REDOX EXPERIMENTAL MEDICINE

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REVIEW

Redox experimental medicine and liver regeneration

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Abstract

The liver is characterized by unique regenerative properties to restore its mass and function after a partial loss. Hepatic regeneration arises after resection or following acute and chronic injuries. Resection and acute liver damage normally induce a regenerative process characterized by phenotypic fidelity, in which each cell type promotes its own replication and replacement. This process fails in chronic liver damage, where trans-differentiation of parenchymal cells or activation of facultative progenitors occurs. Both liver resection and acute/chronic damages alter redox homeostasis, as a consequence of blood flow changes, hypoxia, metabolism modification, and activation of inflammatory response. Even though formerly described as 'oxidative stress', altered redox homeostasis leads to the fine regulation of several pathways involved in liver regeneration, including the proliferation of parenchymal cells, trans-differentiation, and activation of facultative progenitors.

Several redox-dependent transcription factors and pathways implicated in the regenerative process of the liver were described, but pre-clinical experiments using different antioxidants were not fully conclusive. Even though accurate study designs to define appropriate dosages, treatment duration, and routes of administration are required, modulation of redox-dependent molecular pathways to enhance liver regeneration is even more intriguing. Preliminary studies focused on the identification of these targets will pave the way for viable therapies to be tested in clinical trials.

Key Words

- hepatic resection
- liver diseases
- proliferation of parenchymal cells
- trans-differentiation
- facultative progenitors
- redox homeostasis

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Introduction

The liver is an extraordinary organ dedicated to the preservation of whole-body homeostasis. Liver parenchyma is composed mainly of hepatocytes and cholangiocytes, two epithelial cell types that differentiate from common progenitors named hepatoblasts. Hepatocytes control energy metabolism, biosynthesis of molecules, and clearance of endogenous and exogenous toxic compounds, while cholangiocytes structure the biliary system (Rui 2014, Stanger 2015). Hepatocytes and cholangiocytes are also referred as parenchymal liver cells, constituting ~80% of liver mass; the remaining ~20% is composed of nonparenchymal liver cells, which include mainly hepatic stellate cells (HSCs), Kupffer cells (KCs), and liver sinusoidal endothelial cells (LSECs) (Forbes 2014).

The liver is provided with a special regenerative capacity (Fig. 1). Even though the liver is normally characterized by a low cell turnover, it is able to re-establish its original mass and function after damage (Michalopoulos 2007). This process is a very hot topic for both basic and clinical sciences, being accurately regulated and occurring in a very short time after resection of a definite mass amount, not only in animal

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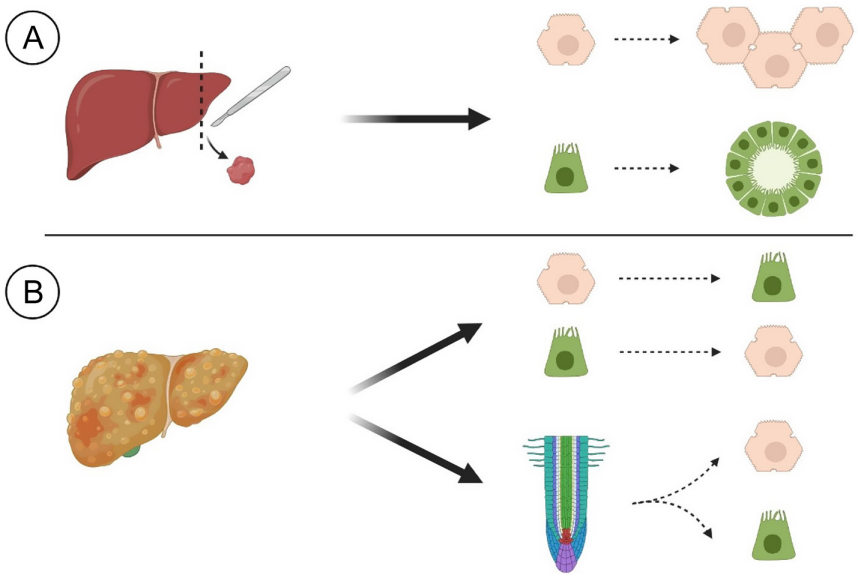

Figure 1
The liver may regenerate through several mechanisms. (A) Hepatic resection activates a process characterized by phenotypic fidelity, that is, replication of every cell through local proliferation. (B) Chronic hepatic injury triggers alternative regenerative processes, trans-differentiation of parenchymal liver cells (upper panel), or differentiation of progenitors toward adult parenchymal cells from a regenerative niche (lower panel).

models (partial hepatectomy (PHx)) but also in humans (partial liver transplantation (PLTx)) (Fausto *et al.* 2006, 2012). Hepatic resection or acute toxic injury are followed by the activation of regenerative activities characterized by phenotypic fidelity that is, replication of every cell through local cell proliferation (Michalopoulos 2007). Nevertheless, a failure of endogenous proliferation, which occurs mostly during persistent hepatic injury, stimulates alternative regenerative pathways, including activation of liver progenitors and/or trans-differentiation of parenchymal liver cells (Michalopoulos & Bhushan 2021).

Damages inducing liver regeneration often induce alterations in redox balance, which may exert an impact on the regenerative process after injury (Kamata *et al.* 2005, Schwabe & Brenner 2006). Although the signaling pathways involved in both the 'canonical' and the alternative regenerative pattern are not completely characterized, several of them may be redox-dependent and may be of interest for both redox biology and redox medicine.

