT5^{\Delta hep/\Delta N}$	Alb-Cre	–	No	–	Increased	No	[124]

$Mdr2^{-/-}$ knockouts represent an established model of cholestasis-induced liver fibrosis. These mice develop fibrotic-related liver tumours at 48 weeks of age with an incidence of 92–100%. [182–184]. While wildtype mice treated with the liver carcinogen DEN normally develop inflammation-associated liver tumours within 32–40 weeks of age with an incidence of 100% [185], CCL_4 treatment in wildtype mice results only in the development of liver fibrosis, but not tumours [124,186]. (Alb: Albumin enhancer/promoter; Alfp: Albumin promoter and alpha-fetoprotein enhancers; Adipoq: adiponectin promoter/enhancer; $STAT5^{\Delta hep/\Delta N}$: One allele encoding STAT5A/B lacking the first 90 amino acids of the N-terminal domain; KO: Knockout; DEN: Diethylnitrosamine; CCL_4: Carbon tetrachloride; NA: Not analyzed; a–k: Phenotypic discrepancies and the use of different promoters are referred to their respective reference).

lipids in the liver and increased uptake of FA by the FA transporter CD36 indicating an impairment in metabolic homeostasis [123,130]. While in some publications it was reported that hepatic deletion of *Jak2* and *Ghr* lead to highly elevated circulating free FA levels, others did not observe this increase in conditional *Stat5* and *Jak2* knockout mice [122,123,125,130,131]. Interestingly, over-expression of hepatic CD36 leads to increased liver FA uptake and triglyceride storage regardless of normal concentrations of circulating free FA levels [35]. This indicates that the increased CD36 expression levels in STAT5 and JAK2 deficient livers likely promote FA uptake and hepatic lipid storage similarly. Interestingly, adipocyte-specific deletion of *Jak2* inhibits lipolysis, increases body fat content and in that way prevents liver steatosis [132]. In addition, chronic GH exposure was shown to promote hepatic insulin resistance and lipolysis in control mice, while in adipose JAK2 deficient mice a diminished susceptibility to the diabetogenic actions of GH was observed [133]. STAT5 signalling in adipocytes was recently reported to control lipid mobilisation in WAT by regulating adipose triglyceride lipase, the rate-limiting protein in lipolysis [134].

It was shown that hepatic *Stat5* or *Jak2* loss, independent of hyper-activated GH signalling, enhances the expression of PPARγ [122,123,125,130,131]. PPARγ is a key regulator of lipogenesis by inducing the transcription of genes involved in FA uptake (*Cd36*) and lipogenesis (*Fasn*, *Scd1*) [135,136]. Recently, it was reported that the expression of *Cd36* is also modulated by the microRNA-20b and this microRNA showed increased expression in STAT5 deficient livers [137]. Accordingly, transcription of *Pparg*, *Cd36* and *Scd1* was suppressed in animals with hyper-activated GH action suggesting that GH-STAT5 signalling negatively regulates the expression of lipogenic genes [131]. Of note, increased expression of *Pparg* and *Cd36* are the key pathways to be deregulated in mouse models with disrupted GH signalling [9,122,123,125,130,131,138]. This indicates that impaired GH-JAK2-STAT5 signalling, via the activity of PPARγ, promotes the development of hepatic steatosis by *de novo* lipogenesis, but also enables additional hepatic FA uptake by the increased expression of *Cd36* [1,40,41,139,140]. Mechanistically, *in vitro* studies indicated that there is a bidirectional inhibitory crosstalk between STAT5 and PPARγ [141,142]. In addition, direct interaction of STAT5 with *Pparg* regulatory promoter regions have been described in non-hepatic cell types [143–145], but are rather associated with an activating than a repressive function. One potential indirect mechanism of how STAT5 deficiency contributes to increased expression of *Pparg* lies in the increased GH-dependent activation of STAT1. In support of this notion, *Pparg* mRNA expression was not affected by ectopic expression of dominant-negative STAT5 in a hepatoma cell line, while expression of dominant-negative STAT1 variant in the same cell line was sufficient to decrease *Pparg* transcription [138]. However, the presence of dominant-negative STAT5 was associated with a prominent induction of *Cd36* mRNA in the same experimental set up. Further, occupancy of STAT5 on regulatory *Cd36* promoter regions in murine livers has been described in the same study. These findings suggest a loss of direct negative regulatory functions on *Cd36* gene expression in the absence of STAT5 activity. This, presumably, already permits increased hepatic FA uptake as it was shown upon adenoviral overexpression of CD36 in livers of mice on a regular diet [35]. Thereby, CD36 might indirectly contribute to PPARγ activation by FA derivatives.

