

THE ROLE OF FLT3 IN HEMOPOIESIS AND LEUKEMIA

Essay

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Submitted by

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List of abbreviation

AKT	Protein kinase B
ALL	Acute lymphocytic leukemia
ALM	Activation loop mutation
AML	Acute myeloid leukemia
ANOVA	Analysis of variance
APL	Acute promyelocytic leukemia
AR	Autosomal recessive
ATP	Adenosine triphosphate
ATRA	All <i>trans</i>-retinoic acid
BCR	Breakpoint cluster region
BM	Bone marrow
BMT	Bone marrow transplantation
CCG	Children's cooperative group
CML	Chronic myeloid leukemia
CR	Complete remission
DC	Dendritic cells
DFS	Disease free survival
DIC	Disseminated intravascular Coagulopathy
ECD	Extracellular domain
EFS	Event free survival
EGF	Epidermal growth factor
EPH B2	Type of receptor
ERK 1/2	Extracellular signal regulated kinase1 and 2
FAB	French American British
FGFR1	Fibroblast growth factor 1 receptor
FISH	Fluorescence insitu hypridization
FLK	Fetal liver kinase
FLT3	Fetal liver tyrosine kinase 3 Fms-like tyrosine kinase 3
G-CSF	Granulocyte colony stimulating factor
GM-CSF	Granulocyte-Macrophage colony stimulating factor

List of abbreviation

GVL	Graft versus leukemia
IGFIR	Insulin like growth factor 1 receptor
ITD	Internal tandem duplication
JM	Juxtamembrane domain
KD	Kinase domain
KI	Kinase insert
LDH	Lactate dehydrogenase
LOH	Loss of heterozygosity
LSC	Leukemic stem cell
MAPK	Mitogen activated protein kinase
MDS	Myelodysplastic syndrome
MLL	Mixed lineage leukemia
MPD	Myeloproliferative disorders
MRD	Minimal residual disease
MS	Myeloid sarcoma
NK	Natural killer cells
OS	Overall survival
PB	Peripheral blood
PCA	Principle component analysis
PDGF	Platelet derived growth factor
PFS	Progression free survival
PI 3K	Phosphoinositide-3-kinase
RAR	Type of gene
RR	Relative risk
RTK	Receptor tyrosine kinase
SCT	Stemcell transplantation
SCTK-1	Stemcell tyrosine kinase-1
STAT5	Signal transducer and activator of transcript
TK	Tyrosine kinase
TKD	Tyrosine kinase domain
TM	Transmembrane domain
UK MRC	United Kingdom medical research council

List of abbreviation

UPN	Unique patient numbers
VEGF-R2	Vascular endothelial growth factor receptor 2
WnT	Wingless type
WT	Wild type

INTRODUCTION

FLT3 (Fms-like tyrosine kinase 3) is a receptor tyrosine kinase expressed in a variety of human cell line of both myeloid and B lymphoid lineage (**Brasel *et al.*, 1995; Turner *et al.*, 1996; Gilliland and Griffin, 2002; Steven Knapper, 2007**).

It is also expressed at high levels in a spectrum of hematological malignancies including 70%-100% of AML (acute myeloid leukemia) of FAB (French-American-British) subtypes, B precursor cell of ALL (Acute Lymphocytic Leukemia), a fraction of T cell ALL & CML (Chronic Myeloid Leukemia) in lymphoid blast crisis as well as myeloid sarcoma (**Rasko *et al.*, 1995; Rosnet *et al.*, 1996; Steven Knapper, 2007**).

FLT3 gene encodes a 993 amino acid protein in humans and is expressed in hemopoietic cells, placenta, gonads and brain (**Rosnet *et al.*, 1993; Ana Marcovic *et al.*, 2005; Steven Knapper, 2007**).

FL is a type I transmembrane (TM) protein that can be released as a soluble homodimeric protein (**Gilliland and Griffin, 2002**). It encodes a 235 amino acid. FL is expressed in cells of hemopoietic bone marrow microenvironment including bone marrow fibroblasts as well as hemopoietic cell lines of myeloid and B and T cell lineage (**Gilliland and Griffin,**

2002). FL acts in synergy with other cytokines to promote expansion of hematopoietic precursors (**Levis *et al.*, 2003).**

FLT3 ligand was found to have several functions includes activation of FLT3, it has a role in immune response and it has an antitumor effect.

Mutations of FLT3 have been detected in about 30% of patients with AML and might play an important role in pathogenesis of AML. Again it is detected in a small number of patients with ALL and MDS and those patients' tend to have poor prognosis in both pediatrics and adults (**Frohling *et al.*, 2001).**

The expression of mutant FLT3 receptor in marrow cells result in a lethal myeloproliferative syndrome and preliminary studies suggest that mutant FLT3 cooperates with other leukemia oncogenes to confer a more aggressive phenotype (**Levis *et al.*, 2002).**

These results suggest that FLT3 is an attractive therapeutic target for kinase inhibitors or other approaches for patients with mutations of this gene.

Mutations in two hot spots of the FLT3 gene lead to autoactivation of the receptor. First, internal tandem duplications in the juxtamembrane region of the receptor (**FLT3/ITD**). Second, mutations in the activation loop, which is

located in the second kinase domain. Point mutations, deletions or small insertions are found at Asp835 (**Dirk *et al.*, 2004; Steven Knapper, 2007).**

It have been demonstrated that FLT3/ITD mutations occur in a subset of patients with myeloid sarcoma. This is of potential importance because several small molecule inhibitors of FLT3 have been developed and are currently in early clinical trials as potential therapeutic agents for AML with FLT3 mutations. (**Levis *et al.*, 2003).**

FLT3-specific antibodies may be useful not only in treating leukemia patients with FLT3/ITD mutations but also in treating those with associated overexpression of the wild-type FLT3 allele. IMC-EB10, as an efficacious and apparently nontoxic FLT3 inhibitor, especially those for whom cytotoxic chemotherapy has failed or those who are too old for more intensive treatment regimens, such as bone marrow transplantation.

Moreover, anti-FLT3 antibody-based therapy may have synergistic effects when combined with other therapies, such as cytotoxic chemotherapy (**Prewett *et al.*, 2002; Yiwen *et al.*, 2004).**

Aim of work

The aim of this work is to elucidate the role of FLT3 mutation in hemopoiesis and leukemia regarding pathogenesis, prognosis and treatment.

THE ROLE OF FLT3 IN HEMOPOEISIS AND LEUKEMIA

FLT3 (FMS-like tyrosine kinase 3) is a Receptor Tyrosine Kinase (RTK) which is expressed by immature hemopoietic cells and is important for the normal development of stem cells and the immune system. FLT3 is also known as FLK-2 (Fetal liver kinase-2) and STK-1 (Human stem cell kinase-1), FLT3 was cloned independently by 2 groups in 1991 (**Mathews *et al.*, 1991; Rosnet *et al.*, 1991a; Rosnet *et al.*, 1991b; Gilliland and Griffin, 2002; Steven Knapper, 2007; Kyu-Tae Kim *et al.*, 2007).**

FLT3 has a strong sequence similarities with other members of class III receptor tyrosine kinase (RTKIII), a receptor family including FMS, FLT3 PDGFR, KIT which are characterized by an extracellular domain comprised of 5 immunoglobulin like (Ig-like) domains, a juxtamembrane domain and 2 kinase domain (KD5) interrupted by a kinase insert (**Rosnet *et al.*, 1993; Agnes *et al.*, 1994; Gilliland and Griffin, 2002; Steven Knapper, 2007).**