This review aims to summarize the redox-dependent mechanisms which may be involved in hepatic regeneration. Description of basic details of redox biology is beyond the scope of this review since several outstanding papers on this topic are available (Serviddio *et al.* 2013, Sies 2015, Flohe 2020, Sies 2020). After a concise presentation of the redox reactions and balance occurring in the liver, we will represent the recent knowledge of the role played by reactive species and redox signaling in the modulation of hepatic regenerative homeostasis, pointing out the most important clinical perspectives.

The hepatic redox homeostasis

The liver accounts for the metabolism of carbohydrates, lipids, and ammonia, biotransformation of endogenous and exogenous toxic compounds, and bile synthesis. The hepatic parenchyma is specialized through metabolic zonation associated with oxygen supply, to let different metabolic pathways proficiently operate in parallel, and to reduce futile cycles (Jungermann & Kietzmann 1996). It is worth to note that proliferating hepatocytes are mostly equidistant from the central and the portal vein (i.e. midlobular), while periportal and pericentral hepatocytes are not proliferating (Minocha *et al* 2017). Gene expression patterns and enzyme distribution in zonation are dynamic and regulated by not only nutrients, hormones but also oxygen and reactive species (Kietzmann 2017). Metabolic reactions in liver cells are modulated by the following:

- subcellular organelles – most oxidative reactions take place in mitochondria and peroxisomes, while reductive reactions occur in the cytosol (Hinzpeter *et al.* 2017);
- coenzyme availability – the couple oxidized/reduced NAD (NAD^+/NADH) in catabolic (oxidative) reactions, and the couple oxidized/reduced NAD phosphate ($NADP^+$/NADPH) in anabolic (reductive) reactions (Xiao *et al.* 2018);
- cellular AMP/ATP ratio – increased ATP utilization and/or decreased ATP production promote catabolism *via* AMP-activated protein kinase (AMPK); on the contrary, high ATP availability inhibits AMPK and switches metabolism toward anabolism (Foretz & Viollet 2011).

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Origin of reactive species in the liver

In this review, the term 'reactive species' will refer to both reactive oxygen and nitrogen species. In the liver, reactive species are produced by several metabolic reactions which take place in different cell types and subcellular compartments.

In the cytosol of hepatocytes, xanthine oxidoreductase (XOR) is involved in the last two steps of purine catabolism, leading to the oxidation of hypoxanthine to xanthine, which is in turn oxidized to uric acid (Battelli *et al.* 2016). XOR mostly acts as a dehydrogenase in the human liver, transferring electrons to NAD^+; nevertheless, XOR can be converted to an oxidase isoform by several stimuli, transferring electrons to O_2 with the production of reactive species (Stirpe *et al.* 2002).

Through the respiratory chain complexes, hepatocellular mitochondria transfer electrons to NAD^+, flavin mononucleotide, and flavin adenine dinucleotide (FAD), which act as carriers to reduce O_2 in a multistep process linked with the production of reactive species (Zorov *et al.* 2014). Liver mitochondria normally produce 13–15% of hepatic H_2O_2 by consuming nearly 2% of O_2 (Boveris *et al.* 1972, Zorov *et al.* 2014). Complexes I and III are the most important mitochondrial sources of reactive species, even though Complex II has also been described as a facultative producer (Moreno-Sanchez *et al.* 2013, Quinlan *et al.* 2013). Other mitochondrial sources of reactive species include monoamine oxidases A/B (Pizzinat *et al.* 1999) and cytochrome b5 reductase (Nishino & Ito 1986) in the outer membrane, α-glycerophosphate dehydrogenase (Mracek *et al.* 2009), dihydroorotate dehydrogenase (Forman & Kennedy 1975), the electron transfer flavoprotein ubiquinone oxidoreductase (Watmough & Frerman 2010), proline dehydrogenase and the branched-chain α-ketoacid dehydrogenase complex (Oldford *et al.* 2019) in the inner membrane, and α-ketoglutarate dehydrogenase and pyruvate dehydrogenase in the matrix (Oldford *et al.* 2019).

Peroxisomes are organelles involved not only in fatty acid catabolism, metabolism of pentose phosphates and D-amino acids but also in alternative alcohol oxidation and NAD^+ regeneration through malate dehydrogenase and/or lactate dehydrogenase (Gronemeyer *et al.* 2013). XOR and the inducible isoform of nitrate synthase are also situated in peroxisomes (Angermuller *et al.* 1987, Tikhanovich *et al.* 2013). In the liver, peroxisomes account for about 20% of O_2 consumption and 35% of H_2O_2 production, generating more reactive species than mitochondria (Fransen *et al.* 2012). H_2O_2 can promptly diffuse through the peroxisomal membrane by a porin-like channel or released in the cytoplasm by crystalloid core tubules (Fritz *et al.* 2007, Rokka *et al.* 2009).

The endoplasmic reticulum (ER) achieves crucial tasks in hepatocytes, including protein synthesis, trafficking and folding, calcium storage, and lipid, steroid, and xenobiotic metabolism (Liu & Green 2019). To oxidize sulfhydryl groups, protein folding needs a high oxidized (GSSG) to reduced (GSH) glutathione ratio in the ER lumen (Chakravarthi & Bulleid 2004). The protein disulphide isomerase (PDI) and ER oxidoreductin 1 (ERO1) are involved in the electron transport for protein folding: PDI directly accepts electrons, while ERO1 transfers electrons to O_2 as final the acceptor, producing ~25% reactive species in hepatocytes (Malhotra & Kaufman 2007, Csala *et al.* 2010). The microsomal monooxygenase system, which includes fatty acid desaturase, squalene monooxygenase, and 7-dehydrocholesterol reductase (involved in lipid and steroid metabolism), is one of the most important sources of reactive species in the ER. Xenobiotic metabolism involves phase I monooxygenation reactions (by cytochromes P450 and the flavoprotein NADPH-cytochrome P450 reductase) and phase II conjugation reactions. The electron transfer from NADPH to P450 in the monooxygenation reaction shows a leakage that promotes the production of reactive species (Zeeshan *et al.* 2016). An additional leakage in the electron transfer process which causes the production of reactive species may occur *via* the NADH-cytochrome b5 reductase in fatty acid desaturation (Samhan-Arias & Gutierrez-Merino 2014).

