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Hepatocyte growth control by SOCS1 and SOCS3

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ABSTRACT

The extraordinary capacity of the liver to regenerate following injury is dependent on coordinated and regulated actions of cytokines and growth factors. Whereas hepatocyte growth factor (HGF) and epidermal growth factor (EGF) are direct mitogens to hepatocytes, inflammatory cytokines such as TNFα and IL-6 also play essential roles in the liver regeneration process. These cytokines and growth factors activate different signaling pathways in a sequential manner to elicit hepatocyte proliferation. The kinetics and magnitude of these hepatocyte-activating stimuli are tightly regulated to ensure restoration of a functional liver mass without causing uncontrolled cell proliferation. Hepatocyte proliferation can become deregulated under conditions of chronic inflammation, leading to accumulation of genetic aberrations and eventual neoplastic transformation. Among the control mechanisms that regulate hepatocyte proliferation, negative feedback inhibition by the 'suppressor of cytokine signaling (SOCS)' family proteins SOCS1 and SOCS3 play crucial roles in attenuating cytokine and growth factor signaling. Loss of SOCS1 or SOCS3 in the mouse liver increases the rate of liver regeneration and renders hepatocytes susceptible to neoplastic transformation. The frequent epigenetic repression of the *SOCS1* and *SOCS3* genes in hepatocellular carcinoma has stimulated research in understanding the growth regulatory mechanisms of SOCS1 and SOCS3 in hepatocytes. Whereas SOCS3 is implicated in regulating JAK-STAT signaling induced by IL-6 and attenuating EGFR signaling, SOCS1 is crucial for the regulation of HGF signaling. These two proteins also module the functions of certain key proteins that control the cell cycle. In this review, we discuss the current understanding of the functions of SOCS1 and SOCS3 in controlling hepatocyte proliferation, and its implications to liver health and disease.

1. Introduction

The liver is one of the largest organs of the body that serves vital homeostatic functions. As the first organ that encounters dietary nutrients via the portal vein, the liver plays a central role in controlling the body metabolism via storage, synthesis and redistribution of carbohydrates, fats, proteins, vitamins (K and A) and minerals (iron and copper) [1]. The liver also produces many plasma proteins (albumin and clotting factors), and secretes bile that helps in digestion and absorption of fats and fat-soluble vitamins. The toxic byproducts of metabolic processes such as ammonia as well as myriad of harmful chemicals that reach the liver from the gut (e.g., ethanol) are detoxified by the liver for safe elimination. Most of these functions are carried out by hepatocytes, which constitute roughly 80% of the liver mass. Even though hepatocytes are long-lived, they undergo damage to a varying extent during the detoxification process. Loss of hepatocytes can also occur from pathogens, particularly hepatitis B and C viruses (HBV, HCV) that establish chronic infections and cause persistent damage to hepatocytes.

In order to maintain the vital homeostatic functions under conditions of extensive hepatocyte damage caused by toxic chemicals and pathogens, or significant loss of tissue by accident, the liver is endowed

Abbreviations: CCl_4, carbon tetrachloride; CDKN1A, cyclin-dependent kinase inhibitor 1A (p21); CRL, Cullin-RING ligase; CytR, cytokine receptors; ECM, extracellular matrix; EGF, epidermal growth factor; DEN, diethylnitrosamine; Gab1, Grb2-associated binding protein 1; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HGF, Hepatocyte growth factor; IFN, interferon; IFNGR, IFN gamma receptor; KIR, kinase inhibitory region; LT, lymphotoxin; MAL, MyD88-adaptor Like; PH, partial hepatectomy; RTK, receptor tyrosine kinases; SOCS, suppressor of cytokine signaling; TGF, transforming growth factor-β; TIR, Toll-Interleukin 1 Receptor (TIR); TIRAP, TIR domain containing Adaptor Protein; TLR, toll-like receptor; TNF, Tumor necrosis factor; TNFAIP3, TNFα-induced protein 3 (A20); TNFR, TNF receptor; TP53, tumor protein 53 (p53); uPA, urokinase plasminogen activator

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with an extraordinary capacity to regenerate at a remarkably rapid rate. The regenerative ability of the liver and the underlying mechanisms are best studied in rodents after removal of two thirds of the liver mass (three of the five lobes in rodent liver) by a surgical technique called partial hepatectomy (PH) [2,3]. Following PH, restoration of the liver mass occurs within 5–7 days in rodents, and within 8–15 days in humans (for instance, following liver transplantation for advanced cirrhosis or hepatocellular carcinoma) [4,5]. This regenerative process begins with proliferation of hepatocytes followed by expansion of non-parenchymal cells and tissue remodeling. Up to 60% of hepatocytes synchronously enter the cell cycle and start synthesizing DNA, which occurs within 24 h in rats and 36 h in mice, followed by proliferation of Kupffer cells, cholangiocytes (48 h) and endothelial cells (96 h), and then a second wave of hepatocyte proliferation [4,6]. Acute hepatocyte damage induced by carbon tetrachloride (CCl_4) is also used to study hepatocyte proliferation, especially in the setting of chronic liver damage [2,5].

Studies on liver regeneration (LR) following PH in rodent models have shown that stimulation of hepatocyte proliferation is preceded by a 'priming' stage within the first 5 h, when activation of nuclear factor-κB (NF-κB), signal transducer and activator of transcription-3 (STAT3) and AP1 transcription factors, and the expression of immediate early genes occur [6,7]. These priming events are elicited by gut-derived lipopolysaccharide (LPS) via the induction of TNFα and IL-6, which are not mitogenic by themselves but enable hepatocytes exit the quiescence state, respond to growth factors and enter the cell cycle (Fig. 1). Phosphorylation of the HGF receptor MET and the EGF receptor (EGFR) is reported to occur within 30–60 min after PH [8]. The loss of the hepatic capillary bed volume due to 2/3 PH causes profound hemodynamic changes in the liver. These physical changes promote the release of active HGF from the extracellular matrix (ECM) via activation of urokinase plasminogen activator (uPA) and also increase the availability of EGF to hepatocytes [4]. Although such profound physical changes do not occur following chemical injury to the liver, the inflammatory processes elicited by cellular damage are likely to induce cytokines that initiate hepatocyte priming. Other mediators such as bile acids and insulin also contribute indirectly to hepatocyte proliferation by respectively promoting hepatocyte priming and general nutrient (glucose) uptake [9].

Hepatocyte proliferation ceases after restoration of the functional liver mass, followed by the removal of surplus cells by apoptosis [4]. A number of factors are implicated in this process, among which transforming growth factor-β (TGFβ) plays a key role. Even though TGFβ is an inhibitor of cell proliferation, its role in terminating liver regeneration is complex, involving production of extracellular matrix, inhibition of uPA and HGF synthesis, all contributing to reduce the availability of bioactive HGF [4]. The increased matrix content also signals via the integrin-linked kinase (ILK) to achieve the final liver mass [10]. Detailed discussions on the various factors that modulate hepatocyte proliferation during the liver regeneration process can be found in many excellent reviews [4,6,7,9].

While physiological hepatocyte proliferation following PH or acute liver injury caused by chemicals, toxins and pathogens is terminated after achieving the 'hepatostat' (homeostatic liver mass), recurrent hepatocyte damage caused by chronic liver injury leads to repeated cycles of hepatocyte proliferation that can promote neoplastic transformation [9] (Fig. 1). Under conditions of such chronic inflammation, cytokines and growth factors (TNFα, IL-6, HGF, EGF) that provide physiological growth stimuli become pathogenic and promote the development of hepatocellular carcinoma. Besides the transforming genetic lesions, deregulation of cytokine and growth factor signaling through increased availability of ligands, overexpression of receptors or

