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Review

Surgical Stress and Liver Response: Injury, Regeneration, and Protection

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ABSTRACT

Liver surgery commonly involves the resection of the liver (loss of liver mass) and the temporary blockage of blood flow to the liver (liver ischemia). The liver immediately responds to overcome any surgical insult by recovering liver mass and function (liver regeneration). Major liver responses include cell proliferation, growth, and death, which are induced and regulated by various intrahepatic and extrahepatic factors. The central molecular machinery that regulates cell proliferation and growth during regeneration of the liver is driven mainly by interleukin-6/janus kinase/signal transducers and activators of transcription-3 and hepatocyte growth factor/phosphoinositide 3-kinase/phosphoinositide-dependent protein kinase 1/v-akt murine thymoma viral oncogene homolog signaling pathways in hepatocytes, respectively. These surgical procedures also induce a deleterious response by hepatocytes, which generate excessive amounts of reactive oxygen species, resulting in certain types of programmed or nonprogrammed cell death (e.g., necroptosis, apoptosis, parthanatos, and necrosis). The janus kinase/signal transducers and activators of transcription-3 and phosphoinositide 3-kinase/phosphoinositide-dependent protein kinase 1/v-akt murine thymoma viral oncogene homolog signals are activated instantly after surgical stress. At the same time, these signals play crucial roles in suppressing cellular oxidative stress and programmed cell death, thereby supporting liver regeneration after surgery. Such molecular machineries work harmoniously and efficiently to induce rapid and reliable liver regeneration that is necessary for life support. This review describes the various molecular and cellular responses of hepatocytes to surgical stress.

General Consideration

The liver is an indispensable organ since it participates in the absorption, digestion, metabolism, and detoxification/purification of different substances. Thus, pathological liver disorders, such as hepatitis and cirrhosis, not only affect basic liver functions but also general homeostasis.[1-5] The liver also has a large reserve capacity and can often respond quiescently to several internal and external stressors.[6]

Various metabolic, biological, or mechanical stressors can cause liver injury.[5,7-13] Excessive stress can deplete the high reserve capability of the liver, which can become life-threatening. Injury to the liver can be acute or chronic in nature. Chronic liver disease, such as alcoholic/viral hepatitis,

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metabolic dysfunction-associated steatohepatitis, and liver fibrosis/cirrhosis, may lead to liver cancer within a few decades.[4,5,10-12,14] Severe acute stress can cause severe injury to the liver, possibly resulting in organ failure. These severe injuries can be inflicted by hepatitis and other viruses, alcohol intoxication, and drug exposure.[15-20] The severity of liver injury is dependent on the degree of liver parenchymal cell death (hepatocyte cell death). If hepatocyte cell death spreads widely and progressively, the severely injured liver will eventually lose the ability to function.

Surgical treatment of the liver will more or less cause injury. Common surgical procedures often involve massive loss of liver mass and liver ischemia (Fig. 1). In partial hepatectomy (PH) or liver transplantation procedures, resection and ischemia can induce liver regeneration to recover mass and function. Since the surgical treatment of liver disease relies on its ability to regenerate both physically and functionally,[6,21-23] insufficient or poor liver regeneration may lead to severe liver failure and impact patient prognoses. This is especially problematic if a patient has underlying disorders, such as diabetes mellitus,[8,22] chronic renal failure, or an infectious disease.[24] Even delayed or insufficient regeneration of the remnant liver can result in major postoperative complications.[13,22,25-27] Failure of the liver to regenerate to an adequate liver volume may lead to severe liver failure, clinical deterioration, and eventual death. Therefore, therapeutic liver resection should be performed in cases where sufficient and immediate liver regeneration is expected.[6,21-23]

Surgical procedures involve common stressors, such as liver resection and ischemia induced by the temporary blockage of hepatic blood flow (Pringle maneuver). Liver resection results in the physical reduction of liver mass, during which liver function may be lost based on the resected amount of liver (hepatocytes). Even if the liver is not resected, injury induced by liver ischemia often results in loss of liver function depending on the degree of liver cell death.[28-34] Loss of liver mass immediately drives the liver to regenerate until it reaches enough volume and function. The procedures to control bleeding inevitably cause liver ischemia and can induce liver injury, depending mainly on the duration of ischemia.[35-41] This may lead to liver failure and even life-threatening postoperative complications if the liver cannot overcome the injury. Especially in cases involving liver transplantation from a live donor, small-for-size liver grafts must regenerate instantly and sufficiently after transplantation. Understanding the pathophysiological features of surgical stress and the response of the liver is, therefore, extremely important and can have clinical benefits.

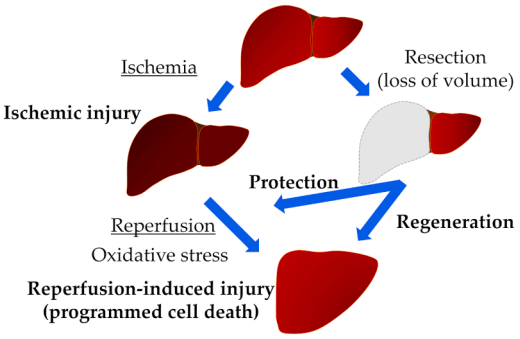

Fig. 1 – Liver response to surgical stress. Liver surgery commonly involves ischemia and resection of the liver. Liver ischemia by itself causes injury, and liver reperfusion (restoration of liver circulation) induces additional injury, referred to as I/R-induced injury. The surgical resection of the liver triggers/initiates regeneration of the remnant liver. Surgical stress involves a combination of ischemia, reperfusion, and volume loss, leading to oxidative stress in the liver. The liver instantly responds to surgical stress by regenerating while protecting against I/R-induced injury.

Following surgical stress, the liver tries to regenerate to restore liver function and maintain essential life activities. The primary liver response for liver regeneration after resection involves cellular proliferation, growth, and programmed cell death. Interestingly, the molecules responsible for driving liver regeneration may also play crucial roles in controlling injury, especially in protecting against oxidative stress and programmed cell death. These processes may be involved in the underlying mechanism for achieving certain liver regeneration.

This review is unique in that it focuses on the liver's response to combined stressors (liver resection with ischemia/reperfusion [I/R]) due to liver surgery. The molecular mechanisms of I/R-induced injury, regeneration, and protection against injury are described, with an emphasis on the mechanisms involved in cell proliferation/growth and cell death.

