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Review

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Key role of interferon regulatory factor 1 (IRF-1) in regulating liver disease: progress and outlook

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Abstract: Interferon regulatory factor 1 (IRF-1) is a member of the IRF family. It is the first transcription factor to be identified that could bind to the interferon-stimulated response element (ISRE) on the target gene and displays crucial roles in the interferon-induced signals and pathways. IRF-1, as an important medium, has all of the advantages of full cell cycle regulation, cell death signaling transduction, and reinforcing immune surveillance, which are well documented. Current studies indicate that IRF-1 is of vital importance to the occurrence and evolution of multifarious liver diseases, including but not limited to inhibiting the replication of the hepatitis virus (A/B/C/E), alleviating the progression of liver fibrosis, and aggravating hepatic ischemia-reperfusion injury (HIRI). The tumor suppression of IRF-1 is related to the clinical characteristics of liver cancer patients, which makes it a potential indicator for predicting the prognosis and recurrence of liver cancer; additionally, the latest studies have revealed other effects of IRF-1 such as protection against alcoholic/non-alcoholic fatty liver disease (AFLD/NAFLD), cholangiocarcinoma suppression, and uncommon traits in other liver diseases that had previously received little attention. Intriguingly, several compounds and drugs have featured a protective function in specific liver disease models in which there is significant involvement of the IRF-1 signal. In this paper, we hope to propose a prospective research basis upon which to help decipher translational medicine applications of IRF-1 in liver disease treatment.

Key words: Interferon regulatory factor (IRF-1); Hepatitis virus; Liver fibrosis; Hepatic ischemia-reperfusion injury (HIRI); Liver cancer

1 Introduction

Interferon regulatory factor 1 (IRF-1), as a primary member of the IRF family, was initially identified as the transcriptional activator to interferon-β (IFN-β), which had been defined as a key cytokine peculiarly bound to the IFN promotor sequence along with IRF-2, even if a competitive inhibitory relationship between IRF-1 and IRF-2 was inescapable (Yan YH et al., 2020). Even so, a cooperative mechanism within IRFs was unmasked in certain conditions. For example, the non-canonical pyroptotic cell death signaling is especially depicted by the synergistic enhancement of cell-type-specific responses by IRF1 and IRF2 through induction of Caspase-4 (Cas4)/Gasdermin D signaling in human samples and mouse models (Thygesen and Stacey, 2019); meanwhile, the DNA-binding domain of IRF-1 interacts with IRF-3 to augment the IRF-3 activation in the innate immune response to virus defense (Wang JJ et al., 2020). These findings indicated that both competitive and cooperative roles might exist within IRFs under certain circumstances.

Human IRF-1 is mapped to the long arm of chromosome 5 (5q31.1) with a total length of 7.72 kb, where a 495-bp promoter contains nine introns and ten exons (Harada et al., 1994). Being acquainted with a multi-fold transcriptional factor, the N-terminus of IRF-1 embraces a conservative DNA-binding domain where it takes the shape of a 3-helix–4-β-sheet–3-loop motif

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to recognize IFN-stimulated response elements (ISREs), while the C-terminus contains the IRF-associated domain 2 that is in charge of interacting with other homologous and heterogeneous proteins (Yanai et al., 2012; Chen et al., 2013). Usually, IFN-γ activated the *IRF-1* gene through the Janus kinase (JAK)/signal transducer and activator of transcription 1 (STAT1) signaling transduction; phosphorylated STAT1 induced γ-activated factor (GAF) activation that was then translocated into the nucleus and coupled on the IFN-γ activation site (GAS) to activate IRF-1 expression. Subsequently, a cluster of IFN-stimulated gene (ISG) sequences (containing conservative ISREs) was launched and thus biological regulatory potency was set off (Rosain et al., 2023). Research has shown that the unpredictable up-regulation of the *IRF-1* gene was revulsive to the stimulation of virus, double-stranded DNA (dsDNA), double-stranded RNA (dsRNA), IFNs, interleukins (ILs), concanavalin A (ConA), and retinoid acid (Pan et al., 2018; Zhou et al., 2022). However, in-depth manifestation revealed that IRF-1 was involved not only in the response to cellular IFN modulation, parasite invasion, virus infection, and cytokines stimulation, but also in the innate immune response to cell growth and oncogene susceptibility transformation, ranging from induction to special cell death patterns such as cell apoptosis, autophagy, pyroptotic death, and ferroptosis (Thygesen and Stacey, 2019; Hojo-Souza et al., 2020; Zhang LM et al., 2022; Zhang Y et al., 2022).

Over the previous several decades, liver diseases have become a focal health issue in humans, with an ascending incidence and a fatality rate at the top rank of all diseases globally. Existing statistics show that over 2 million people die from liver-related diseases each year, with approximately two-thirds occurring in males, accounting for about 4% of all deaths in the world (Devarbhavi et al., 2023). This brutal situation has motivated the development of innovative targets and therapeutic pathways. Recently, the unheeded role of IRF-1 in liver-related diseases has been expounded in the light of experimental and clinical evidence, but the problem of the poor elucidation of its pronounced mechanisms and translational medicine research remains to be explored (Assadiasl et al., 2018; Klune et al., 2018; Yang et al., 2018; Komoll et al., 2021). Therefore, a comprehensive investigation and discussion of IRF-1 and the strength of its multiplicity in liver-related diseases are needed. Thus far, the current review is the first to emphasize summarizing a vast body of literature on the role of IRF-1 in hepatitis, liver fibrosis, hepatic ischemia-reperfusion injury (HIRI), liver cancer, alcoholic/non-alcoholic fatty liver disease (AFLD/NAFLD), and other unappreciated liver diseases (Fig. 1).

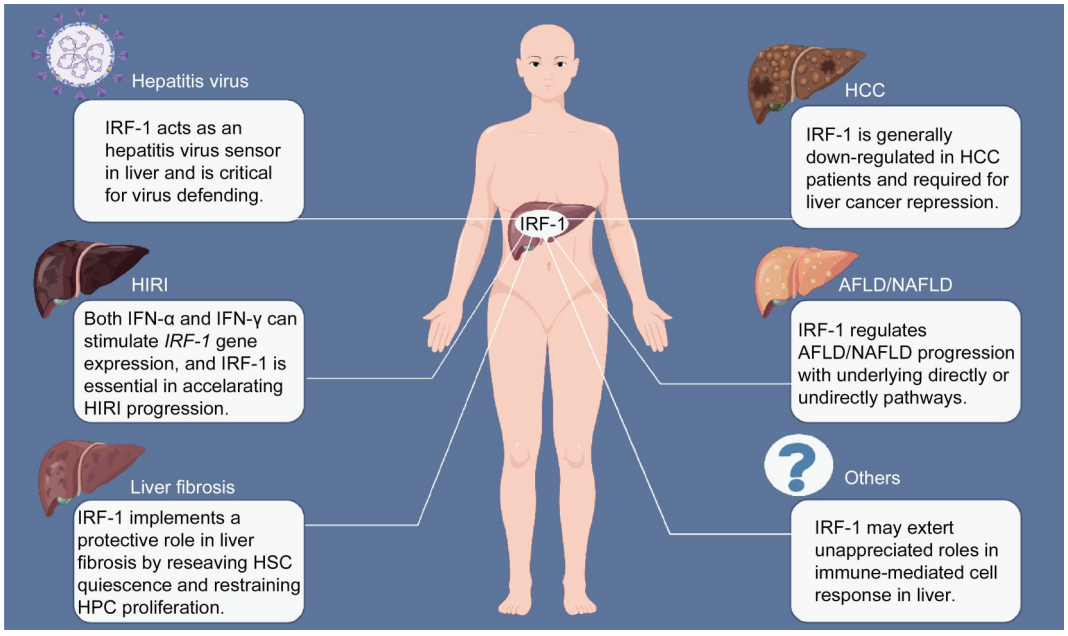

Fig. 1 Overview of the roles of IRF-1 in regulating liver diseases. IRF-1: interferon regulatory factor 1; HCC: hepatocellular carcinoma; IFN: interferon; AFLD/NAFLD: alcoholic/non-alcoholic fatty liver disease; HIRI: hepatic ischemia-reperfusion injury; HSC: hepatic stellate cell; HPC: hepatic progenitor cell.