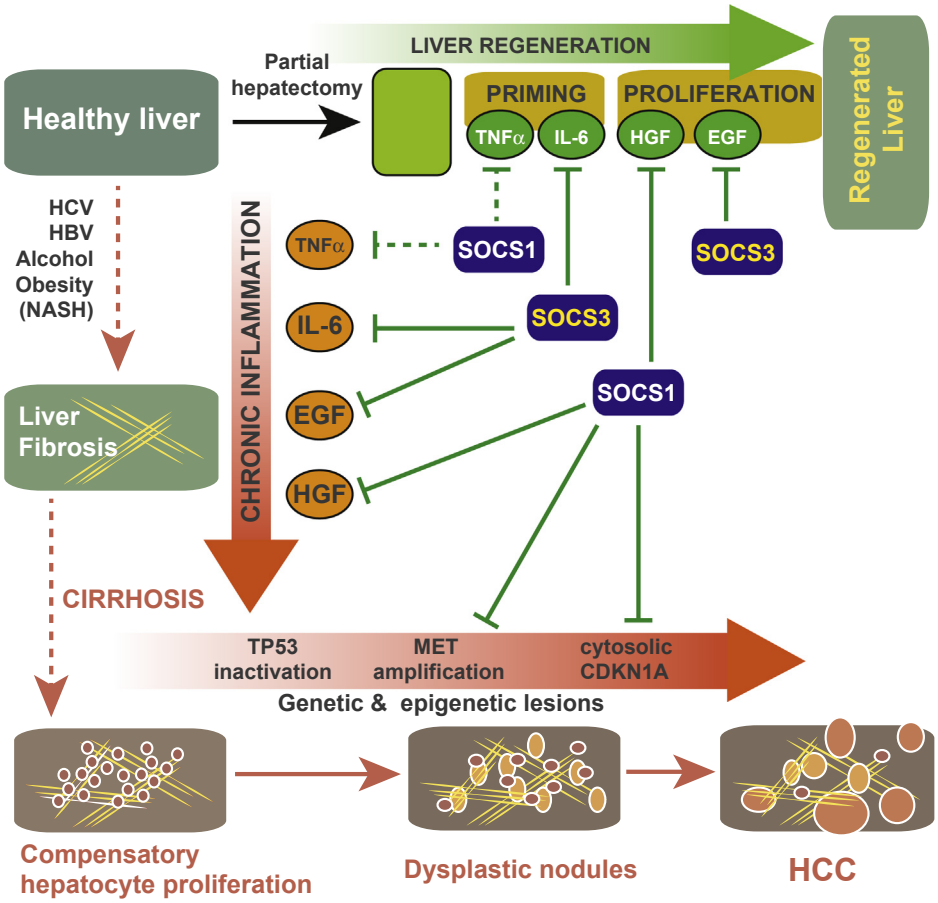

Fig. 1. Key cytokines and growth factors regulated by SOCS1 and SOCS3 in physiological liver regeneration and pathological tumor growth. During liver regeneration following partial hepatectomy, TNFα and IL-6 act as indirect mitogens to 'prime' hepatocytes and render them responsive to mitogenic growth factors HGF and EGF family growth factors. Whereas SOCS3 regulates IL-6 signaling, evidence for SOCS1-mediated control of TNFα signaling remains circumstantial. On the other hand, SOCS1 is needed to control HGF-induced MET receptor signaling whereas SOCS3 is critical to attenuate EGFR signaling pathways. The same cytokines and growth factors are also implicated in hepatocarcinogenesis induced by chronic inflammation and are similarly regulated by SOCS1 and SOCS3 as in normal hepatocytes. Chronic inflammation establishes a mutagenic environment that promotes emergence of potentially neoplastic cells, for example, through inactivation of the 'tumor protein 53' (TP53, widely known as p53), a key tumor suppressor. Both SOCS1 are SOCS3 can cooperate with p53 to promote its tumor suppressor functions (not depicted here; discussed in the text). Besides SOCS1 inhibits the paradoxical oncogenic functions of another tumor suppressor protein, cyclin-dependent kinase inhibitor 1A (CDKN1A, widely referred to as $p21^{Cip1/Waf1}$ or simply p21) in hepatocytes.

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mSOCS1    1 MVARNQVAADNAISPAAEPRRRSEPSSSSSSSSPAAPVRPRPCPAVPAPA  50
                                                .|.....||.....
mSOCS3    1 -----------------------------------MVTHSKFPAAGMSR  14

mSOCS1   51 PGDTHFR--TFRSHSDYRRITRTSALLDACGFYWGPLSVHGAHERLRAEP  98
              |.||..|   ||.|.|:|:.:.....|...||||..::...|:..|.|||
mSOCS3   15 PLDTSLRLKTFSSKSEYQLVVNAVRKLQESGFYWSAVTGGEANLLLSAEP  64

mSOCS1   99 VGTFLVRDSRQRNCFFALSVKMASGPTSIRVHFQAGRFHLDGS-RET---  144
              .||||:|||..:..||.||||..||..::|:.:.|.|.|... |.|
mSOCS3   65 AGTFLIRDSSDQRHFFTLSVKTQSGTKNLRIQCEGGSFSLQSDPRSTQPV  114

mSOCS1  145 --FDCLFELLEHYV-----------------------------AAPRR-  161
              |||:.:|:.||:                             :.|:|
mSOCS3  115 PRFDCVLKLVHHYMPPPGTPSFSLPPTEPSSEVPEQPPAQALPGSTPKRA  164

mSOCS1  162 ------------MLGAPLRQRRVRPLQELCRQRIVAAV-GRENLARIPLN  198
                        :|..|| ...|..||.|||:.:...: ..|.:.::| .
mSOCS3  165 YYIYSGGEKIPLVLSRPL-SSNVATLQHLCRKTVNGHLDSYEKVTQLP-G  212

mSOCS1  199 PVLRDYLSSFPFQI 212 (Uniprot ID: O35716)
            |: |::|..:...:
mSOCS3  213 PI-REFLDQYDAPL 225 (Uniprot ID: O35718)
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Fig. 2. Structure and functional domains of SOCS1 and SOCS3. Curated mouse and human SOCS1 and SOCS3 protein sequences from UNIPROT database were aligned using EMBOSS Needle algorithm (https://www.ebi.ac.uk/Tools/psa/emboss_needle/). Only the mouse SOCS1 and SOCS3 alignment is shown. Human proteins show identical alignment pattern as the mouse proteins (not shown). Color-coded amino acids identify SH2 (green) and SOCS box (magenta) domains, and the extended SH2 (ESS, blue) and KIR (red) sequence motifs. Note that even though mouse and human SOCS1 and SOCS3 show very high degree of sequence conservation, SOCS1 and SOCS3 are divergent and show marked differences within the SH2 domain and the N-terminal sequence that may hold key to distinct growth regulatory and tumor suppression functions of SOCS1 and SOCS3 in hepatocytes. SOCS1 additionally regulates the paradoxical oncogenic potential of the cell cycle inhibitor CDKN1A (see the text and Fig. 5 for details).

the loss of signal regulatory mechanisms may contribute to uncontrolled growth of neoplastic cells. Among the regulators of cytokine and growth factor signaling, the suppressor of cytokine signaling (SOCS) family proteins SOCS1 and SOCS3 have emerged as important tumor suppressor proteins in the liver. In this review, we will focus on SOCS protein-dependent regulation of hepatocyte proliferation during liver regeneration and in malignant growth.

2. SOCS family proteins

SOCS proteins were discovered as feedback negative regulators of the JAK-STAT signaling pathway based on the ability of SOCS1 to inhibit IL-6 signaling, JAK activation and STAT phosphorylation [11–13]. The SOCS protein family is comprised of eight members - SOCS1 through SOCS7 and the earlier known CIS1 [14,15]. All SOCS family proteins harbor a conserved SOCS box domain at the C-terminal end, a centrally located SH2 domain, and a highly variable N-terminal portion. Among the SOCS proteins, only SOCS1 and SOCS3 contain the extended SH2 and kinase inhibitory region (KIR) motifs that precede the SH2 domain [16] (Fig. 2). However, they display substantial differences in their N-terminal regions and in primary amino acid sequence within the SH2 domain. Through SH2 domain interaction with phosphorylated tyrosine residues, SOCS1 can directly bind and inhibit activated JAK kinases, whereas SOCS3 binds to cytokine receptors (CytR) and then forms a complex with JAKs, resulting in both cases occlusion of the substrate-binding pocket of JAKs by the SOCS KIR domain [16–19]. In addition, SOCS binding to CytR can block downstream signaling by preventing recruitment and activation of STAT proteins and other signaling molecules. SOCS3 can bind many cytokine and growth factor receptors that signal via STAT3 and inhibit STAT3 activation [15].

The SOCS box contains sequence motifs that interact with Elongin B/C and a member of the Cullin family proteins that may vary with different SOCS proteins. Together they form a complex with the RING-finger containing protein RBX2 and an E2 ubiquitin (Ub) conjugating enzyme to assemble an E3 Ub ligase of the CRL family (Cullin-RING ligase) (reviewed in [20]). This complex allows SOCS proteins to bring cytokine receptors and downstream signaling molecules to the protein ubiquitination machinery, leading to their ubiquitination and subsequent degradation by proteasomes [21,22]. The SH2 domain also allows SOCS proteins to bind phospho-Tyr residues on growth factor receptor tyrosine kinases (RTK), thereby inhibiting recruitment of downstream signaling molecules as well as by promoting ubiquitination and degradation of receptor chains [23–25]. Some SOCS proteins exert a stronger control over RTK or CytR signaling, whereas SOCS1 and SOCS3 can inhibit both CytR and RTKs (reviewed in [23]).

In vitro studies on various cell types have shown that many cytokines can induce each one of the SOCS proteins, which in turn can inhibit an equally vast array of different cytokines and growth factors [26]. Among the cytokines implicated in hepatocyte proliferation, IL-6 and TNFα induce the expression of SOCS1, SOCS2, SOCS3 and CIS1 in the mouse liver, and IL-6 signaling in mouse primary hepatocytes is sensitive to inhibition by both SOCS1 and SOCS3 [27–29]. However, gene knockout mice have documented the selectivity of cytokines that are regulated by different SOCS proteins [23]. Whereas SOCS1 is essential to attenuate inflammatory signaling by the type-II interferon (IFNγ) via the IFNGR1/IFNGR2 heterodimer in the liver and other vital organs of neonatal mice, SOCS3 deficiency causes embryonic lethality due to defective erythropoiesis in the fetal liver, presumably caused by

deregulated erythropoietin signaling [30–33]. Tissue-specific ablation of SOCS3 has revealed its critical functions in regulating IL-6 signaling in macrophages, T cells and in the liver [34–36].