Surgical Stress and Liver Injury

To date, many studies on the molecular mechanism of I/R-induced liver injury have been conducted in attempts to prevent it.[28,39,41-46] This event may be induced and enhanced by multiple steps that occur sequentially during and after liver ischemia. Thus, we have not yet succeeded in elucidating the comprehensive mechanisms of I/R-induced liver injury and developing a clinically effective therapy.

The degree of ischemic injury depends on the ischemic conditions of the liver (time and temperature).[40] The injury of ischemia by itself usually becomes evident after the restoration of liver circulation (reperfusion), since it is difficult to noninvasively and accurately assess the degree of ischemic injury before reperfusion. Therefore, liver injury emerging after reperfusion reflects both ischemia- and reperfusion-induced injuries.[39,47,48] Immediate injury to the liver/hepatocytes by reperfusion is caused mainly by intracellularly generated reactive oxygen species (ROS).[43,49-59] ROS are generated immediately after reperfusion in cells under prolonged ischemic insult. Although the molecular mechanism of reperfusion-induced injury has not been fully elucidated, the initial injury after reperfusion seems to be evoked by excessively generated cellular ROS in hepatocytes.[43,49-51,53,55-57] These ROS induce various types of programmed cell death[45,46,60-66] and activate proinflammatory transcription factors like nuclear factor kappa B (NFκB).[67-71] Proinflammatory cytokines then induce the migration of immune cells into the reperfused liver tissue, and eventually induce

sterile inflammation that expands I/R-induced injury.[72-75] In this way, I/R-induced liver injury includes injuries caused directly by ischemia or reperfusion, as well as secondary injury enhanced by sterile inflammation (Fig. 2).

Molecular mechanisms of ischemic liver injury

Ischemic injury is caused by procedures that temporarily or permanently block blood flow. Surgical blockade of blood flow into the liver can cause oxygen deprivation in liver cells, resulting in primary liver injury (hepatocyte cell death). Liver ischemia occurs when the oxygen supply is deprived, and adenosine triphosphate (ATP) is rapidly degraded in hepatocytes. This eventually leads to the direct induction of nonprogrammed lytic cell death (necrosis).[76-80] Liver injury induced by ischemia mainly involves necrosis, and apoptosis to some extent.[81]

The duration of liver ischemia is crucial in determining the extent of cellular dysfunction and hepatocyte cell death.[40,82,83] This ultimately depends on how vulnerable cells, tissues, and organs are to ischemia,[82-89] but they can withstand and survive short periods of ischemic insult.[40] An ischemic insult without severe injury allows them to prepare for the next more severe ischemic insult.[90-97] This is a common response to stress in various types of cells/organs, often called "ischemic preconditioning".[98-109] With increased ischemic time, it becomes difficult for cells to withstand ischemia, which can disrupt cell/organelle membranes and structural integrity and induce irreversible and lethal changes in intracellular environments, resulting in cell death.

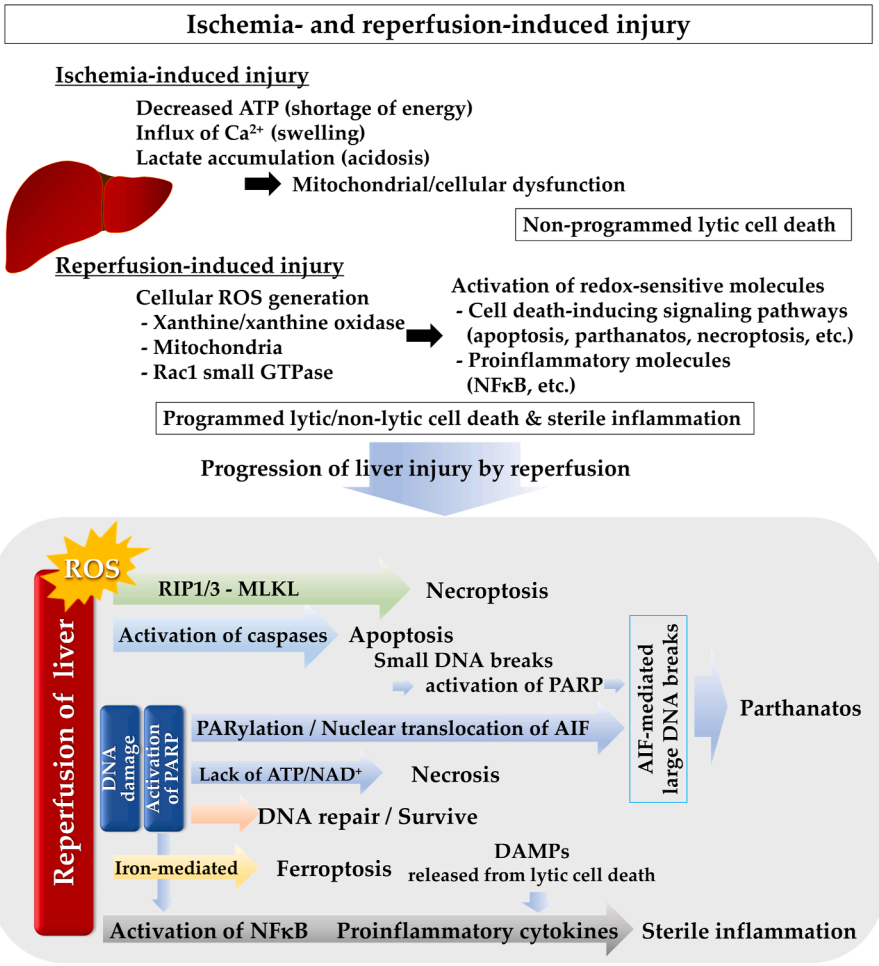

Fig. 2 – Ischemia and ischemia/reperfusion-induced liver injury and inflammation. Ischemia involves the deprivation of oxygen, which inhibits electron transport in the respiratory chain, leading to a decrease in cellular levels of ATP and an intracellular accumulation of Ca^{2+} that activates proteases, lipases, phospholipases, and ATPases. At the same time, anaerobic metabolism causes lactic acidosis, activating intracellular proteases that may cause cellular dysfunction. Increased Ca^{2+} influx into organelles leads to the transition of membrane permeability and therefore mitochondrial dysfunction. These intracellular events result in nonprogrammed lytic cell death (necrosis). The restoration of blood flow to the liver with increased intracellular Ca^{2+} concentrations leads to the excessive generation of ROS via several pathways. This activates several cell death–inducing signaling pathways and proinflammatory molecules such as NFκB. These molecules induce postischemic programmed cell death (apoptosis, parthanatos, necroptosis, etc.) and sterile inflammation through the activation of proinflammatory transcription factors, including NFκB. ATP = adenosine triphosphate; NFκB = nuclear factor kappa B; ROS = reactive oxygen species.