Lysosomes are vital for autophagy, a particularly preserved recycling mechanism consisting of the removal of cellular elements. These organelles maintain hepatocellular energy balance by modulating metabolic enzymes, mitochondria quality, and substrate availability (Madrigal-Matute & Cuervo 2016). Lysosomes are protective against an excess of reactive species by removing injured mitochondria, unfolded proteins, and toxic cellular compounds (Rabinowitz & White 2010, Pohl & Dikic 2019). Lysosomes include an electron transport chain comprising ubiquinone, reduced by cytosolic NADH with O_2 as the final electron acceptor; acidification of the lysosomal matrix induces the partial reduction of O_2, generating reactive species (Gille & Nohl 2000, Nohl & Gille 2002).

Hepatic NADPH oxidase and NO synthases (NOS) are additional sources of reactive species. NADPH oxidase is located in both parenchymal and nonparenchymal liver cells (De Minicis *et al.* 2006). KCs present with a phagocytic form of NADPH oxidase, able to produce high amounts of reactive species (Katsuyama 2010). HSCs are provided with a non-phagocytic NADPH oxidase isoform, able to produce

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mild quantities of reactive species (Bataller *et al.* 2003, Adachi *et al.* 2005, Zhan *et al.* 2006). Hepatic NO synthases are constitutive (eNOS) in LSECs, and inducible (iNOS) in hepatocytes, KCs, HSCs, and LSECs. Production of NO by eNOS is determinant to maintain the hepatic blood flow (Diesen & Kuo 2010). The role of iNOS in the liver is very complex since it can be regulated by several cytokines leading to the formation of reactive species with both protective and harmful effects (Taylor *et al.* 1998, Diesen & Kuo 2010).

Antioxidants in the liver

The liver disposes of several antioxidants to neutralize the excessive production of reactive species and to preserve redox balance. Hepatic endogenous antioxidants may be classified asn enzymatic and non-enzymatic. Endogenous antioxidants work as a complex network of redox reactions between the cytosol and subcellular compartments.

Enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), thioredoxin reductase (TRXR), glutathione peroxidase (GPX), and peroxiredoxin (PRX). SOD isoforms include Cu/Zn (SOD1 and SOD3) or Mn (SOD2) in their active site and account for the dismutation of superoxide anion (Fukai & Ushio-Fukai 2011). Cu/Zn-SOD is mostly located in the cytosol and lysosomes, while Mn-SOD is mostly sited in mitochondria (Okado-Matsumoto & Fridovich 2001). Among human tissues, the liver expresses the highest quantity of both CuZn-SOD and Mn-SOD (Marklund 1980). CAT is an iron-dependent peroxidase which transforms two H_2O_2 into two H_2O and one O_2. CAT activity in the human body is highest in the liver and erythrocytes (Goyal & Basak 2010). The hepatic GR, cytosolic and mitochondrial TRXRs (TRXR1 and TRXR2, respectively) use NADPH to reduce disulfides to dithiols. In the reaction catalyzed by GR, the dithiol reduces GSSG; as selenoproteins, TRXRs form selenothiol pairs which reduce TRX (Miller & Schmidt 2019). GPX isoforms are selenium-dependent peroxidases which are oxidized by the conversion of H_2O_2 into H_2O or organic hydroperoxide (ROOH) to corresponding alcohol (ROH) and are reduced again by GSH. Eight GPX isoforms are reported in humans, but only GPX1, GPX2, GPX4 (phospholipid hydroperoxidase), and GPX7 are located in the liver (Toppo *et al.* 2008). GPX1, GPX2, and GPX7 target H_2O_2 in the cytosol, mitochondria (GPX1), extracellular space (GPX2 and GPX7), and endoplasmic reticulum (GPX7), while GPX4 targets ROOH in the cytosol, mitochondria, and nucleus (Toppo *et al.* 2008). The six isoforms of PRX (thiol hydrolases) can be oxidized by H_2O_2 or ROOH, being reduced again by TRX. The human liver expresses all PRX isoforms, targeting both H_2O_2 and ROOH in the cytosol (PRX1, PRX2, PRX5, and PRX6), mitochondria (PRX3 and PRX5), extracellular space (PRX4), nucleus (PRX5), and endosomes (PRX3 and PRX6) (Rhee *et al.* 2018).

Non-enzymatic antioxidants include GSH, thioredoxin (TRX), and ubiquinone (UQ). GSH, the most concentrated hepatocellular antioxidant, is a tripeptide with a sulfhydryl group in a cysteine residue, which exerts its reductant activity on several oxidized enzymes and antioxidants (Kretzschmar 1996). TRX is a tetrapeptide with two sulfhydryl groups in two cysteine residues exposed to reversible redox reactions by the NADPH-dependent thioredoxin reductase. The reduced form of TRX is necessary to reduce oxidized peroxiredoxin, playing a determinant role in the hepatic redox homeostasis (Okuyama *et al.* 2008). UQ (or coenzyme Q) is contained in all liver cell types and, as lipophilic, is sited within several cell membranes, acting as an antioxidant in its reduced form (ubiquinol, UQH2). However, it can be partially reduced (ubisemiquinone, UQ•-), and the property to go through three different redox states allows it to act as an electron carrier from complexes I and II to complex III in the mitochondrial respiratory chain (Wang & Hekimi 2016). UQ is mostly concentrated in the Golgi vesicles, followed by mitochondria and lysosomes (Kalen *et al.* 1987).