3. Implication of SOCS proteins in hepatocyte proliferation and neoplastic transformation

As TNFα and IL-6 play key roles during liver regeneration, a number of studies have examined the induction of SOCS genes in rodent livers after PH. Campbell et al. reported that PH did not elicit *Socs1* gene expression whereas the *Socs3* gene was rapidly induced in the regenerating mouse liver up to 40-fold within 2 h after PH that lasted for up to 8 h [27]. The *Socs3* gene induction was markedly diminished in mice lacking IL-6. This study also reported that *Socs2* and *Cis1* were weakly induced following PH, although a recent study reported strong induction of *Socs2* within 6 h post-PH [37]. Strong *Socs3* induction following PH was also reported by another group [38]. On the other hand, Sakuda and colleagues observed that the *Socs1* gene was more strongly induced than *Socs3* in the regenerating rat liver [39]. Seki et al. have reported the induction of both *Socs1* and *Socs3* genes in the liver following PH, although *Socs3* was more strongly induced [29]. The variability in SOCS gene expression reported in the above studies warrant a thorough investigation of the kinetics of SOCS gene expression in the regenerating livers, taking into account the age, sex, genetic background and housing conditions (specific pathogen-free versus conventional). The time of surgery and sacrifice should also be considered because the circadian clock can influence hepatocyte proliferation and diurnal changes in the gut microbiome can modulate liver functions [40,41].

Notwithstanding the reported variations in PH-induced expression of *Socs1* and *Socs3* genes, Seki and colleagues implicated both SOCS1 and SOCS3 in regulating liver regeneration [29]. Constitutive expression of either SOCS1 or SOCS3 in the liver through adenovirus-mediated gene transfer inhibited liver regeneration following PH that was accompanied by inhibition of Cyclin D1 expression and DNA replication, and these effects were more pronounced in livers expressing SOCS3 than those expressing SOCS1 [29]. In agreement with this finding, hepatocyte-specific SOCS3 deletion in mice increased hepatocyte proliferation and more rapid restoration of the liver mass following PH [42]. We have shown that *Socs1* knockout mice also showed accelerated hepatocyte proliferation and liver regeneration [43]. The regenerating livers lacking SOCS1 or SOCS3 maintain the 'hepatostat' state, indicating that the growth termination program is not affected by their loss. Consistent with the role of SOCS1 in regulating hepatocyte proliferation, overexpression of miR-155 that targets SOCS1 resulted in increased hepatocyte proliferation with the same accelerated kinetics of liver regeneration, accompanied by increased expression of cyclin D, corroborating the observations in *Socs1* knockout mice [44,45]. Indeed, miR-155 expression was markedly upregulated by PH accompanied by the modulation of SOCS1 expression, whereas ablation of miR-155 resulted in impaired liver regeneration [44]. A recent study showed that SOCS2-deficient mice display increased hepatocyte proliferation up to 48 h post-PH that is attributed to increased levels insulin-like growth factor-I (IGF-I) in the liver [37].

Independent of the studies on *Socs* gene expression following PH and the effect of SOCS deficiency on liver regeneration, a seminal work reported frequent repression of the *SOCS1* gene by promoter CpG methylation in human hepatocellular carcinoma (HCC) specimens in up to 65% of cases [46–48]. This epigenetic mechanism of *SOCS1* gene repression appears to be more frequent in HCC than microRNA-mediated downmodulation, which occurs in other malignancies such as breast cancer [49,50]. *SOCS3* gene was also found to be downmodulated by promoter methylation in HCC specimens, albeit at a much lower frequency (33%) compared to the *SOCS1* gene [51]. These reports predicted a potential tumor suppressor function for SOCS1 and SOCS3 proteins in the liver, a notion that is supported by genetic studies in mice. Yoshimura and colleagues have shown that loss of one copy of the *Socs1* gene in mice increased the susceptibility to diethylnitrosamine (DEN)-induced HCC [52]. We have shown that mice lacking SOCS1 in the whole body or specifically in hepatocytes displayed increased susceptibility to DEN-induced HCC [45]. Loss of SOCS3 in hepatocytes also increases susceptibility to DEN-induced HCC [42,53]. These studies indicate that SOCS1 and SOCS3, despite sharing a high degree of sequence and structural similarities, play essential and non-overlapping functions in regulating physiological liver regeneration and neoplastic growth of hepatocytes. In the following sections, we discuss specific cytokine and growth factor signaling pathways, which are involved in hepatocyte proliferation and regulated by SOCS proteins. We also discuss data that implicate SOCS proteins in cell-intrinsic control mechanisms that thwart deregulated cell proliferation.

4. Regulation of physiological hepatocyte proliferation by SOCS proteins

4.1. SOCS-dependent regulation of the hepatocyte priming

4.1.1. Regulation of hepatocyte TLR signaling by SOCS1

During physiologic liver regeneration, hepatocytes are first primed to exit from quiescent state by the tandem action of two cytokines TNFα and IL-6, which are induced by gut-derived ligands of toll-like receptors (TLR) mainly in Kupffer cells [54]. TLR4 and TLR2/9, which recognize gram-negative and gram-positive bacterial products, respectively, are dispensable for normal liver regeneration. However, participation of MyD88, a critical signaling adaptor shared by most TLR ligands, is critical for the activation of NF-κB in Kupffer cells, and for the production of TNFα and IL-6 in the liver following PH [55]. The priming function of LPS may also result, at least partly, from activation of the complement components C3 and C5, which are essential for efficient liver regeneration, although the underlying mechanisms are unclear [56,57]. A role for SOCS1 in regulating the NF-κB pathway during normal hepatocyte proliferation could be inferred by the requirement of SOCS1 to control TLR signaling [58]. SOCS1-deficient macrophages show increased NF-κB activation and produce elevated amounts of TNFα and IL-6 following LPS stimulation [59,60]. However, two other studies showed that signaling by type-I IFNs, which are also induced by LPS, was shown to be the primary target of SOCS1-mediated regulation in macrophages [61,62]. Nevertheless, SOCS1 has been implicated in regulating TLR activation at multiple signaling nodes [58] (Fig. 3). Recruitment of MyD88 to TLR is facilitated by Toll-Interleukin 1 Receptor (TIR) domain containing Adaptor Protein (TIRAP, also called MyD88-adaptor Like or MAL). SOCS1 has been shown to interact with TIRAP and promote its ubiquitination and proteasomal degradation [63,64]. SOCS1 also targets IRAK1, which is required for the activation of NF-κB downstream of TLR signaling [59,60]. Recent reports show that TRAF6, a component of the IRAK-containing signaling complex is also regulated by SOCS1 and SOCS3 [65]. Finally, the p65 subunit of the NF-κB is itself a target of SOCS1-mediated regulation that was later shown to occur within the nucleus [66–68]. Even though the above studies predict that increased TLR signaling could occur in SOCS1-deficient livers, IL-6 was not elevated in SOCS1-deficient mice after PH [43]. However, this study from our laboratory is confounded by the use of $Socs1^{-/-}Ifng^{-/-}$ mice due to IFNγ-mediated perinatal lethality. Another unanswered question is the identity of the mediators that induce *Socs1* gene expression following PH (Fig. 3). LPS-induced TNFα and IL-6 can stimulate *Socs1* expression. However, it is also possible that TLR-induced type-I IFNs may also contribute to *Socs1* induction, and that SOCS1 might be more critical to regulate IFN-I signaling that can inhibit liver regeneration, than to attenuate TLR signaling as indicated by several studies [61,62,69,70]. Hence, it would be worthwhile to define the role of SOCS1 in hepatocyte priming using, ideally, macrophage- or hepatocyte-specific SOCS1-deficient mice.

