IMMUNE RESPONSE IN TUBERCULOSIS

Essay

Submitted for fulfillment of master degree
In
Medical Microbiology and Immunology

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2008

وقُل ربــي زدنــي علما

صدق الله العظيــم

" سورة طــه آية رقم ١١٤ "

ABSTRACT

Tuberculosis is a major cause of human morbidity and mortality. Host Immune response against tuberculosis involves both the innate and adaptive immune responses. Macrophage represents both the victim and the accused in immune response against tuberculosis. Critical differences exist between adults and children immune response to *M. tuberculosis.* HIV infection remains the most common risk factor for the development of active TB. A vaccine is considered to be the best solution for controlling TB.

KEY WORDS

Tuberculosis, immune response, macrophage, T lymphocytes, HIV, vaccines.

ACKNOWLEDGEMENTS

I would like to express my deep gratitude and cardinal appreciation to ***Prof. Dr. Hala Mohamed Safouh*** *Professor of Medical Microbiology and Immunology, Faculty of Medicine, Cairo University, for her kind guidance, constant encouragement and generous supervision throughout this work.*

I would like to extend my deepest and special appreciation to ***Dr. Iman Ezzat Wali*** *Lecturer of Medical Microbiology and Immunology, Faculty of Medicine, Cairo University, for her great support, close supervision and experienced advice.*

I would like to acknowledge all the professors and lecturers in the department of Medical Microbiology and Immunology, Faculty of Medicine, Cairo University.

Finally I would like to convey my sincere love to my husband, daughters, and my parents.

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LIST OF ABBREVIATIONS

1, 25 $(OH)_2$ D3	1, 25 dihydroxy vitamin D 3
Ag 85 B	Antigen 85 B
AIDS	Acquired immune deficiency syndrome
APC	antigen presenting cell
BCG	Bacillus Calmette- Guérin
C3	Complement factor 3
Ca MK II	Ca2+/calmodulin-dependent kinase II
CCR 2	Chemokine receptor 2
CFP – 10	10 KDa culture filtrate protein
CFU	Colony forming unit
CR 3	Complement receptor 3
DC	Dendritic cell
DC – SIGN	Dendritic cell – specific intercellular – adhesion – molecule – grabbing – non integrin
EEA1	Early endosomal antigen 1
ELISA	Enzyme linked immune sorbent assay
ER	Endoplasmic reticulum
ESAT – 6	6 KDa early secretory antigen target
FAS	Factor of apoptotic signal
FASL	FAS ligand
FGF – 2	Fibroblast growth factor 2
$FoxP_3$	Fork head box P3
GM – CSF	Granulocyte/macrophage colony stimulating factor
HAART	Highly active anti retroviral therapy
HBD – 2	Human beta defensin 2
HIV	Human immune deficiency virus
HLA	Human leucocytic antigen

HNP – 1	Human neutrophil defensin peptide 1
HNP – 2	Human neutrophil defensin peptide 2
IFN – γ	Interferon gamma
Ig	Immunoglobulin
IL	Interleukin
IL – 1R	Interleukin 1 receptor
IL – 1RA	Interleukin 1 receptor antagonist
iNOS	Inducible nitric oxide synthase
IRAK	Interleukin 1 receptor associated kinase
IRIS	Immune reconstitution inflammatory syndrome
LAM	Lipo Arabino mannan
LAMP1	lysosomal-associated membrane protein-1
LBPA	Lysobisphosphatidic acid
LPS	Lipopoly saccharide
LTBI	Latent tuberculosis infection
M. bovis	*Mycobacterium bovis*
M. tuberculosis	*Mycobacterium tuberculosis*
ManLAM	Mannose capped Lipo Arabino mannan
mBD – 3	Murine beta defensin 3
mBD – 4	Murine beta defensin 4
MBL	Mannose binding lectin
MBP	Mannose binding protein
MCP	Monocyte chemotactic protein
MHC	major histocompatibility complex
MIF	Macrophage migration inhibitory factor
MIP	Macrophage inflammatory protein
MR	Mannose receptor
Mtb	*Mycobacterium tuberculosis*

