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Original Article

Lipopolysaccharide promotes tumorigenicity of hepatic progenitor cells by promoting proliferation and blocking normal differentiation

Xiao-Yong Li [a, b, 1], Xue Yang [b, 1], Qiu-Dong Zhao [b, 1], Zhi-Peng Han [b], Lei Liang [a, b], Xiao-Rong Pan [a, d], Jing-Ni Zhu [b], Rong Li [b], Meng-Chao Wu [c, *], Li-Xin Wei [b, **]

[a] Soochow University, Suzhou, China
[b] Tumor Immunology and Gene Therapy Center, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai, China
[c] Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, 225 Changhai Road, Shanghai, 200438, China
[d] Mengchao Hepatobiliary Hospital of Fujian Medical University, Fuzhou, China

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ABSTRACT

Hepatic progenitor cells (HPCs) are bipotential stem cells that can differentiate into mature hepatocytes or biliary epithelial cells (BECs). They are thought to be involved in repair of liver injury and the incidence of hepatic carcinoma. Their physiology is closely associated with the microenvironment where they reside. Lipopolysaccharide (LPS), an important component of the hepatic pathological microenvironment, is stored in the liver and affects many types of cells in various hepatosis. HPCs may also be influenced by LPS. In this paper, mouse ED13.5 E-cadherin^{+} foetal liver cells were isolated as mouse hepatic progenitor cells (mHPCs). Proliferation of mHPCs was promoted under LPS conditions both in vivo and in vitro. Moreover, LPS enhanced colony formation ability of mHPCs, and blocked them differentiation into mature hepatocytes and formation of a bile duct-liked structure. More importantly, long-term treatment with LPS promoted tumorigenesis of mHPCs in nude mice. Thus, we conclude that LPS may promote aberrant proliferation of mHPCs and restrict their normal differentiation. Long-term exposure of mHPCs to LPS increased the risk of tumour formation. These data provide insight into the links between LPS, HPCs fate, and tumorigenesis, and present novel insight into the relationship between HPCs and their microenvironment.

Introduction

Hepatic progenitor cells (HPCs) are adult liver stem cells that are capable of self-renewal and differentiation into mature hepatocytes or biliary epithelial cells (BECs) [17,27]. In general, HPCs remains dormant until they are activated by a severe injury to the liver. They have been demonstrated to be involved in liver regeneration and injury repair. However, some studies have suggested that HPCs are the origin of liver cancer stem cells (CSCs) [1,2]. CSCs, a subpopulation of cancer cells endowed with self-renewal and differentiation capacities, have been suggested to be associated with tumorigenesis, tumour development, and prognosis. Based on their similar phenotype, normal stem cells were considered the resource of CSCs [44]. In the hematopoietic system and solid tissues with a high rate of cell turnover, stem cells have long been thought to be responsible for tumor formation [30,36,43]. Cancer is widely accepted to be a disease of stem cells, since they are the cells that persist in the tissue for a sufficient length of time to acquire the requisite number of genetic changes for neoplastic development [2]. Some liver cancer cells have been reported to express HPC markers [8]. Saha, S. K. et al. found that blocking hepatocyte differentiation promoted the occurrence of biliary cancer [35]. This

Abbreviations: LPS, lipopolysaccharide; HPCs, hepatic progenitor cells; mHPCs, mouse hepatic progenitor cells; BECs, biliary epithelial cells; CSCs, cancer stem cells; NSPCs, enteric neural stem/progenitor cells; TLR4, toll-liked receptor 4; DDC, 3, 5-diethoxycarbony-1, 4-dihydrocollidine; BDR, bile duct reaction; MFC CM, mouse embryonic fibroblasts condition medium; HDM, hepatocytes differentiation induced media; IHC, immunohistochemistry; IF, immunofluorescence; PAS, periodic-acid-schiff's stain; RT-PCR, real-time reverse transcription polymerase chain reaction.

* Corresponding author.
** Corresponding author. Tumor Immunology and Gene Therapy Center, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, 225 Changhai Road, Shanghai, 200438, China. Fax: +86 21 65566349.
E-mail addresses: 13817669673@163.com (M.-C. Wu), weilixin_smmu@163.com (L.-X. Wei).
[1] These authors contributed equally to this work.

