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Review

Liver immunotolerance and hepatocellular carcinoma: Patho-physiological mechanisms and therapeutic perspectives

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Abstract At the moment of the diagnosis of hepatocellular carcinoma (HCC), 70% of patients have only access to palliative treatments, with very few therapeutic options. Liver immunology is very specific, and liver immunotolerance is particularly developed because of the constant and massive influx of antigens. Deregulation of hepatic immunotolerance is implicated in chronic liver diseases development and particularly in liver carcinogenesis. For these reasons, HCC may be an excellent candidate for anticancer immunotherapies such as immune checkpoint inhibitors targeting CTLA-4 and PD-L1/PD-1. Nonetheless, because of the specific immune environment of the liver and the frequent association of HCC with hepatocellular insufficiency, the safety and the efficacy of these new treatments have to be properly studied in this situation. Thus, multiple phase II and III studies are in progress studying immune checkpoint inhibitor monotherapies, combination of different immunotherapies or local strategies such as transarterial chemoembolization combined with immune checkpoint inhibitors. Currently, only the final results of the tremelimumab phase II and the Nivolumab phase I/II study (CheckMate-040) are available. The latter is promising but need to be confirmed by the ongoing phase III studies to confirm the place of immunotherapy in the treatment of HCC. With many new molecular targets and therapeutic combination, immunotherapy represents a new hope in treating HCC patients although serious evaluation is still needed to confirm its interest.

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1. Introduction

Liver cancer is the second cancer-related death worldwide with 750,000 new cases of hepatocellular carcinoma (HCC) per year [1]. When diagnosed, 70% of the patients have only access to a palliative treatment [2,3]. Sorafenib is the only available first-line therapy, with an overall survival (OS) of 10.7 versus 7.9 months with placebo [4], and regorafenib is the first second-line treatment to show an OS benefit [5]. HCC is a very complex disease as more than 160 driver genes were described [6], and the liver constitutes a singular immune environment where immunotolerance is particularly developed. Because tumour initiation and progression are partially due to an escape to immunosurveillance system that fails to detect and destroy cancer cells [7], HCC seems to be a good candidate to immunostimulatory therapies aiming to restore anticancer immunity. These therapies are currently in full swing in HCC with the advent of monoclonal antibodies directed against immune checkpoints.

2. Hepatic immune tolerance and carcinogenesis

Due to intimate relationships with the digestive tract and its systemic filter role, the liver is constantly and massively exposed to many antigens [8]. Consequently, multiple mechanisms of immunotolerance have been developed to prevent autoimmune liver injuries [9].

2.1. Antigen-presenting system

In the liver, classic antigen-presenting cells (APCs) such as resident dendritic cells (DCs) are present, as well as liver-specific APCs such as hepatic stellate cells (HSCs), Kupffer cells (KCs) and more particularly liver sinusoidal endothelial cells (LSECs) [10]. These immune cells present innate immune function thanks to pattern recognition receptors (PPRs), which recognise specific bacterial antigens such as pathogen-associated molecular patterns and host antigens called damaged-associated molecular patterns [11]. PPRs can trigger interleukin (IL)-6-mediated pro-inflammatory responses while they can also decrease tumour necrosis factor (TNF) production by KCs [12] or promote tolerogenic signals through IL-10 secreted by KCs [13] and TGF-β secreted by both KC and LSEC [11] for protective purposes [9,14]. Moreover, as the name implies, these cells have antigen presenting functions. They express major histocompatibility complex (MHC) class-2 molecules, which will bind the T-cell receptor (TCR) [15], leading to CD4+ T-cell activation (also called T helper [T_H]-cells) [10]. Besides, APC expresses CD80 (B7-1) and CD86 (B7-2) ligands, which will activate CD4+ T-cells, through their CD28 receptor [15] (Fig. 1). CD4+ T-cell activation induces CD8+ T-cells (also called cytotoxic T [T_C]-cells) production by antigen cross-presentation [16]. Then, APCs such as LSECs will induce T-cell differentiation in memory T-cells to allow a strong and fast CD8+ T-cells reaction during further antigen exposure [17]. Nonetheless, KC and LSEC, through TGF-β secretion, will also induce CD4+ T-cell differentiation in regulatory T-cells or Tregs (CD4+, FOXP3+ and CD25+), which have an immunosuppressive role [18]. Interactions and mechanisms regulating the imbalance between CD4+ T-cells and Tregs pathways are still insufficiently characterised. Moreover, LSEC role in antigen-presenting is controversial as they also seem to be a key element of liver immunotolerance. They indeed promote immunosuppressive cytokines production by KC as IL-10 and prostaglandin-E2, which decrease MHC class-2 molecules and CD80-CD86 expression by LSEC, impairing their APC activity [19].

Some of these tolerogenic mechanisms are also involved in the remarkable immune tolerance, which can be developed in case of liver allograft, leading sometimes to the ending of immunosuppressive drugs [20,21]. Among these mechanisms, the local attenuation of alloreactive T-cell responses and the production of Treg seem essential [22,23]. Indeed, in a mouse model naturally failing to reject allograft, it was shown that the pharmaceutical inhibition of Tregs with an anti-CD25 therapy induced rejection and was associated with an increase of IL-10 and IL-2 production by graft-infiltrating T cells [24].

2.2. Immune checkpoints

Key factors called immune checkpoints have been described in immunotolerance mechanisms, whose deregulation is involved in chronic diseases pathogenesis and carcinogenesis.

Cytotoxic T-lymphocyte–associated protein 4 receptor (CTLA-4) is constitutively expressed on Tregs, activated T-cells and can also be expressed on naïve T-cells [25]. CTLA-4 has an immunosuppressive role by increasing T-cell differentiation in Tregs and by binding CD80-CD86 ligands on APC with a higher affinity than CD28 [26–28]. This will competitively reduce the CD28-mediated CD4+ T-cell activation and directly induce an intracellular immunosuppressive signals counteracting TCR stimulatory signalling [15,29,30] (Fig. 2A).

Programmed death receptor 1 (PD-1) and its ligands PD-L1/L2 (programmed cell death ligand 1/2) constitute also major factors of immunotolerance. PD-1 is expressed on CD4+ and CD8+ T-cells as well as B-cells and natural killer T-cells [16]. PD-L1 is expressed by KC [31], HSC [32], LSEC [17] and even hepatocytes [33]. PD-1 activation affects antigen-presenting function of LSEC, impairs T-cell activation through an increase of IL-10 secretion by resident DC, KC [16] and monocytes [34], and promotes T-cell differentiation in Tregs [35] (Fig. 2A).

Lymphocyte-activation gene 3 (LAG-3) is a CD4-like molecule, which decreases APC activity by binding their