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Review

Liver inflammation and regeneration: Two distinct biological phenomena or parallel pathophysiologic processes?

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Abstract

The anatomic localization and unique vasculature of the liver, along with its cell properties, make this organ an efficient line of defense against blood-borne infections, either systemic or arising in the abdomen. Liver cells can modify the host immune response by releasing immunomodulatory molecules, interacting with cells of the immune system and acting as scavengers for inflammatory mediators. However, these defensive functions do not protect the liver itself from the severe injury that may be caused by pathogens, toxins or pollutant xenobiotics. Therefore, the mammalian liver has developed a unique adaptation in the form of an astonishing regenerative capability. The complexity of regeneration requires a well-orchestrated system to control this process. Growing evidence suggest the importance of immune mechanisms as a part of this system. It seems likely that the mechanisms that serve to eliminate infections (and may simultaneously cause liver injury) are also active in restoring the structural and functional integrity of the damaged liver.

Keywords: Liver regeneration; Innate immunity; Complement; Cytokines; Immunomodulation

1. Introduction

Occupying a strategic position between the gastrointestinal tract and the rest of the body, the liver plays a crucial role in maintaining metabolic homeostasis. Its functions include 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; detoxification and excretion of endogenous waste products and pollutant xenobiotics into the bile (Crawford, 1994). Its unique dual blood supply, which includes the portal venous system, makes the liver an intermediate filter for most of the venous drainage of the abdominal viscera (Wanless, 1999) (Fig. 1).

These anatomical properties not only support the physiological functions of the liver but also make it vulnerable to a wide variety of metabolic, toxic, microbial, circulatory and neoplastic insults. Some of these insults may cause primary hepatic diseases, such as viral hepatitis and hepatocellular carcinoma. More often, however, hepatic involvement is secondary to extra-hepatic disorders that include some of the most common diseases in humans, such as cardiac decompensation, disseminated cancer, alcoholism and extra-hepatic infections (Isselbacher and Podolsky, 1991). Inflammatory disorders of the liver dominate the clinical practice of hepatology, in part because nearly any insult to the liver can kill hepatocytes and induce the recruitment of inflammatory cells. Indeed, the liver is almost inevitably involved in blood-borne infections, whether systemic or arising within the abdomen (Crawford, 1994).

Although the enormous functional reserve of the liver masks, to a certain extent, the clinical impact of early liver

Abbreviations: CCl_4, carbon tetrachloride; IκBα, inhibitor of nuclear factor-kappa B alpha; LPS, lipopolysaccharide; NF-κB, nuclear factor-kappa B; PHx, partial hepatectomy; STAT3, signal transducer and activator of transcription 3

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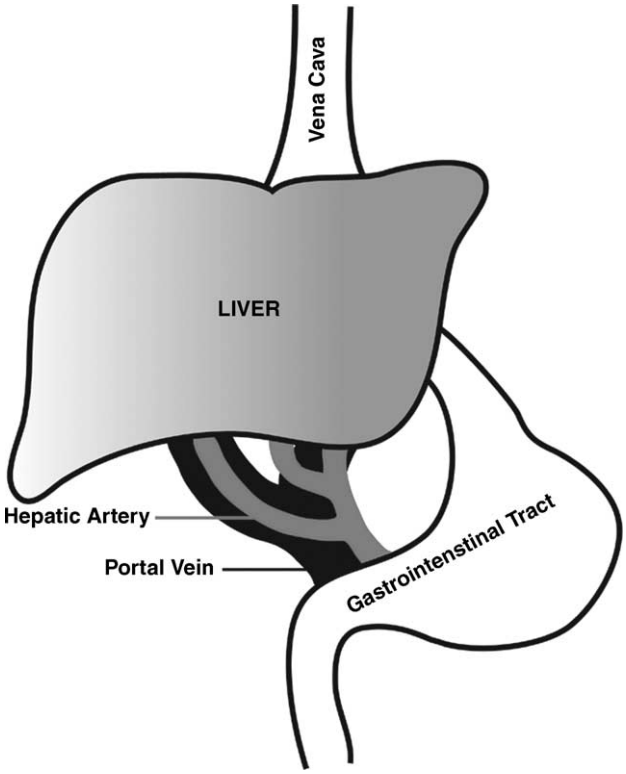

Fig. 1. Dual blood supply to the liver. The liver receives blood to be filtered from the gastrointestinal tract through the portal vein, while oxygenated blood arrives through the hepatic artery. Blood drains from the liver through hepatic veins, which empty into the inferior vena cava.

damage, the progression of diffuse liver disease or strategic disruption of bile flow may lead to life-threatening consequences (Isselbacher and Podolsky, 1991). Therefore, it is expected that an organ accomplishing such important physiological functions and simultaneously being exposed to a wide variety of harmful insults would be additionally equipped with amazing regenerative capabilities, assuring restoration of structural and functional integrity even after severe damage to the parenchyma (Taub, 2004). The liver's capacity to regenerate is evident in the complete recovery occurring after fulminant hepatitis (due either to viral or toxic agents), if the patient can be sustained through the period of acute injury. In this particular situation, the regenerative capabilities of the liver are crucial for the patient's survival after toxic or inflammatory insult. However, this is not always a beneficial process. Architecturally disordered regeneration, in concert with fibrosis, is an essential factor in the development of cirrhosis, and it leads to both disruption of blood flow through the hepatic parenchyma and to uneven hepatocellular function due to the distortion of normal lobular structure (Isselbacher and Podolsky, 1991).