MyD88	myeloid differentiation protein 88
NF-κB	nuclear factor-κB
NK	Natural killer
NO	Nitric oxide
NRAMP – 1	Natural resistance associated macrophage protein 1
PAF	Platelet activating factor
PAS	Para amino salt of aspirin
PBMC	Peripheral blood mononuclear cells
PI(3)P	Phosphatidyl inositol 3 phosphate
PKnG	Protein kinase G
PPD	Purified protein derivative
RANTES	Regulated on activation, normal T expressed and secreted
rBCG	Recombinant Bacille-Calmette- Guérin
rBCG – pfo	Recombinant Bacille-Calmette- Guérin perfringolysin
S1P	Sphingosine 1 phosphate
SATVI	South African tuberculosis vaccine initiative
SLC11A1	solute carrier family 11, member 1
SOD	Superoxide dismutase
TAP	Transporter associated with antigen presentation
TB	Tuberculosis
TGF - β	Transformation growth factor beta
Th1	T helper lymphocyte 1
Th2	T helper lymphocyte 2
TLRs	Toll like receptors
TNF - α	Tumour necrosis factor alpha
TNFR	Tumour necrosis factor receptor
T_{reg}	Regulatory T lymphocytes

TST	Tuberculin skin test
Tγδ	T gamma delta lymphocyte
UreC	Urease gene
VDR	Vitamin D receptor
VEGF	Vascular endothelial growth factor
WHO	World health organization
XDR – TB	Extensively drug resistant TB

INTRODUCTION AND AIM OF WORK

Tuberculosis (TB) remains the single largest infectious disease causing high human mortality leading to 3 million deaths annually. A clear understanding of the immune responses towards the pathogen will be important for achieving optimal immunity, vaccine development, new therapeutic targets, and more precise diagnostic methods for combating this terrible illness **(Skeiky and Sadoff, 2006).**

Genome studies on families affected with tuberculosis have enabled the identification of several candidate genes, human leucocytic antigen (HLA) and non HLA genes that are associated with susceptibility to TB **(Bellamy et al., 2000).**

Essential to effective TB immunity are functioning neutrophils, natural killer (NK) cells, dendritic cells (DCs), mast cells, definsins, and epithelial cells **(Bals, 2004).**

The macrophage is the primary main host cell for *Mycobacterium tuberculosis* (*M. tuberculosis)* **(Means et al., 2001),** and activated macrophages represent a link between innate and cell mediated immunity **(Hestvik et al., 2005).**

Various aspects of macrophage-mycobacterium interactions and the role of macrophage in host response have been discovered, such as binding of *M. tuberculosis* to macrophages via surface receptors, phagosome-lysosome fusion, mycobacterial growth inhibition/killing mechanisms **(Raja, 2004).**

Macrophage apoptosis occurs within the granuloma. This histological process favors host immunity, but *M. tuberculosis* is capable of partially suppressing it. The pro- and anti-apoptotic activities of *M. tuberculosis* may be necessary to establish a persistent infection **(Briken et al., 2004).**

It has become evident that autophagy serves as a powerful mechanism for removal of *M. tuberculosis* infection **(Deretic, 2005).**

The T cell response to *M. tuberculosis* is a complex event which involves a variety of T cell subsets (CD4+ T cells, CD8+ T cells, gamma/delta (γδ) T cells and regulatory T (T_{reg}) cells) involving a combination of protection, cytolysis, and memory immunity **(Keshinro and Diul, 2006),** together with strong T helper 1 (Th1) type T cell immunity, and relative absence of T helper 2 (Th2) type T cell immunity **(Vesosky et al., 2006).**

TB is the commonest opportunistic infection occurring among human immune deficiency virus (HIV) positive persons, with a higher proportion of extra pulmonary or disseminated disease as well as higher frequency of false negative tuberculin skin test (TST) cases **(Rosas-Taraco et al., 2006).**

Critical differences exist between adult and children as regards their TB immunity including deficiencies in macrophages and DCs function, deficiencies in the development of Th1 response to *M. tuberculosis* and the propensity for children to develop Th2 response **(Lewinsohn et al., 2004).**

Although Bacillus Calmette- Guérin (BCG) seems to provide protection against disseminated disease in newborns and children, its efficacy against pulmonary TB in adults is poor, which highlights the need for a better vaccine regimen. Such vaccines include recombinant BCG (rBCG), attenuated strains of *M. tuberculosis,* subunit vaccine approaches and live, non-replicating viral vector-based delivery systems used alone or in prime–boost regimens. A challenge facing the development of these new vaccines is their safety **(Skeiky and Sadoff, 2006).**