

The Role of Double Negative (CD⁴- CD⁸-) T Cells in Chronic Hepatitis B Virus Infection

Thesis

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List of Abbreviations

A nucleotide	Adenine nucleotide
ALPS	autoimmune lymphoproliferative syndrom
ALT	Alanine aminotransferase
Anti-HBc	Anti hepatitis B core antibody
Anti-HBs	Anti hepatitis B surface antibody
APC	Antigen presenting cell
CCRρ	chemokine receptor ρ
CD	Cluster of Differentiation
CMV	cytomegalo virus
CTL	Cytotoxic T lymphocyte
CTLA-ξ	Cytotoxic T-lymphocyte associated antigen- ξ
DC cell	Dendritic cell
DNT	double-negative T cells
DR	Direct repeats
EBV	Epstein-Barr virus
ER	Endoplasmic reticulum
FasL	Fas Ligand
FCERγ	Fragment crystallizable immunoglobulin E receptor gamm
FoxPρ	Forkhead/winged helix transcription factor on T _{reg} cells
GPCR	G-protein coupled receptor
GVHD	Graft-versus-host disease
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immune deficiency virus
HLA	Human leucocyte antigen
IDO	indole aminem ρ, ρ -dioxygenase
IFN	Interferon
IFN-α/β	Interferon alpha/beta

List of Abbreviations

IFN-γ	Interferon gamma
IL-γ	Interleukin- γ
IL-γR	Interleukin- γ receptor
LGL	Large granular lymphocyte
LN	Lymph node
LSEC	liver sinusoidal endothelial cells
mDC cell	Myeloid dendritic cell
MHC	major histocompatibility complex
mRNA	messenger RNA
NALT	nasal-associated lymphoid tissue
NK cell	Natural killer cell
NKT cell	Natural killer T cell
P gene	Polymerase gene
PCR	Polymerase chain reaction
PD-γ	Programmed death- γ
pDC cell	Plasmacytoid dendritic cell
PD-Lγ	Programmed death ligand- γ
PRR	Pattern recognition receptor
SLE	Systemic lupus erythematosus
TCR	T cell receptor
TGF- β	Transforming growth factor- β
Thγ cell	T helper- γ cell
Thγ cell	T helper- γ cell
TNF- α	Tumour growth factor- α
Treg cells	Regulatory T cells

List of Tables

<i>Table</i>	<i>Title</i>	<i>Page</i>
١	Geographical Distribution of HBV Genotypes	١٢
٢	Characteristics of Chronic Hepatitis B at Different Stages	٣٢
٣	The following table summarizes the various hepatitis B tests and their uses	٣٥
٤	The Phenotypes of Treg Subsets	٦٩
٥	Distinctive profile of expression of surface immune proteins by CD٤-٨- T cells	٧٨
٦	Comparison between cases and control regarding the age	١٠١
٧	Comparison between cases and control regarding the sex	١٠٢
٨	Comparison between cases and control regarding liver enzymes ALT and AST levels	١٠٣
٩	Comparison of the percentage of (DN) T Reg cells between cases and control	١٠٧
١٠	Comparison between replicating CHB group and non replicating group, as regard ALT levels	١٠٩
١١	Comparison between the replicating CHB group and the non replicating group, as regard the degree of viremia	١١٠
١٢	Comparison between the replicating CHB group and non replicating group, as regard the percentage of CD٤-CD٨- double (DN)T reg cells.	١١١
١٣	Comparison between CHB patients with mild viremia and with moderate to severe viremia regarding the percentage of (DN)T reg cells	١١٢
١٤	Comparison between CHB patients on treatment versus those who are not regarding the percentage of (DN)T reg cells	١١٣
١٥	Comparison of the percentage of (DN)T reg cells in CHB patients with different treatment duration	١١٣

List of Figures

<i>Fig.</i>	<i>Title</i>	<i>Page</i>
١	A simplified drawing and electron micrograph of the HBV particle and surface antigen	٥
٢	Representation of hepatitis B virus (HBV) genome	٦
٣	Domains of HBV surface proteins	٧
٤	The Replication cycle of HBV	١١
٥	Natural History of HBV Infection	٢٧
٦	The progression from acute to chronic HBV infection	٣٤
٧	Immunoregulatory functions of hepatic natural killer T (NKT) cells	٤١
٨	The cytokine/chemokine cascade through which NK cells recruit T cells	٤٣
٩	Cellular immune responses to HBV	٤٥
١٠	DCs are the most potent APCs	٤٧
١١	Schematic figure of how the B ^V -H ^١ / PD- ^١ pathway may mediate the exhaustion of virus-specific T cells in chronic HBV infection	٥٤
١٢	Causes of HBV-specific T-cell tolerance	٥٦
١٣	Different mechanisms of Treg suppressio	٦٣
١٤	Treg population in the peripheral blood	٧٠
١٥	Gender distribution in cases and control	١٠٢
١٦	BOX PLOT diagram comparing ALT levels between cases and control	١٠٤
١٧	BOX PLOT diagram comparing AST levels between cases and control	١٠٤
١٨	The percentage of (DN) T Reg cells among the control group	١٠٥
١٩	The percentage of (DN) T Reg cells among the cases group	١٠٦
٢٠	Correlation between the ALT level and percentage of (DN) T reg cells among patient group.	١٠٨
٢١	Correlation between the AST level and percentage of (DN) T reg cells among patient group	١٠٨

