PERGAMON

International Journal of Immunopharmacology 22 (2000) 1143–1147

INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY

www.elsevier.com/locate/ijimmpharm

Immunotoxicology: role of inflammation in chemical-induced hepatotoxicity

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Abstract

The liver, which is the major organ responsible for the metabolism of drugs and chemicals, is also the primary target organ for many toxic chemicals. Increasing evidence has indicated that inflammatory processes are intimately involved in chemical-induced hepatotoxic processes, and like other inflammatory diseases, such as autoimmunity, are responsible for producing mediators which can effect liver damage or repair. This review will summarize the authors' current understanding of how inflammatory processes influence hepatic pathology and repair following exposure to established hepatotoxic chemicals including carbon tetrachloride (CCl_4), an industrial chemical, and acetaminophen (APAP), a widely used analgesic.

Keywords: Immunotoxicology; Hepatotoxicity; Acetaminophen

1. Introduction

The vulnerability of the liver to chemical injury is as much a function of its anatomical proximity to the blood supply and digestive tract as to its ability to biotransform and concentrate xenobiotics. Xenobiotics in the blood pass through the portal vein and hepatic artery and then drain through the central and the hepatic veins into the vena cava. The main hepatic duct joins the cystic duct from the gall bladder to form the common bile duct, which drains into the duodenum. Although hepatocytes compromise the bulk of the liver, approximately 35% of liver cells reside in the hepatic sinusoids and represent endothelial cells, Ito cells and, predominantly, Kupffer cells. Kupffer cells, which are responsible for antigen presentation and clearance of particulates from portal circulation, are central to hepatic inflammatory processes.

The liver response to chemical injury can be extremely varied, reflecting the chemical's proper-

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0192-0561/00/$20.00
PII: S0192-0561(00)00073-4

ties, the exposure regimen and animal species examined [1]. Historically, identification and classification of hepatotoxic chemicals has been based upon morphologic changes, in which both the location and type of lesion are considered. However, serum enzyme tests, hepatic excretory tests or alterations in the chemical constituents have proved more sensitive indicators of damage. This classification is not to be confused with mode of action, which is best established by associating molecular and biochemical changes to hepatocellular dysfunction. The liver is also a major inflammatory organ and inflammatory processes participate in a number of pathological (i.e., necrosis and fibrosis), protective and repair events following exposure to hepatotoxic chemicals [2]. The overarching hypothesis that link these effects is summarized in Fig. 1 and is as follows: Initial injury from hepatotoxic chemicals produce focal zones of hepatocellular necrosis that appear predominantly in centrilobular regions where there are high levels of cytochrome P450 mixed function oxidases. The oxidases are responsible for the metabolism of many chemicals to toxic intermediates. The necrosis results from either lipid peroxidation, covalent binding of reactive metabolites to cellular macromolecules, disturbance of biliary production and/or flow or perturbation of calcium homeostasis. Either in response to necrosis or as a direct action by the chemical, Kupffer cells, probably along with adjacent nonparenchymal cells, are activated resulting in the production of proinflammatory cytokines such as IL-1, IL-6 and TNFα. As will be reviewed in the following sections, these cytokines serve as central regulators controlling genes who's products are responsible for either providing cell protection, inducing apoptosis, enhancing cell damage or stimulating hepatocyte proliferation.

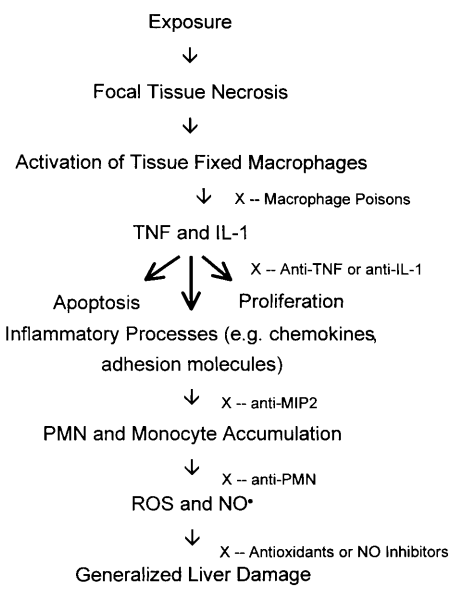

Fig. 1. Proposed model for the role of inflammation in chemical-induced hepatotoxicity.

