Expression of Chemokine Receptor "CXCR4" as a Prognostic Factor in Acute Myeloid Leukemia

Thesis
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AIDS	Acquired immunodeficiency syndrome
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ANLL	Acute nonlymphocytic leukemia
AP	Acid phosphatase
APL	Acute promyelocytic leukemia
APL-V	Acute promyelocytic leukemia- variant
ATRA	All-trans-retinoic acid
BFGF	Basic fibroblast growth factor
BM	Bone marrow
BRCP	Breast cancer resistance protein
C	Single cysteine residue
CAE	Chloroacetate esterase
CAM-DR	Cell adhesion-mediated drug resistance
CBC	Complete blood count
CC	Cysteine-Cysteine
CD	Cluster of differentiation
CEC	Circulating endothelial cells
CGH	Comparative genomic hybridization
CLL	Chronic lymphocytic leukemia
CML	Chronic myeloid leukemia
CNS	Central nervous system
CR	Complete remission
CRc	Complete cytogenetic remission
CSF	Cerebrospinal fluid
CX3C	Cysteine-3aa-Cysteine
CX3CR1	Fractalkine receptor
CXC	Cysteine-aa-Cysteine
CXCR4	CXC Chemokine receptor-4
DAG	Diacyl-glycerol
DARC	Duffy antigen
DC	Dendritic cell
del	Deletion

DFS	Disease free survival
DIC	Disseminated interavascular coagulation
DNA	Deoxyribonucleic acid
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGIL	European Group for the Immunological Characterization of Leukemias
ELR	Three amino acid motif "Glu-Leu-Arg"
EM	Electron microscopy
FAB	French-American-British
FCM	Flow cytometry
FISH	Fluorescence in-situ hybridization
FLT-3	Fms-like tyrosine kinase
FN	Fibronectin
G-CSF	Granulocyte colony-stimulating factor
GDP	Guanosine diphosphate
GM-CSF	Granulocyte Monocyte Colony stimulating factor
Gp	Glycoprotein
GPCRs	G protein-coupled receptors
GTP	Guanosine triphosphate
GVL	Graft-versus-leukemia
Hb	Hemoglobin
HIF-1α	Hypoxia-inducible factor-1 alpha
HIV	Human immunodeficiency virus
HLA	Human leucocyte antigen
HSCS	Hematopoietic stem cells
IL	Interleukin
INFs	Interferons
INF-γ	Interferon-γ
inv	Inversion
IPT	Immunophenotyping
K	Potassium
Kd	Kilodalton
LDH	Lactate dehydrogenase
LESTER	Leukocyte-expressed seven-transmembrane receptor
LFA-1	Leukocyte function-associated antigen-1

LIF	Leukemia inhibitory factor
LM	Light microscopy
LN	Lymph node
LRP	Lung resistance protein
MAP	Mitogen activated protein
M-CSF	Macrophage- Colony stimulating factor
MDR	Multidrug resistance
MDS	Myelodysplastic syndrome
MGSA	Melanocyte growth stimulating activity
MIC	Morphologic-immunologic- cytogenetic
MM	Multiple myeloma
MoAbs	Monoclonal antibodies
MPNS	Myeloproliferative neoplasms
MPO	Myelo-peroxidase
MRD	Minimal residual disease
MSC	Mesenchymal stromal cells
Na	Sodium
NF-κb	Nuclear factor-κb
NHL	Non-Hodgkin lymphoma
NK	Natural killer
NRF-1	Nuclear Respiratory Factor-1
NSE	Non specific estrases
OS	Overall survival
PAS	Periodic acid Schiff
PB	Peripheral blood
PBSC	Peripheral blood stem cells
PBSF	Pre-B-cell growth-stimulating factor
PCR	Polymerase chain reaction
PDGF-R	Platelet derived growth factor receptor
Pgp	P-glycoprotein
Ph+	Malignant Philadelphia chromosome-positive
PIP_2	Phosphatidylinositol 4, 5-biphosphate
PKC	Protein kinase C
PLC	Phospholipase C
PMPs	Platelet-derived microparticles
PR	Partial remission

PRS	Post remission survivals
PT	Prothrombin time
PTT	Partial thrompoblastin time
PTX	Pertussis toxin
RAR	Retinoic acid receptor
Rb	Retinoblastoma
RCC	Renal cell carcinoma
RGS	Regulators of G-protein signaling
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase-polymerase chain reaction
SBB	Sudan black-B
SC	Stem cell
SCID	Severe combined immunodeficiency
SCLC	Small-cell lung cancer
SCT	Stem cell transplantation
SD	Standard deviation
SDF-1	Stromal cell derived factor-1
SKY	Specral karyotyping
t	Translocation
TdT	Terminal deoxynucleotidyl transferase
TGF- β	Transforming growth factor beta
TLC	Total leukocytic count
TNF-α	Tumor necrosis factor-α
TP53	Tumor suppressor gene p53
TSG	Tumor Suppressor Gene
VEGF	Vascular endothelial growth factor
VHL	Von Hippel-Lindau tumor suppressor gene
VLA	Very late antigen
WBC	White blood cell
WHO	World Health Organization
Wt-1	Wilms Tumor-1 Gene
YY1	Ying Yang 1

I) INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous group of diseases characterized by uncontrolled proliferation of myeloid progenitor cells **(Scott et al., 2005)**. The AML is an aggressive malignancy with accumulation of blast cells in bone marrow. Myeloblasts can invade peripheral blood stream, and then localize in extramedullary sites. The regulation of this process has not been clearly explained so far. However, interactions between some chemokines and their specific receptors could be one of the mechanisms responsible for such kind of migration **(Mazur et al., 2007).**

Many critical interactions among cells of the immune system are controlled by soluble mediators called "cytokines". The cytokines are a diverse group of intercellular signaling proteins that regulate, not only local and systemic immune and inflammatory responses, but also wound healing, haemopoiesis and many other biologic processes **(Le et al., 2004).** The chemotactic cytokines, called chemokines, are a super-family of small secreted cytokines that were initially characterized through their ability to prompt the migration of leucocytes (**Koizumi et al., 2007).** They are grouped into four classes based on the position of key cysteine residue: C, CC, CXC, and CX3C **(Barbero et al., 2002).**

The CXCR4 is a G protein-linked seven trans-membrane spanning chemokine receptor that binds stromal-cell derived factor-1 (SDF-1) **(Barretina et al., 2003).** Chemokine receptor (CXCR4) is essential for homing and maintenance of haematopoietic stem cells in distinct stromal cell niches within the marrow **(Burger and Burkle, 2007).**

Recent studies have reported that SDF-1 and functional CXCR4 microparticles are implicated in the pathogenesis and progression of AML. They also proposed that CXCR4 level is potentially valuable as an additional diagnostic AML variable **(Kalinkovich et al., 2006).** The CXCR4 expression in AML is a prognostic marker that can rapidly and easily be determined at disease presentation, **Spoo et al. (2007),** suggested the incorporation of CXCR4 into the risk assessment of AML patients.