In both fulminant hepatitis and cirrhosis, the regeneration of liver parenchyma is a consequence of cell injury resulting from an inflammatory reaction that occurs in the liver tissue. However, fulminant hepatitis is an example of acute inflammation, while liver cirrhosis is most often related to chronic hepatitis, including viral or alcoholic etiology. These examples indicate that both processes – the inflammatory reaction in the liver parenchyma and its regeneration – often co-exist in various clinical situations. However, it is not clear whether the inflammation that occurs in a variety of liver pathologies and is responsible for tissue damage can simultaneously be involved in the initiation and regulation of the regenerative process.

This review focuses on findings that demonstrate the involvement of inflammatory mediators, innate immunity, and in particular, the complement system (an integral part of innate immunity) in the regulation of liver regeneration, and discusses some of the liver functions that extend beyond the traditional role of this organ as a "metabolic factory." Specifically, we will discuss the liver's participation in the immune response as an important line of host defense against invading pathogens. The fact that the liver can act as an immune organ under some circumstances and that liver cells have properties that are traditionally associated with cells of the immune system makes the hypothesis that inflammatory mediators may be involved in regeneration more plausible. Here, we will describe the various liver cell populations and their associations with the immune system. This will be followed by an overview of the regulation of liver regeneration by mediators of innate immunity.

2. Liver cells and their immune functions

The hepatic parenchyma is organized into cribriform, anastomosing sheets or "plates" of *hepatocytes*, seen in microscopic sections as cords of cells radially disposed about a central vein. Between the cords of hepatocytes are vascular sinusoids. Hepatocytes are therefore bathed on two sides by a mixture of portal venous and hepatic arterial blood that represents 25% of the cardiac output, thus making hepatocytes some of the most richly perfused cells in the body. The sinusoids are lined by fenestrated and discontinuous endothelial cells, which demarcate an extrasinusoidal *space of Disse*, into which protrude the abundant microvilli of the hepatocytes. Scattered *Kupffer cells* (tissue liver macrophages) of the monocyte–phagocyte system are attached to the luminal faces of the endothelial cells. Occasional fat-containing *hepatic stellate cells* (HSC, Ito cells) are localized in the space of Disse. In addition, certain populations of *lymphocytes* reside within the liver as part of a defense mechanism against infectious agents (Isselbacher and Podolsky, 1991) (Fig. 2).

2.1. Hepatocytes

2.1.1. Blood-borne infections

The major cell type of the liver that carries out most of its metabolic functions is the hepatocyte (parenchymal cell). Hepatocytes comprise 65% of the cells in the liver and 80% of the hepatic volume (Wanless, 1999). Because of its strategic location between the gastrointestinal tract

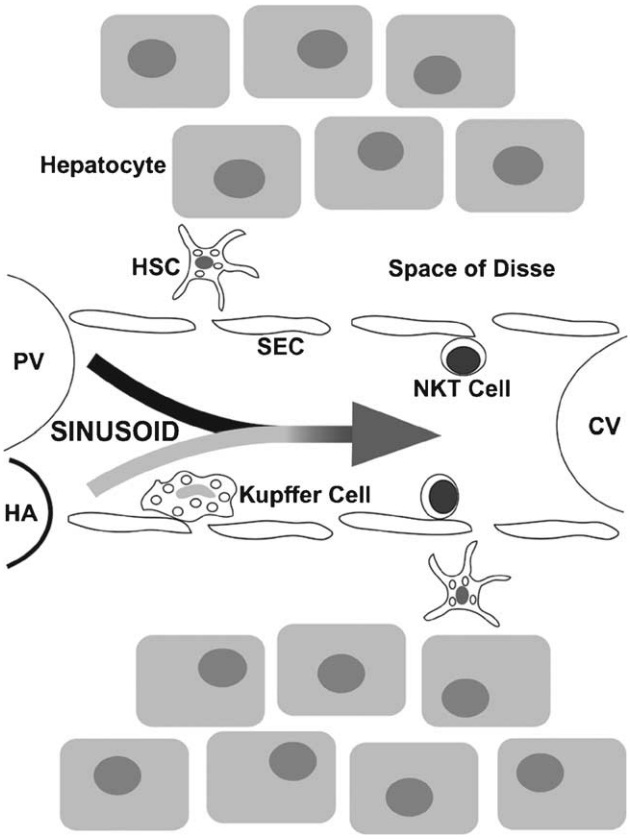

Fig. 2. Schematic architecture of the liver at the cellular level. Hepatocyte cords, radially arranged around central veins, are separated by sinusoids that are lined by fenestrated sinusoidal endothelial cells (SEC). Hepatic stellate cells (HSC) reside in the extrasinusoidal space of Disse, while Kupffer cells are attached to the luminal face of the SEC. Resident lymphocytes, such as NKT cells, are also present in the sinusoidal lumen. A mixture of oxygenated and venous blood deriving from branches of the hepatic artery (HA) and portal vein (PV), respectively, flows through the sinusoids to the central vein (CV).