Interestingly, additional deletion of hepatic *Cd36* in JAK2 deficient livers reduces steatosis only by lowering liver triglyceride content. This finding was further confirmed, when hepatic STAT5-deficient mice were crossed to *Cd36* knockout mice displaying reduced hepatic triglycerides. The expression of lipogenic genes (*Fasn*, *Scd1*) and an alternative transporter for FA uptake (*Fatp1* (fatty acid transport protein 1)) remained elevated, suggesting that inhibition of CD36 does not fully prevent fatty liver disease [37]. The same group reported that treatment of JAK2 deficient mice with a PPARγ-specific antagonist leads to reduced expression of liver *Cd36* and decreased hepatic triglyceride content. Thereby, they demonstrated that inhibition of PPARγ and its downstream targets does not fully inhibit fatty liver development [130]. Another factor involved in changes in hepatic lipid metabolism upon altered GH-STAT5 action is sterol regulatory element binding protein 1c (SREBP-1c). SREBP-1c is a transcriptional master regulator of hepatic *de novo* lipogenesis and its activation is frequently linked to NAFLD [1,146–150]. In case of over-expression of bovine GH, a reduction in hepatic *Srebp-1c* and various lipogenic downstream target genes was observed [151]. *Vice versa*, an up-regulation of *Srebp-1c* was reported under hepatic GHR or STAT5 deficiency [9,122]. Importantly, GH activated STAT5 was shown to bind to the *Srebp-1c* gene promoter, which might contribute to its transcriptional silencing [122].

Chronic livers disease can give rise to HCC and it can progress directly from NAFLD. This links aberrant metabolic processes and HCC development [29,68,71,152]. In patients with NAFLD, persistent fatty degeneration of hepatocytes results in chronic inflammation and oxidative damage, which generates a harmful environment for the liver to promote disease. Although STAT5 activation has been associated with a more favourable prognosis in patients with breast cancer, JAK2-STAT5 signalling was implicated in numerous malignant diseases with poor prognosis [153], such as hematopoietic or prostate cancers [154–157]. In agreement, aberrant activation of STAT5 was found in patients with HBV-related HCC [158,159]. Yet, the role of STAT5 and JAK2 function in fatty liver disease progression to liver cancer is complex. Disruption of GH signalling by STAT5 or JAK2 deficiency leads to similar fatty liver phenotypes. Thus, it might be assumed that fatty liver disease progression and malignant transformation would be similar in both genotypes. However, this is not completely true and studies with transgenic mice indicate a protective role of liver STAT5 rather than a tumour promoting one. Hepatic STAT5 deficiency has been implicated to promote liver disease progression upon genetically- or tetrachloride (CCL_4)-induced liver fibrosis. In a model of cholestatic liver disease, lack of STAT5 associated with disrupted bile acid homeostasis, increased apoptosis due to IGF-1 scarcity, compensatory proliferation, and reduced expression of genes important for hepatocyte integrity and function [160]. Likewise, CCl_4 –treated mice with hepatic STAT5 deficiency were more prone to develop advanced liver fibrosis and, in some cases, liver cancer [124]. Here, loss of STAT5 function and subsequent disease progression were linked to increased oncogenic STAT3 activation and stabilization of the fibrosis promoting transforming growth factor beta (TGF-β) [161]. In a follow up study, STAT5 activity in hepatocytes was further suggested to promote cell cycle arrest upon liver injury by directly inducing the expression of the cell cycle inhibitors *Cdkn1a* and *Cdkn2b*. Its loss consequently favours the activation of survival and proliferation pathways [124,162].