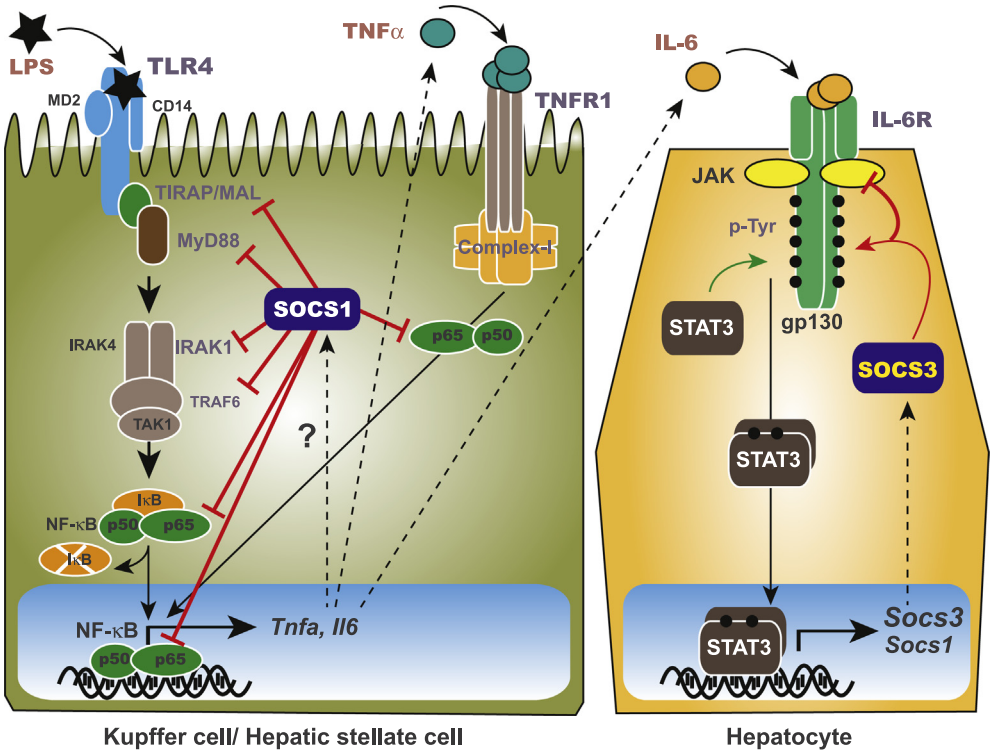

Fig. 3. Regulatory functions of SOCS1 and SOCS3 in hepatocyte priming. Hepatocyte proliferation following partial hepatectomy is dependent on the tandem actions of TNFα and IL-6. LPS arriving via the portal circulation stimulates Kupffer cells and hepatic stellate cells to produce TNFα, which activates the NF-κB pathway to stimulate IL-6 production. IL-6 in turn stimulates hepatocytes by activating STAT3 and increasing cell survival. By controlling several signaling proteins in the LPS-induced TLR4 signaling pathway (TIRAP, MyD88, TRAF6, p65RelA), SOCS1 can potentially regulate the availability of TNFα. SOCS3 induced by IL-6 is a crucial feedback negative regulator of IL-6-stimulated STAT3 signaling during liver regeneration. SOCS3 bind to gp130 subunit of the IL-6 receptor and inhibit JAK activity to mediate its inhibitory functions.

4.1.2. Regulation of TNFα signaling by SOCS1 in hepatocytes

Several studies implicate TNFα and IL-6, produced by Kupffer cells following PH, in promoting hepatocyte survival and proliferation. Whereas IL-6 exerts a direct effect on hepatocytes, TNFα contributes to this process mainly via enhancing IL-6 production [6]. TNFα signals through trimeric TNFR1 receptor complex that can assemble two distinct cytoplasmic signaling platforms called complex-I and complex-II [71,72]. Whereas complex-I activates NF-κB and AP-1 (c-Fos/c-Jun) transcription factors and promotes cell survival, complex-II activates caspases and causes cell death. TNFα can also signal via TNFR2, which activates NF-κB and AP-1, but can indirectly promote the cell death pathway of TNFR1. A fine balance between these cell survival and apoptosis pathways underlie the functions of TNF in maintaining tissue homeostasis. NF-κB activation is crucial for hepatocyte survival during liver regeneration [73]. Early studies on mice lacking TNFR1 showed impaired activation of NF-κB as well as that of AP-1 and STAT3, and reduced DNA synthesis during liver regeneration following PH, implicating TNFα signaling in hepatocyte proliferation [74]. However, these defects were reversed by the administration of IL-6, indicating that TNFα promotes liver regeneration essentially via inducing IL-6 and STAT3 activation. Liver regeneration was not impaired in mice lacking TNFR2 [75]. Surprisingly, a subsequent study on TNFα-deficient mice failed to replicate these findings [76], suggesting the induction of priming signals by factors other than TNFα that activate similar signaling pathways. In this context, it is noteworthy that T lymphocyte-derived lymphotoxin (LT), a member of the TNF family cytokines [77], is implicated in the liver regeneration process via increasing IL-6 production and STAT3 activation [78]. The ability of LTα to bind and signal via TNFR1 could explain why TNFR1 is essential whereas TNFα is dispensable during liver regeneration. TNFR2-deficient mice treated with TNFα strongly upregulate *Socs1*, *Socs2* and *Socs3* genes [79]. Even though the increased rate of DNA synthesis and the rapid restoration of functional liver mass in *Socs1*-null mice [43] could result from the loss of SOCS1-dependent regulation of NF-κB signaling (Fig. 3, discussed in the previous section), direct evidence linking SOCS1 to the regulation of TNFα-induced cell survival and apoptotic pathways in the liver is currently lacking.

4.1.3. Regulation of IL-6 signaling in hepatocytes by SOCS3

IL-6 deficient mice show impaired liver regeneration characterized by markedly reduced induction of the immediate early genes (*c-Myc, c-Fos, c-Jun*) and delayed DNA synthesis [80]. This was also accompanied by necrosis and ballooning degeneration of hepatocytes that are attributed to the lack of STAT3 activation. Delayed proliferation of IL-6-deficient hepatocytes was also confirmed in another report [81]. Subsequent studies addressing the requirement of STAT3 for normal liver regeneration were largely in agreement with these findings. Taub and colleagues reported that DNA synthesis in hepatocyte-specific *Stat3* knockout mice was delayed as in *Il6*$^{-/-}$ mice, but the defective induction of immediate early genes showed differences [82]. Using a similar approach, Haga et al. showed that even though hepatocyte proliferation was impaired in the absence of STAT3, recovery of liver mass was not affected and that this was attributed to AKT-dependent hepatocyte hypertrophy that compensated for the impaired cell proliferation [83]. Similar findings were reported using inducible, hepatocyte-specific STAT3 knockout mice [84]. However, these mice developed an exaggerated inflammatory response during liver regeneration following chemical injury by carbon tetrachloride. These studies indicate that IL-6 signaling has a limited role in normal hepatocyte proliferation but exerts crucial hepatoprotective functions during the acute stress caused by PH or hepatocyte injury.

IL-6 belongs to a cytokine family that signals via receptor complexes containing the gp130 subunit (also known as IL-6Rβ) as the main signal-transducing component [85–87]. As the gp130 chain cannot directly bind IL-6, it relies on the IL-6Rα subunit (also known as gp80) to bind the ligand, which together form a hexameric complex in order to transduce signals. Whereas gp130 is widely expressed in many cell types, IL-6Rα expression is restricted to hepatocytes, hepatic stellate cells, some epithelial cells and leukocytes [88]. However, IL-6Rα can be released in a soluble form, which can bind IL-6 and present it to cells that express gp130. This 'trans-signaling' allows many cell types to respond to IL-6, and plays a key role in mediating the pro-inflammatory functions of IL-6 in immuno-inflammatory diseases and inflammation-associated cancer [89,90]. On the other hand, the classical signaling via membrane-bound IL-6R promotes anti-inflammatory and protective

functions of IL-6 through inhibition of apoptosis and promotion of cell proliferation.

The gp130 subunit of IL-6R complex constitutively interacts with the ubiquitously expressed JAK family kinases JAK1, JAK2 and TYK2, of which JAK1 is crucial for robust IL-6 signaling [91]. JAK3, which is restricted in its expression mostly to hematopoietic lineage cells, is not implicated in IL-6 signaling. Formation of the high-affinity IL-6R complex activates JAK1 through trans-phosphorylation. Activated JAK1 phosphorylates the tyrosine residues on the cytoplasmic domain of gp130 and initiates downstream signaling [85,87,92]. Among the six Tyr residues on gp130, four distal tyrosine residues are implicated in the recruitment and activation of STAT3 and to a lesser extent STAT1 (mostly via the two distal tyrosine residues). Activated STAT3 dimers translocate to the nucleus and bind to response elements in IL-6-inducible genes. Recruitment of SHP2 to the second tyrosine (Y757 in mouse, Y759 in human) on gp130 leads to the activation of RAS-MAPK pathway and NF-IL6 (now called C/EBPβ), which binds to IL-6 response elements in acute phase proteins. IL-6 signaling can also activate the PI3K-AKT pathway and promote cell survival via inducing Mcl-1, which has been reported in primary hepatocytes during liver regeneration and in hepatoma cell lines [87,93,94]. These IL-6 signaling pathways not only promote cell survival and proliferation in the regenerating liver but also contribute to hepatocarcinogenesis [95].

The seminal studies that discovered SOCS family proteins identified SOCS1 through its ability to inhibit IL-6 signaling in macrophages [11,13]. However, subsequent studies using tissue-specific knockout mice have revealed that SOCS1 is dispensable whereas SOCS3 is the key negative regulator of IL-6-induced activation of STAT3 and STAT1 in the liver and macrophages, and that SOCS1 is crucial for attenuating IFNγ signaling [35,96,97]. Systemic injection of IL-6 resulted in rapid and strong induction of SOCS3 in the mouse liver compared to SOCS1, whereas an inverse kinetics was observed following the administration of IFNγ [28]. Both SOCS proteins contribute to balance hepatocyte apoptosis and cell survival during liver injury. Effectively, SOCS1 controls IFNγ-mediated STAT1 activation and apoptosis, while SOCS3 limits IL-6-induced STAT3 activation and pro-survival signaling [98]. Even though STAT3 is activated by a number of cytokines including IL-10 and IFNγ, SOCS3 specially inhibits IL-6 signaling [35,96,97] (Fig. 3). This specificity results from the high affinity interaction of SOCS3 with gp130 chain following its phosphorylation induced by IL-6. Consistent with the requirement of SOCS3 for regulating IL-6 signaling, livers of SOCS3-deficient mice display elevated and prolonged STAT3 activation following PH, and hepatocytes from these mice show sustained STAT3 phosphorylation in response to IL-6 stimulation *in vitro* [42]. Moreover, this study noted that loss of SOCS3 did not result in compensatory *Socs1* gene induction following PH, indicating a crucial role of SOCS3 in controlling IL-6 signaling in hepatocytes.

