

LIVER REGENERATION: A LINK TO INFLAMMATION THROUGH COMPLEMENT

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1. INTRODUCTION

The liver is one of the largest organs in the body, involved in various tasks such as the processing of dietary amino acids, carbohydrates, lipids, and vitamins, phagocytosis of particulate material in the portal circulation, synthesis of serum proteins, biotransformation of circulating metabolites, and detoxification and excretion of endogenous waste products and pollutant xenobiotics into the bile¹. It is strategically located between the gastrointestinal tract and the rest of the body, with a unique dual blood supply including the portal venous system. This makes the liver an intermediate filter for most of the venous drainage of the abdominal viscera, and a vital organ for maintaining metabolic homeostasis². These anatomical properties support the physiological functions of the liver but also make it vulnerable to a wide variety of metabolic, toxic, microbial, circulatory, and neoplastic insults.

The large functional reserve of the liver usually prevents the appearance of clinical symptoms of liver failure even if a significant portion of the parenchyma is destroyed. However, the progression of diffuse liver disease or the strategic disruption of bile flow may lead to life-threatening consequences³, demanding regenerative capabilities from the liver to assure the restoration of structural and functional integrity even after severe damage⁴. Various insults, such as surgery or viral or toxic injury, can signal the mechanisms responsible for liver regeneration⁴. Barring extensive severe injury or other circumstances preventing the

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normal division of hepatocytes, signaling for regeneration results in the reentry of mature quiescent liver cells into the cell cycle. The process of regeneration continues until the liver regains its original size, with complete recovery of tissue architecture⁴. Partial hepatectomy (PHx), in which two-thirds of the liver mass is surgically removed⁵, is one of the most common models used to study the regenerative response. PHx is considered a non-injurious procedure for the remaining liver tissue, which undergoes a compensatory hyperplasia. Conversely, another model involving toxic injury induced by the injection of carbon tetrachloride (CCl₄) results in severe damage to liver tissue. Thus, after CCl₄ injection the liver must both restore lost tissue mass and repair and remove injured parenchyma.

Despite obvious differences between the surgical and injury models, the molecular mechanisms that govern the regenerative response seem to be quite similar. Furthermore, the factors involved in this phenomenon largely overlap with those responsible for the induction of innate immunity, suggesting that liver regeneration may utilize the mechanisms of an inflammatory response⁶. In addition, complement, an important player in innate immune reactions, has been implicated as a crucial factor for liver regeneration.

2. LIVER REGENERATION AND INFLAMMATORY MEDIATORS

Liver regeneration requires the activity of multiple signaling pathways, assuring the synchronized proliferation of liver cells, protection from apoptotic signals, remodeling of extracellular matrix (ECM), and restoration of lobular architecture⁷. The initiation of regeneration through PHx is associated with minimal injury; therefore, an obvious inflammatory reaction that includes a significant inflammatory infiltrate is not seen in the liver parenchyma under these circumstances. However, elevated levels of acute-phase proteins in the blood, activation of liver macrophages, and release of cytokines that are involved in regulation of inflammatory responses to various pathogens suggest that PHx does initiate an inflammatory reaction⁴. Unlike PHx, injection of CCl₄ results in an inflammatory infiltrate in the liver in response to necrosis. In this model, regeneration is associated with significant tissue injury and an inflammatory response not seen after PHx. Though cell death and the inflammatory reaction may interfere with attempts to clearly elucidate the molecular background of regeneration in the CCl₄ model, it can be seen as a better reflection of liver diseases that trigger the regenerative response, such as viral hepatitis and toxic- or drug-induced injury, and of the regeneration of liver parenchyma that occurs after surgical resection carried out in response to various pathologies, including primary or metastatic tumors³.

2.1. Cytokines and Transcription Factors

Lipopolysaccharide (LPS), a strong activator of innate immunity, may be present in increased concentration in the portal blood flow after PHx^{8,9}. This factor is known to be necessary for proper liver regeneration, as both germ-free athymic and LPS-resistant mice show impaired regeneration after PHx¹⁰. LPS is thought to be one of the earliest signals that starts the regenerative process, likely arriving from the gut to engage receptors on Kupffer cells, the resident macrophages of the liver[†]. Activation of Kupffer cells results in production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α) and interleukin (IL)-6. TNF- α activates the nuclear factor-kappa B (NF- κ B) transcription factor in macrophages and hepatocytes.¹¹ This response leads to secretion of IL-6, mainly from Kupffer cells, which in turn activates the transcription factor signal transducer and activator of transcription (STAT) 3 in hepatocytes¹²⁻¹⁴. Studies using mice deficient in TNF receptor 1 (TNFR1)¹⁴⁻¹⁶ or IL-6^{13,17} have shown that these cytokines are necessary for liver regeneration. The ability of IL-6 administration to correct the defect in hepatocyte DNA synthesis seen in TNFR1-deficient mice (TNFR1^{-/-}) after PHx suggests that the role of TNF- α in liver regeneration is mediated by IL-6¹⁴.