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List of Contents

	<i>Page</i>
List of abbreviations.....	I
List of tables.....	III
List of figures.....	IV
Introduction.....	١
Aim of the work.....	٣
Chapter I: Hepatitis B Virus Infection.....	٤
Chapter II: Regulatory T-cells (Tregs).	٥٧
Chapter III: Double Negative DN Treg cells Origin and development of DN Treg cells.....	٧٤
Subjects and Methods.....	٩٧
Results	١٠١
Discussion.....	١١٤
Summary	١٢٢
Conclusion.....	١٢٥
Recommendation.....	١٢٦
References.	١٢٧
Arabic summary.....	--



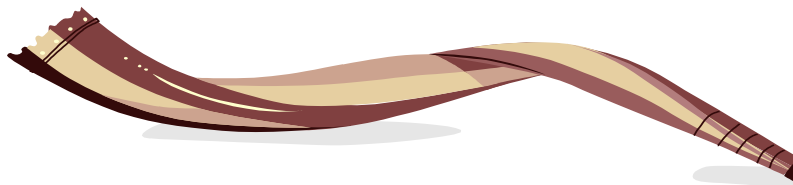
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سُبْحَانَكَ

قَالُوا سُبْحَانَكَ
لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا
إِنَّكَ أَنْتَ
الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم
الآية (٣٢) سورة البقرة

Introduction

Hepatitis B virus infection is a serious global health problem. It has been estimated that 350 million people worldwide are chronic hepatitis B carriers with nearly one million deaths per year (*Lavanchy, 2004*).

Hepatitis B is noncytopathic, DNA virus transmitted sexually, parenterally and from mother to fetus at birth (*Chisari, 1995*). Infection with hepatitis B virus leading to a wide spectrum of clinical presentation ranging from an asymptomatic carrier state to self-limited acute or fulminant hepatitis to chronic hepatitis with progression to hepatocellular carcinoma (HCC) (*Baumert et al., 2007*).

Hepatitis B virus clearance is mediated by a vigorous HBV specific, human leucocyte antigen (HLA) class I restricted cytotoxic T- lymphocytes (CTL) response (*Roh et al., 2001*). Thus, viral persistence or chronicity is associated with an inadequate CTL response to the virus (*Stoop et al., 2005*).

Recent studies have demonstrated that in peripheral lymphoid tissues of normal mice and healthy humans, 1% - 5% of alpha beta T cells receptors positive are CD4⁻ CD8⁺ double negative T cells which are capable of down regulating immune responses. However its origin and developmental pathway is still unclear (*Zhang et al., 2007*).

Double negative T regulatory (T reg) cells are capable of down regulating immune response via direct killing of effector T cells in an antigen specific manner, furthermore, double negative T reg cells have shown to develop regulatory mediated function by acquisition of MHC peptide complexes from antigen presenting cells (APCs). The presentation of allo-antigen on double negative T reg cells allows for specific interaction between double negative T reg cells and allo-antigen reactive T cells. Once the double negative T reg cells have come into contact, killing is then mediated by fas/ fas ligand interaction and perhaps through unidentified pathways (*Chen et al., 2004 and Fischer et al., 2005*).

In addition, double negative T reg cells secrete unique profile of cytokins including TGF- β and IL-10 (*Chen et al., 2004*). So, it is thought that double negative T cells have an important role in immunomodulatory function development of chronic hepatitis and have a role in virus *persistence* (*Zhang et al., 2007*).

Aim of the Work

The aim of this work is to evaluate the role of double negative T cells in chronic HBV infection as a cause of persistence and thus chronicity.

Hepatitis B Virus Infection

Hepatitis B virus infection (HBV) is a serious health problem worldwide. It is one of the most common infectious diseases globally. It is estimated that approximately 2 billion people have serological evidence of past or present infection with more than 1 million new infections occurring yearly. More than 300 million are chronic carriers of HBV and 100,000 to 1.2 million die from HBV infection annually (*Wright, 2007*).

HBV Structure:

HBV is a prototype member of the Hepadnaviridae family, Hepa from hepatotropic and dna because it is a DNA virus (hepatotropic DNA viruses). The mature virion, also known as Dane particle, is 42-48 nm in diameter consisting of an outer lipoprotein layer that encodes the viral envelope proteins, the hepatitis B surface antigen (HBsAg), and surrounds a nucleocapsid core, the hepatitis B core antigen (HBcAg), the nucleocapsid contains the viral genome and viral polymerase. The viruses replicate through RNA intermediate form by reverse transcription, and in this respect they are similar to retroviruses. Although replication takes place in the liver, the virus spreads to the blood (*Fig. 1*) (*Bergua et al., 2007*). In addition to the mature virions, HBV infected serum contains two other distinct subviral particles that are either spherical or filamentous in shape and are approximately 20 nm in width. Subviral particles reach a 100,000 fold higher