Hepatic regeneration

The liver is provided with exceptional features of regeneration triggered by resection as well as different injuries (metabolic, viral, toxic, genetic, or immunologic). Both liver resection and acute/chronic injuries followed by organ regeneration are characterized by perturbations in redox homeostasis. In a healthy liver, functional cells replace the loss of liver mass according to the phenotypic fidelity (Michalopoulos 2013). Nevertheless, a continual or acute liver injury may impair the replicative capacity of mature liver cells, triggering alternative pathways of regeneration. One of these pathways includes the activation and differentiation of hepatic progenitor cells (HPCs, also termed oval cells in rodents) *via* ductular reaction (Espanol-Suner *et al.* 2012). Another pathway is characterized by trans-differentiation of hepatic parenchymal cells, that is, hepatocytes and cholangiocytes act as facultative stem cells for each other (Michalopoulos & Khan 2015).

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Regeneration induced by hepatic resection

Liver parenchymal cells are mitotically quiescent (G0 state), but a loss of liver mass induces quick proliferation of hepatocytes. Current understanding of liver regeneration derives from PHx in rodents, which consists of surgical removal of 70% liver mass, or toxin-induced hepatic injury. Liver regeneration following PHx classically recognizes three phases (immediate/early events, proliferation, and termination; Fig. 2), regulated by orchestrated molecular and cellular pathways which induce activation of nonparenchymal cells and proliferation of the remnant adult parenchymal cells (Michalopoulos & Bhushan 2021).

Increase in portal venous flow is the first event in the hepatic regenerative process, causing hemodynamic changes, which include enlarged sinusoidal diameter, increased fenestration, and widening of the intercellular spaces (Morsiani *et al.* 1998). These changes promote shear stress on LSECs, which in turn release NO-inducing cell proliferation and angiogenesis through vascular endothelial growth factor (VEGF) (Carnovale & Ronco 2012). Furthermore, portal venous flow holds several signaling factors from extrahepatic organs, such as EGF, insulin, glucagon, and bile acids (Michalopoulos & Bhushan 2021). Finally, increased portal venous flow may cause hepatic hypoxia, with consequent activation of the hypoxia-inducible factors (HIFs), additional promoters of liver regeneration (Maeno *et al.* 2005).

An early event following PHx is the activation of a urokinase-type plasminogen activator, which in turn activates metalloproteinases and leads to the breakdown and remodeling of extracellular matrix (ECM) (Kim *et al.* 1997). This results in the activation and release of hepatocyte growth factor (HGF) that, in association with EGF and other signaling molecules, promotes the Ras/Raf/MEK/ERK and the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)–protein kinase B (PKB)–mammalian target of rapamycin (mTOR) pathways, with the transition from G1 to S and from G2 to M phase in proliferating parenchymal cells (Lindroos *et al.* 1991, Fausto *et al.* 2006). The next early event is represented by acute inflammation, with increased levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) and downstream activation of Janus Kinase (JAK)/Signal Transducer and