IRF-1 is generally expressed in normal liver at low levels; however, the imbalanced expression of IRF-1 caused by multiple inducements is a crucial basis for the mediation of various liver-related diseases, including hepatitis, hepatocellular carcinoma (HCC), HIRI, liver fibrosis, AFLD/NAFLD, and other unappreciated diseases.

2 IRF-1 and hepatitis

2.1 IRF-1 and hepatitis B virus

The latest data indicate that 296 million people were tested for being a hepatitis B e antigen-positive ($HBeAg^+$) carrier, and the World Health Organization (WHO) estimates that the prevalence of globally chronic hepatitis B virus (HBV) infection is approximately 3.5% in humans (Jeng et al., 2023). Despite the availability of nucleoside or its analogues being effective in chronic HBV infection, completely curative methods for treating HBV do not currently exist. Some authors consider that the progression of HBV patients is closely linked to the interaction of both host immune status and virus activity (Tan and Schreiber, 2020). IRF-1, as an immune-related factor and an antivirus enhancer for IFN signaling, is thought to have protective effects against HBV infection. In a pioneering study, through backcrossing transgenic mice with a high-level replication of HBV and *IRF-1* knockout mice, $HBeAg^+$ mice with the phenotype of IRF-$1^{+/-}$ or IRF-$1^{-/-}$ were screened, and Guidotti et al. (2002) showed that IRF-$1^{-/-}$ mice manifested a higher capacity of HBV DNA in liver tissue compared to IRF-$1^{+/-}$ mice in the basal condition. Shi and Guan (2009) also studied the role of IRF-1 in Hep2.2.15 cells with high HBV expression; the results showed that HBV expression and HBeAg and hepatitis B surface antigen (HBsAg) secretion were all down-regulated when pretreated with IFN-γ and tumor necrosis factor-α (TNF-α), meanwhile, the expression levels of IRF-1 and downstream Cas7 were up-regulated to ultimately induce Hep2.2.15 cell apoptosis. These studies preliminarily displayed the potential capacity of IRF-1 to fight HBV infection. Moreover, it was discovered that IFN-γ induced immune hepatocyte injury in $HBsAg^+$ transgenic mice through the STAT1/IRF-1 pathway during HBV infection; the mechanisms involved suggested that phosphorylated STAT1 (p-STAT1; phosphorylation at Y701 site) triggered the enhancement of IRF-1 GAS sequence activity to induce IRF-1 expression, which was required for sustaining a positive feedback system for JAK/STAT1 signaling transduction, indicating that the IRF-1 autocrine loop was vital for STAT1 phosphorylation (Chen et al., 2007; Zenke et al., 2018). Importantly, the constitutive expression of IRF-1 still remained intact even though it lacked the STAT1 signal in cells, proving that IRF-1 acted independently to virus-induced resistance responses (Yamane et al., 2019). These pioneering findings revealed a previously unappreciated fact that IRF-1 promotion was a symbolic event for HBV inhibition whatever the involvement of IRF-1 induction was, and similarly suggested that the therapeutic outcome of HBV cessation attributed to IFN treatment depended on the antiviral function of IRF-1 to a certain extent.

Alluding to how IRF-1 directly modulates HBV synthesis and replication, researchers observed that the distinctive sequence in the HBV enhancer-1 region was critical, where IRF-1 could recognize, and through binding to ISRE-like sequence "AGTTTCNNTTTCNC," impact HBV gene expression (Nakao et al., 1999). It was noticeable that the activation of IRF-1 upon transcriptional level from a minimal promoter construct was mediated by the enhancer-1/X gene promoter "ISRE/IRE" (1091–1100 nt) region in the HBV genome. In the enhancer-1/X gene, a single base mutation could influence IFN-α response in chronic HBV patients; for example, single alteration at the fourth base (C to T) might partially alleviate the IFN-α response, and genotype B of HBV had a higher response to IFN-α treatment (Alcantara et al., 2002; Guo et al., 2019). It might be explained by the dubious mutation of the enhancer-1/X promoter in different HBV genomes potentially leading to the inconsistent expression and sensitivity of IRF-1 to IFNs, which causes the different curative effects based on the IFN treatment. Intriguingly, Ku70/80-sensing-mediated IRF-1 was found to activate and translocate into the nucleus; depending on up-regulating C-C chemokine ligand 3 (CCL3) and CCL5 expression, immune effective cells, such as cluster of differentiation 8-positive ($CD8^+$) T and natural killer (NK)/natural killer T (NKT) cells, were recruited and infiltrated in response to rapid HBV replication (Li Y et al., 2016). Regardless, extensive results provide a hint of IRF-1's encouraging effects on anti-HBV activity and replication inhibition, although concrete mechanisms have not been fully uncovered.

2.2 IRF-1 and hepatitis C virus

Hepatitis C virus (HCV) infection has continuously been a growing issue in human hygiene and health, with an estimated 56.8 million infected patients worldwide in 2020. Although the number has started to decrease, the forecast disease burden will not be solved by 2030 according to the WHO (The Polaris Observatory HCV Collaborators, 2022; Thomas et al., 2022). The role of IRF-1 in modulating HCV has been documented as a negative player that inhibits HCV ingredient proteins and sub-genomic replicon. In Huh7 cells barbing the HCV replicon, the observation of baseline ISRE activity was significantly increased and was accompanied by the suppression of the HCV replicon when transfected with the *IRF-1* gene (Kanazawa et al., 2004). As type I IFN stimulated the same cells, it could significantly increase IRF-1 expression and enhance IRF-1 DNA-binding activity during HCV replication (Itsui et al., 2006), which suggested that the anti-HCV response was potentially IRF-1-dependent. In addition, peripheral blood mononuclear cell defects played a negative role in HBV inhibition, which might be related to the dysfunction of IRF-1 (Alhetheel et al., 2020). Interestingly, a previous study revealed that an unappreciated layer of basal IRF-1 transcription could defend against multiple RNA viruses, including hepatitis A virus (HAV) and HCV, but IRF-1 was independently constitutively expressed without IRF-3 or STAT1 signaling stimulation (Yamane et al., 2019). These findings supported the conclusion that IRF-1 has an anti-HCV function.

