Interleukin 7:
A Proposed Role in Primary Immune Thrombocytopenia

Thesis

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Dedication

My special thanks are dedicated to my Mother, Father, my brothers and my lovely sister for their endless support to me, and for pushing me forward all the time.

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List of Contents

List of Tables

Table No. Title

List of Figures

List of Abbreviations

Abb	Full Term
AA	Aplastic Anemia
ADAM TS	A Disintegrin And Metalloprotease with Thrombospondin
ADP	Adenosine Diphosphate
ANA	Antinuclear antibodies
aPTT	Activated partial thromboplastin time
ATG	Antithymocyte globulin
ATIII	Antithrombin III
ATP	Adenosine triphosphate
BFU-MK	Burst-forming unit-megakaryocyte
BFU-MK	MK burst-forming unit
BUN	Blood urea nitrogen
CAMT	Congenital Amegakaryocytic Thrombocytopenia
CBC	Complete blood count
CFU-GEMM	Colony-forming unit
CFU-MK	Colony-forming unit-megakaryocyte
CMP	Common myeloid progenitor
CV	Coefficients of variation
CXCR4	Chemokine type 4 receptors
DIC	Disseminated Intravascular Coagulopathy

DITP	Drug-induced thrombocytopenia
DMS	Demarcation membrane system
EDTA	Ethylene diamine tetra acetic acid
ELISA	Enzyme-linked immunosorbent assay
FDP	Fibrin degradation products
GDP	Guanosine diphosphate
GP	Glycoprotein
GTP	Guanosine triphosphate
HCV	Hepatitis C virus
HIPA	Heparin-induced platelet aggregation test
HIT	Heparin -induced thrombocytopenia
HIV	Human immune deficiency virus
HLA	Human leukocyte antigens
HPA	Human Platelet Antigen-1a
HSC	hematopoietic stem cell
HUS	Haemolytic uraemic syndrome
HUS	Hemolytic uremic syndrome
IC	Intracranial
Ig	Immunoglobulin
IL7	interleukin 7
IL8	interleukin 8
ITP	Idiopathic Thrombocytopenic Purpura
IWG	International Working Group
KMS	Kasabach-Merritt Syndrome
LDH	Lactate Dehydrogenase
MHC	Major histocompatibility complex
MPV	Mean platelet volume
NAIT	Neonatal alloimmune thrombocytopenia
NAP-2	Neutrophil activating peptide 2
No	Nitric oxide

PAF	Platelet activating factor
PAI-1	Plasminogen activator inhibitor-1
PCR	Polymerase chain reaction
PDGF	Platelet-derived growth factor
PF4	Platelet factor 4
PGI2	Prostaglandin I2
POP	Post transfustion purpura
PT	Prothrombin time
PTP	Post transfusion purpura
SCCS	Connected canalicular system
SLE	Systemic lubus erythrematosis
TF	Transcription factors
TFPI	Tissue factor pathway inhibitor
TGF-ß	Transforming growth factor-ß
TMA	Thrombotic microangiopathies
tPA	Tissue plasminogen activator
TPO	thrombopoietin
TSH	Thyroid stimulating hormone
TSP1	Thrombospondin-1
uPA	Urokinase plasminogen activator
VEGF	Vascular endothelial growth factor
VWF	von Willibrand factor
TSLP	Thymic stromal lymphopoietin
RT-PCR	Reverse transcription polymerase chain reaction
PBMCs	Peripheral blood mononuclear cells
BMNCs	Bone marrow mononuclear cells
IFN-g	Interferon-g
TNF-a	Tumor necrosis factor-a

CTL	Cytotoxic T lymphocyte
GWAS	Genome wide association studies
MS	Multiple sclerosis
T1D	Type 1 diabetes
RA	Rheumatoid arthritis
IBD	Inflammatory Bowel Disease
ROC	Receiver operating characteristic curve
Sn	Sensitivity
Sp	Specificity
PPV	Positive predictive value
NPV	Negative predictive value
TH1	T helper 1
TH2	T helper 2

Introduction

Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count <100 × 10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia ***(Rodeghiero et al., 2009).***

The diagnosis of primary ITP remains one of exclusion; no robust clinical or laboratory parameters are currently available to establish its diagnosis with accuracy ***(Cooper et al., 2006).***

The dominant clinical manifestation is bleeding, which correlates generally with severity of the thrombocytopenia. Most cases are considered primary (Thereafter designated ITP), whereas others are attributed to coexisting conditions (secondary immune thrombocytopenia) ***(Stasi and Evangelista et al., 2008).***

The disease and its most widely accepted abbreviation, ITP, has variably been defined as “immune thrombocytopenic purpura”, “idiopathic thrombocytopenic purpura”, and most recently “immune thrombocytopenia” ***(Ruggeri et al., 2008).***

An International Working Group (IWG) consensus panel of both adult and pediatric experts in ITP recently provided guidance on terminology, definitions, and outcome criteria for this disorder.

The IWG defines ITP as newly diagnosed (diagnosis to 3 months), persistent (3 to 12 months from diagnosis), or chronic (lasting for more than 12 months) ***(Rodeghiero et al., 2009).***

Historically, ITP was believed to be caused by increased platelet destruction at a rate that exceeded production by a compensating bone marrow. New knowledge has questioned this model, providing evidence that platelet production is also decreased in many patients with ITP ***(Bromberg, 2006).***

The pathology of ITP is heterogeneous and complex. Besides auto-reactive B lymphocytes secreting antiplatelet antibodies and being considered as the primary immunologic defect in ITP, abnormality of cellular immunity, such as increased Th1/Th2 ratio, T-cell-mediated platelet lysis and reduced numbers and poor functions of circulating regulatory T cells (Tregs), has also been widely demonstrated in ITP ***(Hui-Yuan et al., 2014).***

Interleukin 7 (IL-7), a member of IL-2 family, is produced by bone marrow stromal and epithelial cells ***(Bradley et al., 2005)***. It acts through a receptor that is comprised of two chains: IL-7R alpha (CD127) and gamma chain (CD132). IL-7R is highly expressed on resting T cells except CD4+CD25+ Tregs ***(Seddiki et al., 2006)***.

IL-7 is critical for T-cell development, survival,