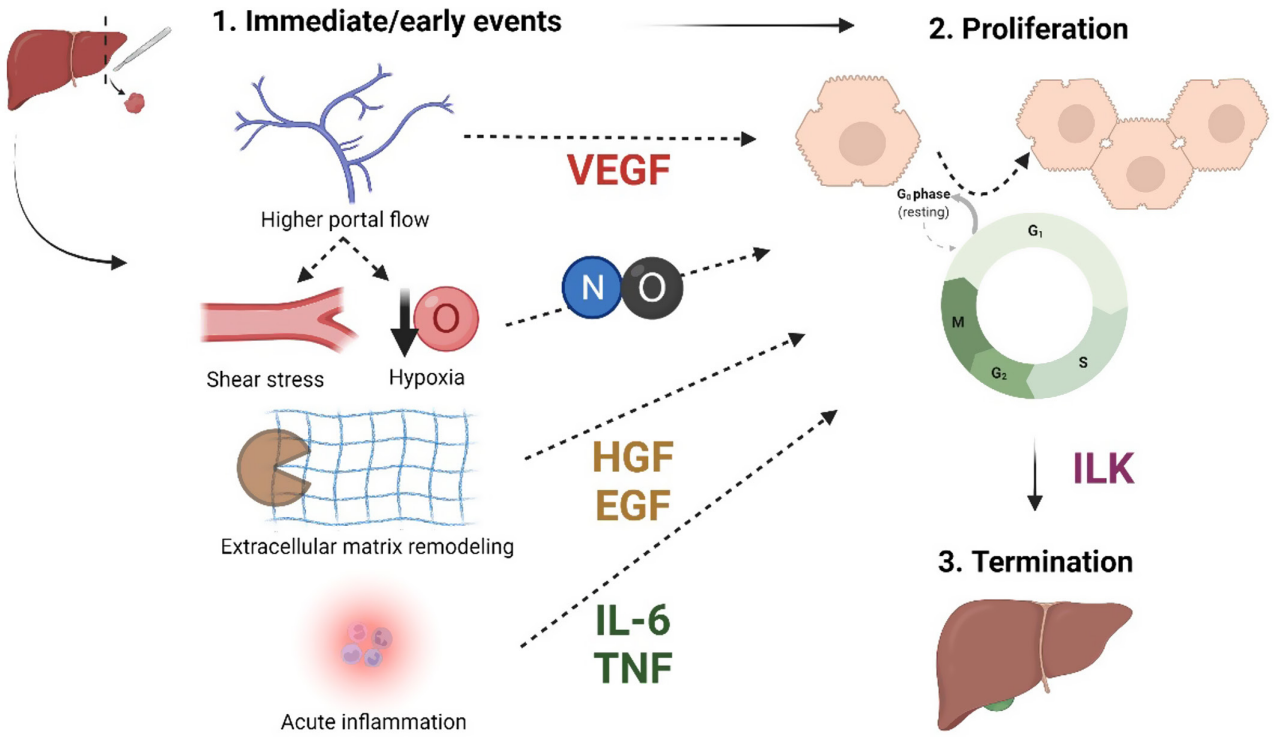

Figure 2
Regeneration following hepatic resection can be schematized in three subsequent stages: (1) immediate/early events include (i) increased hepatic portal flow, with consequent shear stress and hypoxia, leading to the release of vascular endothelial growth factor (VEGF) and nitric oxide (NO), (ii) remodeling of the extracellular matrix followed by the release of hepatocyte growth factor (HGF) and epithelial growth factor (EGF), (iii) acute inflammation which triggers secretion of interleukin-6 (IL-6) and tumor necrosis factor (TNF); (2) proliferation, characterized by the transition of mitotically quiescent (G0 state) toward cycling (G1 state) cells; (3) termination, in during which the integrin-linked kinase (ILK) promotes differentiation and stops proliferation of hepatocytes.

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Activator of Transcription 3 (STAT3) pathway, with the transition from G0 to G1 in quiescent hepatocytes (Cressman *et al.* 1995, Blindenbacher *et al.* 2003).

Proliferation of both parenchymal and nonparenchymal liver cells is regulated by a series of intracellular and extracellular events, controlled by signaling pathways classified according to their effect on hepatic regeneration: (i) complete mitogens, whose ablation stops the process; (ii) auxiliary/partial mitogens, which support the regenerative response, even though their ablation does not abolish it; (iii) complex mediators, which include multiple elements not completely characterized (Michalopoulos & Bhushan 2021). Complete mitogens include HGF and its receptor c-MET, EGF, amphiregulin, tumor growth factor-α (TGF-α), and heparin-αbinding EGF-like growth factor (HB-EGF) as ligands of the EGF receptor (Michalopoulos 2007, Michalopoulos 2013). Several pathways are recognized as auxiliary/partial mitogen signals, including the already cited TNF and IL-6, VEGF and its receptors, bile acids and farnesoid-X-receptor, noradrenalin and its α1 receptor, and different hormones such as insulin, leptin, serotonin, and growth hormone (Cressman *et al.* 1996, Yamada *et al.* 1998, Han *et al.* 2008, Fafalios *et al.* 2011, Borude *et al.* 2012). Complex mitogenic signals include the Wnt-β-catenin system, the Hedgehog and the Hippo-YAP pathways, and the TGF-β1 signaling (Yang *et al.* 2014, Swiderska-Syn *et al.* 2016, Patel *et al.* 2017, Oh *et al.* 2018). In particular, TGF-β1 signaling is a complex pathway controlling the hepatocyte cell cycle and response to mitogens: TGF-β1 inhibits mitosis so that its removal from the liver after PHx is associated with cell proliferation, while its subsequent rise is concomitant to termination of regeneration (Michalopoulos & Bhushan 2021).

Cessation of liver regeneration is characterized by the gradual acquisition of a quiescent phenotype of parenchymal cells, accompanied by the renewal of ECM, a process regulated by a network of signals between hepatocytes and HSCs (Rudolph *et al.* 1999). In this network, a determinant role is played by the integrin-linked kinase (ILK), which induces differentiation and stops the proliferation of hepatocytes (Gkretsi *et al.* 2008).

Alternative mechanisms of liver regeneration

Severe or chronic hepatic damage may induce hepatocellular senescence, causing a disruption in the regenerative mechanisms of liver parenchymal cells (Marshall *et al.* 2005).

In the setting of biliary injury, hepatocytes may exhibit phenotypic plasticity and trans-differentiate toward biliary-like cells to fix a cholestatic damage (Nejak-Bowen 2020). Although several mediators may be involved in this process, YAP activation plays an essential role (Pepe-Mooney *et al.* 2019). More than supplying a pool of cells to help recover injured bile ducts in severe biliary disease, hepatocytes may acquire transient biliary-like functionality (Gadd *et al.* 2020).