Ischemia directly influences the levels of cellular ATP, Ca^{2+}, and intracellular pH.[82,83,110-112] By impairing ATPase-dependent ion transport, ischemia induces an increase in Ca^{2+} levels in cells and mitochondria (Ca^{2+} overload). The regulatory machinery of cell volume is also impaired by the lack of ATP, which finally leads to the lysis of organelles and plasma membranes. As ATP availability declines, ATP-dependent ion channels are inactivated, cell metabolism slows down, and eventually anaerobic glycolysis occurs. Due to the impairment of Ca channels, cellular levels of Ca^{2+} increase and activate Ca-dependent cellular enzymes, including phospholipase C and protein kinase C, thereby inducing hepatocellular necrosis.[113-116] Lactic acid accumulation initially acidifies cells, protects mitochondrial membranes, and postpones cell death.[65] In contrast, the increase in intracellular pH accelerates cell death (pH paradox).[113,117] Both the accumulation of Ca^{2+} and pH imbalance result in a transition in mitochondrial permeability, which is important for necrotic cell death.[65,118-121] This event is characterized by mitochondrial swelling, after which their membrane potential decreases, allowing high molecular weight molecules to pass through "ionic mega channels".[117]

These molecular mechanisms combine to cause necrotic cell death in hepatocytes during liver ischemia.

Molecular mechanism of reperfusion-induced liver injury

In liver surgery, the remnant liver undergoes temporary ischemia followed by reperfusion. In this section, the injury caused by the restoration of liver circulation after ischemia (reperfusion) is described as an "I/R-induced injury."

Generation of ROS in liver after reperfusion

Unless they are generated in excessive amounts, the ROS induced in response to hypoxia are thought to have cytoprotective effects since they activate several signaling pathways.[65,122,123] Under normal (normoxic) conditions, ROS are the by-products of physiological cell metabolism, and their levels are regulated within physiological ranges. When present in physiological amounts, ROS commonly contribute to various physiological events, including cell proliferation, differentiation, survival, and homeostasis.[124-126] However, in some pathological conditions where cellular ROS are produced in excess or not properly degraded, programmed or nonprogrammed cell death can occur. Excessive cellular ROS can play roles as death-inducing second messengers.

The immediate liver injury after reperfusion is provoked mainly by ROS generated in hepatocytes.[6,40,43,45,46,50] ROS are generated immediately in the reperfused liver after 30-60 min of ischemia. If the ischemic time of the liver is much longer or shorter, the generated ROS do not contribute substantially to liver injury.[40] Longer periods of ischemia directly induce massive necrosis of hepatocytes, while ROS are observed only after neutrophil infiltration around the necrotic area at later time points after I/R. Therefore, it seems clear that ROS from neutrophils barely contribute to I/R-induced acute phase injury.[127]

Intracellular enzymatic sources for ROS after I/R have not been fully characterized. The mitochondrial electron transport chain and xanthine oxidase (XO) may be important sources of ROS generated after I/R.[51-55,63,78,128] However, it has become evident that these enzymatic sources of ROS do not fully account for the acute phase ROS generation after I/R. Injury induced by I/R can occur even in XO-deficient organs,[129] and XO inhibitors are not effective in certain I/R-induced injury models.[130-133] These studies have thus questioned whether XO plays a substantial role in I/R-induced injury.

In certain pathological disorders like liver I/R, oxidative phosphorylation of mitochondria and reactions of the oxidative respiratory chain are inhibited, leading to impaired mitochondrial function.[51-53,55,117,120,128] This leads to massive ATP consumption and the eventual generation of large amounts of mitochondrial ROS. Excessive ROS can severely damage mitochondrial structure, function, and energy metabolism, thereby reducing the number of functional mitochondria. Such mitochondrial events can lead directly to cellular necrosis and sometimes apoptosis.[55,63,117] It remains unclear whether excessive ROS of mitochondrial origin are actively involved in the induction of programmed cell death (e.g., apoptosis). Mitochondrial dysfunction undoubtedly causes cell death and liver injury. Extensive and persistent mitochondrial dysfunction eventually causes metabolic dysfunction and liver failure, leading to increased mortality and morbidity.[134,135]

Ras-related C3 Botulinum Toxin Substrate 1 (Rac1), which belongs to the Rho family of guanosine triphosphate degrading enzyme, plays a fundamental biological role in various cell processes, including cytoskeletal reorganization of actin, axonal guidance, induction of DNA synthesis, and cell transformation and migration.[43,50,136-139] In addition, as a second messenger, Rac1 regulates different cellular signaling pathways. It can also regulate intracellular ROS generation in phagocytic[140,141] and nonphagocytic cells[43,49,50,139,142-144] via nicotinamide adenine dinucleotide phosphate oxidase. Rac1 may also positively regulate the generation of ROS in response to I/R *in vivo* and hypoxia/reoxygenation (H/R) *in vitro*, including the liver.[43,50,142,143] Furthermore, Rac1 may play a role in hepatocyte cell death.[50,51,142] Since Rac1 exists close to the cell membrane, Rac1-mediated ROS can act as second messengers and send signals from an external stressor into the cells, thus affecting cell survival, programmed cell death (apoptosis),[43,50] cell proliferation,[144,145] and inflammatory reactions.[43] Interestingly, the posthypoxic activation of heat shock factor is regulated by Rac1-mediated ROS but not by ROS of mitochondrial origin.[49] This suggests that Rac1-mediated ROS are more crucial as second messengers than mitochondria-mediated ROS. In a mouse liver I/R model, Rac1 was involved in ROS generation and liver injury.[43] Rac1 was also involved in NFκB activation in the postischemic liver, indicating that it may regulate a secondary inflammatory reaction after I/R.[43] This suggests that I/R-triggered, Rac1-mediated generation of ROS may contribute to postischemic acute liver injury by inducing programmed cell death (e.g., apoptosis) and a secondary NFκB-dependent inflammatory response.

Programmed Cell Death After Hepatic I/R

When the liver undergoes an ischemic insult, some liver cells die due to a lack of oxygen and ATP. If the ischemic insult is too severe for hepatocytes to overcome, liver failure occurs

soon after reperfusion. Even if they survive ischemic injury, hepatocytes experience oxidative stress right after reperfusion. This can lead to fatal responses in the cells that survive the ischemic insult, which may proliferate, grow, or die in order to stimulate the prompt and efficient regeneration of the liver.

