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Review

What fires prometheus? The link between inflammation and regeneration following chronic liver injury

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Abstract

Liver progenitor cells (LPCs) play a major role in the regeneration process after chronic liver damage, giving rise to hepatocytes and cholangiocytes. Thus, they provide a cell-based therapeutic alternative to organ transplant, the current treatment of choice for end-stage liver disease. In recent years, much attention has focused on unravelling the cytokines and growth factors that underlie this response. Liver regeneration following acute damage is achieved by proliferation of mature hepatocytes; yet similar cytokines, most related to the inflammatory process, are implicated in both acute and chronic liver regeneration. Thus, many recent studies represent attempts to identify LPC-specific factors. This review summarises our current understanding of LPC biology with a particular focus on the liver inflammatory response being associated with the induction of LPCs in the liver. We will describe: (i) the pathways of liver regeneration following acute and chronic damage; (ii) the similarities and differences between the two pathways; (iii) the liver inflammatory environment; (iv) the unique features of liver immunology as well as (v) the interactions between liver immune cells and LPCs. Combining data from studies on the LPC-driven regeneration process with the knowledge in the field of liver immunology will improve our understanding of the LPC response and allow us to regulate these cells in vivo and in vitro for future therapeutic strategies to treat chronic liver disease.

Keywords: Liver progenitor cell; Liver regeneration; Cytokine; Inflammation; T cell

Abbreviations: aFGF, acidic fibroblast growth factor; ALD, alcoholic liver disease; AFP, alpha-fetoprotein; APC, antigen presenting cells; CTL, cytotoxic T lymphocyte; DC, dendritic cells; dlk, delta-like protein-1; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HB-EGF, heparin-binding epidermal growth factor-like growth factor; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HSC, hepatic stellate cells; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; KC, Kupffer cells; KO, knockout; LIF, leukaemia inhibitory factor; LFA, leukocyte functional antigen; LPC, liver progenitor cell; LPS, lipopolysaccharide; LSEC, liver sinusoid endothelial cells; LT, lymphotoxin; MHC, major histocompatibility complex; mTOR, mammalian target of rapamycin; NFkB, nuclear factor kappa B; NK, natural killer; NKT, natural killer T; OSM, oncostatin M; PDGF, platelet-derived growth factor; PHx, partial hepatectomy; SDF1, stromal cell-derived factor-1; SMAD, Sma- and Mad-related protein; SOCS, suppressor of cytokine signalling; STAT, signal transducer and activator of transcription; TGF, transforming growth factor; Th, T helper; TLR, Toll-like receptor; TNF, tumour necrosis factor; TNFRI, tumour necrosis factor receptor I; Treg, regulatory T cell; TWEAK, tumour necrosis factor-like weak inducer of apoptosis; VCAM, vascular cell adhesion molecule.

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1. Introduction

1.1. Distinctive features of the liver

In many ways the liver is a special organ. First it carries out a wide range of functions in the body including metabolism and synthesis, detoxification and host defence, making it an important and vital organ. Second the liver has an enormous regeneration potential like no other organ in the body: it can completely restore its weight and architecture when reduced to 10% of its original mass. Unlike other tissues, e.g. muscle, this involves adult liver resident cells, not stem or progenitor cells. When this repair mechanism is impaired or exhausted, another cell type becomes involved in the regeneration process: the liver progenitor cell (LPC). Third although not considered a lymphoid organ, the liver performs complex immune functions that are differentially regulated from the well-studied immune responses triggered in lymphoid organs. Induction of tolerance against food antigens and allogenic liver transplants are some of the features that are still not well understood.