



Article

# Redox-Dependent Modulation of Human Liver Progenitor Cell Line Fate

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**Abstract:** Redox homeostasis is determinant in the modulation of quiescence/self-renewal/differentiation of stem cell lines. The aim of this study consisted of defining the impact of redox modifications on cell fate in a human hepatic progenitor line. To achieve this, the HepaRG cell line, which shows oval ductular bipotent characteristics, was used. The impact of redox status on the balance between self-renewal and differentiation of HepaRG cells was investigated using different methodological approaches. A bioinformatic analysis initially proved that the trans-differentiation of HepaRG toward bipotent progenitors is associated with changes in redox metabolism. We then exposed confluent HepaRG (intermediate differentiation phase) to oxidized (H<sub>2</sub>O<sub>2</sub>) or reduced (N-acetylcysteine) extracellular environments, observing that oxidation promotes the acquisition of a mature HepaRG phenotype, while a reduced culture medium stimulates de-differentiation. These results were finally confirmed through pharmacological modulation of the nuclear factor (erythroid-derived 2)-like 2 (NRF2), a principal modulator of the antioxidant response, in confluent HepaRG. NRF2 inhibition led to intracellular pro-oxidative status and HepaRG differentiation, while its activation was associated with low levels of reactive species and de-differentiation. In conclusion, this study shows that both intra- and extracellular redox balance are crucial in the determination of HepaRG fate. The impact of redox status in the differentiation potential of HepaRG cells is significant on the utilization of this cell line in pre-clinical studies.

**Keywords:** redox balance; HepaRG; liver regeneration

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## 1. Introduction

Stem cells rely on their capacity to maintain pluripotency, self-renew, or activate/differentiate to promote regeneration on intricate signals in their niches. Characterized by special regenerative properties, the liver is able to respond to different stimuli, activating several pathways for mass restoration: indeed, acute organ loss induces hepatocellular proliferation characterized by phenotypic fidelity (canonical pathway), while chronic hepatic injury may activate the trans-differentiation of parenchymal cells or activation of facultative progenitors (alternative pathways) [1,2]. In particular, this latter regenerative mechanism involves a bipotent cell line located in the smallest branches of the ductular tree (regenerative niche), capable of differentiating toward hepatocyte or biliary cell lineages [3–6].

To study regeneration and differentiation, the HepaRG cell line was used as an alternative to progenitors showing human oval ductular bipotent characteristics [7,8]. Indeed, confluent HepaRG cells supplemented with dimethyl sulfoxide (DMSO) are stimulated

# Modulation Of Liver Cell Expression

**M.P. Manns**



## **Modulation Of Liver Cell Expression:**

**Modulation of Liver Cell Expression** Werner Reutter,1987-01-01      **Modulation of Liver Cell Expression** ,1987

**Dietary Modulation of Gut Microbiota-X axis** Bowen Li,Yang Yuhui ,Francesca Bottacini,2025-10-24 The field of dietary modulation of gut microbiota has gained significant attention due to its profound impact on human health The gastrointestinal tract hosts a diverse community of microorganisms collectively known as the gut microbiota which plays a crucial role in regulating overall health Recent research has underscored the importance of these microbial communities in not only aiding digestion but also in bolstering the body s defense mechanisms against various illnesses A key aspect of this relationship is the gut microbiota s role as a primary regulator of peripheral organ health through multiple communication pathways This intricate network highlights the critical function of the gut microbiota in maintaining systemic well being and organ function Despite these advancements there remain gaps in understanding the complex interactions between diet gut microbiota and peripheral organs often referred to as the X axis Current studies have linked gut microbiota dysbiosis to numerous health conditions including inflammatory bowel disease rheumatoid arthritis and neurological disorders However more research is needed to fully elucidate these connections and develop effective interventions      *Cooperation of Liver Cells in Health and Disease* Z. Kmiec,2013-06-29 It is only during the last decade that the functions of sinusoidal endothelial cells Kupffer cells hepatic stellate cells pit cells and other intrahepatic lymphocytes have been better understood The development of methods for isolation and co culturing various types of liver cells has established that they communicate and cooperate via secretion of various intercellular mediators This monograph summarizes multiple data that suggest the important role of cellular cross talk for the functions of both normal and diseased liver Special features of the book include concise presentation of the majority of detailed data in 19 tables Original schemes allow for the clear illustration of complicated intercellular relationships This is the first ever presentation of the newly emerging field of liver biology which is important for hepatic function in health and disease and opens new avenues for therapeutic interventions      *Lap (NF-IL6) is a Modulator of Liver-specific Transcription and Hepatic Cell Proliferation* Martina Buck,1996      *Liver Growth and Repair* A. Strain,A.M. Diehl,2012-12-06 Nelson Fausto The Greek myth of Prometheus with its picture of a vulture feasting on its chained victim has traditionally provided a visual image of liver regeneration It is a powerful and frightening representation but if one were to substitute the vulture by a surgeon and Prometheus by a patient laying on a properly prepared operating table the outcome of the procedure would not differ significantly from that described by Greek poets Yet few of us who work in the field have stopped long enough to ask where this myth originated Did the poet observe a case of liver regeneration in a human being Was it brilliant intuition or perhaps literally just a gut feeling of a poet looking for good rhymes that led to the prediction that livers grow when part of the tissue is removed This book does not attempt to solve these historical issues It does instead cover in detail some of the major modern themes of research on liver regeneration injury and repair As indicated in