As second messengers, cellular ROS generated after reperfusion can activate several redox-sensitive signaling pathways to trigger programmed cell death and liver injury.[43,50,146-148] To date, ROS-mediated programmed cell death following H/R or I/R has been extensively studied, mainly with a focus on apoptosis,[43,63,66,81,115,146,149] a nonlytic programmed cell death mechanism that is caspase-dependent and redox-sensitive. Caspases are cysteine proteases that escalate cascade reactions leading to cell death.[150-153] Interestingly, caspases also contribute to immune system regulation by activating proinflammatory cytokines (interleukin [IL]-1β).[150,154] Some caspases, such as caspases-1, -4, -5, -11, and -12 in mice or humans, are involved in the processing/activation of proinflammatory molecules and are often referred to as "proinflammatory caspases".[154-156] To date, because most studies have focused exclusively on caspase activation and apoptosis in organ injury, these enzymes have been investigated as possible therapeutic targets in various diseases, including injury induced by I/R.[157-159] However, caspase inhibition often results in the partial suppression of I/R-induced liver injury, suggesting that other molecules, independently of caspases, may play important roles and induce different programmed cell death processes under these conditions.

Researchers have identified several programmed cell death processes in pathophysiological conditions for many organs (apoptosis, necroptosis, parthanatos, ferroptosis, and others).[30,34,60,81,160-167] Of these, apoptosis is one of the most well-known and plays a part in various disorders such as postischemic liver injury and chronic/acute hepatitis.[30,66,149]

Fas antigen (CD95) is expressed constitutively in both noncancerous and cancerous hepatocytes, and may regulate various pathological cell death processes.[33,168-170] Fas-ligand can induce apoptosis redox-dependently in a caspase-mediated manner and is involved in many pathological conditions, including postoperative liver injury,[168,171,172] hepatitis B and C,[171] and alcoholic hepatitis.[5,168]

Several molecules that induce apoptosis, including tumor necrosis factor-α (TNF-α), can also trigger necrotic cell death in certain circumstances.[46,160-162,167] This programmed necrosis is known as "necroptosis". TNF-α is also known to regulate the signaling pathways for cell survival and cell death, which can be divided into necroptotic and apoptotic pathways.[173,174] Binding of TNF-α to its cell surface receptor leads to the formation of Complex I, which contains receptor interacting protein kinase 1 (RIP1), tumor necrosis factor receptor-associated factor 2, TNF receptor–associated death domain (TRADD), and tumor necrosis factor receptor-associated factor 5. These molecules are commonly polyubiquitinated if the cells are not under any particular stress. However, RIP1 moves to form Complex II when the molecules are deubiquitinated through the actions of certain proteins. Complex II contains caspase-8, TRADD, Fas-associated protein with a death domain, RIP3, and RIP1. Cleavage and activation of caspase-8 lead to the inactivation of RIP3 and RIP1. As a result, apoptosis occurs by subsequent activation of downstream caspases (caspases-3, -6, and -7).[45,46,175] If the cells lose caspase activity for some reason, they can undergo necroptosis, which may act as a "backup" cell death mechanism. Recent studies have suggested that necroptosis may be pathologically involved in the progression of acute pancreatitis, myocardial infarction, and I/R-induced liver injury.[45,46,162,176,177]

DNA breaks lead to the activation of poly (adenosine diphosphate-ribose) polymerase (PARP), an enzyme that repairs DNA.[178-183] PARP primarily mediates repair processes in cells with DNA damage, in order to prevent cell death. Poly [adenosine diphosphate-ribose] (PAR) is generated from PARP and is added to target proteins. PAR generated by PARP then acts as a scaffold to recruit various enzymes that repair DNA damage.[178,184,185] PARP and PAR play additional roles in pathological conditions involving cell death and inflammation.[183,186] In certain conditions, PARP may induce programmed/nonprogrammed cell death processes, including necroptosis, parthanatos, and necrosis, in many cell types.[45] PARP that is excessively activated will consume both ATP and nicotinamide adenine dinucleotide to induce necrosis. Parthanatos, a lytic programmed cell death process, is the result of DNA breaks, excessive PARP activation, and PAR production. With the addition of PAR, apoptosis-inducing factor is liberated from the mitochondria and travels into the nucleus, inducing parthanatos.[180,183] Reportedly, RIP and PARP may also interact, suggesting that PARP could be involved in inducing necroptosis.[183,187,188]

It is unclear how these cell death processes (necroptosis, apoptosis, parthanatos, and necrosis) interact with each other and affect different pathological conditions such as I/R. However, H/R, I/R, or oxidative stress can certainly induce these cell death processes in hepatocytes.[45] In particular, parthanatos and necroptosis appear to be more redox-sensitive than apoptosis. Furthermore, PARP may be involved in postischemic liver inflammation through activation of the proinflammatory transcription factor NFκB.[179,189,190]

Inflammation after hepatic I/R

An important transcription factor in the induction and expansion of I/R-induced injury is proinflammatory NFκB.[191] NFκB is usually found in the cytoplasm bound to the inhibitory protein inhibitor of κB (IκB).[192-195] During oxidative stress, IκB is degraded, promoting the nuclear translocation of NFκB. When activated, NFκB can stimulate the transcription of genes such as cytokine-inducible nitric-oxide synthase, cytokines (e.g., TNF-α), adhesion molecules (e.g., intercellular adhesion molecule-1), and chemokines.[191,196] ROS generated within a few minutes after hepatic reperfusion activates redox-sensitive molecules including NFκB.[40] NFκB is activated less than a few hours after reperfusion,[43] and induces an increase in proinflammatory cytokines in the reperfused liver tissue (IL-1β, IL-6, and TNF-α).[191] Although ROS generation and the proinflammatory reaction occur within a few minutes and hours, respectively, postischemic liver injury and inflammation become evident late after reperfusion. Histologically, liver injury can be observed 24 h after reperfusion although serum markers (lactate dehydrogenase, alanine aminotransferase,

aspartate aminotransferase) may be increased earlier.[40] Inflammatory cell infiltration only becomes apparent 24 h after liver reperfusion. This indicates that ROS originating from infiltrating neutrophils in the postischemic liver barely contribute to the early phase of I/R-induced liver injury. Redox-dependently activated NFκB mediates proinflammatory cytokine production and induces a secondary liver injury later after reperfusion.[40]

Surgical Stress and Liver Regeneration

Regeneration of the liver is indispensable in almost all liver surgeries. The molecular mechanisms by which liver mass is restored after PH to maintain sufficient liver function, especially in terms of hepatocyte proliferation and growth, will be described in the next section.