Severe hepatocellular injury may induce direct conversion of cholangiocytes to hepatocytes (Deng *et al.* 2018). Nevertheless, it is possible that less severe injury might also trigger de-differentiation of cholangiocytes to a bipotent progenitor state, through the so-called 'ductular reaction' (Sell 1998). The intrahepatic bile ductules (or canals of Hering, located between hepatocytes and the bile ducts) represent the anatomical site of hepatic regenerative niches, in which HPCs expressing both hepatocyte and cholangiocyte markers emerge and proliferate in response to severe or chronic liver injury (Xiao *et al.* 2003, Miyajima *et al.* 2014). HPC activation is accompanied by ECM remodeling, macrophage infiltration, and myofibroblast stimulation, involving several signaling pathways mediated by Wnt/β-catenin, Notch, and TNF-related weak inducer of apoptosis (TWEAK) (Jakubowski *et al.* 2005, Boulter *et al.* 2012). Moreover, YAP and mammalian target of rapamycin complex 1 (mTORC1) signals have been recently reported as determinants for HPC activation, since these pathways positively modulate the growth of cholangiocyte-derived organoids and the proliferation of HPCs in mice (Planas-Paz *et al.* 2019). Proliferation of HPCs is further regulated by several inflammation-related cytokines (TNF, IL-6) and growth factors (HGF/MET, VEGF, and TGF-β) (So *et al.* 2020). The origin of HPCs was defined by lineage tracing studies, which described cholangiocytes as sources of HPCs in several models (Schaub *et al.* 2014, Tarlow *et al.* 2014*a*, Raven *et al.* 2017). However, different lineage tracing investigations in chronic liver injury models reported hepatocytes as a supplementary source of HPCs through metaplastic process (Yanger *et al.* 2013, Tarlow *et al.* 2014*b*, Yanger & Stanger 2014). Mechanisms supporting hepatocyte metaplasia involve both YAP and Notch signaling (Yanger *et al.* 2013, Yimlamai *et al.* 2014, Pepe-Mooney *et al.* 2019). It is worth to note that HPC-dependent hepatic regeneration is not effective in repairing the loss of liver mass in severe or chronic liver diseases (Weng *et al.* 2015). Furthermore, the persistence of undifferentiated HPCs amplifies inflammation and fibrosis (Lukacs-Kornek & Lammert 2017). On the contrary, stimulating HPC differentiation may simultaneously lead to functional parenchymal cells and mitigation of fibrosis.

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Redox control of hepatic regeneration

Although formerly considered harmful, reactive species are progressively involved in several cell fate outcomes and signalling pathways (Holmstrom & Finkel 2014). In the liver, oxidants modulate several processes that may impact hepatic regeneration. We will elucidate redox-dependent mechanisms implicated in liver regeneration occurring after PHx/PLTx or in severe or chronic liver diseases (Table 1).

Redox involvement in regeneration after hepatic resection

Hepatic resection induced by PHx or PLTx is characterized by an excess of reactive species, which were mainly ascribed to intermittent inflow occlusion (Guerrieri *et al.* 1999, Senoner *et al.* 2019). It is conceivable that molecular pathways regulated by reactive species would be determinant in the process of regeneration following hepatic resection. On the other side, antioxidant treatments demonstrated to improve liver regeneration, suggesting that high concentrations of reactive species might be harmful in this process (Zeng *et al.* 2015, Cordoba-Jover *et al.* 2019). Thus, current evidence indicates that redox homeostasis is a determinant for the outcome of hepatic regeneration.

Modification of redox status in immediate/early events

Liver resection induces significant perfusion changes in the organ remnant, which influence hepatic functions *via* immediate modifications in O_2 supply, followed by indirect alterations of cellular metabolism. Indeed, since hepatic arterial and venous blood flow and pressure compensate for each other, increase in portal pressure is balanced by contraction of the hepatic artery (hepatic arterial buffer response) (Eipel *et al.* 2010). This means that the liver remnant receives a high portal and a low arterial blood flow, with reduced O_2 tension (Smyrniotis *et al.* 2002).

NO is a short-lived and highly unstable reactive species acting as both intra- and extracellular signaling molecule to modulate vasodilation and angiogenesis (Cooke & Losordo 2002). Hepatic NO concentration and metabolism are increased immediately after resection, associated with liver-specific cytokine-dependent overexpression of iNOS (Hortelano *et al.* 1995). More than regulating vascular dynamics in regenerating liver, NO is involved in the induction of DNA synthesis, even though it can partially promote lipid peroxidation (Carnovale *et al.* 2000). It is worth to note that NO is not the only redox-related mediator for hepatic vasodilation after resection since an upregulation of heme-oxygenase 1 (HO-1) by KCs promotes the production of carbon monoxide to contribute to vasodilation (Eipel *et al.* 2010).

Table 1 Redox-dependent modulators of hepatic regeneration.

Type and phase of regeneration		Regulatory factor	Role	References
Regeneration following liver resection	**Immediate/early phase**	Nitric oxide	Vasodilation Induction of DNA synthesis	Carnovale *et al.* (2000)
		HIF-1α	Hepatocellular metabolism	Maeno *et al.* (2005)
			Angiogenesis	Tajima *et al.* (2009)
		HIF-2α	Angiogenesis	Kron *et al.* (2016)
	Proliferation	H_2O_2	Induction of HB-EGF and amphiregulin	Miyazaki *et al.* (1996)
		NF-κB	Induction of TNF and IL-6	Mullen *et al.* (2020)
		NRF2	Induction of IL-6	Wruck *et al.* (2011)
			Activation of insulin/IGF-1R	Beyer *et al.* (2008)
		Nucleoredoxin	Inhibition of Wnt/β-catenin	Funato *et al.* (2006)
		FOXOs	Inhibition of cell cycle	Essers *et al.* (2005)
		HIF-1α	Activation of Hedgehog	Bijlsma *et al.* (2008)
		TRX1	MST1 inhibition	Chae *et al.* (2012)
			YAP activation	Wang *et al.* (2019)
	Termination	O_2^-	ILK inhibition	Saito *et al.* (2004)
		NO	ILK impairment	Reventun *et al.* (2017)
Alternative pathways of liver regeneration		NRF2	p21 signaling	Fan *et al.* (2014)
			Activation and differentiation of HPCs	Bellanti *et al.* (2021)

FOXOs, forkhead box O transcription factors; HB-EGF, heparin-binding EGF-like growth factor; HIFs, hypoxia inducible factors; HPCs, hepatic progenitor cells; IGF-1R, insulin-like growth factor-1 receptor; IL-6, interleukin-6; ILK, integrin-linked kinase; MST1, mammalian sterile 20-like kinase-1; NF-κB, nuclear factor-κB; NRF2, nuclear factor erythroid 2-related factor 2, TNF, tumor necrosis factor; TRX1, thioredoxin-1; YAP, yes associated protein.