In brief, the HCV ingredient proteins were key to nullifying IRF-1 activation, among which nonstructural protein 5A (NS5A) was one of the most lucid and understandable proteins impacting HCV replication. As an important nonstructural protein of HCV, NS5A exerted a regulatory function on IFN response by target-inhibiting RNA-dependent protein kinase R (PKR)-binding domain and PKR–IRF-1–ISG antiviral signaling (Colpitts et al., 2020); meanwhile, the IRF-1 was generally down-regulated under the condition of NS5A stimulation, which is related to both the weakening immunity response by inducing complement C4 expression and the decreasing cellular IRF-1 transcription level through repressing human RNA polymerase II subunit 10α (hRPB10α), a common submit of RNA polymerase (Jung et al., 2007; Banerjee et al., 2011). Colpitts et al. (2020) provided a mechanistic insight into PKR–IRF-1 signaling resistance to HCV that HCV NS5A protein co-opted the host cyclophilin A (CypA) to aid innate antiviral evasion and invalidate the antiviral response of the PKR–IRF-1 axis. Furthermore, IRF-1 controlled a peculiar independent IFN antiviral response in infected hepatocyte, and HCV appeared to be more sensitive to IRF-1 restriction (Yamane et al., 2019). Broadly speaking, the lack of a PKR–IRF-1-dependent program is indicatively adverse to HCV inhibition; importantly, the enhancement of IRF-1 target is also self-governed without canonical PKR activation (i.e., PKR autophosphorylation) to defend HCV (Colpitts et al., 2020). Additionally, the core protein of HCV seems to have parallel effects by restraining the IRF-1-inducing anti-HCV phenotype. In peripheral monocytes, the HCV core protein acted on the monocytic membrane via interacting with Toll-like receptors (TLRs) and promoting the IL-10 secretion to restrain both the IRF-1 and the subsequent type I IFN generation (Pang et al., 2016). Since feeble T-cell immunity is a major phenomenon in chronic HCV patients and is often accompanied by major histocompatibility complex (MHC) inhibitory maturation, it seems that both HCV core and NS5A proteins involved antigen-presenting inhibition, which was regulated by IRF-1, and this might imply a promising approach in the IRF-1 target enhancer for the induction of cellular and humoral responses in HCV patients (Kim et al., 2012; Hajikhezri et al., 2021). In fact, the IFN–IRF-1 axis mediating antiviral pathways in HCV infection cells was acknowledged and the antiviral model was IFN-dependent; however, Nandakumar et al. (2013) found that the condition of IFN absence could also monitor the anti-HCV activity through IRFs, inducing an IFN-independent mechanism in the IRF-1, IRF-5, and IRF-7 knock out (KO) cells, which indicated that the IRFs, including IRF-1, might act as “fail-safe” protective factors when the virus circumvents the IFN response. These findings suggested the core value of IRF-1 for anti-HCV therapy through dependent or independent ways. Interestingly, a recent study explored that IRF-1, as a competitor, facilitated *IFNL2* gene transcription and triggered an autophagic death pattern to resist HCV in HepG2 cells (Zhang MQ et al., 2020). It highlighted the unappreciated role of endogenous IRF-1 in mediating special HCV-infected cell death models, indicating that it deserves further exploration.

Genetic polymorphism in an infective host contributes to HCV susceptibility in human beings; in this context, the diverse levels of *IRF-1* gene expression in host individuals may be associated with the vital genetic variation that is depicted for single-nucleotide polymorphism (SNP). Saito et al. (2005) analyzed the treatment bias between individual SNP variation in the IRF-1 promoter and the IFN-β monotherapy in HCV patients. The results showed a lower virus load and a sustainable viral response in certain IRF-1 SNP phenotype patients (−415C/−410A/−300A), which was also associated with higher IRF-1 promoter activity and a significantly greater number of Th1 $CD4^+$ cells. In addition, the findings of an SNP examination of IRF-1 promoter also indicated the possibility of a better prognosis and IFN-α therapy response to HCV in −300AA IRF-1 genotype individuals (Wietzke-Braun et al., 2006). Another study involving 400 Turkish HCV patients who received SNP genotyping analysis even raised the possibility that the special site of *IRF-1* gene-type (−410, −388) is a discriminating gene marker for deciding HCV susceptibility and development (Korachi et al., 2013). Taken together, and based on IRF-1 SNP detection, this may provide an effective prospect when looking for those HCV patients who are more sensitive to IFNs or other forceful therapies.

2.3 IRF-1 and other hepatitis viruses

Given the significance of innate immunity in defending against viral infection, there is a deep understanding of how IRF-1 induces the mechanisms inhibiting HBV/HCV; however, the role of IRF-1 in other hepatitis viruses is still unclear. Xu et al. (2017) used Huh7.5-p6 cells to test the potential anti- or pro-viral effects of ISGs on hepatitis E virus (HEV) replication, and three ISGs, including *IRF-1*, showed serious inhibition of HEV luciferase activity, of 50% compared to the control group. In separate cell lines harboring HEV replication, IRF-1 showed significant HEV repression and the anti-HEV effect was dominated by a binding pattern with the STAT1 promoter region where Tyr701 site phosphorylation was IFN stimulation-independent. More importantly, the IRF-1 enhancer and ribavirin combination amplified the ISG induction and the following anti-HEV effects (Xu et al., 2016). Except for the underlying function of IRF-1 in resisting HEV, the utility of the IFN-based regimen for HAV inhibition was minor; however, three types of IFNs and IL-29 have produced interesting results as an HAV remedy (Gabrielli et al., 2023), but it is still unclear whether the IFN–IRF-1 axis plays a similar role in HAV repression and this deserves more consideration.

3 IRF-1 and hepatic fibrosis

Hepatic fibrosis is a complex and progressively aggravated outcome of fibrous scar formation that requires multiple pathogenic factors and certain kinds of cells dysfunction in the liver, representing an excessive accumulation of fibrous proteins and the deposition of collagen in the extracellular matrix (ECM). Abnormal activated of hepatic stellate cells (aHSCs) is a habitual and key phenomenon involved in inducing the fibrogenesis process that is attributed to the accumulation of ECM proteins during chronic liver injury. Other marked myofibroblasts in the liver, such as activated portal fibroblasts with mesenchymal stem cell features, epithelial–mesenchymal transition (EMT)-associated and bone marrow-derived myofibroblasts, have been recognized as major collagen-producing cells in response to fibrosis caused by certain special types of liver injury (Kisseleva and Brenner, 2021; Lei et al., 2022).

Several studies have suggested that IRF-1 might play a protective role in liver fibrogenesis. A recent study indicated that IRF was associated with the regulation of the HSC phenotype and, as a lineage-specific transcriptional factor, played a crucial role in maintaining quiescent status in human and mouse HSCs (Liu et al., 2020). In vivo, $IRF\text{-}1^{-/-}$ mice showed a lower degree of hepatic fibrosis and inflammation than wild type (WT) mice in the IFN-γ pretreatment condition after 3,5-methoxycarbonyl-1,4-dihydrocollidine (DDC) feed, which was consistent with the anti-fibrotic function of IFN-γ via STAT1-inducing HSCs apoptosis (Jeong et al., 2006; Weng et al., 2013). The cell-cycle arrest of HSCs in the G1 phase was observed in another similar study using individual IFN-γ treatment, although apoptosis genes including *IRF-1* were not altered simultaneously; however, if HSCs were released from G1 phase arrest, the apoptosis ability of IRF-γ was enhanced by activating *IRF-1*, *FAS*, and *IFN-γRβ1* genes (Oh et al., 2017). What we hint at, drawing on these findings, is that both the stimulative

responsiveness of the IFN-γ/IRF-1 axis to apoptosis and the promotion of the cell-cycle arrest pathway may point to a way to target the undesirable growth of HSCs. Nevertheless, the role of IRF-1 in HSCs has a double-face in dealing with distinct liver injuries. In the acute liver injury model, endogenous IRF-1, by which the HSCs generated were released to neighboring hepatocytes to initiate hepatocyte apoptosis, deteriorated liver injury (Rani et al., 2018). Therefore, the protective and injurious function of IRF-1 relies on the type of hepatic injury (acute or chronic), and this may also further make sense of whether the exhibition of the different effects of HSCs in hepatic fibrosis and acute liver injury is due to IRF-1 generation or not. Apart from proving that IRF-1 could act as an inhibitor of HSC activation in the liver, it was also indicative that IRF-1 was associated with the expression of programmed cell death protein ligand 1 (PD-L1) in pancreatic stellate cells (Ebine et al., 2018), which elevated the possibility that IRF-1 targeting stellate cells might regulate certain tumor immunity applications.