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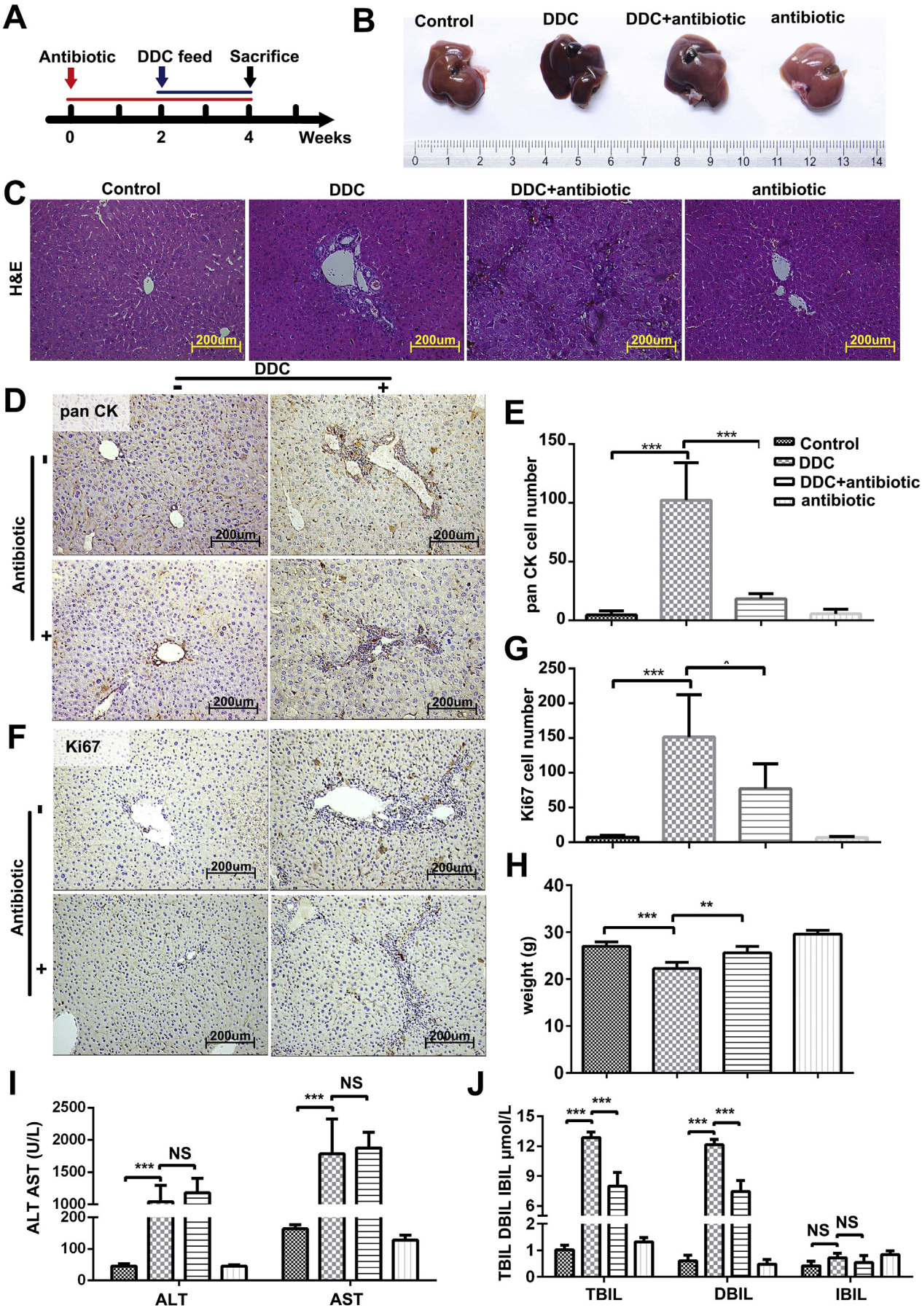
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