The Role of Double Negative (CD٤- CD٨-) 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
CCR٥	chemokine receptor ٥
CD	Cluster of Differentiation
CMV	cytomegalo virus
CTL	Cytotoxic T lymphocyte
CTLA-٤	Cytotoxic T-lymphocyte associated antigen-٤
DC cell	Dendritic cell
DNT	double-negative T cells
DR	Direct repeats
EBV	Epstein-Barr virus
ER	Endoplasmic reticulum
FasL	Fas Ligand
FCER١γ	Fragment crystallizable immunoglubulin E receptor gamm
FoxP٣	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 ٢،٣-dioxygenase
IFN	Interferon
IFN-α/β	Interferon alpha/beta

List of Abbreviations

IFN-γ	Interferon gamma
IL-٢	Interleukin-٢
IL-٢R	Interleukin-٢ 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-١	Programmed death-١
pDC cell	Plasmacytoid dendritic cell
PD-L١	Programmed death ligand-١
PRR	Pattern recognition receptor
SLE	Systemic lupus erythematosus
TCR	T cell receptor
TGF- ß	Transforming growth factor-ß
Th١ cell	T helper-١ cell
Th٢ cell	T helper-٢ cell
TNF- α	Tumour growth factor- α
Treg cells	Regulatory T cells

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أهمية الخلايا الليمفاوية تى المزدوجة السلبية(سى دى- ٤، سى دى-٨) في مرض الالتهاب الكبدي الوبائي المزمن ب

رسالة توطئة الحصول على درجة الماجستير في الباثولوجيا الإكلينيكية والكيميائية

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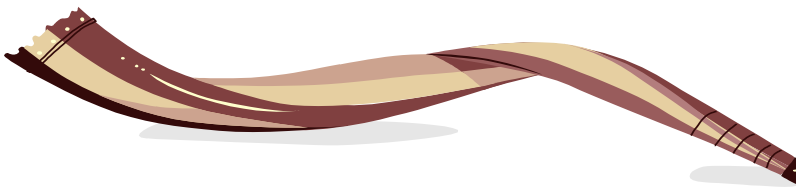

I would like to thank my husband who encouraged and supported me all the time, to him I dedicate this work.


قَالُوا سُبْحَانَكَ
لاَ عِلْمَ لَنَا
إِلاَّ مَا عَلَّمْتَنَا
إِنَّكَ أَنتَ
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 ٣٥٠ million people worldwide are chronic hepatitis B carriers with nearly one million deaths per year (***Lavanchy, ٢٠٠٤).***

Hepatitis B is noncytopathic, DNA virus transmitted sexually, parenteraly and from mother to fetus at birth ***(Chisari, ١٩٩٥)***. 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., ٢٠٠٧)***.

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., ٢٠٠١)***. Thus, viral persistance or chronicity is associated with an inadequate CTL response to the virus ***(Stoop et al., ٢٠٠٥).***

Recent studies have demonstrated that in peripheral lymphoid tissues of normal mice and healthy humans, ١٪ - ٥ % of alpha beta T cells receptors positive are CD٤- CD٨- double negative T cells which are capable of down regulating immune responses. However its origin and developmental pathway is still unclear ***(Zhang et al., ٢٠٠٧)***.

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., ٢٠٠٤ and Fischer et al., ٢٠٠٥)***.

In addition, double negative T reg cells secrete unique profile of cytokins including TGF-β and IL-١٠ (***Chen et al., ٢٠٠٤)***. 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., ٢٠٠٧)***.

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 ٢ billion people have serological evidence of past or present infection with more than ٥٠ million new infections occurring yearly. More than ٣٥٠ million are chronic carriers of HBV and ٥٠٠،٠٠٠ to ١,٢ million die from HBV infection annually ***(Wright, ٢٠٠٦)***.

HBV Structure:

HBV is a prototype member of the Hepadnaviridae family, Hepa from hepatotrophic and dna because it is a DNA virus (hepatotropic DNA viruses). The mature virion, also known as Dane particle, is ٤٠-٤٢ 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.) (Bergua et al.,)***. 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 ٢٠ nm in width. Subviral particles reach a ١٠،٠٠٠ fold higher