Through elegant structural studies, Nicola and Babon have elucidated the molecular basis of SOCS3-mediated inhibition of IL-6 signaling [19,99]. This study showed that SOCS3 can bind and inhibit JAK1, JAK2 and TYK2, the JAK family kinases that constitutively associate with gp130 and share an evolutionarily conserved motif called GQM, which is essential for SOCS3 binding and inhibition of IL-6 signaling [19]. The lack of this sequence motif in JAK3 renders it non-susceptible to inhibition by SOCS3 as well as by SOCS1 [19,100]. SOCS3 simultaneously binds activated gp130 and JAKs, and this receptor-mediated proximity positioning is critical for inhibiting JAK activity, whereas the high affinity interaction of SOCS1 with JAKs even in their non-phosphorylated state obviates the need for prior binding to an activated receptor chain to access JAKs [100].

4.1.4. Central role of IL-6-induced SOCS3 in regulating the cell cycle

Even though STAT3 activation by IL-6 is critical for hepatocyte priming and liver regeneration, hyperstimulation of this pathway, achieved through transgenic expression of human soluble gp80 and infusion of human IL-6, inhibited hepatocyte proliferation and delayed liver regeneration [101]. This unexpected inhibition of liver growth by IL-6 was attributed to stronger induction of cyclin-dependent kinase inhibitor 1A (CDKN1A, previously known as p21Waf1/Cip1, generally known as p21), which harbors STAT3 binding sites in its gene promoter [102,103]. Similar observations were reported on primary mouse hepatocytes *in vitro*, wherein IL-6 stimulation inhibited cell proliferation via induction of p21 [104]. This study also showed that hepatocytes from *Socs3*$^{+/-}$ mice (deficient in SOCS3-dependent regulation of IL-6 signaling) are more sensitive to IL-6 mediated inhibition *in vitro*, however hepatocyte proliferation *in vivo* following PH was significantly enhanced in these mice. Moreover, genetic ablation of SOCS3 in hepatocytes strengthened STAT3 signaling following partial hepatectomy and these mice also show increased hepatocyte proliferation and accelerated liver regeneration [42]. The reason for this discrepancy - increased IL-6 signaling is inhibitory in the presence of SOCS3 but not in its absence - is not well understood. Gao and colleagues showed that the IL-6-mediated inhibition of hepatocyte proliferation *in vitro* was abolished by HGF available from non-parenchymal cells [104]. As discussed below and in section 5.3, increased p21 expression observed in *Socs3*$^{+/-}$ hepatocytes appears to involve IL-6-mediated induction of SOCS3 and subsequent SOCS3-dependent modulation of the p53 pathway and this may contribute to growth inhibition by IL-6.

The tumor protein 53 (TP53, better known as p53), which is inactivated in many cancers, is a key tumor suppressor protein that induces genes involved in cell cycle arrest, DNA repair, senescence and apoptosis [105]. The induction of *Cdkn1a* is occurs mainly via the p53-dependent transcriptional activation [106] and this pathway has been implicated in the regulation of hepatocyte proliferation during liver regeneration. Following PH, the induction of immediate early genes *c-Myc*, *c-Fos* and *c-Jun* by cytokines and growth factors promote hepatocyte survival and proliferation (Fig. 4, step 1) [4,7,80]. Ablation of *c-Jun* impairs liver regeneration, whereas concomitant deletion of either p53 or CDKN1A has been shown to abrogate the defective hepatocyte proliferation caused by c-Jun deficiency [107,108]. Therefore, c-JUN seems to promote liver regeneration by inhibiting p53-mediated upregulation of CDKN1A (Fig. 4, step 2). CDKN1A has been previously shown to regulate liver regeneration as its deletion increased hepatocyte proliferation [109]. Studies in mouse embryo fibroblasts suggested that SOCS3 could be involved in p53-mediated upregulation of CDKN1A [110]. Subsequently, Gao and colleagues have shown that SOCS3 interacts with p53 and promote its activation in hepatic stellate cells [111]. Therefore, it is possible that SOCS3, which is rapidly induced following PH, presumably following IL-6-mediated STAT3 activation, likely plays a key role in regulating hepatocyte proliferation priming via SOCS3/p53-mediated induction of CDKN1A (Fig. 4, step 3). We propose that impaired liver regeneration caused by transgenic expression of soluble gp80 or infusion of human IL-6 could result from hyper-induction of SOCS3 and SOCS3/p53-mediated upregulation of p21 and blockade of the cell cycle (Fig. 4, step 4), whereas this pathway will be abrogated in *Socs3*-null hepatocytes allowing IL-6-mediated hepatocyte survival and priming to accelerate liver regeneration unhindered.

In the above scenario, it would also be necessary to modulate the regulatory functions of SOCS3 in order to facilitate an orderly progression of liver regeneration. Indeed, such regulation seems to be initiated by TNFα while IL-6 is also being induced. The TNFα-induced protein 3 (TNFAIP3, commonly known as A20) induced by TNFα mediates many hepatoprotective functions by inhibiting pro-inflammatory NF-κB signaling. Ferran and colleagues have shown that A20 also potentiates IL-6/STAT3-mediated proliferation of hepatocytes following PH through downmodulation of SOCS3 and CDKN1A (Fig. 4, step 5) [112,113]. While the downmodulation of SOCS3 has been correlated to the induction of miR-203, it remains to be addressed whether the A20-mediated CDKN1A downmodulation is secondary to reduced SOCS3 expression.

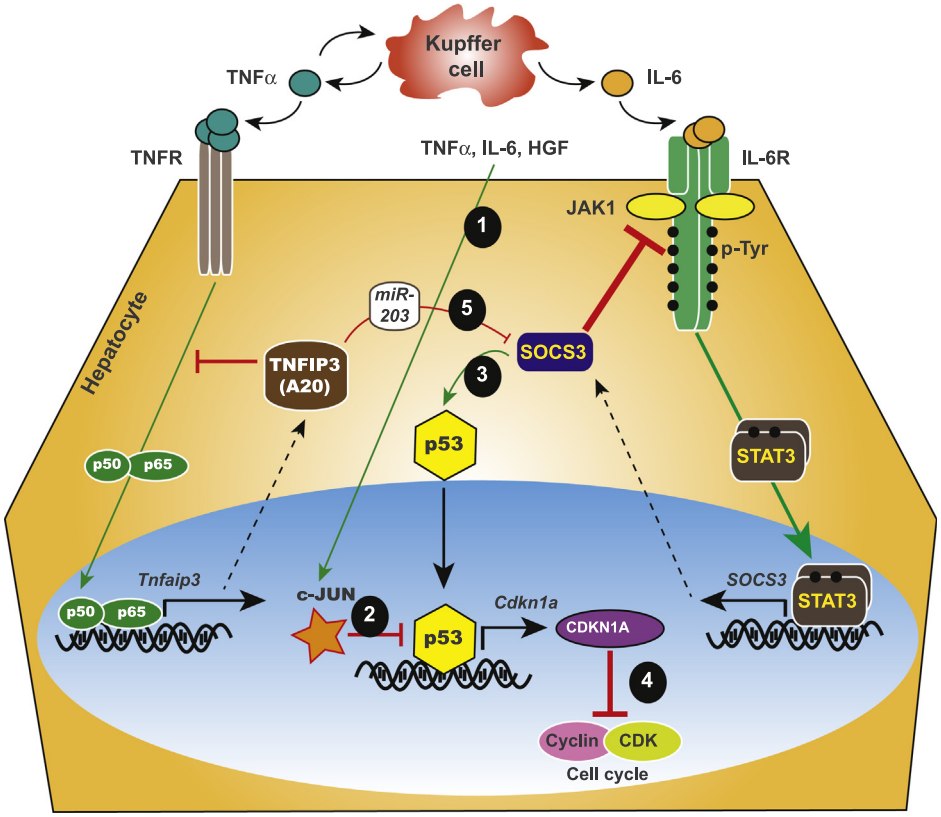

Fig. 4. Intricate functions and regulation of SOCS3 in hepatocyte stimulation by IL-6. In addition to inhibiting IL-6-stimulated JAK-STAT pathway, SOCS3 may also mediate p53-mediated growth regulation. Following PH, cytokines and growth factors induce c-JUN (step 1), which blocks p53-mediated growth inhibition (step 2). Circumstantial evidence suggests that the latter could be mediated, at least partly, by IL-6 stimulated SOCS3, which can activate p53 (step 3) to induce CDKN1A, which inhibits CDK/cyclin complexes and cell cycle progression (step 4). This SOCS3-dependent regulatory pathway could be regulated by TNFAIP3 (a feedback inhibitor of TNFR signaling, also called A20) via inducing miR-203 that targets SOCS3 (step 5). The loss of the SOCS3-dependent regulation of both IL-6 signaling and p53-mediated growth inhibition could explain why SOCS1 deficiency increases liver regeneration, whereas administration of IL-6 inhibits it, presumably via potentiate the p53-medaited inhibitory pathway. See text for details.

