International Immunopharmacology 54 (2018) 12–23

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Inflammation is regulated by the adenosine derivative molecule, IFC-305, during reversion of cirrhosis in a CCl_4 rat model

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ARTICLE INFO

Keywords:
Cirrhosis
CCl_4
Hepatotoxicity
Hepaprotective molecule
Liver immune response
Inflammation
Anti-inflammatory response
Liver immune response
Inflammation

ABSTRACT

Cirrhosis is a liver pathology originated by hepatocytes, Kupffer and hepatic stellate cells interactions and transformations. This pathology is associated with inflammation and fibrosis, originated by molecular signals secreted by immunological and parenchymal cells, such as cytokines and chemokines, like IL-1β, IL-6, TNF-α or MCP-1, driven by Kupffer cells signals. As part of inflammation resolution, the same activated Kupffer cells contribute to anti-inflammatory effects with IL-10 and MMP-9 secretion. In a Wistar rat model, cirrhosis induced with CCl_4 is characterized by increased inflammatory cytokines, IL-6, IL-1β, MCP-1, and TNF-α, in plasma and liver tissue. The IFC-305 compound, an adenosine derivative salt, reverses the cirrhosis in this model, suggesting that immune mechanisms related to inflammation should be explored. The IFC-305 reduced inflammatory cytokines, supporting the anti-inflammatory effects induced by the elevation of IL-10, as well as the reduction of M1 inflammatory macrophages ($CD11b/c^+/CD163^+$) and the increase of M2 anti-inflammatory macrophages ($HIS36^+/CD11b^+$), measured by flow cytometry. Furthermore, the IFC-305 enhances the metabolic activity of arginase and moderates the inducible nitric oxide synthetase, evaluated through biochemical and immunohistochemical methods. These results contribute to understand the function of the IFC-305, which modulates the immune response in the Wistar rat model of CCl_4-induced cirrhosis and support the hepatic protective action through an anti-inflammatory effect, mainly mediated by Kupffer cells.

1. Introduction

Cirrhosis is a pathological condition that represents the 14th most common cause of death worldwide [1]. In recent years, many studies have been conducted to understand the mechanisms involved in the development of this disease and its resolution, at cellular and molecular levels. It has been demonstrated that the immune response is one of the main mechanisms involved in the progression and repair of this liver pathology [2].

Liver injuries provide a proper model of inflammation and repair, showing a complex interaction of epithelial cells, myofibroblasts, and the extracellular matrix (ECM), all are components of the mammalian wound-healing response. In almost all etiologies, cirrhosis is preceded by fibrosis and inflammation, with elements of innate and adaptive immune response that are crucial in regulating these processes [3]. The most common etiologies for cirrhosis are: hepatitis B and C alcohol abuse [4,5], non-alcoholic steatohepatitis [6], and chronic infection with parasites such as *Schistosoma mansoni* and *Schistosoma japonicum* [7]. The efforts to confront these fibrotic diseases are focused on finding specific marks that transform an acute inflammation to a chronic one, and to use them as therapeutic aims for treatment and reversion of these phenomena [8]. The immune response plays an essential role in this transformation, mainly due to diverse cellular phenotypes [9]. This dynamic environment in the complex hepatic structure and intercellular communication produces an irreversible tissue fibrosis, cirrhosis, and, in many cases, hepatocellular carcinoma [10]. The participation of immune cells, such as Kupffer cells (KC) as initial effectors, is responsible for cirrhosis development [11,12], and they represent an immune cell population related to liver fibrosis treatment.

The resident liver macrophages and KC present diverse activation phenotypes: M1 related to inflammation and M2 anti-inflammation [13], both are regulated by extracellular signals, such as adenosine [14]. This activation has been described as a product of the signals related to inflammation and resolution of inflammation processes [15,16].

In liver diseases, the phenomenon, in a canonical way, occurs when

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http://dx.doi.org/10.1016/j.intimp.2017.10.019
Received 17 January 2017; Received in revised form 3 October 2017; Accepted 17 October 2017
1567-5769/ © 2017 Published by Elsevier B.V.