Hepatic fibrosis has another feature, the abnormal expansion of hepatic progenitor cells (HPCs); to be specific, the balance will tip towards HPC expansion when hepatocytes suffer inclusively TGF-β-mediated apoptosis in a fibrotic environment where TGF-β was sustaining their existence (Goonetilleke et al., 2021). Previous experimental results have implied that HPC proliferation is conducive to fibrosis, depending on the mitogen of the TNF-like weak inducer of apoptosis (TWEAK) activation, which binds to the fibroblast growth factor-inducible-14 (Fn14) receptor; the administration of recombinant TWEAK-neutralizing antibody would lead to the inhibition of HPC proliferation, thus preventing fibrogenesis response in fibrotic mice after 70% hepatectomy (Kuramitsu et al., 2013; Gu et al., 2023). In vitro, IFN-γ directly alleviated the proliferation and expansion of HPC line cells in WT mice compared with the cells from IRF-1$^{-/-}$ mice, and also indirectly had an inhibitory effect via suppressing HSC activation. The same effect in vivo, obstructing IFN-γ and its downstream *IRF-1* gene, directly increased HPC proliferation and hepatic fibrosis in DDC-challenged mice (Weng et al., 2013). A recent report seemed to provide an explanation of how IRF-1 repressed the fibrotic progress. In patients with keloids, in whom ECM deposition was common and TWEAK/Fn14 signaling was universally down-regulated; however, TWEAK/Fn14-induced protein 65 (p65) expression could bind to the IRF-1 promoter to restrict the *ECM* gene in normal skin (Gu et al., 2023). This means that the IRF-1-mediated TWEAK/Fn14 signaling may play a similarly restrictive role in liver fibrosis. It, therefore, can be predicted that, as well as holding back the growth of HSCs, restraining HPC proliferation via the IRF-1-mediated route will be another way to combat hepatic fibrosis, despite the elaborate mechanisms of IRF-1 in regulating HPCs and HSCs having not yet been comprehensively exposed.

4 IRF-1 and HCC

The incidence of liver cancer is increasing worldwide, and it is estimated that one million people per year will be affected by 2025 (Villanueva, 2019). Recently, several IRFs have been found to be closely related to neoplasia and the progress of HCC, such as IRF-2 (Wang DP et al., 2020), IRF-3 (Kim et al., 2021), IRF-5 (Sy et al., 2018), and IRF-8 (Wu et al., 2022), among which IRF-1 seemed to be the most embedded and thoroughly studied. A groundbreaking finding from 32 HCC patients revealed that lower *IRF-1* messenger RNA (mRNA) expression was predisposed to adjacent non-cancer tissue rather than cancer tissue, and those well/moderately-differentiated HCCs had a higher IRF-1 expression tendency with a longer survival rate (Moriyama et al., 2001). Yan YH et al. (2020) and Zekri et al. (2010) also documented that well-differentiated or early HCC patients had an increased *IRF-1* mRNA; once gene alteration of *IRF-1* occurred, it would portend worse overall survival based on relative database and clinical analyses. Coincidentally, our previous findings further illustrated that *IRF-1* gene expression could guide the prognosis for patients who underwent liver transplantation (LTx) for HCC beyond the Milan criteria, and IRF-1 might be used as a potential target in HCC treatment on account of its ability to impact tumor cell autophagy and apoptosis (Zhang et al., 2016). In contrast, IRF-2 released the accelerative capacity in tumorous malignant phenotypes such as osteosarcoma and colorectal cancer (Lu et al., 2018; Sun et al., 2019), which might be ascribed to its competition with the same IRF-1-binding site in IFN-inducible gene regulatory elements,

and the neoplasia effect of IRF-2 might be re-enacted with a rapid decrease of IFN concentration in the tumor microenvironment. Considering the independence and interaction of two IRFs, the IRF-2/IRF-1 ratio perhaps provides a more valuable reference for liver cancer or other relevant tumors in clinical treatment and prognosis evaluation.

Until now, numerous manifestations have been interpreted, indicating that IRF-1 directly inhibits antitumor growth and enhances the recognition of immune cells in liver cancer. The mechanism that governs tumor cell-cycle arrest may be a general and significant switch that contributes to a much more robust anti-tumor symphony against cancer cell growth when IRF-1 is irritated. IFN- and TGF-β-induced $p21^{WAF-1}$ synthesis is known to command cell-cycle arrest at the G1 phase via inactivation of cyclin E-associated kinase, cyclin-dependent kinase (*CDK*), and lessened DNA synthesis (Tada et al., 1998; Miyazaki et al., 2004; Armstrong et al., 2012). Notably, IRF-1 in its upstream is indispensable, in a binding-promoter manner, to $p21^{WAF-1}$ in HCC (Yano et al., 1999; Miyazaki et al., 2004). Moreover, p53 was inductively generated by primary hepatocytes after IFN-γ management in presenting cell-cycle arrest ability and was also responsible for the p53-dependent apoptosis and angiogenesis in HCC (Zhu et al., 2019; Zhang YC et al., 2020). IRF-1 is an upstream transcriptional player for p53 in the IRF-γ pathway, which suggests a synergistic reaction of IRF-1 and p53 in HCC cell-cycle regulation. Interestingly, two key regulatory factors, p27 (Kip1) and human telomerase reverse transcriptase, possess specialties in regulating cell cycle, respectively, by inhibiting the activity of several Cyclin/CDK complexes and limiting 5' DNA end telomere extension, which all showed a potential IRF-1-like binding site in their homologous gene promoters (Moro et al., 2000; Lee et al., 2003). Regardless, these concerning findings hinted that the regulation of IRF-1 in the cell cycle might be a promising target for HCC treatment.

Cell autophagy is an evolutionarily conserved subtype of programmed cell death in some circumstances such as cell starvation, damage, and other stress. Both special signal transduction and gene activation are required for the purpose of surviving response and energy gain, which have been proved in applications for anticancer therapies. In HCC, autophagy promotion was a linchpin governing tumor cell growth by the IRF-1-mediated phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mechanistic target of rapamycin (mTOR) autophagy pathway, although our findings appeared to exhibit a little discrepancy after employing different HCC lines (Li PY et al., 2012; Zhang HM et al., 2016). On one hand, it is understandable that autophagy generates HCC programmed death and it is beneficial for alleviating tumor load. On the other hand, it is paradoxical that autophagy is seemingly required for the conversion of benign tumors to malignant HCC, and autophagy also promotes tumorigenesis via maintaining oxidative metabolism or expressing the oncogenic *Ras* gene (Mathew and White, 2011; Liu et al., 2018). We believe that the IRF-1-mediated autophagy pathway in HCC tumorigenesis is mysterious and a promising target for deeper research. Additionally, the enhancement of tumor cell apoptosis is another meaningful approach along with IRF-1 up-regulation to provoke anti-growth in HCC. MicroRNAs, including microRNA-23a (*miR-23a*) (Yan et al., 2016), *miR-301a* (Dong et al., 2020), and *miR-31* (Wan et al., 2020), were pinpointed to up-regulate in HCC. Relying on acting with the IRF-1 3' untranslated region (UTR)-binding model, microRNAs employed the decrease of *IRF-1* expression and subsequently accelerated the HCC deteriorating phenotype via apoptosis suppression. Recently, researchers found that endogenous *IRF-1* up-regulation led to HCC apoptosis depending on the increase of *miR-195* and checkpoint kinase 1 (*CHK1*) inhibition (Yan YH et al., 2021b). CHK1 was deemed a vital player in DNA damage response signaling depending on its interaction with several factors or pathways in the tumor microenvironment, and was positively related to advanced HCC stage and poor prognosis. A recent insight indicated that a combination of CHK1 inhibition and cisplatin induced more DNA damage and HCC apoptosis progression, thus accelerating IRF-1 expression and in turn recruiting the NK and $CD8^+$ T cell infiltration to activate antitumor immunity (Li XC et al., 2023). Therefore, both the "double-sword effect" of IRF-1 inducible activation of autophagy-relevant genes and uncharted mechanisms of cell death involving IRF-1 activation ought to shed new light in the future.