In situations of additional challenges, such as elevated WAT derived free FA uptake because of combined hypercortisolism [122] or hyper-activated GH signalling [125], liver cancer developed in the background of progressive steatosis. Here, malignant transformation occurred without substantial hepatic fibrosis or inflammation. Aberrant activation of STAT3 was linked to accelerated liver tumorigenesis in STAT5-deficient livers [122–125]. As abnormal activation of STAT3 is JAK2-dependent, a compensatory activation of STAT3 was not observed in JAK2 deficient livers [131]. In contrast to STAT5 deficiency, loss of hepatic JAK2 deficiency in a GH transgenic background leads to decelerated tumour formation [131]. Moreover, liver *Jak2* loss diminished tumour formation when treated with the liver carcinogen diethylnitrosamine (DEN) [163]. Along this line, we observed that STAT5-deficiency in hepatocytes delays liver tumorigenesis in a DEN model of chemically-induced carcinogenesis. This indicates that STAT5 acts as an oncogene in the DEN-model [164] and suggests that the role of STAT5 in liver cancer is dependent on genetic factors and the nature of the insult.

4.1. Hepatic GH-JAK2-STAT5 signalling in oxidative stress and damage management

As described, the pathogenesis of NAFLD is characterised by changes in FA uptake, synthesis, oxidation and export, which ultimately lead to marked fat accumulation in hepatocytes. Several studies have shown that liver injury in the course of NAFLD is induced by oxidative stress, promoting the risk for liver tumorigenesis [49–52,152,165–167]. Oxidative stress represents a disequilibrium between oxidant and antioxidant agents [165]. However, the link between JAK2-STAT5 signalling and oxidative stress in hepatocytes and its possible contribution to liver cancer development is not well appreciated. Our studies demonstrated that disruption of the JAK2-STAT5 pathway by either hepatic *Stat5* or *Jak2* deletion led to the accumulation of cytoplasmic ROS in hepatocytes [122,131], probably the result of chronic fatty degeneration seen in these livers. Moreover, STAT5B deficiency resulted in enhanced hepatic PPARα-dependent peroxisomal FA oxidation [168], which might contributes to additional oxidative stress and damage in hepatocytes. In contrast, ROS production was stimulated by STAT5-induced expression of NADPH-Oxidase 4 (NOX4), a ROS generating enzyme. However, this was assessed in mouse embryonic fibroblasts and not in STAT5-deficient livers [169]. Another study conducted in JAK2 deficient mice did not observe any differences in lipid peroxidation, a consequence of increased ROS generation, which led them to the conclusion that ROS production was unchanged in JAK2 deficient mice. However, they showed elevated expression of genes involved in endoplasmic reticulum stress, which assumes cellular stress and most likely increased ROS production in those mice [163,170]. Oxidative stress does not only induce liver damage but also acts as a strong activator of stress-activated protein kinases, including tumour-promoting c-Jun N-terminal kinase (JNK), p38 MAPK, and extracellular signal-regulated kinase (ERK) signalling [171]. In particular, JNK1 and ERK signalling have been implicated to fulfil oncogenic functions in murine and human liver cancer [172–174]. ERK activation was unchanged upon hepatic deletion of either *Stat5* or *Jak2* independent of hyper-activated GH signalling. However, activation of hepatic JNK1 and cellular Jun (cJun) (a downstream target of JNK1) was increased in tumorigenic liver samples of GH transgenic STAT5-deficient mice and of mice with a hepatic deletion of *Stat5* and the *Gr* [122,125], endorsing that ROS is generated upon STAT5 deficiency. By contrast, aberrant activation of JNK was not present in tumorigenic livers of JAK2 deficient mice when treated with DEN [163]. In line, it has been reported that JNK1 deficiency prevents DEN-induced liver cancer in mice [175]. Moreover, hepatic deficiency of cJun resulted in reduced liver tumours upon DEN treatment validating that JNK1 and cJun play a crucial role in liver tumorigenesis [176]. Consequently, JNK1 might be an additional risk factor that contributes to the differences in liver cancer development seen in STAT5 and JAK2 deficient livers. Notably, *Stat5* loss was linked to abolished p53 activity suggesting that DNA damage repair and/or removal of damaged hepatocytes was diminished, thereby contributing to early liver tumorigenesis [125]. Furthermore, STAT5 can induce several downstream targets of p53 in mouse embryonic fibroblasts, which was reversed upon STAT5 deficiency [169]. These results may suggest a regulatory role of STAT5 in the control of p53 function in liver. However, the exact mechanism behind this observation still awaits clarification. Prolonged exposure to ROS-induced oxidative stress results in oxidative damage, i.e. oxidation of proteins, lipids and DNA, which leads to structural and functional abnormalities of cellular molecules ultimately resulting in malignant transformation [165]. Interestingly, although both genotypes (STAT5 and JAK2 deficient livers) developed similar disease-related phenotypes, e.g. fatty livers characterised by lipogenic expression profiles accompanied by similar increased ROS production, oxidative damage was only present in STAT5 deficient mice [131]. Our study led to the assumption that the difference seen in tumorigenesis was partly attributed to differences in glutathione S-transferase (GST) expression and activity [131]. GSTs belong to a major antioxidant defence mechanism and act on oxidised macromolecules such as lipids and amino acids to prevent cell damage [177]. In situations of insufficient ROS clearance, GSTs promote the conjugation of the reduced form of glutathione to oxidized macromolecules thereby detoxifying the cellular environment [178]. Only JAK2 deficiency/inhibition led to increased detoxification capacity by increasing the expression and activity of GSTs, which was associated with abolished hepatic oxidative damage. This leads to the conclusion that blocking JAK2 function protects hepatocytes against oxidative damage by regulating the activity of GSTs [131,163]. By contrast, STAT5 deficiency resulted in unaffected GST expression and activity, which was linked to enhanced oxidative damage predisposing the liver for malignant transformation. Recently, JAK2-independent activation of STAT5 was associated with increased ROS mediated DNA damage in chronic myeloid leukaemia cells by abolishing antioxidant enzymes [179,180]. This suggests tissue-specific functions of JAK2- STAT5 signalling in regulating antioxidants and it emphasizes the need to further study its involvement and precise mechanism in the regulation of the antioxidant defence systems. Given that oxidative stress exhibits a crucial role in chronic liver diseases, increasing knowledge about underlying mechanisms would allow better understanding of the pathogenesis and therapeutic avenues to counteract NAFLD.

