A Possible Role in Immune Response Modulation after Autologus Bone Marrow Stem Cell Transplantation in Type 1 DM

Thesis

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بسم الله الرحمن الرحيم

وأنـزل الله عـليك
الكتاب والحكمة
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صدق الله العظيم

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Hanan Mahmoud Ali Mahmoud

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List of Abbreviations

AAgs   : Antibodies to islet autoantigens

ACE   : Angiotensin-converting enzyme

AD   : Autoimmune disease

ADA   : American Diabetes Association

ADSCs   : Adipose tissue derived stromal cells

AGEs : Advanced glycation end products

AHSCT   : Hematopoietic stem cell transplantation

ALL   : Acute lymphoblastic leukemia

ALT   : Alanine Amino transferase

AML   : Acute myeloid leukemia

APC   : Antigen-presenting cells

ARBs   : Angiotensin receptor blockers

ASCs   : Adult stem cells

ASCT : Autologous stem cell transplantation

ASL   : Amyotrophic lateral sclerosis

AST   : Aspartate Amino transferase

BM   : Bone marrow

BR   : Breast cancer

BW   : Balance Weight

CBC   : Complete blood count

CHD   : Chronic heart disease

CLL   : Chronic lymphocytic leukemia

CML   : Chronic myeloid leukemia

CNS   : Central nervous system

CRC   : Colorectal cancer

CRP   : C-reactive protein

List of Abbreviations *(Cont...)*

CV	: Cardiovascular
CVD	: Cardiovascular disease
CY	: Cyclophosphamide
DAG	: Diacylglycerol
DCCT	: Diabetes control clinical trial
DCs	: Activated dendritic cells
DCs	: Dendritic cells
DKA	: Diabetic ketoacidosis
DLI	: Donor's lymphocyte infusion
DM	: Diabetes mellitus
DMARDs	: Disease-modifying anti-rheumatic drugs
DMD	: Duchenne muscular dystrophy
DOPA	: Dopamine precursor
DPP-4	: Dipeptidyl peptidase-4 inhibitors
EBMT	: European Bone Marrow Transplantation
EF	: Ejection fraction
ESCs	: Embryonic stem cells
FISH	: Fluorescence in situ hybridization
FISH	: Fluorescence in situ hybridization
FPG	: Fasting plasma glucose
GAD	: Glutamic acid descarboxilase
GAPDH	: Glyceraldehyde 3-phosphate dehydrogenase
G-CSF	: Granulocyte colony-stimulating factor
GD	: Gestational Diabetes
GFAT	: Glucosamine-glutamine, fructose-6-phosphate amidotransferase

List of Abbreviations *(Cont...)*

GLUTs	: Glucose transporters
GSH	: Glutathione
GVHD	: Graft-versus-host disease
GVT	: Graft versus tumor
HbA1c	: Haemoglobin A1C
HCL	: Hydrochloric acid
HD	: Huntington's disease
HDC	: High dose chemotherapy
HHS	: hyperosmolar hyperglycemic state
HLA	: Human leukocyte antigen
HSCs	: Haematopoietic stem cells
ICA	: Islet cell antibody
ICM	: Inner cell mass
IFG	: Impaired fasting BG
IFN-γ	: gamma interferon
IgG	: Immunoglobin G
IHA	: Immune haemolytic anemia
IL	: Interleukin
ITP	: Immune thrombocytopenia purpura
JIA	: Juvenile idiopathic arthritis
KLAT	: Keratolimbal allograft transplantation
LC	: Lung cancer
LDH	: Lactate dehydrogenase
LSCD	: Limbal SC deficiency
MAPK	: Mitogen-activated protein kinase

List of Abbreviations *(Cont...)*

MF	: Macrophages
MHC	: Major histocompatibility complex
MI	: Myocardial infarction
Mo	: Monocytes
MODY	: Maturity-onset diabetes of the young
MS	: Multiple Sclerosis
MSC	: Mesenchymal stem cells
NADPH	: Nicotinamide adenine dinucleotide phosphate
NF	: Nuclear factor
NOD	: Non-obese diabetic
OA	: Osteoarthritis
OC	: Ovarian cancer
OGTT	: Oral glucose tolerance test
PCR	: Polymerase chain reaction
PD	: Parkinson's disease
PD	: Processing Disposable(s)
PDGF	: Platelet-derived growth factor
PMN	: Polymorphonuclear
PPMS	: Primary progressive MS
RA	: Rheumatoid arthritis
RAGE	: Receptor for AGE
RCC	: Renal cell cancer
RICT	: Reduced intensity conditioning regimens
RIST	: Reduced-intensity SC transplantation
ROS	: Reactive oxygen species
SC	: Cesarean section