Intriguingly, a small number of studies supply other new insights about IRF-1 in relation to metastasis and anti-cancer immunity treatment in HCC. For example, recently, endogenic IRF-1 was found to enhance the

anti-tumor immunity effects with NK and $CD8^+$ T cells by the axis of IRF-1/C-X-C chemokine ligand 10 (CXCL10)/C-X-C chemokine receptor 3 (CXCR3) activation in the HCC microenvironment (Yan YH et al., 2021a). The IRF-1-mediated mTOR/STAT3/AKT signaling pathway was verified to take part in EMT and metastasis in HCC (Yu et al., 2017), and IRF-1 was referred to as the inhibitor of invasion and migration by inducing *miR-130b* in hepatoma samples (Lin et al., 2015). A recent report highlighted the potential immunomodulatory capacity of the HCC-derived forkhead box family 1 (FOXO1), a transcription factor with diverse functions, and re-educated tumor-associated macrophages (TAMs) by the IRF-1/nitroxide axis-induced IL-6 reduction in the HCC microenvironment (Cui et al., 2023). These implications validated the antitumor role of IRF-1, which not only targeted the cancer cell, but also interacted with the immune cells surrounding HCC.

It is worth mentioning that multiple studies have confirmed that IRF-1 can exert tumor inhibitory effects on liver cancer through extensive and complicated mechanisms; however, IRF-1 can bind to the promoter of PD-L1 in tumorous cells and trigger immune cell dysfunction to allow immune escape in HCC. Wang R et al. (2022) explored the immune escape role of IRF-1 in HCC and TAMs under the IFN-γ stimulation condition in which IRF-1 enhanced human endogenous retrovirus-H long terminal repeat-associating 2 (*HHLA2*) expression via binding to the promoter region in *HHLA2*. Thus, on one hand, it promoted the PD-L1 expression in primary and xenograft tumors, and on the other hand, induced M2 polarization and chemotactic migration in TAMs. A recent report also revealed that the dysfunction of NK cells in HCC intratumoral regions was related to the higher expression of nuclear receptor subfamily 4, group A, member 1 (*NR4A1*), a cancer-associated immune exhaustion gene of great value, and IFN-γ/p-STAT1/IRF-1 signaling pathway activation also took part (Sorrentino et al., 2021; Yu et al., 2023). Interestingly, several studies seemed to account for the underlying mechanism by which IRF-1 induced "contradictorily PD-L1 expression." For one thing, in the presence of inflammation cytokines such as IFN-γ, which were generated and infiltrated in the HCC periphery, the balance between the IRF-1-mediated HCC inhibition and PD-L1 escape effect would be disequilibrated (Yan YH et al., 2020). On the other hand, the dysfunction of several IRF-1 inhibitors might contribute to PD-L1 phenotype alteration, such as an increase in small ubiquitin-like modifier pattern of IL-33 and a decrease in epigenetic modification by enhancer of zeste 2 polycomb repressive complex 2 submit (*EZH2*) (Xiao et al., 2019; Wang et al., 2023). This peculiarity prompts the possible combination of targeting the programmed cell death protein-1 (PD1)/PD-L1 inhibitor and the undeveloped activator/synergist of IRF-1 for overcoming HCC, especially in refractory HCC patients (Fig. 2).

The promotion of IRF-1 remarkably reduced the HCC malignant phenotype via facilitating HCC autophagy and apoptosis. IRF-1 directly induced mTOR/STAT3/AKT signal activation and interacted with microRNAs (*miR-31*, *miR-23a*, and *miR-301a*) to accelerate the tumor cell malignant phenotype; however, *miR-345* and *miR-130b* inhibited EMT and the metastasis of HCC via the IRF-1-mediated mTOR/STAT3/AKT pathway. IRF-1 coupled on the p21 promoter to increase CDK4's cell cycle arrest ability and Cyclin E inhibition, as well as lessening DNA synthesis. Meanwhile, IRF-1 might also combine with p53 to have an anti-tumor effect due to p53-induced apoptosis signaling and angiogenesis repression in HCC. It is noticeable that IRF-1 on the one hand activates NK and $CD8^+$ T cells via the CXCL10/CXCR3 axis in the HCC microenvironment and, on the other hand, HCC-derived IRF-1 acts with TAMs to inhibit the IL-6/STAT3 signal to enhance the anti-tumor immunity effect. Additionally, IRF-1 may also represent malignant phenotype promotion by enhancing PD-L1 expression in the presence of inflammation and HHLA2.

5 IRF-1 and HIRI

HIRI not only makes a pivotal contribution to hepatic resection, LTx, or hypovolemic shock due to trauma, but also serves as the principal cause of acute hepatic injury or failure (Monga, 2018; Ni et al., 2019). At present, there are no effective treatments to tackle HIRI because of the lack of understanding of the mechanisms underlying of HIRI. However, accumulating evidence has shown that IRF-1 is a key ingredient in HIRI occurrence and evolution. Clearly, not only the HIRI itself, IFNs, TNF-α, and self-DNAs released by scathing hepatocyte, but also the ILs (IL-1, IL-6,

