Expression of Fibromodulin gene as a tumor associated antigen in B-cell chronic lymphocytic leukemia

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Abstract

Fibromodulin (FMOD) is an extracellular matrix protein, it was recently proposed to be a novel tumor associated antigen (TAA) in B-cell chronic lymphocytic leukemia and it was found to be one of the most overexpressed genes in CLL. In this study, using reverse transcription-polymerase chain reaction (RT-PCR), fibromodulin gene was found to be expressed in 46% of patients with B-CLL in comparison to control group which was 0% (P value 0.006). There were significant relations between fibomodulin expression and some clinical and laboratory data such as lymphadenopathy, splenomegaly, hepatomegaly, lower hemoglobin level, lower RBCs count and lower platelet count. The reason for the expression of fibromodulin in B-CLL is unknown. Understanding the biological function of fibromodulin in B-CLL is critical because this molecule may be involved in the pathophysiology of B-CLL and may be used as a target for therapeutic intervention.

Key words:
CLL
FMOD
TAA
RT-PCR

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List of abbreviations

Ab	:	Antibody.
Ag	:	Antigen.
AIHA	:	Auto immune hemolytic anemia.
APCs	:	Antigen presenting cells.
ATM	:	Ataxia - telangectasia mutated.
Bcl-2	:	B-cell lymphoma/ leukemia- 2.
BCR	:	B cell receptor.
BM	:	Bone Marrow.
B2M	:	Beta 2 microglobulin.
bp	:	Base Pair.
B-PLL	:	B- Prolymphocytic leukemia.
CAP	:	Cyclophosphamide, doxorubicin and prednisone.
CBC	:	Complete blood count.
CD	:	Cluster of differentiation.
CD40L	:	CD40 Ligand.
CHOP	:	Cyclophosphamide, vincristine, prednisone and adriamycin.
CLL	:	Chronic Lymphocytic Leukemia.
CLL/PLL	:	Chronic Lymphocytic Leukemia/ Prolymphocytic leukemia.
CMV	:	Cyto-megalovirus.
COMP	:	Cartilage oligomeric matrix protein.
COP	:	Cyclophosphamide, vincristine and prednisone.
CR	:	Complete remission.
CS	:	Condroitin sulphate.
CTL	:	Cytotoxic T lymphocyte.
Cys	:	Cysteine.

DAT	:	Direct antiglobulin test.
DCs	:	Dendritic Cells.
Del	:	Deletion.
DNA	:	Deoxy-ribonucleic acid.
DLIs	:	Donor lymphocyte infusions.
DS	:	Dermatane sulphate.
EBV	:	Epstien Barr Virus.
ECM	:	Extra Cellular Matrix.
EDTA	:	Ethylene diamine tetra acetic acid.
EGF	:	Epithelial growth factor.
FC	:	Fludarbine, Cyclophosphamide.
FCR	:	Fludarbine, Cyclophosphamide, Rituximab.
FISH	:	Flurescent insitu hybridization.
FL	:	Follicular Lymphoma.
FMOD	:	Fibromodulin.
GAG	:	Glycosaminoglycan.
G0	:	Gap 0.
GvL	:	Graft versus- Leukemia.
Hb	:	Hemoglobin.
HCL	:	Hairy cell Leukemia.
HCT	:	Hematopoietic cell transplantation.
HLA	:	Human leucocytic antigen.
HSCT	:	Hematopoietic stem cell transplantation.
Id	:	Idiotype.
Ig	:	Immunoglobulin.
IGVH	:	Immunoglobulin variable region of heavy chain.
IL	:	Interleukin.
KDa	:	Kelodalton.

KS	:	Keratan sulphate.
LDH	:	Lactate dehydrogenase.
LDT	:	Lymphocytic doubling time.
LRR	:	Leucin Rich Repeat.
MBL	:	Monoclonal B - Lymphocytosis.
MCL	:	Mantle cell lymphoma.
MDM2	:	Murine double – minute 2 oncoprotein
MGUS	:	Monoclonal gammopathy of undetermined significance.
MHC	:	Major Histocompatibility Complex.
MMP1&MMP13	:	Collagenases.
MZL	:	Marginal Zone Lymphoma.
NCI-WG	:	National Cancer Institute – Working Group.
NK	:	Natural Killer cell.
nPR	:	Nodular partial response.
OFAiLRP	:	Oncofetal antigen – immature laminin receptor protein.
P	:	Petit arm of chromosome.
P53	:	Tumor suppressor gene.
PB	:	Peripheral Blood.
PBMCs	:	Peripheral Blood Mononuclear Cells.
PD	:	Progressive Disease.
PGs	:	Proteoglycans.
Plts	:	Platelets.
PR	:	Partial Response.
q	:	Long arm of chromosome.
Rb1 gene	:	Retinoblastoma 1 gene.
RHAMM	:	The Receptor for hyaluronic acid mediated motility.
RNA	:	Ribonucleic acid.
r.p.m	:	Round per minute.

RT-PCR	:	Reverse Transcriptase – Polymerase Chain Reaction.
SAC	:	Staphylococcus aureus cowan strain-1.
SD	:	Stable Disease.
SEREX	:	Serological identification by recombinant expression cloning.
sIg	:	Serum immunoglobulin.
SLL	:	Small Lymphocytic Lymphoma.
SLRPs	:	Small Leucin Rich Repeat Proteoglycan.
SLVL	:	Splenic Lymphoma with villous lymphocytes.
SmIg	:	Surface membrane immunoglobulin.
SMZL	:	Splenic Marginal Zone Lymphoma.
sTK	:	Serum thymidine kinase.
t	:	Translocation.
TAA	:	Tumor Associated Antigen.
TAE	:	Trisbase, Acetic acid, EDTA.
TGF-α	:	Tumor Growth Factor - α.
TGF-β	:	Tumor Growth Factor - β
TNF-β	:	Tumor Necrosis Factor - β.
TRM	:	Transplant – related mortality.
UVA&UVB	:	Ultraviolet A & Ultraviolet B.
ZAP-70	:	Zeta - associated protein - 70 kilo-Dalton.
1q32	:	It is long arm of chromosome 1.

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INTRODUCTION

AND

AIM OF WORK

Introduction

B-cell chronic lymphocytic leukemia (B-CLL) is the most common leukemia of adults in western countries. Allogenic hematopoetic cell transplantation (HCT) is the only potentially curative therapy for B-CLL, but due to the high treatment-related mortality and advanced age of most patients, the procedure is not applicable for the majority of B-CLL patients. Therefore there is a fervent need for novel therapeutic strategies (***Schmidt et al., 2007***).

Immunotherapy promises to mitigate the complications of chemotherapy and potentially provide for curative treatment. Effective strategies for this will have to overcome the disease-related acquired immune deficiency and the capacity of the leukemia-cell to induce T-cell tolerance, thereby compromising the activity of even conventional vaccines in patients with this disease (***Arnon et al., 2007***).

Recently, it has been described that vaccination with allogenic dendritic cells (DCs) pulsed with tumor cell lysate generated specific cytotoxic CD8+ T cell response against the leukemia-associated antigens such as fibromodulin which was detected in patients with B-CLL (***Hus et al., 2008***).

For the development of T-cell based therapies, the definition of immunogenic tumor-associated antigens (TAAs), which are expressed in malignant cells from leukemia / cancer patients but not in tissues of healthy volunteers, constitutes a cornerstone. RHAMM /CD168, fibromodulin, survivin and the oncofetal antigen immature laminin-