2. Results and discussion

Increasing evidence indicates that inflammation adds to chemical-induced liver damage through a complex series of events involving sequentially: the activation of non-parenchymal cells, specially Kupffer cell and their release of proinflammatory cytokines; the induction by inflammatory cytokines of adhesion molecules and C–C and C–X–C families of chemokines such as IL-8, MIP-2 and MCP-1; the chemokine-induced recruitment of activated neutrophils and circulating monocytes to the liver and; ultimately, nitric oxide production, degranulation and release of neutral proteinase and generation of superoxide anions (O_2^-) from infiltrating leukocytes via NADPH-oxidase during the respiratory burst. It has been shown that O_2^-, which itself mediates tissue damage, can be further reduced to other cell damaging reactive oxygen intermediates (ROIs), including H_2O_2 and hydroxyl radical ($OH^\bullet$) [2]. The ultimate toxicity of O_2^- may depend on its ability to bring about the reduction of Fe^{3+} to Fe^{2+}, providing for the generation of $OH^\bullet$ from H_2O_2, and to interact with $NO^\bullet$ to generate peroxynitrite ($ONOO^\bullet$) and subsequently $OH^\bullet$. The overall effect of this complex series of events would be additional cellular damage and depending upon severity and chronicity, fibrosis. In respect to the latter, it has recently been shown that IL-6 deficient mice are resistant to liver fibrosis induced by CCl_4 administration [3].

There is ample evidence to support the hypothesis that inflammatory responses exacerbate chemical-induced hepatotoxicity. For example, treatment of Kupffer cells or hepatocytes with hexpatotoxic chemicals such as acetaminophen, ethanol, heavy metals or H_2O_2 results in the expression and release of inflammatory cytokines and chemokines [4–7]. Secondly, inflammatory cell infiltrates [7–9] and proinflammatory cytokines are found in the liver of rodents exposed to hepatotoxic chemicals such as acetaminophen, cadmium [10], αnapthyl isothiocyanate [11], dimethylnitrosamine [12] or carbon tetrachloride [13,14]. Lastly, administration of proinflammatory cytokines, such as TNFα, mediates many of the pathological effects seen with hepatotoxic chemicals including inflammatory cell infiltrates, lipogenesis, fibrogenesis and cholestasis [15]. While these studies indicate that inflammation is associated with hepatotoxicty, it does not provide evidence for a causal relationship. More direct evidence that inflammation is responsible for exacerbating hepatotoxicity is suggested by studies demonstrating that inactivation or depletion of Kupffer cells by gadolinium chloride, dextran sulfate or methyl palmitate decreases toxicity from exposure to hepatotoxins and, when studied, also reduces inflammatory cytokine levels [16–21]. Additionally, hepatotoxicity is reduced in experimental animals which have been therapeutically treated or genetically modified to prevent the production of inflammatory cytokines, such as has been demonstrated in TNF receptor knockouts [8,10,13].

While inflammatory processes can exacerbate chemical-induced hepatotoxicity, in certain cases they have been shown to participate in liver repair [14]. Similar to that observed in regeneration models following partial surgical hepatectomy and consistent with previous observations that TNFα is a hepatocyte mitogen [22], neutralization of TNFα or IL-6 prior to CCl_4 delays the ability of the liver to repair itself [14]. TNFα/IL-6 induction occurs within minutes following CCl_4 exposure and is responsible for the activation of nuclear transcription factors including AP-1, NF-κB, and STAT 3 [14,22,23], which regulate genes involved in cell growth. One of the growth factors that is regulated via this pathway is transforming growth factor-α (TGFα), a potent hepatocyte growth factor. In this respect, it has recently been demonstrated that TNFα, induced in the liver following CCl_4 exposure, is responsible for TGFα production [24].

The role of inflammation in toxicological processes is viewed with considerable interest by many toxicologists as increasing numbers of occupational and environmental disease, as well as adverse drug reactions, are believed to manifest an over-exuberant inflammatory component that contributes, albeit to varying degrees, to disease severity. Regarding the liver, over 600 000 workers, including painters and newspaper printers, are exposed chronically to organic solvents and have a relative risk for cirrhosis ranging from 1.6 to 2.1 [25]. Liver cirrhosis is the third most common cause of death in urban dwellers aged 25–64 with an annual incidence estimated between 150 and 200 cases per million in Western countries [26]. Approximately 15–20% of these are classified as cryptogenic cirrhosis in which no identifiable cause (metabolic, alcoholic or viral) can be established. Case reports of individuals accidentally exposed to large doses of CCl_4 or other chlorinated organic solvents revealed fulminate hepatic necrosis and has lead to routine screening of solvent exposed populations for liver enzyme changes, such as hepatic transaminase [27]. Acetaminophen, a commonly used pain reliever, is strongly associated with hepatotoxicity, particularly when combined with alcohol and represents one of several drugs where the recommended dose is relatively close to that which can cause toxicity.

In summary, only recently have toxicologists come to appreciate the role inflammation plays in classical toxicological processes. This relationship can be extremely complex, as inflammation may well be only one facet of a time- and dose-dependent continuum of toxicological and repair processes. Although many mediators are responsible for these processes, pro-inflammatory cytokines have received the most attention as they represent central mediators involved in regulating this process. Not surprisingly, considerable efforts are being undertaken using the newly found understanding of molecular control to develop specific

and safe biological and molecular inhibitors of TNFα for potential therapeutic use. The understanding of the molecular basis for inflammatory diseases has also provided additional opportunities to improve human health risk assessment. For example, the identification of functional polymorphisms for many of the genes which code for inflammatory mediators should allow for a better estimate of determining susceptible populations and help improve human risk assessment.

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