and peripheral circulation, the liver filters blood from the splanchnomesenteric vascular bed. This region is especially subject to vasoconstriction and bacterial translocation during sepsis (Dhainaut et al., 2001). Hepatic dysfunction during severe sepsis is characteristic of this disorder and occurs most often in response to shock and hypoperfusion, leading to severe complications that include disseminated intravascular coagulation and often hemorrhage (Root and Jacobs, 1991). However, the liver is not only a passive victim of bacterial systemic infections. The liver parenchyma is actively involved in the immune response (to promote host defense) and in the metabolic shift toward gluconeogenesis (to reprioritize protein synthesis to ensure cellular repair). Hepatocytes modify their metabolism toward amino acid uptake, ureagenesis and gluconeogenesis, as well as increased synthesis and release of pro-coagulant and complement factors, antiproteolytic enzymes and a variety of other acute phase proteins (Vary and Kimball, 1992). These metabolic changes occur as a response to endotoxin, cytokines, vasoactive substances or other inflammatory mediators. Liver parenchymal cells express a rich repertoire of receptors on their surface that assures the direct involvement of these mediators in cellular processes (Baumann et al., 1987; Dinarello, 1984; Pomposelli et al., 1988).

2.1.2. Immunomodulation

Another characteristic of hepatocytes that points to their active involvement in the immune response is the expression of various molecules on their surface that are known to be involved in immunomodulatory activities. Resting hepatocytes express major histocompatibility complex (MHC) class I molecules (Bumgardner et al., 1990), CD1 and intercellular adhesion molecule (ICAM)-1 (Bertolino et al., 2002). MHC class II molecules such as CD40L and costimulatory molecules such as CD80 are not constitutively expressed; however, they are upregulated following inflammation. Therefore, resting hepatocytes may only act as antigen-presenting cells (APC) for CD1- or MHC class I-restricted T-cells, whereas after inflammation they may present antigen to a wider range of lymphocytes. It has been reported that hepatocytes can act as very efficient APC for naive $CD8^+$ T-cells in vitro. T-cell activation mediated by hepatocytes has been found to be as efficient as that by mature splenic dendritic cells (DC) in terms of the number of APC required to achieve an equivalent degree of T-cell proliferation (Bertolino et al., 1998). The same group has also shown that hepatocytes may activate $CD8^+$ T-cells in vivo. However, this activation was found to be restricted to high-avidity naive $CD8^+$ T-cells that have been activated by liver parenchymal cells directly without priming in lymph nodes (Bertolino et al., 1995).

2.2. Kupffer cells

2.2.1. Blood-borne infections

Kupffer cells (hepatic macrophages) constitute approximately 80% of body macrophages (Wanless, 1999). Like other cells of the monocyte–phagocyte system, they have migratory and phagocytic capabilities. They continuously patrol liver sinusoids and establish a solid line of defense against portal bacteremia and endotoxemia. They prevent bacteria (Katz et al., 1991) and endotoxins (Mathison and Ulevitch, 1979) from entering the systemic circulation. In addition, they are able to remove bacteria from peripheral circulating blood.

2.2.2. Immunomodulation

Kupffer cells share with other macrophages the ability to initiate and regulate immune responses through the production and release of immunomodulatory mediators. Once primed and activated, Kupffer cells produce cytokines (Decker, 1990; Luster et al., 1994) that either regulate hepatocyte and endothelial cell function via paracrine interactions or are released into the systemic circulation (Fong et al., 1990). For example, lipopolysaccharide (LPS) stimulation leads to the secretion of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1-α/β, IL-6, IL-12, IL-18

and granulocyte macrophage-colony stimulating factor (GM-CSF) (Freudenberg and Galanos, 1991; Groopman et al., 1989; Van Zee et al., 1991; Wakabayashi et al., 1991). Conversely, Kupffer cells are potent scavengers of systemic and gut-derived inflammatory mediators, immune complexes, toxic products and cytokines (Andus et al., 1991) and thus appear to play a crucial role in limiting the extent of the systemic inflammatory response.

Kupffer cells are ideally located to encounter circulating lymphocytes in the sinusoidal lumen. They express MHC class II molecules and ICAM-1 (Mehal et al., 1999), as well as low levels of CD80 and CD86 (Leifeld et al., 1999; Lohse et al., 1996). In vitro experiments suggest that although Kupffer cells appear to be less efficient than splenocytes and extra-hepatic macrophages (Lohse et al., 1996; Rubinstein et al., 1986, 1987), they can function as APC for all $CD4^+$ T-cells (Lohse et al., 1996; Nadler et al., 1980; Richman et al., 1979; Squiers et al., 1993) and Th1 clones (Roland et al., 1994).

2.3. Sinusoidal endothelial cells (SEC)

2.3.1. Immunomodulation

The liver sinusoids form a specific capillary network system in which a variety of metabolic substances are exchanged between the hepatic blood flow and parenchymal cells. The major component of this system is the endothelium. Its structural characteristics, such as its ability to act as a membrane sieve and its lack of a basement membrane, facilitate the establishment of direct contact between soluble and insoluble serum substances and the hepatic parenchymal cells (Wisse, 1970, 1972). In addition, SECs are now regarded as scavenger endothelial cells, which have the potential to eliminate a variety of macromolecules from the blood by receptor-mediated endocytosis (Smedsrod et al., 1990). It has been reported that the types of molecules preferentially eliminated by SEC are denatured or modified proteins such as advanced glycation end products, extracellular matrix components (including hyaluronic acid) and some lipoproteins (Blomhoff et al., 1984; Nagelkerke et al., 1983; Smedsrod et al., 1985). In the liver, Kupffer cells and dendritic cells, both of which belong to the macrophage lineage, are known to have antigen-presenting functions. It has been noted that SEC also have antigen-presenting functions, similar to those of dendritic cells (Lohse et al., 1996); in fact, they express molecules relevant to antigen presentation, such as CD40, CD54, CD80, CD86 and MHC classes I and II (Knolle et al., 1999). Furthermore, this function of SEC apparently leads to immunological tolerance rather than enhancement of immunity against specific antigens through $CD8^+$ T-cells, resulting in suppression of excessive immunological responses against various dietary antigens (Knolle and Gerken, 2000; Limmer et al., 2000). These studies suggest a new dimension to the function of SEC that involves regulation of the local hepatic immune response in concert with Kupffer cells and hepatic dendritic cells (Enomoto et al., 2004).