The regeneration process after surgical liver resection consists of a network of complex interactions between the liver and extrahepatic organs.[6] Within the liver, various hepatic cells, including hepatocytes, hepatic stellate cells (HSCs), sinusoidal endothelial cells (SECs), and Kupffer cells, coordinate with each other to achieve liver regeneration.[6,197-201] Cytokines (IL-6, TNF-α, and interferon-γ) and growth factors (transforming growth factor [TGF]-α and -β, hepatocyte growth factor [HGF]) will mediate the cell-cell interactions. This multifactorial control system allows for the efficient and reliable regulation of liver regeneration. At the same time, these extremely organized intrahepatic cells may closely collaborate with extrahepatic organs, such as the thyroid gland,[202,203] adrenal gland, pancreas,[203,204] duodenum,[205] platelets,[205,206] spleen,[207,208] and autonomic nervous system.[209] These extrahepatic organs induce various signaling pathways in parenchymal/nonparenchymal liver cells to directly achieve liver regeneration through growth factors (TGF, epidermal growth factor [EGF]) and hormones (T3, norepinephrine, insulin, serotonin, glucagon, and somatostatin). These networks between the liver and other organs essentially coordinate to regulate liver regeneration processes.

Liver regeneration consists of five phases as follows: priming, initiation, progression, maintenance, and termination.[6,210] The basic hepatocyte functions/behaviors (i.e., cellular proliferation, growth, and death) have pivotal roles to play during each phase. Regeneration of the liver is initiated by hepatocyte proliferation and growth, which are cooperatively and respectively regulated via IL-6/janus kinase (Jak)/signal transducers and activators of transcription-3 (STAT3) and phosphoinositide 3-kinase (PI3-K)/phosphoinositide-dependent protein kinase 1 (PDK1)/v-akt murine thymoma viral oncogene homolog (Akt) signals[197,199,201,211-213] (Fig. 3). For normal, healthy liver regeneration, programmed cell death (apoptosis) may play an important role during the termination phase.[6]

Hepatocyte proliferation via Jak/STAT3 signals

Activated Kupffer cells predominantly secrete IL-6, which transmits mitogenic signals to hepatocytes via activation of the Jak/STAT3 pathway and is an important factor during the initiation phase of liver regeneration.[6,197,198,214-216] STAT3 does not activate post-PH in IL-6–deficient mice,[217] suggesting that STAT3 activation post-PH is only induced by IL-6, although other cytokines, including granulocyte colony stimulating factor[218] and leptin,[219] can also activate STAT3. Activation of STAT3 by its phosphorylation at Tyr705 immediately after PH sends strong mitogenic signals to hepatocytes, and may therefore trigger liver regeneration.[201,203,213,215] In post-PH mice, activated STAT3 instantly moves into the nucleus and binds target DNA sites within a few hours.[197,199,201,212]

The activation of the IL-6/Jak/STAT3 signaling pathway occurs in the following manner[220,221]: IL-6 binds to its corresponding receptor, leading to the binding of the gp130 protein to the IL-6 receptor and Jak activation. Jak activates STAT3 mainly through the phosphorylation of the tyrosine residue Tyr705. After STAT3 activation, it is released from gp130 and travels to the cytosol, where a dimer is formed involving its Src homology2 domain and the phosphorylated tyrosine

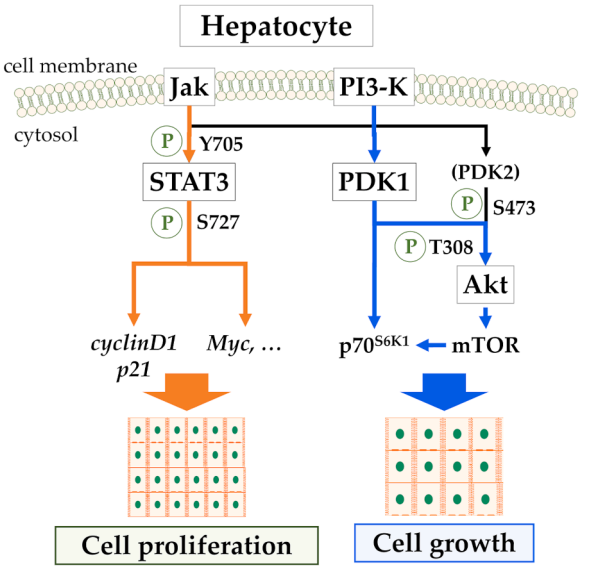

Fig. 3 – Signal transduction of cell proliferation and growth during liver regeneration. After surgical resection, the liver regenerates essentially through cell proliferation and growth, which are mainly regulated by the IL-6/Jak/STAT3 and HGF/PI3-K/PDK1/Akt signaling pathways. During regeneration, cell proliferation is predominantly regulated by activated STAT3. However, when the STAT3-induced mitogenic response is disturbed, Akt is activated in compensation and tries to maintain normal liver regeneration. Jak/STAT3 positively controls cell proliferation by targeting cyclinD1, p21, and Myc. PI3-K/Akt positively controls cell growth by phosphorylating/activating mTOR and $p70^{S6K}$. HGF = hepatocyte growth factor; IL-6 = interleukin-6; Jak = janus kinase; mTOR = mammalian target of rapamycin; PDK1 = phosphoinositide-dependent protein kinase 1; PI3-K = phosphoinositide 3-kinase; STAT3 = signal transducers and activators of transcription-3.

Tyr705 on its counterpart. The STAT3 dimer then undergoes nuclear translocation, and binds certain DNA sites to upregulate gene expression of its targets. Reportedly, during STAT3 activation, it is also phosphorylated at Ser727, which may be necessary for its full activation. However, recent studies also suggest that phosphorylation at Ser727 may negatively regulate STAT3 activity by dephosphorylating Tyr at 705, indicating a negative control mechanism for STAT3 activity.[222] Cell proliferation after PH has also been analyzed in liver-specific STAT3-deficient mice.[6,199,212] In hepatocytes for these post-PH mice, mitogenic activity and DNA synthesis are almost lost and cyclinD1 expression is substantially reduced. STAT3-C (the constitutively active mutant of the STAT3 gene) may also be useful for the study of STAT3 function.[33,42,211,223] STAT3-C gene induction within hepatocytes leads to transcriptional upregulation of cyclinD1, p21, and c-myc, thereby stimulating cell proliferation.