NF- κ B and STAT3 participate in the induction of immediate-early genes important for liver cell growth and hepatoprotection^{13,18}. NF- κ B regulates the cell cycle regulator cyclin D1^{19,20}. Stimulation of the IL-6 receptor (IL-6R/gp130) by IL-6 promotes cell growth not only through STAT3 activation²¹, but also through activation of the mitogen-activated protein kinase (MAPK) signaling cascade²². There is some debate that IL-6 may be more important as a hepatoprotective factor rather than as a mitogen^{17,23,24}. IL-6 activates the pro-survival proteins phosphoinositol 3 kinase (PI3K) and Akt in addition to STAT3, which is also involved in hepatoprotection^{25,26}. NF- κ B has also been shown to be an anti-apoptotic factor during liver regeneration. When NF- κ B activation is inhibited, such as through the action of a superrepressor transgene of the NF- κ B inhibitor, I κ B α , or by treatment with gliotoxin, liver regeneration after PHx is impaired and apoptosis of hepatocytes occurs instead of proliferation^{27,28}. NF- κ B regulates genes for anti-apoptotic proteins²⁹⁻³⁵ and prevents TNF- α -induced hepatocyte death³⁶⁻⁴¹.

The cytokines and transcription factors mentioned here, along with some of their targets, are also involved in inflammation. Most notable of these is TNF- α , which is released by mast cells and macrophages in the initial phase of the inflammatory response⁴². In endothelium, TNF- α (along with IL-1, which is involved in the acute-phase response in the liver⁷) induces a spectrum of changes, mostly regulated at the transcriptional level, referred to as endothelial activation⁴³. In particular, TNF- α induces the synthesis of endothelial adhesion molecules, other cytokines, chemokines, growth factors, eicosanoids, nitric oxide, and enzymes associated with matrix remodeling.⁴³ Additionally, it increases the surface thrombogenicity of the endothelium⁴⁴. TNF also causes aggregation and

priming of neutrophils, leading to augmented responses of these cells to other mediators and release of proteolytic enzymes from mesenchymal cells, thus contributing to tissue damage^{45,46}.

LPS, thought to be an initial stimulator of liver regeneration, also activates the complement system through the alternative pathway⁴⁷. In fact, there are many potential connections between complement and liver regeneration based on what is known about interactions of the factors discussed above with the complement pathways. The anaphylatoxin C5a, the effector molecule resulting from cleavage of complement protein C5, acts on macrophages to induce cytokine release, including TNF- α ^{48,54}. The role of the C3a anaphylatoxin (originating from cleavage of C3) in modulation of TNF- α and IL-1 β production and release in macrophages is not as well characterized as that for C5a, but some published data indicate that C3a and C3a desArg may stimulate production of these cytokines⁵⁵. C3a signaling appears to be costimulatory to LPS signaling and, depending on the pathophysiological background and target cell population, may have stimulatory as well as inhibitory characteristics⁵⁵. C3a and C5a may therefore contribute to the induction of transcription factors indirectly through their effects on cytokines. Indeed, both C3a and C5a are known to enhance the release of IL-6 in response to LPS in peripheral blood mononuclear cells and Kupffer cells in the liver⁵⁶⁻⁵⁸. C5a is also important for NF- κ B- and MAPK-dependent release of IL-6 by neutrophils during sepsis⁵⁹. Additionally, C5a activates the lipoxygenase pathway of arachidonic acid (AA) metabolism in neutrophils and monocytes, leading to acceleration of eicosanoid production by these cells⁶⁰. Previous reports have emphasized the importance of eicosanoids, specifically prostaglandins and their potential effect on CREB transcription factor signaling, in liver regeneration after PHx^{61,62}.

