THE ROLE OF CIRCULATING CD4+CD25HIGH REGULATORY T CELLS IN CHRONIC HEPATITIS B VIRUS INFECTION

Thesis

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SUMMARY

There are more than 2 billion individuals with serological evidence of HBV infection worldwide. Of these 400 million are chronic carriers and 500,000 to 1.2 million die annually from cirrhosis and HCC. HBV infection has serious consequence such as chronic hepatitis, cirrhosis and HCC that ultimately causes death of infected persons.

Many studies have confirmed that the pathogenesis of HBV is largely due to the host immune system particularly the cellular immune response.

Regulatory T cells represent about (5-10%) of CD4 T cells known as suppressor T cells. Their major role is to shut down T cell –mediated immunity toward the end of an immune reaction and to suppress auto-reactive T cells. Two major classes of CD4 regulatory T cells have been described, naturally occurring T regulatory cells and adaptive T regulatory cells.

Regulatory T cells, are crucial for the maintenance of immunological tolerance.

There is increasing evidence that $CD4^{+}CD25^{+}$ T Reg contribute to the immunological hyporesponsiveness against several pathogens including HBV, resulting in chronic infection.


بسم الله الرحمن الرحيم
وَأَنْزَلَ اللهُ
عَلَيْكَ الْكِتَابَ
والْحِكْمَةَ
وَعَلَّمَكَ مَا لَمْ
تَكُنْ تَعْلَمُ
وَكَانَ فَضْلُ
اللهِ عَلَيْكَ
عَظِيمًا
صدق الله العظيم
سورة النساء آية

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LIST OF ABBREVIATIONS

Abbrev.	Full term
ALT	Alanine aminotransferase
Anti-HBc	Anti hepatitis B core antibody
Anti-HBs	Anti hepatitis B surface antibody
A nucleotide	Adenine nucleotide
APC	Antigen presenting cell
CD	Cluster of Differentiation
cccDNA	covalently closed circular DNA
CTL	Cytotoxic T lymphocyte
CTLA-4	Cytotoxic T-lymphocyte associated antigen-4
DC cell	Dendritic cell
DR	Direct repeats
ER	Endoplasmic reticulum
FasL	Fas Ligand
FoxP3	Forkhead/winged helix transcription factor on T_{reg} cells
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
HSPGs	Heparan sulphate proteoglycanes
IFN	Interferon
IFN-α/β	Interferon alpha/beta

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Full term
IFN-γ	Interferon gamma
IL-2	Interleukin-2
IL-2R	Interleukin-2 receptor
IPEX	Immune dysregulation, polyendocrinopathy, enteropathy X-linked syndrome
LGL	Large granular lymphocyte
LN	Lymph node
mDC cell	Myeloid dendritic cell
moDC cell	Monocyte derived dendritic cell
mRNA	messenger RNA
NK cell	Natural killer cell
NKT cell	Natural killer T cell
NS2 protein	Non-structural 2 protein
PAMPs	Pathogen associated molecular pattern
PCR	Polymerase chain reaction
pDC cell	Plasmacytoid dendritic cell
PD-1	Programmed death-1
PD-L1	Programmed death ligand-1
PEG-IFN	Pegylated interferon
P gene	Polymerase gene
PRR	Pattern recognition receptor
TCR	T cell receptor
TGF- ß	Transforming growth factor-ß
TNF- α	Tumour growth factor- α
T nucleotide	Thymine nucleotide
Th1 cell	T helper-1 cell
Th2 cell	T helper-2 cell
Treg cells	Regulatory T cells

INTRODUCTION

Hepatitis B virus (HBV) infection is a major threat worldwide with a particularly high prevalence in Asia & Africa, approximately 400 million people suffer from chronic hepatitis B infection. This includes 350 million chronic carriers of the virus ***(Xue-Ping et al., 2010).***

Transmission of hepatitis B virus results from exposure to infectious blood or body fluids. The acute illness causes liver inflammation, vomiting, jaundice and rarely death. Chronic hepatitis B may eventually cause liver cirrhosis and liver cancer, a fatal disease with very poor response to current chemotherapy. The infection is preventable by vaccination ***(Barker et al., 1996).***

Many studies have confirmed that the pathogeneses of HBV is largely due to the host immune system particularly the cellular immune response ***(Xue-Ping et al., 2010).***

Regulatory T cells represent about (5-10%) of CD4 T cells in human, formerly known as suppressor T cells. Their major role is to shut down T cell –mediated immunity toward the end of an immune reaction and to suppress auto-reactive T cells that escaped the process of negative selection in the thymus ***(William et al., 2004).***

Two major classes of CD4 regulatory T cells have been described naturally occurring T regulatory cells (CD4,CD25 T regulatory cells) arise in the thymus and adaptive T regulatory cells (Th3cells) may originate during a normal immune response ***(Barton et al., 2000).***

It is suggested that increase frequency of CD4(+) CD25(high) T regs may inhibit the cellular immune response against HBV and affect viral clearance, leading to the persistence of chronic HBV infection ***(Schwarz and Bhandoola, 2006).***

AIM OF THE WORK

The aim of this study is to analyze the frequency of circulating CD4(+) CD25(+)^{high} T regulatory cells in patients with chronic hepatitis B and assess its role in virus persistence.