Hepatocyte growth via PI3-K/PDK1/Akt signals

The mitogenic response driven by IL-6/STAT3 plays a crucial role during regeneration of the liver.[197,198,212-214,217] However, deletion of the STAT3 gene in mouse hepatocytes does not impair liver regeneration at all after PH, even if cell proliferation does not occur.[201] As a backup mechanism, immediate cell growth may occur to achieve liver regeneration without delay by compensating for cell numbers with cell size.[6,198,201,214]

The PI3-K/PDK1/Akt pathway plays a major role in various essential cellular functions, including cell growth (cell size).[224-228] PI3-K/PDK1/Akt signals are activated by receptors coupled to G proteins or receptor tyrosine kinases, which are stimulated by IL-6,[229] TNF-α,[230] HGF,[231] epidermal growth factor,[232,233] and insulin-like growth factor-1.[234] Akt is activated via its phosphorylation at Thr308 in the active domain and Ser473 in the hydrophobic domain. Although Thr308 phosphorylation may be enough for Akt activation, phosphorylation of both Thr308 and Ser473 is required for its full activation.[234,235] Mammalian target of rapamycin (mTOR) has been established as an important Akt target in cell growth.[236] mTOR stimulates the activation of $p70^{S6K1/S6K2}$ and eIF4E-inhibiting 4E-BP1, which mediate essential cellular functions such as protein synthesis, glucose homeostasis, cell proliferation, and cell growth.[237]

Disruptions in STAT3-driven cell proliferation lead to the compensatory activation of the PI3-K/PDK1/Akt pathway in an attempt to maintain normal liver regeneration.[6,199,214,237] For liver-specific STAT3-deficient mice, the liver restoration rate after PH was not significantly different from that in their control littermates. Instead, hepatocyte size in the STAT3-deficient mouse liver was transiently and significantly larger than that in control mice, but eventually returned to the original size within 14 days post-PH with sufficient restoration of the liver. In contrast, in liver-specific PDK1-deficient mice, phosphorylation of Akt at Thr308 was greatly reduced and $p70^{S6K}$/mTOR activation (phosphorylation) therefore declined after PH. This can lead to severe impairment in recovery of liver function and mass post-PH, which can potentially be ameliorated through the revival of PDK1-Akt signaling.[199,201] These findings suggest that the PI3-K/PDK1/Akt pathway plays a major role in post-PH liver regeneration by enlarging and retaining cell size/function, especially when there are disruptions in the early mitogenic response after this procedure.

In brief, the complementary Jak/STAT3 and PI3-K/PDK1/Akt pathways contribute to regeneration of the liver in a coordinated manner via cellular proliferation and growth.

Hepatocyte Protection During Post-PH Liver Regeneration

Liver stress following liver surgery induces cellular ROS of various origins in the liver/hepatocytes, as described in previous sections. Intracellularly generated ROS after hepatic reperfusion easily activate redox-sensitive signaling pathways to trigger programmed cell death.[43,50,146-148] A mechanism that protects against injury and stress in vital organs is justified in order to maintain essential life activities. Similar to other mammalian cells, hepatocytes have endogenous scavenging enzymes for protection against excessive ROS, including glutathione peroxidase, catalase, and superoxide dismutase (SOD).[33,42,238,239] However, once the level of ROS formed is above that to be removed/suppressed by such enzymes, this triggers multiple harmful cellular events that eventually result in programmed cell death and inflammatory cytokine production.

Interestingly, both STAT3 and Akt not only play important roles in liver regeneration (cellular proliferation and growth) but also protect against oxidative stress and injury (cellular death), which will be described in the next sections (Fig. 4).

Jak/STAT3 signals for liver protection

Apoptosis, as a programmed cell death process, has been widely investigated and is induced by a series of cascade reactions of caspases. The activities of these caspases are redox-dependently regulated even in the absence of ligands.[45,46,240] Following postischemic oxidative stress, Fas-associated protein with a death domain and caspases-8 and -10 are recruited into cytoplasmic death domains to form a death-inducing signaling complex, eventually activating caspases-8 and -10. Caspase-8 and -10 recruitments can be competitively inhibited by fas-associated protein with death domain -like interleukin-1β-converting enzyme-like-inhibitory protein to eventually inhibit downstream signals.[33] Activated caspase-8 then activates caspase-3 either directly or indirectly via a mitochondrial pathway regulated by BH3-only proteins.[150,151] Proapoptotic proteins, such as Bax and Bak, induce mitochondrial outer membrane permeabilization, which is inhibited by the antiapoptotic B-cell lymphoma-extralarge and B-cell lymphoma 2 (Bcl-2).[150,151,241]

STAT3 activated immediately after PH through IL-6 can reduce cellular ROS (i.e., oxidative stress) in liver cells[33,42] by upregulating redox factor-1 (Ref-1)[33] and manganese superoxide dismutase (Mn-SOD)[42] genes. In addition, the proapoptotic pathway is directly inhibited by activated STAT3 through fas-associated protein with death domain -like interleukin-1β-converting enzyme-like-inhibitory protein, B-cell lymphoma-extralarge, and Bcl-2 gene upregulation.[33]