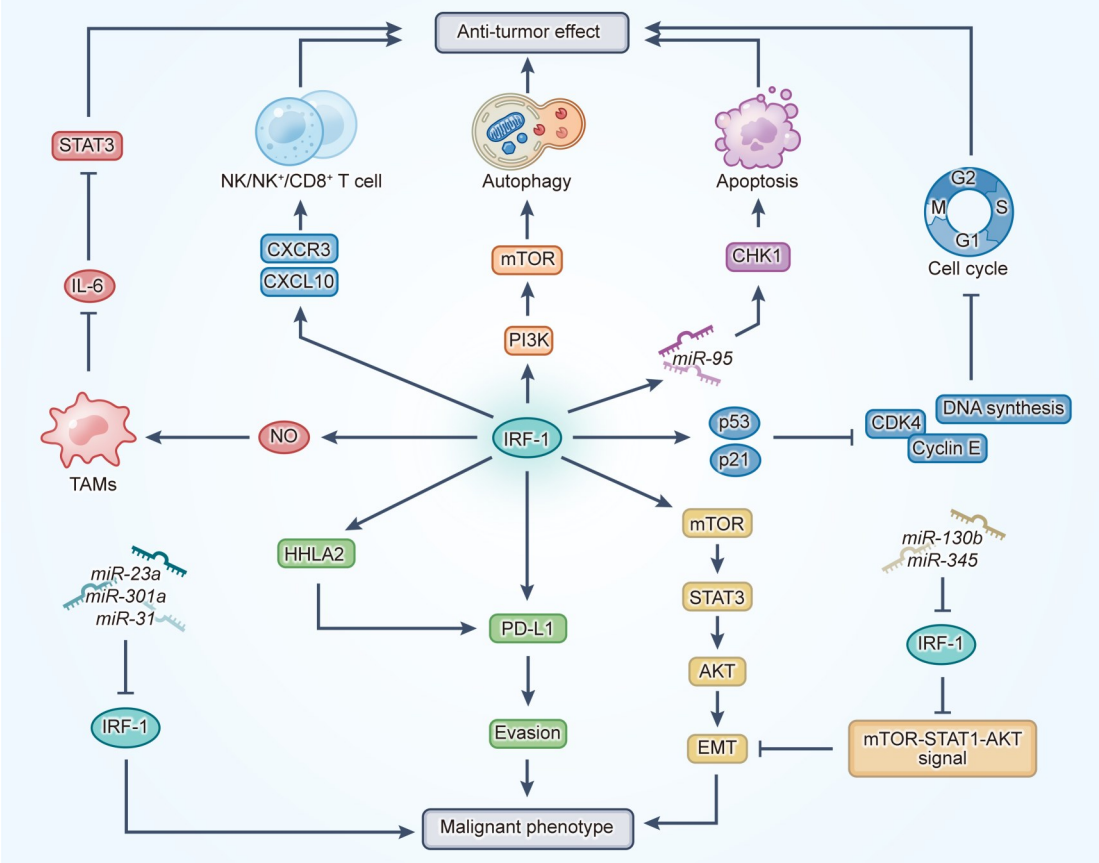

Fig. 2 Roles of IRF-1 in regulating HCC progression. IRF-1: interferon regulatory factor 1; HCC: hepatocellular carcinoma; STAT: signal transducer and activator of transcription; IL: interleukin; TAMs: tumor-associated macrophages; miR: microRNA; NK: natural killer; CD8+: cluster of differentiation 8-positive; CXCR3: C-X-C chemokine receptor 3; CXCL10: C-X-C chemokine ligand 10; NO: nitric oxide; HHLA2: human endogenous retrovirus-H long terminal repeat-associating 2; mTOR: mechanistic target of rapamycin; PI3K: phosphoinositide 3-kinase; PD-L1: programmed cell death protein ligand 1; CHK1: checkpoint kinase 1; AKT: protein kinase B; EMT: epithelial–mesenchymal transition; p53: protein 53; CDK4: cyclin-dependent kinase 4.

IL-23, and IL-27) have all been verified as initiating elements that directly/indirectly control the transcription level of IRF-1 in its gene's upstream promoter district (Fujita et al., 1989; Bender et al., 2009; Klune et al., 2018).

Earlier investigators observed the alteration of IRF-1 and attempted to elucidate its internal effects on HIRI in the field of LTx (Tsung et al., 2006; Ueki et al., 2010). Tsung et al. (2006) determined IRF-1's characters in HIRI using LTx to imitate warm ischemia/reperfusion (I/R) in both WT and *IRF-1* KO mice; the result showed that the expression of IRF-1 was remarkably up-regulated after warm HIRI in the WT group. Following research identified IRF-1 as an important regulator in HIRI after LTx in mice (Kim et al., 2009). Ueki et al. (2010) also conducted LTx in WT and IRF-1$^{-/-}$ mice within 24 h of cold storage and found that the up-regulation of *IRF-1* mRNA was commonly seen in WT mice that were prone to significantly elevated serum alanine aminotransferase (ALT) level and a more distensible liver necrosis area 12 h after LTx compared to IRF-1$^{-/-}$ mice. A clinical study evaluated the relationship between *IRF-1* gene expression and liver enzymes in the acute period after HBV-infected patients underwent LTx; the results showed that *IRF-1* might intensify organ rejection and liver inflammation injury (Nabavizadeh et al., 2018). Moreover, a recent bioinformatic analysis for predicting potential immune-related genes involving HIRI after LTx showed nine identified hub genes, including *IRF-1*, screened from human sample datasets (Guo et al., 2023). Of particular note is that ILs and IFN-γ, as important inflammation cytokines (Soyoz et al., 2021), lead to IRF-1 expression and a rejection response in clinical

treatment, which implies the clinical possibility of using IRF-1 examination to replace the level of inflammation cytokines in recipients suffering from LTx rejection. Overall, reports on IRF-1 expression in LTx immune rejection and inflammation supply a new pathway to alleviate graft rejection by targeting IRF-1. They also suggest its value in terms of rejection severity prediction, although the clinical study and subsequent proof have not been reported.

Concerning how IRF-1 releases abilities in the downstream regulation of HIRI, a few factors and pathways have been discovered that involve exorbitant inflammation eruption, unexpected cell death pattern activation, and immune cell participation. IRF-1, induced by IFN-γ secretion originating from the non-parenchymal cells in the liver, has an effect on generating death ligands and up-expressing death receptor 5 (DR5) and FAS, which lead to Caspase cascade activation (Cas8 and Cas3) and secondary apoptosis in HIRI (Ueki et al., 2010). Castellaneta et al. (2014) provided insight into the mechanism by which self-DNA from damaged hepatocytes could be deemed damage-associated molecular patterns (DAMPs), irritate TLR9 in plasmacytoid dendritic cells (DCs), and accelerate IFN-α production in promoting HIRI; this depends on activating the IRF-1/FAS/DR5 apoptosis pathway. When IFN-α neutralization intervenes, *IRF-1* gene transcription and subsequent hepatocyte I/R are relieved.

Moderate autophagy is a highly conserved form of cell death that occurs through an autophagosome-mediating pattern, which is ubiquitous in organisms. It involves the degradation of damaged organelles or other cellular components that maintain normal physiological activity and homeostasis. Nevertheless, what we found in past studies was that immoderate hepatocyte autophagy was of significance in exacerbating HIRI over time in an IRF-1-dependent manner; under the IRF-1 induction condition, c-Jun N-terminal kinase (JNK) signal activation and β-catenin inhibition kicked off severe autophagy in the context of HIRI (Yan B et al., 2020; Li et al., 2021). One of the DAMPs, high-mobility group box 1 (HMGB1), was taken as a main transmitter to mediate and deprave HIRI by the HMGB1/TLR4 pathway in Kupffer and DCs (Tsung et al., 2007; Ni et al., 2021). Our previous work also pinpointed that HIRI induced an increase in IRF-1 transcription and IRF-1 was directly united with the endo-nuclear *HMGB1* gene, resulting in HMGB1 protein production, which then translocated and interacted with intracellular Beclin 1 and displaced B cell lymphoma protein-2 (Bcl-2) to promote autophagy (Cui et al., 2018). In addition, Dhupar et al. (2011) discovered the inherent translocation mechanism, where the acetylation of HMGB1 was associated with nucleocytoplasmic shuttling and IRF-1 mobilized HMGB1 acetylation via combining with HAT p300. Hence, IRF-1-induced acetylation of HMGB1 to augment autophagy in HIRI might be supplied as a highlight in settling HIRI. Of note, research on I/R injury is currently focusing on non-coding RNA exosomes engaged in autophagy pathways and other cell death pathways, especially ferroptosis and copper-induced cell death (Zhang L et al., 2020; Chen et al., 2023; Zhu et al., 2023; Zuo et al., 2023); whether the cross-talk of IRF-1 to non-coding RNAs or distinctively induced cell death patterns impacts the HIRI or not is worthy of further exploration.