5. Summary and concluding remarks

Hepatic GH-JAK2-STAT5 signalling is centrally involved in fatty liver disease progression and relevant for liver cancer development. Impairment of this signalling pathway by conditional deletion of either *Stat5* or *Jak2* results in whole body alterations in lipid metabolism leading to marked accumulation of lipids in hepatocytes accompanied by increased peripheral lipolysis and increased hepatic lipid anabolism promoting a NAFLD-phenotype. STAT5 and JAK2 are both crucial for the metabolic homeostasis of the liver by preventing liver steatosis through regulation of lipogenic genes involved in FA uptake and synthesis. However, STAT5 and JAK2 are differently involved in liver cancer development, partly due to differences in ROS generation and clearance (Fig. 4). While STAT5 deficiency leads to early liver cancer formation in a background of hyper-activated GH signalling, JAK2 deficiency clearly delays liver tumorigenesis. STAT5 deficiency is linked to malignant transformation of hepatocytes on account of: 1) decreased expression of hepatoprotective factors. 2) Increased activation of oncogenic STAT3 caused by rerouting of GH signalling towards STAT3 instead of STAT5. 3) Increased activation of oncogenic JNK1 and cJun. 4) Decreased expression of p53. 5) Decreased expression and activity of GSTs, which results in increased oxidative damage that sensitizes hepatocytes for tumorigenic transformation. By contrast, JAK2 deficiency in hepatocytes is associated with delayed liver tumorigenesis, which is linked to: 1) Normal expression and absent oncogenic STAT3 and JNK activation. 2) Increased expression and activity of GSTs to prevent oxidative damage (i.e. oxidation of lipids, protein and DNA). The prospect to reduce oxidative stress might provide a reason to target JAK2 in chronic liver disease and thereby preventing subsequent development of liver cancer. However, JAK2 has pleiotropic functions affecting e.g. also myelopoiesis or immunity. Thus, future research is still required to elucidate in more detail hepatic JAK2 function in the regulation of GSTs and the potential of JAK2 inhibition to prevent oxidative liver damage.