2.4. Liver lymphocytes

2.4.1. Innate immune response/immunomodulation

The liver is selectively enriched for cells involved in innate immunity, including natural killer T (NKT) cells (Exley and Koziel, 2004). This lymphocyte subset is rare in most tissues but is unusually abundant in bone marrow and liver (Crispe and Mehal, 1996; MacDonald, 1995). NKT cells share features of both classical T and natural killer (NK) cells (Exley and Koziel, 2004). The major subset of these cells is defined by reactivity against CD1d, which is one of the known glycolipid-binding non-polymorphic major histocompatibility complex class 1-like glycoproteins (Porcelli and Modlin, 1999). These glycoproteins facilitate the recognition of non-protein antigens, in particular glycolipids, including those present in mycobacterial species. CD1d is constitutively expressed on a variety of hematopoietic-derived APC cells, as well as on parenchymal liver cells (Castano et al., 1995; Kawano et al., 1997). Once activated, NKT cells can produce large amounts of interferon-gamma (IFN-γ) and IL-4 (Bendelac et al., 1995; Exley et al., 1997), two cytokines that are hallmarks of Th1 and Th2 responses, respectively. These cells also display CD1d-specific cytotoxicity, thus contributing to responses against various pathogens and tumor cells (Cui et al., 1997; Exley et al., 1998; Kawamura et al., 1998; Metelitsa et al., 2001).

The properties of liver cells, together with the liver's particular anatomic localization and unique vasculature, make it an effective barrier against both systemic infections and those arising in the abdomen or gastrointestinal tract. Moreover, it can influence the activity of the whole immune system through the immunomodulation mediated by certain cell populations. Finally, through its role as a scavenger, it may limit the magnitude of the systemic inflammatory response.

3. Liver regeneration

3.1. Definition and models

Liver regeneration is a compensatory hyperplasia and hypertrophy that occurs as a response to viral or toxic liver injury or hepatic resection (Taub, 2004). The capacity of adult liver cells, both parenchymal and non-parenchymal, to re-enter the cell cycle reflects the uniqueness of this process (Taub, 2004). Under normal conditions, only 0.5–1.0% of liver cells are regularly undergoing DNA replication (Cotran et al., 1994). However, upon stimulation, individual hepatocytes have a remarkable replicative capacity, as only a few hepatocytes are required to restore liver mass after profound injury (Taub, 2004). The ability of hepatocytes to undergo cellular growth and proliferation during regeneration, while continuing to carry out their metabolic tasks, makes possible a relatively rapid restoration of the delicate homeostatic equilibrium even after serious insult to the liver. Liver regeneration requires the activity of multiple signaling pathways,

assuring synchronized proliferation of liver cells, protection from apoptotic signals, remodeling of extracellular matrix and restoration of lobular architecture (Fausto, 2001).

The most commonly applied experimental model for studying liver regeneration is 70% surgical resection of the rodent liver (partial hepatectomy, PHx), a technique introduced by Higgins and Anderson (1931). In this model, approximately two-thirds of the liver is surgically removed, and the remaining liver lobes enlarge until the original liver mass is restored, at which point regeneration stops. The majority of the data elucidating the molecular mechanisms of the regenerative response of the liver has been derived from studies that utilized PHx. Surgical liver resection is associated with only minimal injury; therefore, an obvious inflammatory reaction that includes a significant inflammatory infiltrate is not seen in the liver parenchyma under these circumstances. However, some alterations in body homeostasis observed after PHx indicate that an inflammatory reaction does occur in this experimental situation. These changes include elevated levels of acute phase proteins in the blood, activation of liver macrophages and the release of cytokines that are involved in the regulation of inflammatory responses to various pathogens (Taub, 2004).

The liver can also regenerate after induction of parenchymal damage by hepatotoxins, such as carbon tetrachloride (CCl_4), or by systemic introduction of Fas ligand. In these two models, regeneration is a response to massive liver cell necrosis as well as secondary necrosis that occurs after apoptotic cell death (Taub, 2004). The inflammatory infiltrate seen in histological liver sections is a naturally occurring reaction of the system to necrotic tissue. Indeed, in these models, regeneration is unavoidably associated with significant tissue injury and an inflammatory reaction. Therefore, there are certain doubts whether experiments employing models of hepatic injury may clearly elucidate the molecular background of regeneration, since cell death and an inflammatory reaction may interfere with the delicate homeostatic balance of living systems. However, models employing cell damage as an initiator of liver regeneration might be seen as a better reflection of liver diseases that trigger the regenerative response, such as viral hepatitis, toxic- and 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 tumors (Isselbacher and Podolsky, 1991). Nevertheless, despite the obvious differences between the surgical and injury models, the basic molecular mechanisms that govern the regenerative processes seem to be quite similar.