Additionally, the abnormal activation of immune cells seems to broaden the horizon on how immune mechanisms contribute to HIRI. IL-15 was transferred from macrophages and DCs to NK, NKT, and memory $CD8^+$ T cells through binding to IL-15 receptor α-subunit (IL-15Rα), leading to enhanced cytotoxicity and IFN recruitment (Guo et al., 2017). It has been found that hepatocytes could express the IL-15/IL-15Rα complex and hence provide a preferable environment to initiate T cell activation and $CD8^+$ T cell differentiation (Tao et al., 2021). Based on the preceding findings, Yokota et al. (2015) found that the soluble IL-15/IL-15Rα complex was generated chiefly in the liver and was the major inducer of unleashing HIRI in LTx. IRF-1 was noted to directly act on the IL-15/IL-15Rα complex to augment NK and $CD8^+$ T cell numbers and facilitate the cytotoxic inflammatory response. Neutrophils, as a dominating immune cell population in HIRI, could be activated and recruited during HIRI (Nakamura et al., 2019). In terms of the potential triggering pattern of neutrophilic activation, IRF-1 played the dominant role in the excretion of neutrophil extracellular vesicles, which regulated Rab27a transcription by binding its prompter region and ultimately relied on the neutrophil TLR-4 pathway to attack HIRI (Yang et al., 2018). Intriguingly, the inducible nitric oxide synthase (iNOS) promoter had a potential transcription-binding site to IRF-1 and the

iNOS/IRF-1 pathway was involved in myocardial I/R injury and oxidative stress. Importantly, the iNOS/nitric oxide (NO) signal and a positive feedback loop between iNOS and IRF-1 were required for IRF-1 continually activating during HIRI (Du et al., 2020; Jiang et al., 2022). It has been clarified that iNOS is an important junction in the enablement of warm HIRI utilizing apoptosis via the NO-mediating cyclic guanosine monophosphate (cGMP)-dependent protein kinase (PKG)/Cas3 signal or other possible molecules, such as heme oxygenase-1 (HO-1) and heat shock protein 70 (HSP70) (Liu et al., 2017; Qiao et al., 2019, 2020), which suggested that IRF-1 exerted parallel effects on HIRI via unappreciated iNOS signal and deserves further consideration (Fig. 3).

IRF-1 was triggered by IFN generation during HIRI and iNOS/NO signal activation in hepatocytes directly stimulated by the *IRF-1* gene translation when HIR was perceived and where a positive feedback loop stood between IRF-1 and iNOS. Both IRF-1-induced hepatocyte apoptosis and necrosis could be seen as DAMPs to promote DC activation to generate IFN-α; on the other hand, HIRI-induced nonparenchymal cell excitation could irritate the *IFN-γ* gene to exacerbate IRF-1 expression. The activated IRF1 aggravated both severe autophagy and apoptosis pathways, and IRF-1 provided a deteriorative connection to immune cells including neutrophil, Kuppfer cells, NK, and $CD8^+$ T cells to amplify HIRI.

6 IRF-1 and other liver diseases

6.1 IRF-1 and cholangiocarcinoma

In addition to the several clinically common liver disease patterns mentioned above, recently, several studies have found that IRF-1 may also exploit latent regulatory effects on special types of liver disease. By

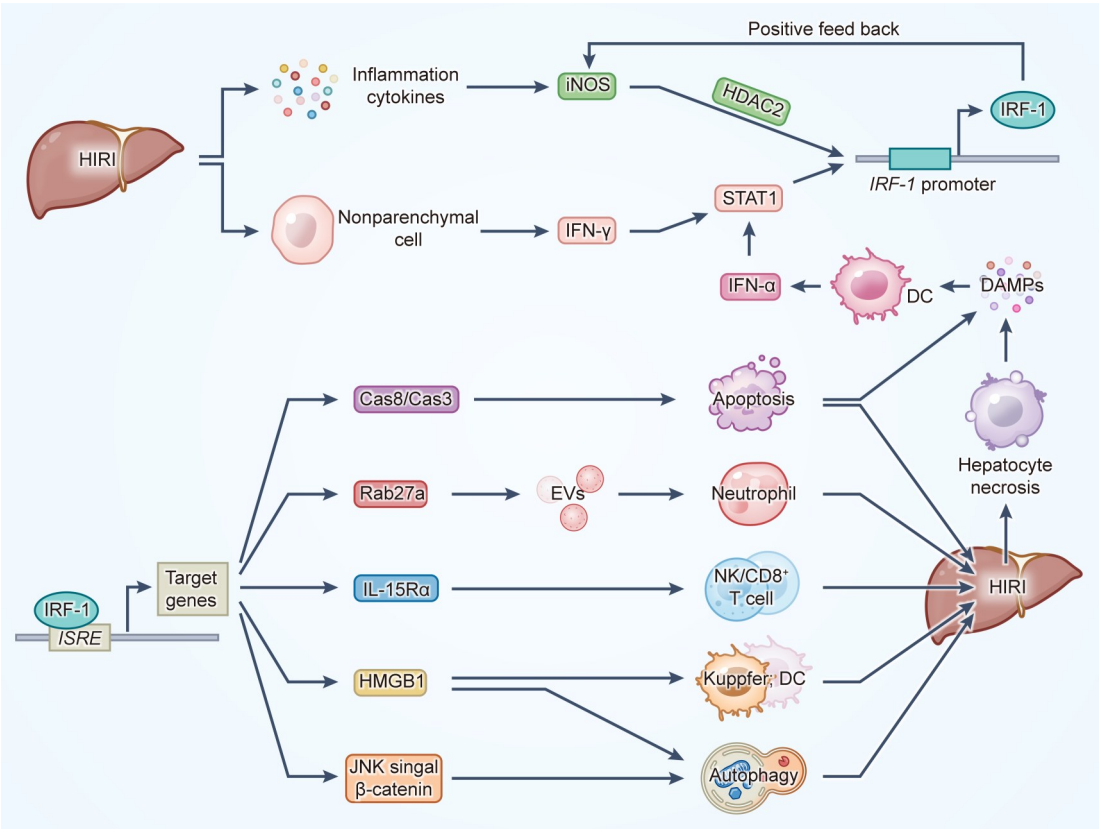

Fig. 3 Mechanisms of IRF-1 in inducing HIRI. IRF-1: interferon regulatory factor 1; HIRI: hepatic ischemia-reperfusion injury; ISRE: interferon-stimulated response element; iNOS: inducible nitric oxide synthase; HDAC2: histone deacetylase 2; IFN: interferon; STAT1: signal transducer and activator of transcription 1; DAMPs: damage-associated molecular patterns; IL: interleukin; HMGB1: high-mobility group box 1; DC: dendritic cell; NK: natural killer; $CD8^+$: cluster of differentiation 8-positive; Cas: caspase; EVs: extracellular vesicles; JNK: c-Jun N-terminal kinase.

using HuCCT1, a cholangiocarcinoma cell line, Miyazaki et al. (1998) attempted to reveal the biological process to which transforming growth factor-β (TGF-β) refers; the findings showed significant repression of HuCCT1 growth in a TGF- and time-dependent manner under TGF stimulation, and that, in the wake of the p21/Waf1/Cyclin pathway, down-regulation through IRF-1 induction was involved. Moreover, both clinical trials on cholangiocarcinoma and in vitro experiments indicated that IRF-1 was highly expressed in cholangiocarcinoma, which was closely related to clinical progress and prognosis. A further demonstration revealed that miR-383 inhibited the malignant phenotype of proliferation, migration, and invasion via targeting *IRF-1* gene 3' UTR, which bears out the broad spectrum of IRF-1 tumor suppression and would be useful for cholangiocarcinoma treatment (Wan et al., 2018a, 2018b). Of note, in the presence of liver inflammation, a sharp increase in the expression of IFN-γ induced IRF-1 up-regulation and then dramatically eliminated the let-7a cluster in circulating colorectal cancer cells, which led to a reverse EMT and adhesion process and attenuated colorectal cancer liver metastasis (Cheng et al., 2018). This highlighted an unappreciated method of using IRF-1 in the treatment of rare types of liver cancer and metastatic hepatica carcinoma, especially those advanced metastatic carcinomas that can be easily metastasized to the liver.