2.2. Growth Factors, Metalloproteases, Adhesion Molecules, and Acute Phase Proteins

Growth factors, including hepatocyte growth factor (HGF), also contribute to hepatocyte proliferation during regeneration. Active HGF is produced by cleavage of pro-HGF by urokinase plasminogen activator (uPA) and plasminogen proteases, a part of the fibrinolysis system^{63,64}. The involvement of this system in inflammation can be illustrated by the role of plasminogen activator (released from endothelial cells and leukocytes activated during the inflammatory response) in cleaving plasminogen to generate the matrix protease plasmin, a multifunctional enzyme, which in turn can cleave complement C3 to produce C3 fragments. Also, plasminogen can degrade fibrin to form fibrin split products, which may have permeability-inducing properties⁶⁵, and plasmin can activate Hageman factor, which can trigger multiple cascades to amplify the inflammatory response⁶⁵.

When uPA is blocked, production of HGF is delayed, as is liver regeneration.^{4,66} HGF can activate pathways for PI3K, ERK (an MAPK protein), and Akt,

which are involved in growth and hepatoprotection, as mentioned above⁶⁷. Conditional knockout mice for the HGF receptor Met have increased sensitivity to hepatocyte apoptosis and impaired recovery from damage when the liver is injured, further indicating that the HGF–Met pathway is involved in hepatocyte survival⁶⁸. Interestingly, delayed recovery in these mice is associated with a persistent inflammatory reaction. C3 may promote the release of HGF from adhesive granulocytes and monocytes⁶⁹, while in alveolar macrophages uPA and C5a act synergistically to upregulate TNF- α production, suggesting another potential link between complement and cytokine production during regeneration⁷⁰.

Proteases, especially metalloproteases (MMP), are intricately involved in liver regeneration by regulating activation of certain signaling factors, including HGF, and contributing to angiogenesis for restoration of liver architecture. Aside from being involved in HGF processing, plasminogen may also contribute to angiogenesis in the liver, as plasminogen-deficient mice have an impaired increase in microvessel density during regeneration⁷¹. Lack of tissue inhibitor of metalloprotease (TIMP)-1 leads to increased MMP activity in the regenerating liver and may result in greater release of HGF from the ECM. Indeed, an increase in activated HGF is observed in TIMP-1-deficient (TIMP-1^{-/-}) mice⁷². TNF- α can be shed from the cell surface by TNF- α -converting enzyme (TACE), which is inhibited by TIMP-3⁷³. TIMP-3 deficiency results in overproduction of hepatic TNF- α , leading to hepatocyte apoptosis and liver failure⁷⁴. VEGF is another important angiogenic factor for liver regeneration, involved in the reconstruction of liver sinusoids through proliferation of sinusoidal endothelial cells, which promotes hepatocyte proliferation⁷⁵. It can be released from the ECM to initiate signaling, perhaps by MMP-9, which is induced during liver regeneration^{72,76,77}. Intriguingly, C5a can also be involved in angiogenesis. C5a-stimulated HUVECs reveal increased expression of genes involved in endothelial adhesion, migration, and angiogenesis⁷⁸. In some cases, MMPs may be detrimental to the liver. After injection of CCl₄, MMP-2 expression is increased in IL-6^{-/-} livers, which show greater damage and liver failure compared to wild-type livers⁷⁹. Additionally, injury and apoptosis in IL-6^{-/-} livers is reduced when MMP-2 is inhibited. Providing yet another link between the complement system and liver regeneration, complement proteins have been shown to interact with MMPs as targets and regulators of these enzymes⁸⁰⁻⁸⁴.

Adhesion molecule expression is necessary for interactions between endothelial cells and leukocytes during extravasation and migration, one of the most important events that occurs soon after induction of the innate immune response⁸⁵. This process results in leukocytes leaving the bloodstream and entering the interstitial space to travel to the site of inflammation. Anaphylatoxins, mainly C5a, participate in endothelial activation during extravasation and migration. C5a-stimulated HUVECs upregulate genes for E-selectin, ICAM-1, VCAM-1, and IL-6⁷⁸. Anaphylatoxins also influence the expression of adhesion molecules on leukocytes. It has been postulated that C5a is involved in eosinophil adhesion to bronchial epithelial cells during allergic inflammation in the

airways⁸⁶. Another study showed that C5a is an activator of integrin-dependent adhesion and transmigration in eosinophils and neutrophils⁸⁷. These examples indicate that anaphylatoxins can play a role in the process of extravasation, directly influencing the expression of adhesion molecules on endothelial cells as well as leukocytes. However, anaphylatoxins are also indirectly involved in this process through regulation of TNF- α and IL-1 expression. These two cytokines appear to be major regulators of adhesion molecule expression on both leukocytes and endothelium. Adhesion molecules are also necessary for liver regeneration. Mice deficient in ICAM-1 show impaired regeneration, with a decrease in the recruitment of leukocytes and levels of TNF- α and IL-6⁸⁸. Complement, which regulates ICAM-1 expression during inflammation, may potentially regulate ICAM-1 expression during regeneration, as well, perhaps to increase recruitment of lymphocytes to the liver through adhesion to sinusoidal endothelial cells⁸⁹.