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Blood flow changes after liver resection cause local hypoxia with consequent activation of the redox-dependent transcription factors HIFs. HIF-1α is able to regulate hepatocellular metabolism and angiogenesis during liver regeneration induced by PHx (Maeno *et al.* 2005, Tajima *et al.* 2009). HIF-2α is also activated by resection-induced hypoxia, to coordinate the proliferation of hepatocytes with VEGF-driven LSECs reconstruction and angiogenesis (Kron *et al.* 2016). This redox-sensitive mechanism can be pharmacologically modulated to accelerate the process of liver regeneration, as suggested by studies using prolactin-induced HIF-1α-VEGF axis or prolyl hydrolase inhibitors (Olazabal *et al.* 2009, Schadde *et al.* 2017). Furthermore, blood flow changes induced by PHx alter the remodeling of sinusoids affecting shear stress-induced eNOS, accounting for senescent LSECs *via* Notch activation, but Sirtuin 1 inhibition was able to promote liver regeneration by abolishing Notch-induced senescence (Duan *et al.* 2022). The latter is the first study demonstrating that LSEC senescence is triggered by endothelial Notch activation, with Sirtuin 1 as a direct target of Notch (Duan *et al.* 2022).

Redox modulation of proliferation pathways

Redox balance is involved in the regulation of several growth factors implicated in the proliferation of hepatocytes. HGF and its receptor c-MET, main regulators of hepatocellular proliferation, are also key modulators of the cellular redox state in a multimodal manner, but particularly upregulating the antioxidant GSH system, and repressing NADPH oxidase and CYP2E1 (Clavijo-Cornejo *et al.* 2013). In gastric mucosal cells, hydrogen peroxide is able to induce the expression of HB-EGF and amphiregulin in a concentration-dependent manner, and this induction is blocked by co-treatment with the antioxidant N-acetylcysteine (Miyazaki *et al.* 1996). In rat liver cells, hydrogen peroxide induces phosphorylation of EGF receptor, promoting transformation (Huang *et al.* 2001).

Cytokine-associated pathways involved in regeneration after hepatic resection are greatly influenced by the redox state. Mild concentrations of reactive species activate the transcription factor nuclear factor-κB, a potent inducer of TNF, IL-1β, IL-6, and its downstream STAT3 molecule expression (Mullen *et al.* 2020). Of interest, the IL-6 promoter matches an antioxidant response element and is strongly activated by the nuclear factor erythroid 2-related factor 2 (NRF2), one of the most important redox-sensitive transcription factors (Wruck *et al.* 2011). TGF-β inhibits hepatocyte proliferation, while its inactivation leads to increased proliferative response after liver resection (Russell *et al.* 1988, Romero-Gallo *et al.* 2005). The family of NADPH oxidases is recognized targets of TGF-β, mediating many of its effects on several liver cells and influencing liver regeneration after resection (Herranz-Iturbide *et al.* 2021).

Hormones involved in liver regeneration after PHx/PLTx may be modulated by cellular and extracellular redox state, including norepinephrine, growth hormone, insulin, and thyroid hormone, all of which in turn induce the Ras/Raf/MEK/ERK and PI3K/PKB/mTOR signaling pathways (Abu Rmilah *et al.* 2020). Of note, the contribution of insulin/insulin growth factor-1 receptor signaling in liver regeneration after PHx requires NRF2, since its inactivation leads to oxidative stress-related insulin resistance, impairing the activation of anti-apoptotic and pro-mitogenic pathways (Beyer *et al.* 2008). Of interest, NRF2 is dynamically regulated following PHx, showing activation in the presence of a pro-oxidant agent (such as ethanol) or antioxidant compounds, suggesting that this pathway may be triggered by liver resection independently of redox status (Morales-González *et al.* 2017).

Redox homeostasis alterations affect all the complex mitogenic signals involved in liver regeneration after PHx/PLTx. Overexpression of nucleoredoxin, a TRX family protein, selectively inhibits the Wnt/β-catenin pathway, while its ablation accelerates cell proliferation through Ras or MEK (Funato *et al.* 2006). Low amounts of reactive species promote the interaction between β-catenin and forkhead box O (FOXO) transcription factors, inhibiting the cell cycle progression (Essers *et al.* 2005). On the other side, Wnt/β-catenin signaling is necessary for hepatocyte protection against reactive species-mediated apoptosis, inducing the phosphorylation of FOXO3 and increasing hepatocyte proliferation (Tao *et al.* 2013). The Hedgehog cascade may be triggered by HIF-1α through hypoxia consequent to hepatic resection (Bijlsma *et al.* 2008). It is also worth to note that Hedgehog is a target of Wnt/β-catenin in the liver, suggesting a redox-dependent crosstalk between these pathways in regeneration following hepatic resection (Gebhardt 2014). The Hippo-YAP pathway is variably modulated by redox homeostasis, producing different functional outcomes. YAP, the main downstream effector of the Hippo cascade, is inactivated by the mammalian Ste20-like kinases 1/2 (MST1/2). Interestingly, TRX1 may prevent MST1 activation, while reactive species trigger MST1 activity, with opposite effects on YAP (Chae *et al.* 2012, Wang *et al.* 2019). Furthermore, the redox state may directly regulate YAP expression and activity in the liver (Wu *et al.* 2013).