4.2. Control of growth factor receptor signaling by SOCS proteins

Even though SOCS proteins were initially discovered and extensively studied as negative regulators of the cytokine-stimulated JAK-STAT pathway, several studies recognized their ability to attenuate growth factor signaling via receptor tyrosine kinases (RTK) as well. Summarizing these data, Trengove and Ward assigned SOCS proteins to three partially overlapping groups that mainly controlled the JAK-STAT pathway, predominantly regulated the RTKs or attenuated both [23]. SOCS1 and SOCS3, which share the maximum homology among SOCS proteins fall in the category that can regulate both JAK-STAT and RTK signaling pathways. Among the several growth factor receptors that are implicated in hepatocyte proliferation, the HGF receptor c-MET and the EGF receptor EGFR (ErbB1) play critical roles in liver regeneration. Indeed, HGF and EGF are designated as 'direct mitogens' whereas other growth factors, cytokines and hormones are considered auxiliary factors that aid in hepatocyte proliferation during liver regeneration [6,9,114]. Both c-Met and EGFR become phosphorylated within 60 h after PH [8], and are clearly regulated by SOCS family proteins as discussed in the following sections.

4.2.1. Regulation of HGF-induced MET signaling by SOCS1

HGF, produced mainly by hepatic stellate cells and stored in the ECM, is released through the activation of matrix metalloproteinases during liver regeneration [115]. Following PH, *de novo* HGF synthesis occurs not only in the liver but also in kidneys and lungs [9]. As the deletion of *Hgf* gene results in embryonic lethality [116], the critical requirement for HGF-induced MET signaling for liver regeneration was demonstrated by deleting MET in adult liver or specifically in hepatocytes in mice, as well as by downmodulating HGF or MET expression using short hairpin RNA (shRNA) in rats [117–119]. These animals showed reduced activation of ERK, delayed cell cycle entry and impaired liver generation following PH, highlighting the crucial role of HGF-MET signaling in hepatocyte proliferation.

The role of SOCS1 in regulating HGF signaling in hepatocytes came to the limelight from our observations that the increased rate of liver regeneration in *Socs1*$^{-/-}$*Ifng*$^{-/-}$ mice (the use of these mice was necessary to overcome the lethality caused by uncontrolled IFNγ signaling in the absence of SOCS1) was not associated with increased IL-6 production or STAT3 activation but was accompanied by increased phosphorylation of ERK and Grb2-associated binding protein 1 (GAB1) [43]. GAB1 is a large adaptor molecule with many tyrosine residues that can recruit myriad of signaling molecules and is implicated in amplifying signaling pathways downstream of many RTKs, particularly MET and EGFR [120,121]. HGF induces phosphorylation of Tyr residues on MET, leading to (i) recruitment of the adaptor protein Grb2 both directly and indirectly that activates the Ras-Raf-ERK pathway, (ii) recruitment and activation of PI3K that results AKT and NF-κB pathways, and (iii) recruitment and activation of STAT3, which collectively promote cell survival and proliferation [122]. GAB1 contains a MET-binding site (MBS) that allows its direct interaction with MET. GAB1 provides docking sites for additional signaling molecules that amplify and sustain the GF-induced signaling pathways [120,121,123–125]. Among these, amplification of the ERK pathway is crucial to MET signaling [122,126]. Forced expression of SOCS1 in hepatocytes has been reported to inhibit HGF-induced STAT3 phosphorylation and intravenous administration of recombinant adenoviral SOCS1 construct inhibited STAT3 activation in the regenerating liver [29]. However, SOCS1 deficiency did not affect hepatic STAT3 activation following PH [43], presumably resulting from unimpaired IL-6 signaling. Nonetheless, in agreement with the finding of Seki et al., forced SOCS1 expression inhibited HGF-induced STAT3 phosphorylation in several hepatoma cells [24,29,43]. Hence, increased and prolonged phosphorylation of ERK and GAB1 in the regenerating livers of SOCS1-deficient livers [43] indicate that endogenous SOCS1 is essential to attenuate only a subset of HGF-induced MET signaling pathways that cannot be controlled by other regulators such as protein Tyr phosphatases [127–129]. Curiously, SOCS1-deficient primary hepatocytes show increased phosphorylation of MET, GAB1 and AKT following HGF stimulation, but not ERK phosphorylation that was amplified in the regenerating liver,

suggesting context-dependent modulation of MET signaling pathways by SOCS1 in hepatocytes that may result, possibly, from co-operation of MET with other GF receptors *in vivo* [24,43,129]. In addition to SOCS1, SOCS3 has also been reported to inhibit HGF-induced STAT3 phosphorylation in hepatocytes [29].

Investigating the mechanisms underlying the SOCS1-dependent regulation of MET signaling using hepatoma cell lines forcibly expressing SOCS1, we have recently shown that SOCS1 directly interacts with MET via the SH2 domain [130]. MET tyrosine kinase activity was dispensable for this interaction even though active MET kinase interacted more strongly with SOCS1. Recent data on the intricacies of SOCS1 binding to JAK kinases even in their non-phosphorylated state indicate that the availability of SOCS1 is the critical parameter for regulating the JAK-STAT pathway [100]. This raises the possibility that the same mode of interaction may occur in SOCS1-mediated regulation of the MET RTK. We have also shown that SOCS1 promoted polyubiquitination of MET via K48-dependent ubiquitin chain elongation leading to proteasomal degradation of the MET receptor, and that this pathway occurred independently of the CBL-mediated MET downmodulation that occurs via the endosomal pathway [131]. Our unpublished data indicate that SOCS1 also regulates the stability of GAB1, although this may occur secondary to MET downmodulation.

The increased activation of MET in the regenerating livers of SOCS1-deficient mice may also result from increased bioavailability of HGF. The promoter region of HGF contains IL-6 response elements, and increased expression of IL-6 following PH could contribute to the raising levels of systemic HGF in the regenerating liver [4,132]. Even though neither loss of SOCS1 nor that of SOCS3 augments serum IL-6 levels following PH [42,43], hepatic HGF levels may be modulated by SOCS1. HGF is stored in abundant quantities within the extracellular matrix of the liver and is rapidly released by the action of uPA following partial hepatectomy [133]. Hepatic uPA becomes activated throughout the remnant liver within 5 min of PH [4]. Cleavage by uPA renders the inactive, ECM-bound monomeric HGF into active homodimers. Other matrix remodeling enzymes also influence the release of matrix-associated HGF following PH [115,134]. The induction of matrix metalloproteinase 9 (MMP9) by TNFα could also be responsible for its priming effect on liver regeneration via releasing HGF from the ECM [135,136]. The potential role of SOCS1 in regulating TLR signaling (discussed earlier) raises the possibility that SOCS1 may regulate hepatic HGF levels during liver regeneration.

4.2.2. Regulation of EGFR signaling by SOCS3

EGFR signaling can be elicited by many of the seven EGF family members, particularly EGF, TGFα and amphiregulin [137]. Whereas EGF is constantly produced by duodenal Brunner's glands and salivary glands and can act on hepatocytes in an endocrine fashion, heparin-bound EGF (HB-EGF) produced by Kupffer cells, and TGFα and amphiregulin produced by hepatocytes can act in paracrine and autocrine manner, respectively, during liver regeneration [114]. Whereas genetic ablation of TGFα does not affect liver regeneration, removal of salivary gland source of EGF and deletion of or HB-EGF or amphiregulin compromises liver regeneration indicating partially overlapping roles of EGFR ligands [138–141]. Unlike HGF which signals via the MET homodimer, EGF signals via EGFR1 (ErbB1) that can form a homodimer or a heterodimer with EGFR2 (ErbB2) or ErbB3, and stimulate Ras-Raf-ERK and PI3K-AKT signaling pathways to promote cell growth, adhesion and migration [137]. That EGFR signaling is crucial for uninterrupted liver regeneration was demonstrated by hepatocyte-specific ablation of EGFR in adult mice and shRNA-mediated inhibition of EGFR expression in rats, resulting in reduced expression of cyclin D1, delayed cell cycle entry, increased TNFα expression and cell death in the regenerating liver [142,143]. Even though increased MET expression was observed in the EGFR-downmodulated rats, obviously this did not compensate for the loss of EGFR signaling, indicating non-overlapping roles of these RTK pathways in liver regeneration [143].

SOCS1 and SOCS3 are induced by EGF in epithelial cells, followed by their recruitment to the Tyr-phosphorylated EGFR, resulting in its ubiquitination and proteasomal degradation [144]. However, in hepatocytes, only SOCS3 but not SOCS1 was able to attenuate EGFR-stimulated STAT3 phosphorylation [29]. Indeed, the ability of SOCS3 to attenuate STAT3 activation downstream of IL-6, MET and EGFR presumably accounts for the severe impairment of liver regeneration in mice overexpressing SOCS3 in hepatocytes than in mice expressing SOCS1 [29]. Following EGF stimulation, SOCS3-deficient primary hepatocytes showed increased activation of STAT3 and ERK, which also occur in the regenerating livers of hepatocyte-specific SOCS3 knockout mice *in vivo* following PH [42]. These reports highlight the requirement of SOCS3 to attenuate EGFR signaling during physiological liver regeneration.

Two other SOCS family members, SOCS4 and SOCS5 have also been shown to bind EGFR and attenuate signaling. An early study on orthologs of SOCS proteins in drosophila showed that transgenic expression of SOCS36E, the ortholog of human SOCS5, resulted in developmental defects similar to those caused by exacerbated JAK-STAT or EGFR signaling [145]. EGFR signaling in drosophila was shown to induce SOCS36E, which attenuated EGFR-stimulated normal cell growth and neoplastic transformation caused by EGFR overexpression [146]. Following the initial description of SOCS36E, human SOCS5 and its closest relative SOCS4 were reported to be induced by EGFR signaling in human HeLa cells [147]. Human and mouse SOCS5 promoted the degradation of EGFR in a SOCS-box-dependent manner that occurred independently of ligand binding [147,148]. SOCS4 has also been reported to promote degradation of EGFR [149]. Whether SOCS4 or SOCS5 can modulate EGFR-mediated hepatocyte proliferation is not yet reported, but it is likely that they may play a secondary role as SOCS3 exerts a dominant regulation over EGFR signaling.