Dr N Bucher's chapter the modern phase of experimental studies on liver regeneration started in 1931 with the publication by Higgins and Anderson of a method to perform a two thirds resection of the liver of a rat. The technique described has 3 remarkable features: 1 it is highly reproducible resulting in the removal of 68% of the liver; 2 it has minimal if any mortality; and 3 it consists only of blood vessel ligation and does not involve cutting through or wounding hepatic tissue. *Liver Diseases (2 Vols.)* Shakir Ali, 2006-01-03. This book presents state of art information summarizing the current understanding of a range of liver diseases and reviews some key diagnostic and therapeutic advances. The book is a collection of selected clinical and scientific topics divided into two volumes each divided into two sections. The first volume treats the cellular biochemical and Hepatic Metabolism and Disposition of Endo- and Xenobiotics Karl-Walter Bock, 1991-06-30.

*Pathology of the Liver* Roderick N. M. MacSween, 1994. This text describes the basic mechanisms which operate in the normal and abnormal liver, the pathological and clinical features of disease and their histological appearance. The third edition includes a new chapter on pathological lesions that can develop after hepatic transplantation. *Cholestatic Liver Diseases* M.P. Manns, 1998-08-31. Many liver diseases may be associated with cholestasis and in some of them cholestasis is the leading symptom. This book the proceedings of Falk Symposium No 102 Part I of the Liver Week Freiburg 1997 gives an update on the anatomy, physiology and pathophysiology of bile formation and secretion. Significant progress has been achieved in recent years due to the application of molecular biology which led to the identification of the specific transporters involved in bile formation and secretion. Furthermore medical treatment in cholestatic liver diseases has made progress recently due to the introduction of ursodeoxycholic acid and other medical procedures. Finally cholestatic liver diseases are major indications for liver transplantation. Primary biliary cirrhosis has been the first disease where liver transplantation was shown to increase survival and improve quality of life. A completely separate but also heterogeneous group are patients with paediatric cholestatic liver diseases. Some of them are also treated with liver transplantation while in others genetic defects are being identified. The purpose of the symposium was to bring together well known scientists and clinicians from around the world to discuss the recent progress on the physiology and pathophysiology of bile formation and secretion. Furthermore the molecular basis of and the therapeutic developments in cholestatic liver diseases and its progress were discussed. This volume deals with most if not all modern aspects of cholestatic liver diseases with contributions on pathology, biochemistry, pharmacology, physiology, hepatology, immunology, paediatrics and last but not least surgery.

**Cumulated Index Medicus**, 2000. *Hepatic Fibrosis* Pablo Muriel, 2022-04-23. *Hepatic Fibrosis Mechanisms and Targets* is a complete volume of liver extracellular matrix biology including molecular signaling pathways, cells and factors that modulate fibrogenesis and fibrosis. The book uses an integrated approach toward the molecular and cellular mechanisms involved in the synthesis and degradation of hepatic fibrotic tissue, emphasizing the possible molecular targets to fight fibrosis. This important reference describes in detail and didactically the cellular and molecular events that are conducive to

fibrosis that leads to cirrhosis hepatocellular carcinoma and death The provided information allows readers to understand the molecular mechanisms of hepatic fibrogenesis to accelerate the development of new therapies Presents progression from inflammation to fibrosis with a special focus on the molecular mechanisms involved Didactically explains the participation of cells cytokines and factors in profibrogenic pathways Illuminates the causative participation of free radicals in liver fibrogenesis Explains the role of gut dysbiosis in chronic liver diseases leading to fibrosis Provides experimental models to study liver fibrosis and describes available noninvasive monitoring methods

**Trichothecene-induced Modulation of Cytokine Gene Expression in T Cells** Yanli Ouyang,1995

**Cholestasis** Paolo Gentilini,1994 Contains contributions dedicated to intracellular mechanisms leading to cholestasis The book emphasizes the plasma membrane in order to explain altered uptake and secretion of bile salts

**The Liver** Irwin M. Arias,James L. Boyer,2001 The first major text to link the discoveries of basic biology to the understanding and clinical management of liver diseases The Liver Biology and Pathobiology has long been a classic in gastroenterology and hepatology Now this landmark work has been thoroughly revised and updated to reflect recent groundbreaking achievements in the laboratory and clinic More than 100 world renowned investigators provide a definitive account of current concepts on the structure and function of the liver and the mechanisms underlying liver diseases This edition has been pared down to a smaller more user friendly size and focused more sharply on the most important advances A Brandon Hill recommended title

**Mechanisms of Immune Modulation by Transforming Growth Factor-** Susan C. McKarns,2001

**Modulation of 17[beta]-estradiol-induced Responses in Fish by Cytochrome P4501A1 Inducing Compounds** Michael James Anderson,1995

*Liver and Biliary Diseases* Neil Kaplowitz,1996

**The Journal of Cell Biology** ,1994 No 2 pt 2 of November issue each year from v 19 1963 47 1970 and v 55 1972 contain the Abstracts of papers presented at the Annual Meeting of the American Society for Cell Biology 3d 1963 10th 1970 and 12th 1972

*Culture of Epithelial Cells* R. Ian Freshney,1992-02-11 Designed for cell and molecular biologists this reference work covers many of the most commonly used epithelia It presents in a practical fashion the specific protocols for their cultivation and characterization

## The Enigmatic Realm of **Modulation Of Liver Cell Expression**: Unleashing the Language is Inner Magic

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