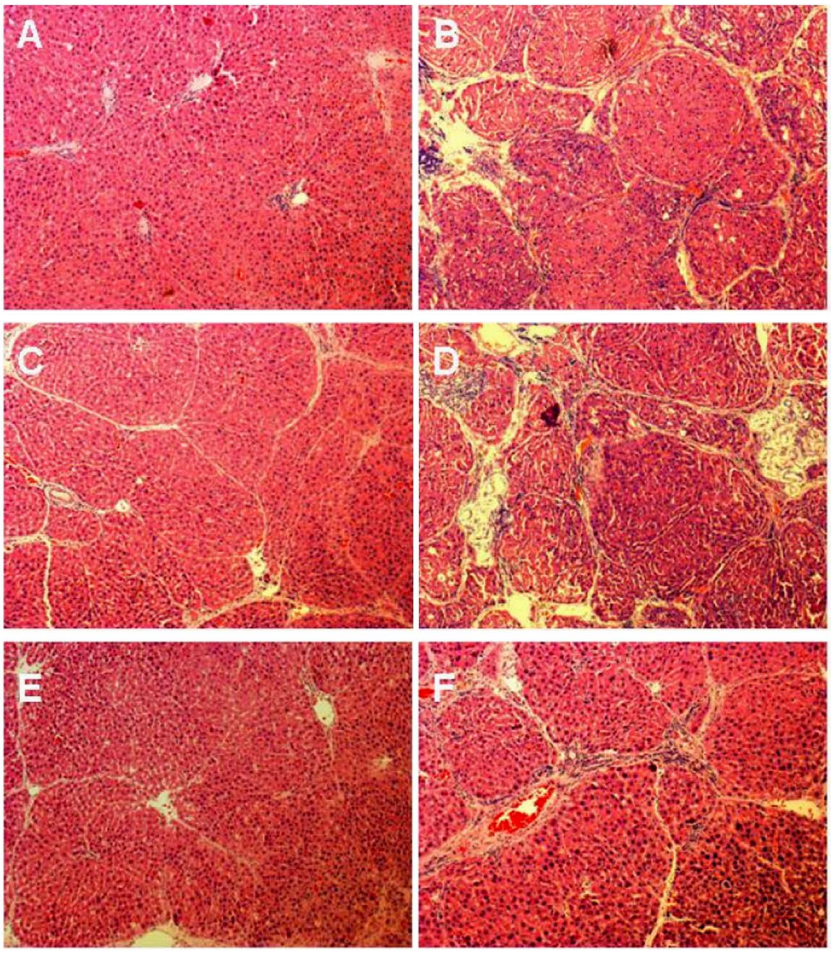

Fig. 1. Effects of IFC-305 on liver tissue samples stained with haematoxylin. (10X). (A) HC; (B) Ci; (C) Ci IFC 5w; (D) Ci SS 5w; (E) Ci IFC 10w; (F) Ci SS 10w.

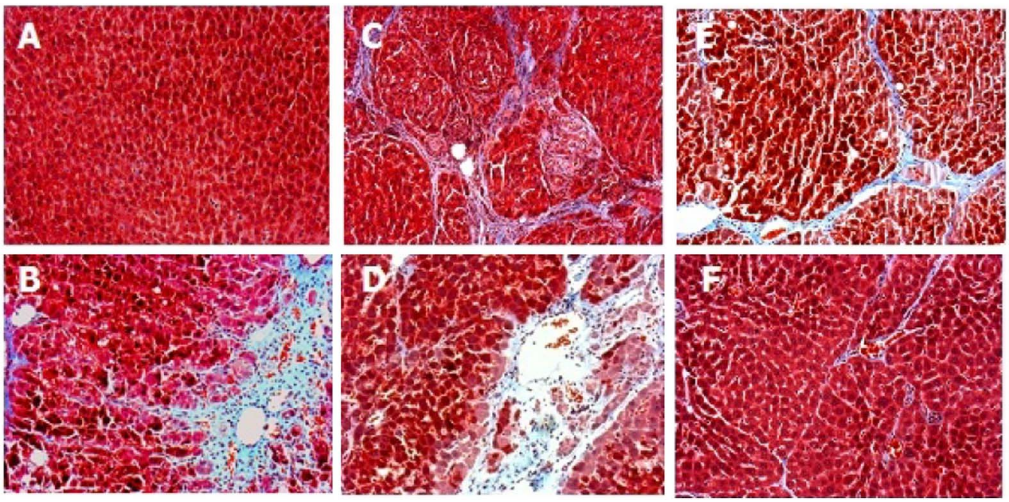

Fig. 2. Effects of IFC-305 on liver tissue samples stained with Masson's trichrome 10X. (A) HC, (B) Ci, (C) Ci SS 5w, (D) Ci SS 10w, (E) Ci IFC 5w, (F) Ci IFC 10w.

the activated Kupffer cells regulate the activation of hepatic stellate cells (HSC) and other molecular and cell interactions associated to the establishment of cirrhosis [17,18]. KC also interact with other cells, like neutrophils, hepatocytes, etc., mainly through molecules directly associated to inflammation and fibrosis, like cytokines and chemokines, such as IL-1β, IL-6, TNF-α, and MCP-1 [19]; KC could be contributing to anti-inflammatory effects with IL-10 and other cytokines involved in tissue repair [20]. Cytokines are hormone-like molecular mediators that are synthesized by a variety of cells in response to various stimuli, including inflammation and tissue damage. The liver is the main organ that produces and removes cytokines; all cell types in the liver, parenchymal and non-parenchymal, are capable of cytokines production [21,22].

Besides the knowledge of the pathological mechanisms involved, the therapeutic options for the treatment of liver diseases, such as cirrhosis, are limited. We have previously reported that the IFC-305 compound, an adenosine derivative salt, was shown to be able to reverse cirrhosis induced by CCl_4 in a rat model [23]. Part of these effects has been associated with the inhibition of HSC activation [24] and regulation of the cell cycle and the proliferative capacity of the liver

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