3.2. Regulation by innate immunity

3.2.1. Cytokines

Liver regeneration is essentially regulated by the interplay between cytokines and growth factors (Taub, 2004). Cytokines are pleoitropic molecules that are crucial for the regulation of immune responses associated with both innate and adaptive immunity. In this context, they are produced in response to pathogen recognition. Cytokines coordinate cellular and tissue events that occur during the progression of an inflammatory response, the ultimate goal of which is to eliminate the pathogen. At the same time, the host tissue must be protected against excessive damage caused by the actions of these inflammatory mediators. If the innate immune response is unable to clear the infection, an adaptive immune response develops (Janeway et al., 2001).

Macrophages, which are widely distributed throughout the body, are among the first responders to infections. Upon activation, they release a variety of mediators, including cytokines that launch an inflammatory reaction. Among these are TNF-α and IL-6, which are produced as an integral part of the induction of innate immunity (Janeway et al., 2001). Both are also known to be involved in the priming phase of liver regeneration (Taub, 2004). In response to PHx, Kupffer cells release TNF-α, which activates the nuclear factor-kappa B (NF-κB) transcription factor in macrophages and hepatocytes in both an auto- and paracrine manner (Taub et al., 1999). This response leads to the secretion of IL-6, which in turn activates the transcription factor signal transducer and activator of transcription 3 (STAT3) (Cressman et al., 1995; Yamada et al., 1997). Studies in IL-6-deficient (Cressman et al., 1996; Sakamoto et al., 1999) and TNF-α receptor 1 (TNFR1)-deficient (Yamada et al., 1997) mice have shown that normal liver regeneration requires these cytokines. To some extent, the role of TNF-α in liver regeneration is mediated by IL-6, since the defect in DNA synthesis that occurs in TNFR1-deficient mice after PHx can be corrected by administration of IL-6 (Yamada et al., 1997).

The activation of transcription factors by cytokines results in both cellular proliferation and protection from cell death. NF-κB regulates the transcription of cyclin D1, a cell cycle regulator that is upregulated after PHx (Cressman et al., 1996; Guttridge et al., 1999; Hinz et al., 1999). Stimulation of the IL-6 receptor (IL-6R/gp130) by IL-6 promotes cell growth not only through STAT3 activation (Levy and Lee, 2002), but also through activation of the mitogen activated protein kinase (MAPK) signaling cascade, which is crucial for cell proliferation (Talarmin et al., 1999).

Some recent studies have emphasized the hepatoprotective role of IL-6 more strongly than its mitogenic activity (Blindenbacher et al., 2003; Sakamoto et al., 1999; Wuestefeld et al., 2003). IL-6 activates the pro-survival kinases phosphoinositol 3 kinase (PI3K) and Akt in addition to STAT3, which is also involved in hepatoprotection (Alonzi et al., 2001; Webster and Anwer, 2001). The activity of TNFR1 leads to NF-κB activation; however, when this activation is inhibited, such as through the action of a super-repressor transgene of the NF-κB inhibitor, IκBα, or of gliotoxin, liver regeneration after PHx is impaired and apoptosis of hepatocytes occurs instead of proliferation (Iimuro et al., 1998; Plumpe et al., 2000). NF-κB is also known to regulate certain anti-apoptotic genes, including Fas-associated death domain-like interleukin-1 beta-converting enzyme (FLICE)-

inhibitory protein (FLIP), cellular inhibitor of apoptosis protein (c-IAP) 1 and inducible nitric oxide synthase (iNOS) (Diaz-Guerra et al., 1997; Hatano et al., 2001; Krikos et al., 1992; Manna et al., 1998; Micheau et al., 2001; Opipari et al., 1992; Taylor et al., 1998; Wang et al., 1998), and it prevents TNF-α-induced hepatocyte death (Beg and Baltimore, 1996; Liu et al., 1996; Reinhard et al., 1997; Van Antwerp et al., 1996; Wang et al., 1996; Xu et al., 1998) (Fig. 3). In summary, along with their downstream targets (transcription factors), cytokines, as mediators of innate and adaptive immunity, coordinate proliferative and pro-survival signaling pathways that are crucial for successful regeneration of liver parenchyma.

3.2.2. LPS

The release and production of IL-6 and TNF-α are initiated, at least in part, by components of the innate immune system (Cornell et al., 1990; Strey et al., 2003). It has been suggested that LPS, a strong activator of innate immunity, is present in increased concentration in the portal blood flow after PHx (Cornell, 1985a,b). Moreover, both germ-free athymic and LPS-resistant mice show impaired regeneration after PHx (Cornell et al., 1990). LPS resistance is associated with a mutation of the gene encoding toll-like receptor 4 (TLR4), which, via an interaction with surface CD14 on macrophages, is involved in TNF-α release after LPS stimulation (Rhee and Hwang, 2000).