5. SOCS-dependent regulation of neoplastic hepatocyte growth

Most of the cytokines and growth factors involved in physiological liver regeneration also play a key role in neoplastic hepatocyte growth leading to HCC. Whereas hepatocyte proliferation during physiological liver regeneration occurs rapidly and is terminated upon achieving a functional liver mass, the failure to achieve hepatostat is a key driving force behind neoplastic hepatocyte growth that eventually escape the physiological control mechanisms that regulate cell proliferation, restrict the liver size and cause HCC. In most instances, HCC arises in cirrhotic livers that result from chronic inflammation in response to persistent and recurring injury to hepatocytes caused by hepatitis viruses, alcohol abuse and obesity. Progressive replacement of the liver parenchyma with fibrous tissue results in compensatory hepatocyte proliferation and acquisition of stem cell-like properties, which are driven by cytokines and growth factors (e.g., TNFα, IL-6, HGF, TGFα) that become abundant in the inflammatory milieu of the fibrotic liver [150–153]. The recurring cycles of hepatocyte proliferation promotes accumulation of genetic and epigenetic lesions leading to activation of oncogenic signaling pathways (e.g., CTNNB1, NFE2L2, TERT) and/or inactivation of tumor suppressor proteins (e.g., TP53, PTEN, SOCS1, SOCS3, etc.) [152,154–157]. Accumulation of multiple genetic lesions enables the pre-neoplastic cells to gain the ability to undergo ligand-independent proliferation (e.g., MET receptor amplification), resist cell death, invade tissues and undergo extra-hepatic metastasis. In the following sections, we briefly discuss the cytokines and growth factors implicated in the development of HCC and are regulated by SOCS proteins.

5.1. SOCS proteins in inflammation-driven liver cancer

Chronic hepatic inflammation associated with hepatitis virus infections, noxious chemicals and obesity promotes hepatocarcinogenesis through increased production of inflammatory cytokines, among which

TNFα and IL-6 play key pathogenic roles [158,159]. Consistent with the role of lymphotoxin in hepatocyte proliferation (discussed in Section 4.1.2), recent studies implicate other TNF-family cytokines LTβ and LIGHT derived from CD8+ T lymphocytes and natural killer T cells in HCC pathogenesis [160,161]. Whereas the TNF family cytokines promote HCC via canonical and non-canonical pathways of NF-κB activation (TNFR: IKKβ/p65-RelA; LTβR: IKKα/p52-RelB), IL-6 potentiates oncogenic STAT3 activation [162–164]. Deregulated NF-κB pathway can promote HCC via stimulation of pro-inflammatory cytokine production, particularly IL-6, as well as via inducing anti-apoptotic proteins such as BCL-2, FLIP, c-IAP, etc., which can counter TNFα-induced apoptosis pathways in hepatocytes and in stellate cells that promote liver fibrosis [162,165]. On the contrary, IKKβ kinase activated by TNFα exerts a tumor suppressor role by attenuating ROS accumulation and inhibiting the consequent activation of pro-carcinogenic JNK and STAT3 activation in hepatocytes [166]. Indeed, STAT3 activation, which occurs in 60% of human HCC, shows an inverse with NF-κB activation, supporting NF-κB-mediated negative regulation of STAT3 activation. Therefore, sustained pro-inflammatory signaling and STAT3 activation downstream of IL-6 and growth factors (EGF, HGF) appear to be the major oncogenic mechanisms in HCC pathogenesis [162,166]. Increased IL-6 production and consequent STAT3 activation underlies the increased susceptibility of male mice to DEN-induced carcinogenesis [158]. Female sex hormones attenuate IL-6 production and HCC, which explains the preponderance of HCC among men. Work from the Karin Lab has also shown that HCC progenitor cells acquire the ability to produce autocrine IL-6 that promote cancer progression [167]. STAT3 signaling promotes HCC mainly by increasing hepatocyte survival and proliferation via induction of anti-apoptotic proteins BCL2, BCL-xL and MCL1 and cyclin D1, although its non-nuclear functions that promote cell metabolism and migration may also contribute to tumor progression [162,168].

In the liver, SOCS1 and SOCS3 exert cell-intrinsic antitumor functions within hepatocytes as revealed by increased susceptibility of mice with hepatocyte-specific ablation of *Socs1* and *Socs3* genes to HCC [42,45,53]. SOCS1 and SOCS3 can control hepatocarcinogenesis by regulating hepatic fibrogenesis and thereby reducing inflammatory cytokine and growth factor production by stellate cells and macrophages [36,52,169,170]. SOCS3-deficient livers show increased STAT3 phosphorylation following DEN injection that was accompanied by increased expression of genes coding for BCL2, BCL-xL, MYC and Cyclin D1 [42,53]. Given that SOCS3-deficient hepatocytes show elevated and sustained STAT3 phosphorylation following IL-6 or EGF stimulation [42], attenuation of oncogenic STAT3 signaling appears to be a key tumor suppressor mechanism of SOCS3 in hepatocytes. Whether IL-6 and STAT3 are crucial for the increased susceptibility of hepatocyte-specific SOCS3-deficient mice to HCC, and whether SOCS3 binding to the gp130 subunit of IL-6R is essential for its tumor suppression, are key questions that remain to be addressed. In contrast to SOCS3, SOCS1 does not appear to control inflammatory cytokine signaling within hepatocytes during HCC pathogenesis. SOCS1 can potentially regulate TLR, TNF and IL-6 signaling in hepatocytes (discussed in earlier sections), but SOCS1 deficiency did not affect TNF induced NF-κB phosphorylation, systemic IL-6 production or hepatic STAT3 phosphorylation following DEN injection, suggesting that the antitumor function of SOCS1 is exerted on other oncogenic pathways [45,58].

5.2. Regulation of growth factor RTKS by SOCS proteins in HCC

Additional tumor suppressor functions for SOCS3 in the liver was indicated by the ability of SOCS3 to attenuate EGF and HGF signaling in hepatocytes and increased EGF-induced STAT3 and ERK phosphorylation in SOCS3 deficient hepatocytes [29,42]. Seki et al. also reported inhibition of HGF-induced STAT3 activation by SOCS1, however SOCS1-deficient hepatocytes did not show increased or sustained STAT3 activation, presumably due to the availability of SOCS3, but showed increased ERK activation downstream of MET signaling [29,43]. In HCC cells, SOCS1 attenuated HGF-stimulated MET signaling pathways, cell proliferation and migration. Mechanistically, SOCS1 interacts with the MET receptor and promotes its ubiquitination and proteasomal degradation of activated MET [130]. Whether EGFR and MET oncogenic signaling pathways are crucial targets of tumor suppression by SOCS3 and SOCS1 has not been addressed yet. Similarly, how methylation of SOCS1 and SOCS3 impacts on MET and EGFR protein levels in human HCC specimens needs to be examined. Nonetheless, the preclinical models of mice lacking SOCS1 or SOCS3 in hepatocytes provide additional support for therapeutic targeting of RTK signaling in HCC [24,171].

5.3. SOCS-dependent regulation of cell cycle control mechanisms in HCC

While investigating the cellular senescence program induced by oncogenic STAT5 signaling in fibroblasts, Ferbeyre and colleagues discovered that SOCS1 enables p53 activation by acting as a bridge between p53 and its upstream kinases ATM and ATR, which phosphorylate p53 and promote its transcriptional activity [172]. Following this seminal report, a similar role for SOCS3 was reported in hepatic stellate cells [111,172]. By regulating DNA repair, senescence, apoptosis and cell proliferation, p53 functions as a master tumor suppressor and thus is often mutated in many cancers [105]. Most p53 mutations in HCC seem to occur late during pathogenesis in the western world, even though aflatoxin, prevalent in certain geographical areas, can cause p53 mutation specifically at codon 249 [154]. Therefore, the reports implicating SOCS1 and SOCS3 in p53 functions raise the possibility that loss of SOCS1 or SOCS3 in HCC may compromise the tumor suppressor functions of wildtype p53 early during tumorigenesis. Testing this prediction in SOCS1 deficient mice revealed that SOCS1 deficiency did not impair p53 activation or induction of its target genes in the liver following genotoxic stress induced by DEN [45]. However, SOCS3 appears to substitute for SOCS1 in activating p53 following genotoxic stress to hepatocytes in SOCS1-deficient mice (Khan et al., manuscript in preparation), suggesting that at least part of the tumor suppressor functions of SOCS1 and SOCS3 could be mediated via p53. As a corollary, at least part of the p53 functions as tumor suppressor would require SOCS1 and SOCS3, and this may have implications for therapeutic strategies aimed at restoring wildtype p53 functions in HCC [173].