6.2 IRF-1 and AFLD/NAFLD

Additionally, IRF-1 appears to play a crucial role as a profound mediator in AFLD/NAFLD mouse models. Long-term excessive alcohol intake inevitably causes alterations to physiological metabolism and the activation of macrophage autophagy in hepatic cells. In the AFLD model, macrophage autophagy could further facilitate the p62-dependent IRF-1 degradation process and inhibit the transcription of CCL5 and CCL10, which are both noticeable molecules that trigger hepatic inflammation in the development of AFLD (Liang et al., 2019). In alcohol-associated liver injury patients, the activation of Cas1 inflammasome mediated by IRF-1 may participate in the pro-inflammatory process (Li HD et al., 2024). On the other hand, the fibrosis process and inflammation accumulation are unescapable events in NAFLD evolution. The c-Mer tyrosine kinase (MERTK), a profound receptor that modulates efferocytosis, indeed adjusted the activation of HSCs, steatosis, and apoptosis in Kupffer cells (Cai et al., 2020). In two Italian cohorts of NAFLD patients, MERTK expression and polymorphism were observed to have a close relationship with liver fibrosis at the F2–F4 stages (Petta et al., 2016). Based on the differential analysis of transcriptional binding sites in alleles, Cavalli et al. (2017) confirmed by chromatin immunoprecipitation (ChIP)-sequencing and an electrophoresis mobility shift assay (EMSA) experiment that IRF-1 could be used as an inhibitory factor to inhibit the A allele on MERTK rs6426639 and to down-regulate the MERTK expression. These findings might imply an unknown cross-talk between MERTK and IRF-1 in the pathogenesis of NAFLD, by direct or indirect pathways.

6.3 IRF-1 and acute cellular rejection

Of note, recent several articles reported that the alternative target of IRF-1 might be key to the prevention of specific liver disease and may help to establish adaptive immunity in certain disease settings such as acute cellular rejection (ACR) (Hama et al., 2009) and acute-on-chronic liver failure (Rueschenbaum et al., 2021). The related ACR research has found elevated gene expression profiling of IRF-1 in both the early phase (Hama et al., 2009) and the tolerance induction phase (Cordoba et al., 2006) in a mice allograft LTx model using microarray detection. Meanwhile, IRF-1 was also intensively related to other ACRs via the release of regulating immune mediators during heart transplantation and islet β cell allografts (Erickson et al., 2004; Solomon et al., 2011). A clinical, controlled study showed that the down-regulated *IRF-1* mRNA tended to be concentrated in HBV patients without rejection after LTx (Janfeshan et al., 2017). Intriguingly, IRF-1 repression has demonstrated ACR prevention through the use of docosahexaenoic acid (DHA), which involved iNOS promoter inhibition with elements of IRF and nuclear factor-κB (NF-κB) (Kielar et al., 2000). These findings afford us a broader view of the role of IRF-1 in ACR and its potential use in clinical therapy and early intervention.

7 Perspective and conclusions

This review first highlights the profound role of IRF-1 in liver diseases and mainly focuses on the

underlying regulatory applications for hepatitis infection, HCC, HIRI, liver fibrosis, and other uncommon liver-related diseases. On one hand, IRF-1 can inhibit hepatitis virus replication and alleviate the progression of hepatic fibrosis. On the other hand, the expression of IRF-1 displays aggravation of HIRI, meanwhile, its role in restricting the malignant phenotype of HCC has been explored and is thought to be an indicator that can be used to predict HCC prognosis, although IRF-1 may have a capacity for PD-L1 promotion under inflammation conditions. Targeting IRF-1 may also be relevant in other areas related to liver diseases, such as cholangiocarcinoma, AFLD/NAFLD, and ACR.

Although the perception of IRF-1 targeting has raised the possibility of its huge therapeutic potential, at least for now, IRF-1-induced pathogenesis in hepatic disease is still not fully understood. Interestingly, several compounds have shown liver protective functions, in which IRF-1 has been significantly involved (Table 1). However, to our knowledge, little attention is being paid to its clinical applications and role in translational medicine. Therefore, paying additional attention to understanding IRF-1 by adopting advanced technologies including omics/single-cell metabolomics analysis, single-molecule protein sequencing, and clustered regularly interspaced short palindromic repeats (CRISPR) editing will be beneficial for clarifying the more intrinsic mechanisms and functional characteristics of IRF-1-mediated signaling pathways (Eisenstein, 2023).

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Author contributions

Tao CHEN designed, planned, and drafted the paper. Jianjun ZHANG gave suggestions and revised the primary manuscript. Tao CHEN, Shipeng LI, Dewen DENG, and Weiye ZHANG performed the literature search, interpretation, and manuscript drafting. Jianjun ZHANG and Zhongyang SHEN designed and supported the foundation to this paper, and finally revised the manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Table 1 Compounds involving the IRF-1 signal in liver diseases

Compound	Model	IRF-1 signaling involvement	Main effects and outcomes	Reference
Zhankuic acid A	ConA-induced hepatitis in mice	Inhibited IFN-γ/STAT1/IRF-1 pathway	Anti-inflammation; inhibited lymphocyte activation	Chen et al., 2014
(5R)-5-Hydroxytriptolide	ConA-induced hepatitis in mice	Activated IFN-γ/STAT1/IRF-1 pathway in spleen	Eliminated activated T cells; decreased inflammatory cytokines; blocked mRNA expression of chemokines	Zhou et al., 2006
Huganbuzure granule	ConA-induced immune liver injury in mice	Inhibited JAK1/STAT1/IRF-1 signaling	Inhibited the production of inflammatory factors; inhibited hepatocyte apoptosis; regulated balance of immunity cells	Wang et al., 2021
Glycyrrhizic acid ammonium salt	ConA-induced immune liver injury in mice	Inhibited JAK1/STAT1/IRF-1 signaling	Decreased hepatocyte apoptosis; suppressed oxidative stress; regulated balance of Th cells	Tian et al., 2019
Chlorogenic acid	HIRI in mice	Reduced IRF-1/HMGB1/TLR4/NF-κB signaling	Decreased oxidative stress, mitochondrial damage, and apoptosis	Li K et al., 2023
Anethole	HIRI in mice	Reduced both nuclear translocation of IRF-1 and IRF-1/HMGB1/TLR signaling	Decreased pro-inflammatory factors and alleviated HIRI	Cho et al., 2013
Ginsenoside Rh2	Liver fibrosis in mice	Up-regulated IRF-1 to reduce SLC7A11 expression in HSCs	Promoted HSC ferroptosis and HSC inactivation	Lang et al., 2023

IRF-1: interferon regulatory factor 1; ConA: concanavalin A; IFN-γ: interferon γ; STAT1: signal transducer and activator of transcription 1; mRNA: messenger RNA; JAK1: Janus kinase-1; Th: T helper; HMGB1: high-mobility group box 1; TLR4: Toll-like receptor; NF-κB: nuclear factor-κB; HIRI: hepatic ischemia-reperfusion injury; SLC7A11: solute carrier family 7 member 11; HSCs: hepatic stellate cells.

Compliance with ethics guidelines

Tao CHEN, Shipeng LI, Dewen DENG, Weiye ZHANG, Jianjun ZHANG, and Zhongyang SHEN declare that they have no conflicts of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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