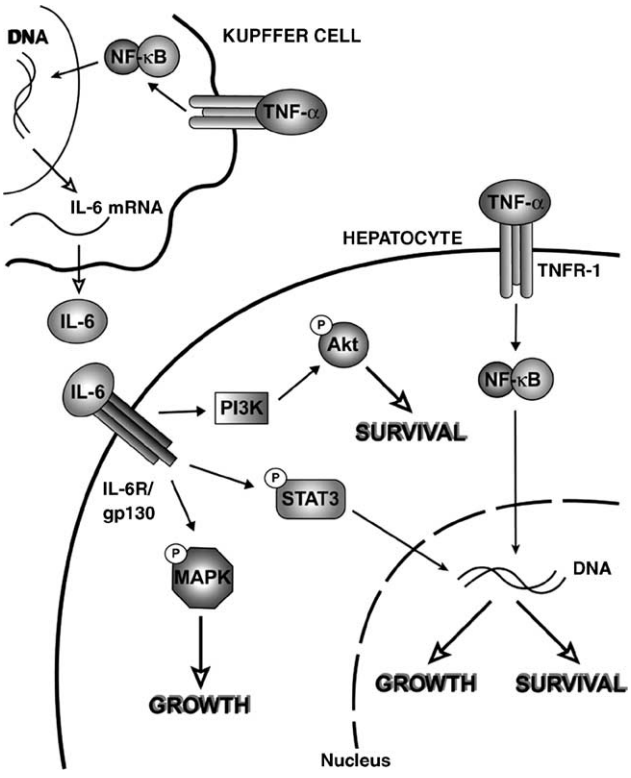

Fig. 3. Cytokine signaling during liver regeneration. TNF-α action on Kupffer cells through the TNF receptor 1 (TNFR1) results in activation of NF-κB and production and release of IL-6. Both of these cytokines can act on hepatocytes. Induction of NF-κB by TNF-α in these cells leads to the transcription of genes involved in both cell growth and survival. IL-6 acts through the IL-6R/gp130 complex to stimulate several signaling pathways. MAPK activity leads cell growth, while STAT3 additionally induces anti-apoptotic gene expression. IL-6 simultaneously activates PI3K/Akt to further promote hepatoprotection.

3.2.3. NKT cells

The liver NKT cell population expands very quickly after PHx in mice, and this expansion is dependent upon signaling through adrenergic receptors (Minagawa et al., 2000). These findings raise the possibility that NKT cells play a role in liver regeneration. The observation that adrenergic-receptor blockers inhibit the accumulation of NKT cells in the regenerating liver suggests that these cells are activated as part of a "stress response". The limited diversity of their T-cell receptor (TCR) and its specificity for glycolipids presented by CD1 suggests that glycolipids may be "damage signals" that recruit NKT cells regardless of the mechanism of tissue injury (Ahmad and Alvarez, 2004; Exley and Koziel, 2004). NKT cell expansion sometimes leads to impaired liver regeneration. The number of NKT cells can increase as a result of IL-12 stimulation, and this increase exacerbates injury during the early phases of liver regeneration (Ito et al., 2003). This effect is, at least to some extent, related to the increased IFN-γ-producing capacity of NKT cells after IL-12 stimulation, given the role of IFN-γ in hepatitis-induced acute liver failure (Ando et al., 1993).

3.2.4. Complement

Indications of an association between liver and the complement system rely not only on the fact that liver parenchyma is a major site of complement protein synthesis but also on growing evidence suggesting the importance of the liver as a target organ for effector complement compounds. This complement activity is obvious in regard to liver cells of myeloid origin, since these cells express a rich repertoire of receptor molecules that may interact with complement proteins (Schieferdecker et al., 2001). However, it has recently become more apparent that complement activity in the liver is not restricted to non-parenchymal cells, but that hepatocyte functions can also be modified by active fragments of complement proteins (Schieferdecker et al., 2001).

Complement effector molecules can act on the liver in a direct or indirect manner. Direct effects can be exerted through complement receptors (for example, the receptors for anaphylatoxins) expressed on the surface of liver cells. Indirect complement activity can be illustrated by the release of cytokines induced by complement and their subsequent action on liver parenchyma. Sometimes direct and indirect complement actions overlap: hepatic macrophages, for instance, can be stimulated by direct interaction of the C5a anaphylatoxin with its receptor (C5aR), which is expressed on these cells, to secrete cytokines that in turn may exert their functions on a variety of cells, including the macrophages themselves (Cavaillon et al., 1990;

Montz et al., 1991; Okusawa et al., 1987; Scholz et al., 1990).

Anaphylatoxins are potent effector molecules of complement as well as potent inflammatory mediators. They are generated as a result of activation of the complement cascade through limited proteolysis of C3 and C5 by respective convertases. As a result, C3a and C5a are released into the circulation or interstitial fluid (Ember et al., 1998; Wetsel et al., 2000). Anaphylatoxin effects at the periphery include degranulation of mast cells, contraction of smooth muscle cells, an increase in vascular permeability and the chemotaxis and activation of neutrophils, with the release of reactive oxygen species, eicosanoids and cytokines (Ember et al., 1998; Kohl, 2001; Mastellos and Lambris, 2002). Anaphylatoxin functions in the liver are less well-characterized; however, significant progress in this area has been made in recent years. In the normal rat liver, C5aR is expressed by non-parenchymal cells (Schieferdecker et al., 2001). Therefore, the direct effect of C5a can be seen only on these cells. C5a enhances the LPS-dependent release of IL-6 from Kupffer cells (Cavaillon et al., 1990; Mack et al., 2001; Montz et al., 1991) and induces the release of prostanoids from both Kupffer cells and HSC (Hespeling et al., 1995; Ramadori and Christ, 1999). These mediators, in turn, influence the function of hepatocytes. The release of prostanoids indirectly leads to C5a-mediated enhancement of glycogen phosphorylase activity, and thus to glucose output from hepatocytes (Puschel et al., 1996), while increased LPS-dependent IL-6 secretion enhances transcription of the α_2-macroglobulin gene in these cells (Schieferdecker et al., 2001). C5aR has been found to be upregulated on hepatocytes under various inflammatory conditions; for example, exposure of rats to IL-6 results in de novo expression of functional C5aR in hepatocytes (Schieferdecker et al., 2000). In this experimental model, C5a directly initiates glucose output from hepatocytes.