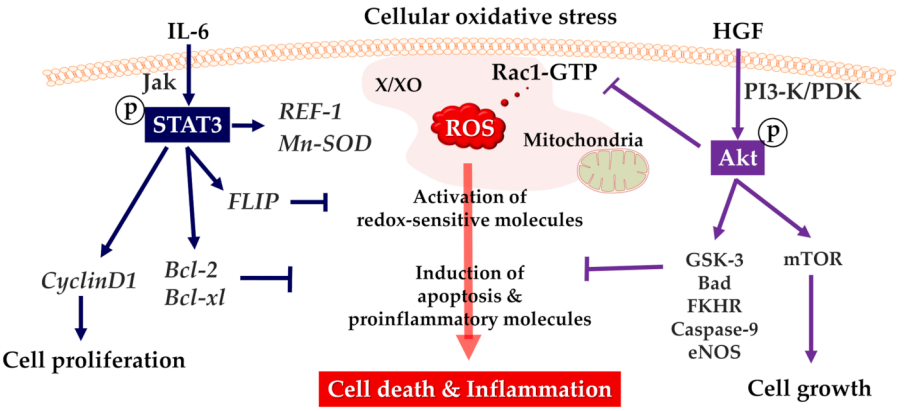

Fig. 4 – Protection of ROS-mediated cell death and inflammation by Jak/STAT3 and PI3-K/PDK1/Akt pathways. STAT3 targets and upregulates antioxidative (REF-1, Mn-SOD), antiapoptotic (Bcl-2/Bcl-xL), and mitogenic (cyclinD1) genes. Akt activates antiapoptotic/survival signaling, and additionally phosphorylates (inactivates) Rac1 to reduce oxidative stress. Suppression of cellular oxidative stress inhibits a post-PH inflammatory reaction by inhibiting the activation of the proinflammatory transcription factor NFκB. Bcl-xL = B-cell lymphoma-extralarge; PH = partial hepatectomy; Bcl = B-cell lymphoma 2; eNOS = endothelial nitric oxide synthase; FKHR = forkhead transcription factor; FLIP = fas-associated protein with death domain -like interleukin-1β-converting enzyme-like-inhibitory protein; GSK-3 = glycogen synthase kinase-3; HGF = hepatocyte growth factor; IL-6 = interleukin-6; Jak = janus kinase; Mn-SOD = manganese-dependent superoxide dismutase 2; mTOR = mammalian target of rapamycin; Mox = mitogenic oxidase; NFκB = nuclear factor kappa B; Nox = nicotinamide adenine dinucleotide phosphate oxidase; PDK1 = phosphoinositide-dependent protein kinase 1; PI3-K = phosphoinositide 3-kinase; Ref-1 = redox factor-1; ROS = reactive oxygen species; STAT3 = signal transducers and activators of transcription-3.

Upregulation of these apoptosis-inhibiting molecules inhibits the induction pathway of apoptosis. Similarly, deletion of IL-6 or STAT3 genes extends liver injury in various pathological models.[33,217,242] The activation of STAT3 promotes liver regeneration by stimulating hepatocyte proliferation, but at the same time, protects against liver injury by suppressing apoptosis and oxidative stress. This may be a rational molecular mechanism for hepatocytes to ensure liver regeneration after PH.

PI3-K/PDK1/Akt signals for liver protection

The crucial PI3-K/PDK1/Akt survival pathway decreases oxidative stress[50,243] and apoptosis,[244,245] and promotes protein synthesis.[6,199,201] This signaling pathway is activated via the binding of the specific receptor tyrosine kinase (cMet) by HGF, one of the major ligands for hepatocytes. After binding to cMet, HGF promotes several biological effects primarily through PI3-K, PDK1, and Akt activation, including antioxidation and antiapoptosis.[50,246,247] The antioxidant ability of Akt is somehow dependent on heme oxygenase-1, nuclear factor-erythroid 2-related factor 2, and Cu/Zn-SOD.[248-251] As previously mentioned, Rac1 is positively involved in cellular ROS generation during H/R or I/R. Under normoxic conditions, Rac1 is phosphorylated (Ser71) and therefore inactivated in hepatocytes. H/R dephosphorylates (activates) Rac1 to generate cellular ROS, inducing apoptosis. HGF-activated Akt inactivates Rac1 again via phosphorylation, and therefore inhibits ROS production regulated by Rac1. This eventually suppresses the H/R-induced apoptosis of hepatocytes.[50] Akt also functions as an antiapoptotic molecule by phosphorylating the apoptosis-regulating Bcl-2 agonist of cell death, forkhead transcription factors, caspase-9, and IκB kinase, to influence NFκB.[247] The multifunctional role of Akt allows it to play a protective role against I/R-induced injury in several organs other than the liver.

Numerous reports have also highlighted the protective effect of STAT3 and Akt against necroptosis[252,253] and that of Akt against parthanatos.[254] Necroptosis and parthanatos are redox-dependently induced in hepatocytes, similar to apoptosis.[46] Therefore, considering their antioxidative properties, it is unsurprising that STAT3 and Akt have a protective effect against necroptosis and parthanatos induced after liver I/R.

The protective mechanisms of the Jak/STAT3 and PI3-K/PDK1/Akt pathways against different programmed cell death processes in I/R-induced injury are seemingly complex. Further investigation is warranted to analyze the contributions of these pathways with regard to programmed cell death mechanisms, including necroptosis, apoptosis, parthanatos, and other types.

In Table 1, the key molecules highlighted in this review and their effects/roles in liver regeneration, injury, and protection are summarized.

The Unique Immune Microenvironment of the Liver and Its Injury, Regeneration, and Protection

Various immune cells can be found dispersed throughout the liver and are located very close to liver parenchymal cells (hepatocytes). This unique microenvironment may make it

Table 1 – Key molecules and their major effects/roles in liver injury, regeneration, and protection.

Key molecules/organelles/intracellular environments	Effects/roles	References
Oxidative stress after hepatic I/R		
Key molecules/organelles	Effects on cellular ROS and redox-sensitive signals	
X/XO	ROS generation	51-55,78,128-133
Mitochondria	ROS generation	60,63,117,134,135
Rac1 small GTPase	ROS generation & activation of redox-sensitive signals (e.g., NFκB)	43,49,50,139-146,255
Liver injury (programmed or nonprogrammed cell death) after I/R		
Key molecules/Intracellular environments	Types of induced cell death (cell death pattern)	
ATP/NAD^+(↓), Ca^{2+}(↑), pH(↓), acidosis	Necrosis (nonprogrammed, lytic)	65,82,83,110-121
RIP1/3 (redox-sensitive)	Necroptosis (programmed, lytic)	45,46,163,176-178
Caspases (redox-sensitive)	Apoptosis (programmed, nonlytic)	150-153,155-160
PARP/AIF (redox-sensitive)	Parthanatos (programmed, lytic)	45,179,181,184,187-191
Fe^{2+}	Ferroptosis (nonprogrammed, lytic)	60
Liver regeneration and protection after liver resection and I/R		
Key molecules	Effects on hepatocytes (molecules involved)	
IL-6/Jak/STAT3	Cell proliferation (induction of CyclinD1)	6,33,197,202,213,223,224
	Antioxidant (induction of Mn-SOD and Ref-1)	33,223
	Antiapoptosis (induction of FLIP, Bcl-2, and Bcl-xL)	33,242,243
HGF/PI3-K/PDK1/Akt	Cell growth (activation of $p70^{S6K}$ and mTOR)	6,197,199,200,225-229,237
	Antioxidant (suppression of Rac1 activity)	50,247,248
	Antiapoptosis (suppression of Bad and caspases)	50,247,248
Sterile liver inflammation		
Key molecules/substances	Effects on secondary inflammation after I/R	
DAMPs/NFκB (redox-sensitive)	Production of proinflammatory cytokines	67-75