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Redox commitment in termination of regeneration

ILK is a key determinant for termination of liver regeneration after Phx, since its ablation causes enhanced proliferation of parenchymal cells and hepatomegaly, associated with Hippo-YAP activation (Apte *et al.* 2009). A model of transient focal cerebral ischemia showed that superoxide inhibits ILK, while SOD expression is associated with increased ILK level (Saito *et al.* 2004). In damaged vascular endothelium, ILK protein stability and signaling cascade were impaired by high amounts of NO produced by iNOS (Reventun *et al.* 2017). These studies support the hypothesis that ILK is repressed by reactive species (including NO) in the early and intermediate phase of liver regeneration; when termination is approaching, redox balance tunes toward a reduced status, allowing ILK signaling to coordinate termination of regeneration.

Redox-dependent modulation of alternative liver regeneration pathways

The mechanisms underlying liver parenchymal cell trans-differentiation or ductular reaction involve key regulators of transcription (such as YAP, Wnt/β-catenin, Notch, TWEAK, and mTORC1), cytokines (TNF and IL-6), and growth factors (HGF/c-MET and VEGF). As already described, all these pathways are redox-responsive and take place following liver resection. Nevertheless, redox modifications are not triggered by blood flow modifications with reduced O_2 tension and shear stress. On the contrary, the impairment of redox homeostasis characterizing acute and chronic liver conditions contributes to disease pathogenesis, accounting for dysfunction or death of parenchymal cells (Medina & Moreno-Otero 2005, Mari *et al.* 2010). Hepatocellular trans-differentiation and ductular reaction are associated with metabolic changes, which include downregulation of oxidative pathways and mitochondrial dysfunction (Serviddio *et al.* 2013, Caldez *et al.* 2018).

When hepatocyte proliferation is impaired by loss of β1-integrin or p21 overexpression, cholangiocytes may behave as facultative progenitors to contribute to hepatocellular regeneration (Raven *et al.* 2017). Evidence from a model of toxic liver injury suggests that p21 signaling follows oxidative burst and is coordinated with the NRF2 pathway, expression of antioxidant genes, and control of the oxidative injury (Fan *et al.* 2014). Hepatic damage induced by thioacetamide (TAA) or 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) is followed by regeneration sustained by biliary epithelial cells (Deng *et al.* 2018). Of note, liver damage induced by both TAA and DDC administration is associated with alterations of redox homeostasis which induce upregulation of the NRF2 cascade (Stankova *et al.* 2010, Demirel *et al.* 2012, Singla *et al.* 2012). These data indicate that the master antioxidant regulator NRF2 could play a determinant role in the trans-differentiation process of liver parenchymal cells, but further specific investigations need to address this hypothesis.

Persistent hepatic chronic damage leads to an excess in reactive species with consequent oxidative stress, which may induce a senescent phenotype of parenchymal cells, impairing their capacity to proliferate (Roskams 2006, Bellanti & Vendemiale 2021). Thus, the ductular reaction occurs as a response to an oxidative injury, leading to HPC activation in a specialized microenvironment defined as a regenerative niche (Michelotti *et al.* 2016, Govaere *et al.* 2019, Overi *et al.* 2020). Nevertheless, the contribution of HPC activation and differentiation from hepatic niches is questioned, because of a lower efficiency with respect to phenotypic fidelity and trans-differentiation (Michalopoulos & Bhushan 2021). The final fate of HPC differentiation process is determined by different signaling pathways occurring in the niche, which is dependent on the etiology of liver injury (Boulter *et al.* 2012, Govaere *et al.* 2019). Regenerative niches are sites of multifaceted immunological events played by both immune and non-immune cells, and redox signaling is determinant in the fine tuning of the immune response in the HPC niche (Bellanti *et al.* 2020). More than modulating the immune signals within and around the niche, recent evidence demonstrates that the redox-dependent transcription factor NRF2 is a key determinant of HPC fate since its inhibition triggers their activation and differentiation (Bellanti *et al.* 2021). Further research is needed to clarify whether other redox-dependent transcription factors may potentially regulate the commitment of undifferentiated progenitors toward specific hepatic lineages.

Concluding remarks

Changes in redox homeostasis occur both following hepatic resection and during acute or chronic liver injuries. Understanding of several redox-dependent transcription factors and pathways implicated in the regenerative process of the liver has significantly improved in the last years. Several studies tested the hypothesis that antioxidants would boost liver regeneration by counteracting the negative effects of reactive species. Pre-clinical experiments using silymarin, quercetin, curcumin, resveratrol, baicalein, geraniol, and melatonin showed controversial results, suggesting the need for accurate study designs to define appropriate

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dosages, treatment duration, and routes of administration (Canbek & Yaylaci 2018). Furthermore, pharmacological modulation of redox-dependent molecular pathways to enhance liver regeneration represents a fascinating aim of the research. Indeed, pioneering reports suggest that potent pharmacologic activation of NRF2 is a potential approach to improve hepatic regeneration (Dayoub *et al.* 2013, Chan *et al.* 2021). Pre-clinical studies aimed at the definition of these targets will identify viable therapies to be tested in human trials.

Declaration of interest

The authors have no competing interests to declare. Francesco Bellanti is an Editor of Redox Experimental Medicine. Francesco Bellanti was not involved in the review or editorial process for this paper, on which he is listed as an author.

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F B wrote the first draft of the manuscript. G V and G S wrote sections of the manuscript and substantially contributed to the conception of the new version of the work. All authors contributed to manuscript revision, read, and approved the submitted version.

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