Activation of transcription factors after PHx leads to upregulation of acute phase proteins, such as serum amyloid protein, hemopexin, and complement (C)-reactive protein^{13,90,91}. Upregulation of serum amyloid A, serum amyloid A2, and haptoglobin precursor after PHx has also been noted in our recent study on the liver proteome⁹². Increased synthesis of acute-phase proteins is a hallmark of acute inflammatory reactions mediated by the innate immune system⁸⁵. Complement is also involved in the acute-phase response. C5a contributes to production of several acute-phase proteins in liver cell lines⁹³. C5a has also been shown to act synergistically with LPS to enhance production of the acute-phase protein α_2 -macroglobulin in hepatocytes⁹⁴. It is possible that C5a acts during liver regeneration, either directly or indirectly through other signaling factors, to upregulate production of acute-phase proteins required for liver mass restoration.

2.3. Natural Killer T (NKT) Cells

NKT cells display characteristics common to both classical T and natural killer (NK) cells⁹⁵. Most NKT cells are reactive against the glycolipid-binding non-polymorphic major histocompatibility complex class I-like glycoprotein CD1d⁹⁶. Interestingly, besides being expressed on antigen-presenting cells of the immune system, CD1d is constitutively expressed on parenchymal liver cells^{97,98}. NKT cells can contribute to both the Th1 and Th2 adaptive immune responses through their production of large amounts of, respectively, interferon-gamma (IFN- γ) and IL-4 upon activation^{99,100}. IL-4 production by a liver population of NKT cells can also lead to production of antibody that activates complement to promote recruitment of T cells during contact sensitivity¹⁰¹.

Recently, NKT cells have been suggested to play a role in liver regeneration. The number of NKT cells in the liver in mice increases very quickly after PHx, dependent upon signaling through adrenergic receptors¹⁰². Blocking of adrenergic receptors inhibits accumulation of NKT cells in the regenerating liver⁹⁵. It is possible that expansion of the NKT cell population can impair re-

generation of the liver. In one study, an increase in NKT cell numbers due to IL-12 stimulation was shown to exacerbate injury during the early phases of liver regeneration¹⁰³. Increased production of IFN- γ by the expanded population of NKT cells could partly explain this detrimental effect, as IFN- γ is known to play a role in hepatitis-induced acute liver failure¹⁰⁴. Increased NKT cells could potentially lead to increased C3 production by liver epithelial cells as well. A mitogen for T-lymphocytes, which also contributed to NKT cell expansion in one study¹⁰⁵, stimulated C3 release from rat epithelial cells in the liver¹⁰⁶. In this case, increased C3 may further contribute to liver damage caused by NKT cells.

3. THE ROLE OF COMPLEMENT IN LIVER REGENERATION

The complement system plays a crucial role in the early innate immune response, and we have thus far postulated several potential links between this system and regeneration of the liver based on factors common to both. However, recent studies have provided evidence for a definitive role for complement in the regenerative response. C3 appears to be activated early after the initiation of liver regeneration, as cleavage products are observed in the serum 2–3 hours after CCl₄ injection¹⁰⁷ and PHx (personal observation). Exemplifying the reciprocal nature of complement proteins and cytokines, C3 and C5 have been shown to be involved in cytokine production during early liver regeneration. Following PHx, increases in TNF- α and IL-6 mRNA are observed¹⁰⁸. In mice lacking C3 (C3^{-/-}) and in mice treated with an inhibitory antagonist for the C5a receptor (C5aR), there is a reduction in TNF- α and IL-6 mRNA levels. Further, both of these cohorts also show impaired activation of NF- κ B and STAT3¹⁰⁸. Thus, both C3 and C5 (most likely through the activities of C5a) are necessary for the initial priming events of liver regeneration. Due to this defect in priming, hepatocytes in both C3^{-/-} and C5^{-/-} mice do not enter the cell cycle and overall proliferation is greatly reduced during liver regeneration¹⁰⁷⁻¹⁰⁹. This lack of cell proliferation results in an inability of complement-deficient mice to completely restore their liver mass after insult.