Recent studies in our laboratory have demonstrated that the complement system is involved in the regulation of liver regeneration after PHx and CCl_4-mediated injury (Mastellos et al., 2001; Strey et al., 2003; Markiewski et al., 2004). Complement activation occurs in two waves during the course of the regenerative process after CCl_4-mediated injury. C3 cleavage fragments appear in the serum of experimental animals in the first few hours after toxin injection (first wave of activation), while a second, even more pronounced wave is seen between 24 and 60 h after injection of CCl_4 (Markiewski et al., 2004). The time frame for the primary complement activation correlates with the priming phase of liver regeneration, when cytokine signaling activates transcription factors (NF-κB, STAT3) that are critical to this process. Both peaks of complement activation in serum are associated with deposition of complement proteins in the liver tissue (Markiewski et al., 2004). Local deposition of complement components indicates that activation may occur in situ, in the liver parenchyma, as a response to stimuli that trigger regeneration. The timing of the second peak of complement activation corresponds to the time at which damaged liver tissue is being resolved by macrophages.

Since C3 fragments (C3b and iC3b) are known be involved in the clearance of apoptotic cells (Mevorach et al., 1998), we hypothesize that secondary complement activation may be important for this process. Indeed, animals deficient in C3 display delayed clearance of injured liver cells (Markiewski et al., 2004). C3 deficiency is also associated with significantly impaired proliferation of hepatocytes in both the surgical and the toxicity models of liver regeneration (Strey et al., 2003; Markiewski et al., 2004). In addition, C3-deficient mice experience massive tissue injury after PHx that is usually not seen in wild-type animals (Strey et al., 2003). A similar phenotype is observed in C5-deficient mice, although hepatocyte proliferation is only delayed after CCl_4-mediated injury and is not as dramatically reduced as in C3-deficient livers (Mastellos et al., 2001; Markiewski et al., 2004). An exacerbated phenotype is seen in C3/C5 double-deficient mice, with barely visible proliferation of hepatocytes and massive damage to liver parenchyma (Strey et al., 2003).

The regenerative wild-type phenotype has been restored in deficient strains through reconstitution with recombinant and synthesized anaphylatoxins (Markiewski et al., 2004; Mastellos et al., 2001; Strey et al., 2003); this successful reconstitution points to the involvement of anaphylatoxins in liver regeneration. Moreover, experiments performed with C3aR-deficient mice and wild-type mice treated with C5aR antagonist have confirmed that anaphylatoxins exert their functions on liver regeneration through their respective receptors (Markiewski et al., 2004; Mastellos et al., 2001; Strey et al., 2003). Pharmacological blockade of C5aR in the PHx model results in decreased induction of mRNA for TNF-α and IL-6 in the first few hours after surgery (Strey et al., 2003). The inhibition of cytokine induction correlates with the lower NF-κB and STAT3 binding activity observed in nuclear extracts from livers of C5aR antagonist-treated mice (Strey et al., 2003). Similar results regarding the activity of transcription factors have been obtained from experiments using C3-deficient mice (Strey et al., 2003); these findings were expected because C3 is an upstream regulator of C5 cleavage (C3b is required to form C5 convertase, which cleaves C5 to C5a and C5b). Summarizing, the plausible scenario is that complement activation occurs simultaneously with the initiation of liver regeneration and leads to the generation of potent inflammatory mediators, the anaphylatoxins C3a and C5a which, acting on their receptors expressed on liver cells (mainly Kupffer cells), participate in the regulation of the cytokine release and/or production that in turn stimulates the induction of transcription factors that are crucial for regeneration (Fig. 4). The presence of massive tissue injury in complement-deficient mice after surgical resection may also indicate the involvement of complement in hepatoprotective functions. Whether this involvement is only indirect, acting via cytokine signaling, or whether other mechanisms play a role requires further investigation.