List of Abbreviations *(Cont...)*

SCLC : Small cell lung carcinoma

SDH : Sorbitol dehydrogenase

SF : Synovial fluid

SLE : Systemic lupus erythematosus

SPMS : Secondary progressive MS

SSc : Systemic sclerosis

T1DM : Type 1 diabetes mellitus

Th : T helper

TLRs : Toll-like receptors

TMB : Tetra methyl benzidine

TNF : Tumour necrosis factor

TNF-β : Tumor necrosis factor beta

TZDs : Thiazolidinediones

UCB : Umbilical cord blood

UCE : Umbilical cord blood

UCE : Umbilical cord epithelium

UTI : Urinary tract infection

2hPG : 2-hour plasma glucose

α : Alpha

β : Beta

γ : Gamma

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Introduction

Type 1 DM comprises only 5% to 10% of all diabetic etiologiesbut is associated with a high frequency of vascular complicationsand compromises quality and expectancy of life*(Rubin and Peyrot, 1999)*.Combination of genetic, immunologic, and non genetic factors contributes to the onset and progression of Type 1 DM *(Atkinson and Maclaren, 1994; Lipton et al., 1992)*. Specific HLA antigens, in particular DR3 and DR4, have been associated with increased risk for Type 1 DM development *(Lipton et al., 1992; Barbesion et al., 1997)*, while DR2 alleles generally have been described as "protective" of Type 1 DM *(Thorsby and Ronningen 1993)*. In addition to HLA predisposing factors, viral infection, psychological factors, and dietary factors have been described as predisposing factors *(Beyhum et al., 1997; Robinson and Fuller, 1985)*.

Pathologically autoimmune diabetes is characterized by mononuclear cell infiltration into the pancreatic islets, termed insulinitis. These mononuclear cells consists of CD4 + and CD8+ T cells, B cells, NK cells, and macrophages *(Kawamoto et al., 2001)*. B-cells are among the earliest cells to infiltrate the pancreatic islets of NOD mice, and auto antibodies against islet antigens indicate disease onset in humans and mice. Despite this, autoantibody production is not sufficient to initiate disease and is disconnected from the occurrence of diabetes and insulitis *(Lehuen et al., 1990)*. Rather, B-cells are multifunctional and are crucial antigen-presenting cells (APCs)

for priming proinflammatory T-cell responses to β-cell antigens *(Bouaziz et al., 2007)* Transient B-cell depletion after the first signs of disease onset using anti-BLyS mAb also arrests diabetes progression and maintains NOD mice in a "honeymoon" state for extended periods *(Zekavat et al., 2008).* However, in general, T lymphocytes play the most pivotal role in initiating the disease process *(Sempe et al., 1991).*

In 1986, *Mosmann et al* reported that upon activation CD4+ T cells will differentiate into two distinct T helper (Th) cell clones expressing distinct cytokine profiles and effector functions, thus giving rise to a unifying Th1/Th2 paradigm. Central to this are the specific requirements for induction of Th1 and Th2 activities, including the nature of APC (macrophages, dentritic cells, or B cells) *(Macatonia et al., 1993; Duncan and Swain 1994)*, strength of TcR binding to processed antigen, and Th1 and Th2 cytokines *(Romagnani, 1995)*. Th1 cells produce IL-2 and gamma interferon (IFN- γ), while Th2 cells produce IL-4, IL-5, IL-10, and IL-13 *(Robinson and Fuller, 1985)*.

Th0 cells, which produce both Th1 and Th2 cytokines, are generally regarded as precursors for Th1 and Th2 cells, being swayed into differentiating into either pathway in response to external stimuli and also in response to Th1 and Th2 cytokines *(Swain et al., 1990; Sad and Mosmann 1994)*.

Th1 cytokines induce Th1 activity and block Th2 activity *(Hsieh et al., 1993)*, whereas Th2 cytokines promote Th2