Complement is also involved in protection of the liver from damage during regeneration, perhaps again through its role in liver cell priming. After PHx, both C3^{-/-} and C5^{-/-} livers display severe damage and, in some animals, liver failure and mortality¹⁰⁸. A similar defect in liver regeneration is observed in C5^{-/-} mice after CCl₄ injection. Though CCl₄ normally induces damage in livers, C5^{-/-} mice have a much more diffuse and extensive pattern of liver necrosis and apoptosis after injection of CCl₄ compared to wild-type mice, along with an increase in lipid content, known to be detrimental to liver regeneration and function^{109, 110}. Thus, both C3 and C5 are necessary to prevent injury during the restoration of liver mass.

C3 and C5 are not only separately required for cell division and hepatoprotection but also function in a cooperative manner. When both complement pro-

teins are absent, in double-deficient C3/C5^{-/-} animals, an even greater reduction in hepatocyte proliferation is observed after PHx than that seen in singly deficient livers. In addition, the injury observed in C3/C5^{-/-} livers is more severe than damage occurring in C3^{-/-} or C5^{-/-} livers.¹⁰⁸ This additive effect suggests that C3 and C5 each have specific functions during regeneration of the liver, and do not just control redundant mechanisms.

C3 and C5 are cleaved into their effector fragments following activation of the complement system. Further analysis of liver regeneration after PHx and CCl₄ injection in complement-deficient mice has demonstrated the importance of these effector molecules, especially the anaphylatoxins C3a and C5a. Defects in cytokine signaling and transcription factor activation have already been noted when mice were treated with a C5aR antagonist. These mice also display impaired liver regeneration and increased liver injury and mortality after PHx¹⁰⁸. Reconstitution of C5^{-/-} mice with murine C5 restores cell division and greatly diminishes injury to near-wild-type levels following injection of CCl₄¹⁰⁹. C5a has been shown to be the main effector for this improvement in recovery, as it can be accomplished through reconstitution with only the C5a component of C5, while blockage of the C5aR with antagonist impairs regeneration in a manner similar to that seen in C5^{-/-} mice. C3a has also been shown to be involved in proper liver regeneration. Reconstitution of C3^{-/-} mice with murine C3a restores hepatocyte proliferation to wild-type levels and reverses post-PHx liver damage seen in C3^{-/-} mice^{107,108}. The importance of both anaphylatoxins has been demonstrated by single or double reconstitution of C3/C5^{-/-} mice following PHx. When these mice are treated with only C3a or C5a, defects in regeneration are only partially corrected. However, double reconstitution with both anaphylatoxins restores regenerative parameters to levels similar to those seen in wild-type mice, further confirming the cooperative effects of C3 and C5¹⁰⁸. Finally, cell division in C3aR^{-/-} mice after CCl₄ injection is impaired, again showing the importance of C3a for regeneration¹⁰⁷. However, the defect is not as severe as in C3^{-/-} mice, suggesting that C3 may have other functions aside from those mediated by C3a.

In fact, C3 does appear to have an additional function. It is not only necessary for promoting liver cell growth and preventing injury through the actions of C3a, but also for clearing damaged tissue through deposition of C3b/iC3b. As mentioned, C3 cleavage products are present in serum soon after the initiation of liver regeneration. Twenty four to 36 hours after injection of CCl₄, a second, even greater wave of C3 cleavage occurs. The timing of this second wave correlates with local deposition of C3 within damaged liver parenchyma¹⁰⁷. Though wild-type and C3^{-/-} mice show similar levels of initial liver injury early after CCl₄ injection, there is delayed clearance of damaged parenchyma in C3^{-/-} mice. Phagocytosis of necrotic and apoptotic tissue is facilitated by engagement of the CR3 receptor on macrophages with C3b/iC3b deposited in areas of injury^{111, 112}. Thus, the delayed clearance of damaged tissue in C3^{-/-} mice is caused by the absence of C3 deposition in these areas.