Even though SOCS1 deficiency alone did not compromise p53 activation, this study revealed an unexpected role of SOCS1 in controlling the deleterious functions of cyclin-dependent kinase inhibitor CDKN1A (p21) [45]. By inhibiting CDKs at several stages of the cell cycle, CDKN1A functions as a tumor suppressor. However, many studies have reported elevated CDKN1A expression in tumor tissue specimens of many cancers including HCC (Reviewed in [106]). Indeed, CDKN1A can become oncogenic by phosphorylation events that impair its nuclear translocation and promote its cytosolic retention, where it can inhibit apoptotic pathways (Fig. 5). In the livers of SOCS1-deficient mice exposed to DEN, the *Cdkn1a* gene is upregulated and CDKN1A protein accumulates in the cytosol [45]. Primary hepatocytes from SOCS1-deficient mice indicate that increased activation of the PI3K-AKT pathway downstream of RTK signaling promotes CDKN1A phosphorylation and cytosolic retention. In addition to transcriptional upregulation, SOCS1 regulates the protein levels of CDKN1A by promoting its ubiquitination and proteasomal degradation [45]. This study from our laboratory indicates that loss of SOCS1-dependent regulation of RTK signaling not only promotes cell proliferation but also relieves the regulatory control exerted by CDKN1A. The inability of SOCS3 to compensate for SOCS1 deficiency to regulate CDKN1A protein levels in hepatocytes partly explains the non-overlapping tumor suppressor roles of SOCS1 and SOCS3 in the liver.

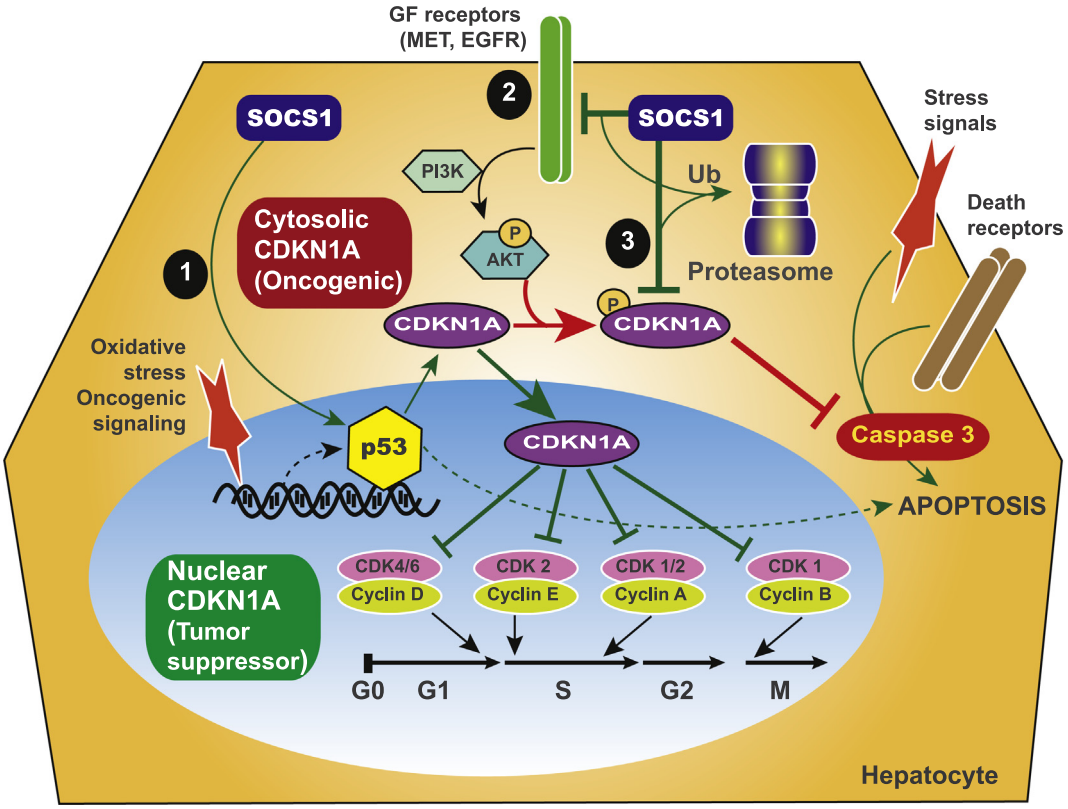

Fig. 5. SOCS1-dependent regulation of the proto-oncogenic roles of CDKN1A. SOCS1 can exerts its tumor suppressor role in hepatocytes by three mechanisms: (1) by inducing p53 activation and induction of p53-dependent tumor suppressor genes, (2) inhibition of oncogenic MET signaling by promoting its ubiquitination and proteasomal degradation, and (3) by blocking the paradoxical oncogenic roles of CDKN1A. Within the nucleus CDKNA inhibits CDK/cyclin complexes and blocks cell cycle progression. However, AKT-dependent phosphorylation of CDKN1A downstream of deregulated growth factor signaling (for example, increased MET signaling in the absence of SOCS1) retains it in the cytosol, wherein it inhibits apoptosis pathways and promotes oncogenesis. SOCS1 inhibits cytosolic CDKN1A by promoting its ubiquitination and proteasomal degradation.

6. Exploitation of SOCS proteins to modulate hepatocyte growth for therapy

The knowledge on SOCS-dependent control of hepatocyte proliferation can be exploited for therapeutic purpose in two ways. On one hand, SOCS1 and SOCS3 could be used to inhibit cancer growth. On the other hand, they may be targeted to enhance hepatocyte proliferation in order to promote liver regeneration or to produce engineered liver for transplantation.

6.1. Using SOCS proteins and their derivatives to inhibit cancer growth

The pioneering works of Johnson and colleagues led to the development of a SOCS1-mimetic peptide based on hydropathic complementarity to the JAK2 activation loop (reviewed in [174]). This peptide, called Tkip, shows a partial homology to SOCS1 KIR domain and was able to inhibit inflammatory cytokine signaling and inhibit prostate cancer cell proliferation, and attenuate the severity of inflammatory and autoimmune diseases such as psoriasis and experimental autoimmune encephalomyelitis [175,176]. Subsequent studies from this group used the SOCS1-KIR peptide that was also equally effective in attenuating inflammatory cytokine signaling *in vivo* [177,178]. Another group led by Marasco and colleagues used linear peptides of SOCS1-KIR and SOCS3-KIR regions, improved their ability to inhibit JAK2 kinases, and showed their utility to attenuate inflammatory skin conditions and growth of triple negative breast cancer cells [179–181]. Hawiger and colleagues rendered full length SOCS1 and SOCS3 cell permeable and reported their efficacy in attenuating inflammatory conditions of the liver [182,183]. The findings that SOCS1 and SOCS3 are released in exosomes and that these microvesicles are effective in attenuating inflammation in lungs raise the possibility of using this approach for SOCS delivery to cancer cells [184]. SOCS1 gene therapy using adenoviral vectors has been shown to be effective in inhibiting tumor growth in preclinical models of diverse cancers including HCC by cooperating with other cancer treatments such as chemotherapy, radiation, oncolytic virus and immune checkpoint therapy [185–188]. These reports raise the hope of exploiting SOCS1 and SOCS3 to complement the conventional and emerging cancer treatment approaches, but achieving this goal depends on optimizing safe and efficient ways of delivering SOCS proteins and their biologically active derivatives to tumors.

6.2. Targeting SOCS proteins to promote liver growth

Liver transplantation remains the only curative therapy for terminal liver illnesses caused by infectious diseases, fibrosis, cancer and, in recent decades, the obesity-associated non-alcoholic steatohepatitis. However, the demand for liver tissue for transplantation far exceeds the supply of donor livers, and this trend is only expected to worsen in the next two decades [189]. To tackle this situation, various approaches of liver regenerative medicine are being pursued. These efforts range from repopulating the liver with healthy primary hepatocytes, or hepatocytes differentiated from mesenchymal stem cells and induced pluripotent stem cells, to *in vitro* engineering of liver tissue through organoid culture and three-dimensional bioprinting of hepatocytes and stromal cells. Despite impressive advances, these approaches face significant challenges that could be mitigated by progressively exploiting the tremendous increase in our understanding of the cellular components and signaling pathways involved in liver regeneration [190]. For example, manipulating hepatocytes to improve their proliferative capacity would

boost the expansion of infused hepatocytes and transplanted liver tissue. In this context, transient silencing of SOCS1 or SOCS3 in infused hepatocytes and engineered liver tissues could be considered to boost their expansion potential. This can be achieved, for example, through the use of microRNAs targeting SOCS1 (miR-155 [44]) or SOCS3 (miR-203 [191]) or antagonistic peptide such as the one described for SOCS1 [192].

7. Conclusion

SOCS1 and SOCS3 are the most closely related members of the SOCS family, yet they control distinct cytokine and growth factor signaling pathways implicated in hepatocyte proliferation. At the hepatocyte priming stage, the functions of SOCS1 remain nebulous whereas SOCS3 is crucial to attenuate IL-6 signaling. In the hepatocyte proliferation stage, SOCS1 controls MET signaling whereas SOCS3 regulates EGFR signaling. SOCS1 and SOCS3 share the ability to activate the p53 tumor suppressor, whereas SOCS1 additionally controls the paradoxical oncogenic functions of CDKN1A. Loss of these regulatory controls caused by epigenetic repression of *SOCS1* and *SOCS3* genes in HCC likely contributes to cancer progression. Whereas SOCS1 and SOCS3 could be exploited in cancer therapeutics, targeting them may find application in regenerative medicine to restore the liver mass.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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