I/R = Ischemia/reperfusion; ROS = Reactive oxygen species; X/XO = Xanthine/Xanthine oxidase; ATP = Adenosine triphosphate; NAD^+ = Nicotinamide adenine dinucleotide; Ca^{2+} = Calcium ion; RIP1/3 = Receptor interacting protein kinase 1/3; IL-1β = interleukin-1β; PARP = Poly (adenosine diphosphate-ribose) polymerase; AIF = Apoptosis-inducing factor; Fe^{2+} = Iron ion; Jak = janus kinase; STAT3 = Signal transducers and activators of transcription-3; Ref-1 = redox factor-1; SOD = superoxide dismutase; FLIP = fas-associated protein with death domain -like interleukin-1β-converting enzyme-like-inhibitory protein; Bcl-2 = B-cell lymphoma 2; Bcl-xL = B-cell lymphoma-extralarge; PI3-K = Phosphoinositide 3-kinase; PDK1 = phosphoinositide-dependent protein kinase 1; Akt = v-akt murine thymoma viral oncogene homolog; $p70^{S6K1}$ = 70 kDa ribosomal protein S6 kinase 1; mTOR = Mammalian target of rapamycin; Rac1 = Ras-related C3 Botulinum Toxin Substrate 1; Bad = BCL2 associated agonist of cell death; DAMPs = Damage associated molecular pattern; NFκB = Nuclear factor kappa B; HGF = Hepatocyte growth factor; GTPase = guanosine triphosphate degrading enzyme.

possible for the liver to react quickly to surgical stress. In particular, Kupffer cells (resident macrophages) probably play a central role in the liver response (injury, inflammation, regeneration, and protection) to surgical stress. Kupffer cells are scattered throughout the liver, and are rapidly activated once the liver is subjected to surgical stress. Activated Kupffer cells secrete proinflammatory cytokines (e.g., IL-6 and TNF-α), which induce the migration of circulating inflammatory cells into the liver. Induction of sterile inflammation by these cytokines and inflammatory cells aggravates postischemic liver injury.[6,214] IL-6 plays another substantial role in liver protection and regeneration by rapidly transmitting signals to nearby hepatocytes and activating STAT3.[33,198] Similar to Kupffer cells, HSCs and SECs are scattered within the liver. These cells are important especially in liver regeneration (proliferation) and protection. The growth factor HGF is secreted as a pro-HGF from the extracellular matrix, HSCs, and SECs, and is then activated by the fibrinolytic system (urokinase type plasminogen activator). It then acts on nearby hepatocytes and contributes to immediate proliferation as well as protection after surgical liver stress.

Discussion From the Aspects of Clinical Application and Relevance

Clinical trials to prevent postoperative liver injury and promote regeneration through preoperative administration of drugs

To date, several drugs have been clinically administered to suppress liver injury after hepatectomy or liver transplantation procedures, including steroids, insulin, antioxidants, and herbal medicines.[256-259] Preoperative

administration of these drugs at high doses was able to suppress postoperative liver inflammation and injury and/or promote regeneration after liver resection and transplantation. Most effects are adequately supported by the mechanisms presented in this review, thus highlighting their validity. The development of more effective drugs based on these molecular mechanisms is warranted so that they can be used in future clinical treatment.

Preoperative maneuvers and liver regeneration

Liver surgery maneuvers, including portal vein embolization/ligation and associating liver partitions and portal vein ligation for staged hepatectomy (ALPPS) are performed in cases of extended liver resection.[260-262] These maneuvers are often performed preoperatively to induce better liver regeneration with sufficient functional reserve and prevent postoperative liver failure. Some studies have investigated the mechanism of improved regeneration for the remnant liver using these maneuvers, and have highlighted the possible involvement of humoral factors (e.g., IL-6, IL-1β, TNF-α, HGF, and vascular endothelial growth factor-α) and Kupffer cells as well as the impact of hemodynamic changes.[262,263] Under these conditions, it is clear that similar signaling molecules (e.g., STAT3 and Akt) are activated in hepatocytes of the remnant liver, leading to better liver regeneration with less injury.

Tolerance time for hepatic ischemia

The allowed duration for liver ischemia is of great interest to surgeons. Although a postoperative liver injury is the result of combined ischemia and reperfusion injuries, the degree of postoperative liver injury primarily depends on warm ischemic time. It may be difficult to infer/predict how long the liver can tolerate ischemia during common liver surgeries. In humans, the safe tolerance time for warm liver ischemia is reportedly at least 60 min.[38,264] Although there are huge differences between humans and animals, similar findings were also observed in the mouse liver I/R model (30-90 min of ischemia) where 60 or 75 min of liver ischemia induced hepatic ROS after reperfusion, followed by moderate liver injury.[40] The generation of ROS after reperfusion suggests that the liver and its hepatocytes are still viable and functioning, although they may be injured. Thirty or 45 min of liver ischemia did not induce significant ROS or liver injury after reperfusion, indicating that the stress was not strong enough to provoke excessive hepatic ROS and injury. However, severe liver injury was induced after reperfusion following 90 min of liver ischemia, without any ROS generation at all. The results in the animal model suggest that warm ischemia spanning less than 45 min is not very stressful and may be well-tolerated without causing significant liver injury. In contrast, 90 min of warm ischemia is considered to be fatal and intolerable. These findings indicate that the limit of tolerance time for warm ischemia is also around 60 min in mice. By activating or inhibiting key molecules in the mechanisms proposed here, it may be possible to increase the liver's tolerance time for ischemia.

Conclusions

In this review, surgical stress to the liver and the subsequent liver response are described. Liver surgical procedures often involve hepatectomy (loss of liver mass) and the temporary blockage of blood flow to the liver. These procedures inevitably induce several liver responses to rapidly recover liver mass and function. The major molecular mechanisms that regulate cell proliferation and growth during regeneration of the liver involve IL-6/Jak/STAT3 and HGF/PI3-K/PDK1/Akt signals. In addition to liver regeneration, these pathways play important roles in suppressing postoperative liver injury by preventing cellular oxidative stress and programmed cell death. These molecular mechanisms work harmoniously and efficiently to stimulate rapid and reliable liver regeneration for optimal patient outcomes.

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CRediT authorship contribution statement

Michitaka Ozaki: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Sanae Haga:** Writing – review & editing.

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