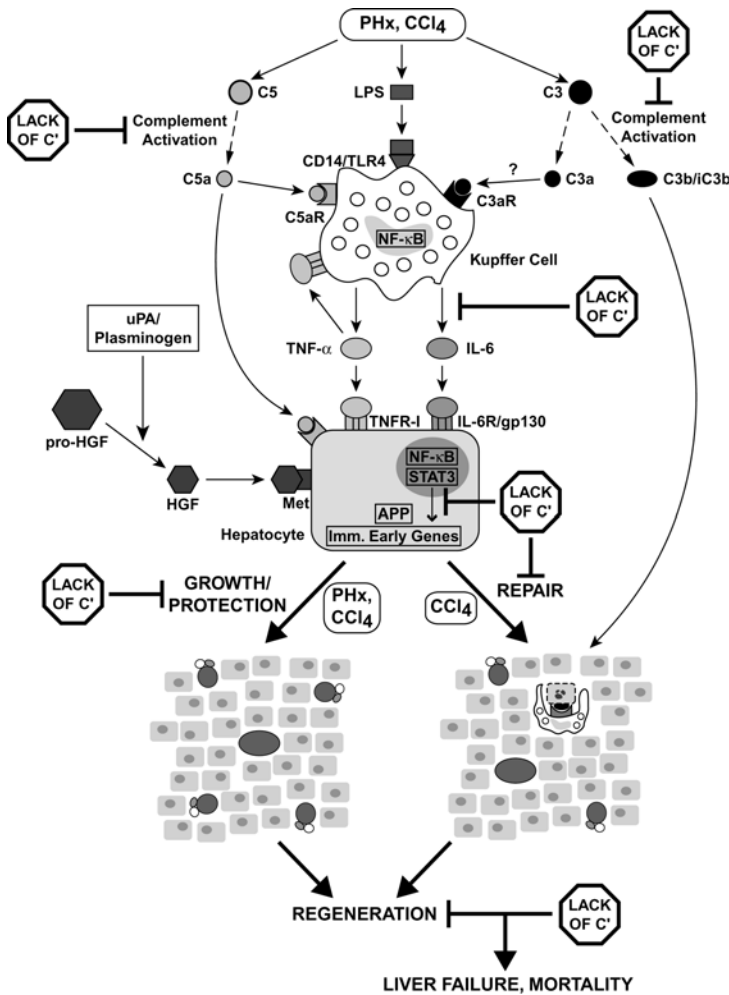


Figure 1. Complement involvement in liver regeneration. Initiation of liver regeneration signals complement activation. C5a and possibly C3a bind to their receptors (C5aR, C3aR) on Kupffer cells, and, together with LPS signaling through Toll-like receptor (TLR) 4, stimulate release of TNF- α and IL-6. TNF- α acts in an autocrine manner on Kupffer cells and, with IL-6 and C5a, activates the NF- κ B and STAT3 transcription factors in hepatocytes. HGF binds to the Met receptor on hepatocytes after cleavage of pro-HGF by urokinase plasminogen activator (uPA) and plasminogen proteases. Immediate-early gene products and acute-phase proteins (APP) induced by NF- κ B and STAT3, along with HGF, stimulate cell growth and hepatoprotective pathways. Complement also contributes to the clearance of damaged tissue, through C3b/iC3b deposition and its interaction with the CR3 receptor on macrophages. When complement components (C') are absent or inhibited, regeneration can be impaired at any of these steps, resulting in liver failure and occasional mortality.

A schematic representation of liver regeneration and the steps in which complement is involved is shown in Figure 1. In summary, complement seems to have multiple functions during liver regeneration: C3a and C5a are necessary for proper priming of liver cells and progression through the cell cycle, promoting growth and inhibiting cell death, while C3b/iC3b is needed to promote clearance of injured tissue and prevent development of a more severe inflammatory response that may lead to further injury.

Without C3 and C5, the liver is unable to undergo proper tissue repair and cell proliferation. In many cases, this leads to liver injury, failure, and increased mortality. These studies demonstrate the important functions of complement during liver regeneration, and strengthen the connection between regeneration and the inflammatory response.

4. CONCLUSION

We have emphasized here the similarities that exist between the inflammatory and regenerative responses in terms of mediators involved, providing evidence that liver regeneration includes an inflammatory reaction. Particular emphasis has been placed on the role of complement, an early and fundamental player in innate immunity, in regeneration of the liver. During the inflammatory response there are multiple interactions existing between several complement proteins and the network of pleiotropic mediators, the cytokines. Through cytokine functions, complement is involved in precise and balanced regulation of innate and adaptive immune responses and the control of cellular growth and apoptosis. Additionally, through cytokine signaling and other, more direct processes, complement is now known to be vital for proper liver regeneration. Thus, the interactions between various complement proteins and cytokines are essential for both immune responses and tissue regeneration, and provide a new link in the expanding chain connecting these two biological phenomena.

5. ACKNOWLEDGMENTS

This work was supported by National Institutes of Health Grants AI 30040, GM-62134, DK-059422, and CA112162 to JDL.

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