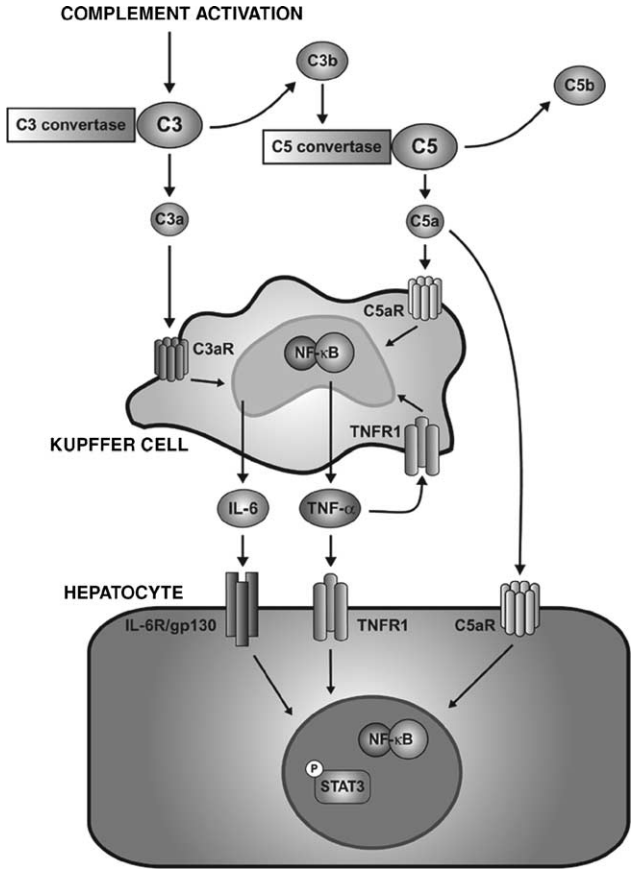

Fig. 4. The role of anaphylatoxins in liver regeneration. Activation of the complement cascade leads to limited proteolysis of C3 (by the C3 convertase) and release of C3a and C3b. C3a acts as a signal for Kupffer cells through the C3a receptor (C3aR). C3b participates as part of the C5 convertase in cleaving C5. C5a, which is released as a consequence of this cleavage, acts as a ligand for the C5a receptor (C5aR) on Kupffer cells and hepatocytes. Anaphylatoxin signaling results in activation of NF-κB and release of TNF-α and IL-6 from Kupffer cells. These cytokines signal through their respective receptors on hepatocytes, along with C5a, to promote cell growth and survival through the actions of transcription factors.

3.2.5. *Acute-phase proteins (APP)*

Up-regulation of APP after PHx has been noted in several reports, including our recent study on the liver proteome (Strey et al., 2005). Increased synthesis of these proteins is a hallmark of the acute inflammatory reactions mediated by the innate immune system (Janeway et al., 2001).

3.2.6. *Adhesion molecules*

One of the most important events that occur soon after induction of the innate immune response is the process of leukocyte extravasation and migration to sites of inflammatory reactions. This process requires the interaction of adhesion molecules on the surfaces of leukocytes and the endothelium (Janeway et al., 2001). ICAMs expressed on endothelial cells after the initiation of inflammatory reactions are crucial for leukocyte extravasation and have also been shown to be required for normal liver regeneration after PHx (Selzner et al., 2003).

3.2.7. *Urokinase-type plasminogen activator (uPA)*

uPA and plasminogen proteases cleave pro-hepatocyte growth factor (pro-HGF) and thereby release HGF, a potent hepatocyte mitogen that is involved in regeneration (Currier et al., 2003; Pediaditakis et al., 2001). Plasminogen activator (released from enodothelial cells and leukocytes activated during the inflammatory response) cleaves plasminogen and generates plasmin, a multifunctional protease, which in turn can cleave C3 to produce C3 fragments; it can also degrade fibrin to form fibrin split products, which may have permeability-inducing properties (Collins, 1999). Plasmin can also activate Hageman factor, which can trigger multiple cascades to amplify the inflammatory response (Collins, 1999).

4. Concluding remarks

Brief descriptions of the complex biological processes that take place in vivo necessarily run the risk of oversimplifying or omitting important aspects of particular biological events. Although some of the concepts in this review have been streamlined, our discussion represents an attempt to summarize the multifaceted involvement of inflammatory reactions in liver regeneration. The concept that an inflammatory reaction is indeed involved in the initiation and regulation of the liver's regenerative response has sometimes been seen as controversial. This skepticism is due, at least in part, to a belief that the most commonly applied model for studying liver regeneration, PHx, is not associated with an ongoing inflammatory reaction. However, our own experience and that of others has led us to conclude that the mechanisms used by living organisms to neutralize infections also apply to the control of liver regeneration.

Our understanding and appreciation for the exceptional role of inflammation in human pathology has increased significantly since the first century A.D., when Celsus originally defined inflammation as a process characterized by "rubor, calor, dolor and tumor." Inflammation is seen today as an intellectually challenging problem in a variety of contemporary scientific fields and is one of the most common targets for medical therapeutic interventions. Inflammation can currently be viewed, as described by Nathan (2002), "as a complex set of interactions among soluble factors and cells that can arise in any tissue in response to traumatic, infectious, post-ischaemic, toxic or autoimmune injury." This process is usually beneficial for the host and leads to both neutralization of the causative factor and tissue recovery. However, under certain circumstances, when the actions of the various compounds of the "inflammatory machinery" are not properly orchestrated, inflammation may lead to significant pathology. There is already a long list of human diseases in which an inflammatory reaction plays a pathogenic role. Some of these diseases were previously categorized as degenerative disorders, but new insights into the mechanisms involved in their pathogenesis have dramatically altered this old classification.

Examples include chronic gastric ulcer, multiple sclerosis, atherosclerosis and a lengthy list of autoimmune disorders (Nathan, 2002).

Finally, our view on the role of inflammation in cancer has recently undergone important modifications. Traditionally, it was thought that the inflammatory reaction present at the periphery of malignant tumors represented a defense mechanism triggered by the immune system, indicating a better prognosis for cancer patients. However, recent data have bolstered the concept that inflammation is a critical component of tumor progression, and the presence of inflammatory cells and mediators favors, to some extent, the growth of the tumor. It is now becoming clear that the tumor microenvironment, which is crucial for malignant cell proliferation, survival and migration, is controlled by inflammatory cells (Coussens and Werb, 2002). Several molecular mechanisms used by cancer cells to proliferate effectively may also apply to proliferating liver cells during regeneration, further supporting the concept that inflammatory mediators are indeed involved in the regulation of this unique process.

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