Expression of CD39 and CD73 by Chronic Lymphocytic Leukemia B-cells

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ
قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ
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Yasmine Magdy

Contents

List of Abbreviations

ADO	:	Adenosine
ADP	:	Adenosine diphosphate
AMP	:	Adenosine monophosphate
APAF-1	:	Apoptotic protease activating factor 1
ATM	:	Ataxia telangectasia mutation
ATP	:	Adenosine triphosphate
BCRs	:	B-cell receptors
BM	:	Bone marrow
CD	:	Cluster of differentiation
CLL	:	Chronic lymphocytic leukemia
CTL	:	Cytotoxic T cells
DDT	:	Dichlorodiphenyltrichloroethane
DISC	:	Death-inducing signaling complex
EBV	:	Epstein Barr virus
ELISA	:	Enzyme Linked Immunosorbent Assay
E-NTPDase	:	Ectonucleoside triphosphate diphosphohydrolase
FAB classification: French American British classification		
FAS	:	FAS receptor
FASL	:	FAS ligand
FDC	:	Follicular dendritic cell
FITC	:	Fluorescin isothiocyauate
GPI	:	Glycophosphatidylinositol
HBV	:	Hepatitis B-virus
HCV	:	Hepatitis C virus
HIV	:	Human immunodefficieney virus
HMS	:	Hyperactive malarial splenomegaly
IL	:	Interleukin
INF	:	Tumor necrosis factor
IQR	:	Interquartile range
IWCLL	:	International workshop on CLL

List of Abbreviations (Cont.)

K_2 EDTA	:	Di Potassium-ethylene diamine tetra acetic acid
LDH	:	Lactate dehydrogense
LDT	:	Lymphocyte Doubling time
MRD	:	Minimal residual disease
MZ	:	Mantle zone
NCI.WG	:	National cancer institute working group
NHC	:	Non Hodgkin lymphoma
NPV	:	Negative predictive value
NT'5E	:	Ecto-5'-nucleotidase
PBS	:	Phosphate buffer saline
PBSC	:	Peripheral blood stem cell
PCNA	:	Proliferating cell nuclear antigen
PCR	:	Polymerase Chain Reaction
PE	:	Phycoerythrin
PPV	:	Positive predicate value
ROC	:	Receiver operator characteristic curve
RT-PCR	:	Real time Polymerase Chain Reaction
SCD23	:	Soluble CD23
SCID	:	Severe combined immunodeficiency
SD	:	Standard deviation
sICAM	:	Soluble intercellular adhesion molecule
SLL	:	Small lymphocytic lymphoma
SLVL	:	Splenic lymphoma with villous lymphocytes
TK	:	Thymidine kinase
TL	:	Tumor load
UA	:	Uric acid
VEGF	:	Vascular endothelial growth factor
WBC	:	White blood cells.

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Introduction

Chronic lymphocytic leukemia (CLL), the most common leukemia in adults, is a lymphoproliferative disorder with a highly variable clinical course. CLL is characterized by the clonal expansion of mature antigen stimulated CD5+/CD23+ B-lymphocytes in blood, secondary lymphoid tissue and the bone marrow ***(Chiorazzi et al, 2005)***.

The clinical staging systems developed by Rai and Binet remain the standard methods for risk assessment in CLL, but they don't allow predictions about the risk of disease progression in early stage disease patients, which is the majority of patients. A sizable number of studies investigated prognostic markers, which can be helpful for predicting the individual risk at an early stage of the disease ***(Sivina et al, 2011).***

The most accepted and widely used prognostic markers in CLL are the mutation status of immunoglobulin variable gene segments (IgVH), the expression of CD38 and ZAP-70 as well as cytogenetic risk groups ***(Catovsky and Montserrat, 2011).***

Extracellular nucleotides and nucleosides such as adenosine triphosphate (ATP) and adenosine (ADO) respectively, may participate in creating favourable conditions that promote tumour growth and survival, CD39 hydrolyses ATP or ADP to adenosine monophosphate (AMP). AMP is then rapidly degraded to ADO by soluble or membrane bound CD73. ADO production is an integral component of the suppressive machinery of regulatory T-cells, blunting effector T-cell proliferation and secretion of T-helper 1-type cytokines, thus promoting tumor growth and survival ***(Serra et al, 2011).***

Elevated expression and activity of CD73 have been reported in several types of solid tumors and in certain types of

leukemia, suggesting that it may be benificial to the survival of tumour cells and could promote metastatic spread ***(Stagg et al, 2010).***

On these grounds, it is justified to hypothesize that expression of CD39 and CD73 by CLL cells might have an impact on the course of the disease in CLL patients and that this warrants further studies.

Aim of the Work

In this work we aim to study the expression of CD39 and CD73 and its clinical significance among a group of Egyptian B-CLL patients.

Chronic Lymphocytic Leukemia

Introduction:

Chronic lymphocytic leukemia (CLL) is the most common adult form of leukemia ***(Xu et al, 2008)***. It is a monoclonal disorder characterized by a progressive accumulation of functionally incompetent lymphocytes ***(Puente et al, 2013).***

CLL follows an extremely variable clinical course with overall survival times ranging from months to decades. Some patients have no or minimal signs and symptoms during their entire disease course and have a survival time similar to age-matched controls. Other patients experience rapidly deteriorating blood counts and organomegaly and suffer from symptoms at diagnosis or soon thereafter necessitating therapy ***(Crowther-Swanepoet et al, 2013)***.

Epidemiology:

Prevalence and Incidence:

It is the most common leukemia in the western world with an incidence of 4:100 000/year. The incidence increases to >30:100 000/year at age >80 years ***(Eichhorst et al, 2010).*** Generally, it creates more than 30% of all types of leukemia, with a median age at time of diagnosis of 72 years. Incidence rates increase with age and are higher among men than women ***(Panovská et al, 2010).*** In Asian countries, CLL represents only 5% of leukemias, with the T-cell phenotype predominating. This geographic difference in incidence is most likely the result of genetic factors ***(O'Brien and Keating, 2005).***