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7. Author contribution

DK, MT, KMM, and RM collected and analyzed literature

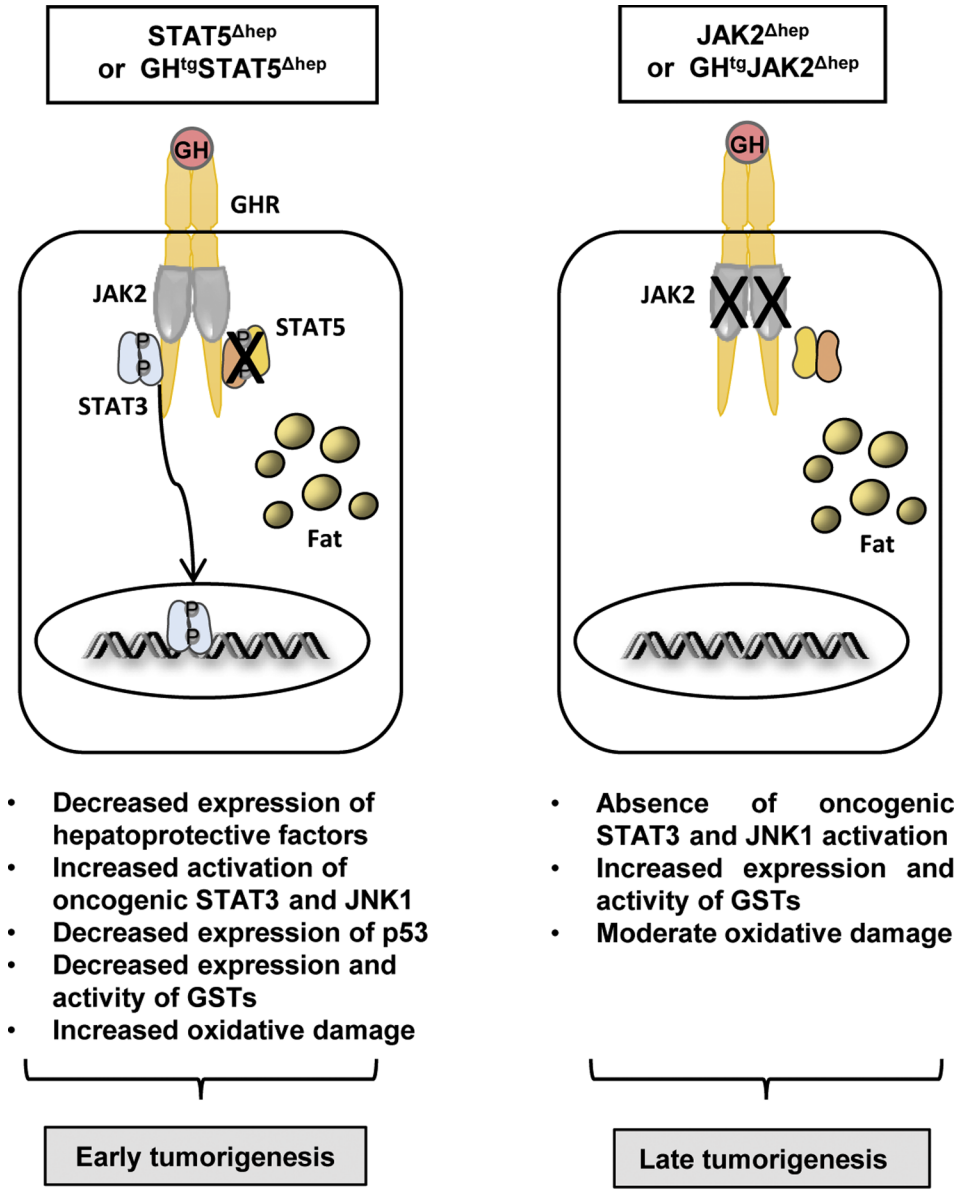

Fig. 4. Schematic illustration of the major differences between hepatic STAT5 and JAK2 deficiency that potentially contribute to variances in tumorigenesis. Loss of hepatic STAT5 or JAK2 (with or without hyper-activated GH signalling) lead to increased lipid accumulation. However, STAT5 deficiency accelerates tumour development that is associated with increased activation of STAT3 and oxidative damage. In contrast, JAK2 deficiency delays tumour formation which is characterised by the absence of oncogenic STAT3 activation and diminished oxidative damage compared to STAT5 deficiency. The diminished oxidative damage seen under JAK2 deficiency can partly be attributed to increased expression and activity of glutathione S-transferases (GSTs), which are detoxifying enzymes.

information, designed the concept for the review article and created the figures and the table. All authors further contributed to the content, edited and approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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