Role of Fibroblast Growth Factor 2 in Chronic Myeloid Leukemia

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Abstract

Background: WBCs recovered from CML patients contained only small amounts of the 24 kDa isoform of FGF-2, although the level of soluble FGF-2 in plasma was significantly increased. While searching for the potential source of FGF-2 in the blood of these patients, with exclusion of the possibility of a concomitant occurrence of solid tumors and noncancer diseases. Nevertheless, other possible sources of FGF-2 in plasma of CML patients should be considered. One of them is the rapidly proliferating blasts that are present in bone marrow, while being rare in peripheral blood. During progression of CML, especially in its terminal stages, large numbers of proto-differentiated blasts are released into the bloodstream. FGF2 expression was increased in CML and AML stroma during the development of resistance to kinase inhibitors, indicating that FGF2 expression is a regulated autocrine growth factor for stroma. In stress hematopoiesis (highly complex and dynamic process that involves crosstalk between HSPCs, bone marrow stromal cells, and nonhematopoietic tissues to sense apathogenic organism and convert the signal of an infection into the signal for myeloid differentiation), FGF2 stimulates expansion of both supportive marrow stromal cells and hematopoietic stem/progenitor cells to regenerate the marrow. There is evidence that stress hematopoiesis is a frequent event in CML, because up to 35% of CML patients treated with Imatinib (IM) and newer agents develop transient cytopenias.

Keywords: Fibroblast Growth Factor 2, Chronic Myeloid Leukemia

Introduction

Chronic myeloid leukemia (CML) is myeloproliferative neoplasm (MPN) in which granulocytes are the major proliferative component. It is a widely described malignant disorder of hematopoietic stem cells (HSCs) that accounts for 15%–20% of all cases of leukemia in adults**.**Worldwide, CML has an annual incidence varies from as low as 0.4/100,000 persons in some non-Western countries to 1.75/100,000 in the United States. In western countries the median age of CML patients is about 57 years Patients older than 70 years make up more than 20% and children and adolescents <5% **(1).**

CML is more common in males than in females with male-to-female ratio varying between 1.2 and 1.7.The incidence in CML increases by age, at least up to 75–80 years, with an annual incidence rising from 0.39 in young (20–29 years) to 1.52 in those 70 years or more**.** In Asia and in Africa the median age at diagnosis is <50 years, reflecting in part the lower median age of the population.The first Arab Leukemia Net (ALN) reports demonstrated that age specific rates for CML in Egypt and Arab nations are lower by at least two decades compared to western population [highest in age group 30 -35 years **(1).**

Pathophysiology and Etiology:

CML is an acquired abnormality that involves the hematopoietic stem cells. It is characterized by a cytogenetic aberration consisting of a reciprocal translocation between the long arms of chromosomes 22 and 9 t (9; 22). The translocation results in a shortened chromosome 22. The Philadelphia (Ph) chromosome is detected in 95% of patients; this translocation relocates an oncogene called ABL from the long arm of chromosome 9 to a specific breakpoint cluster region (BCR) in the long arm of chromosome 22. The ABL oncogene encodes a tyrosine protein kinase. The resulting BCR/ABL fusion gene encodes a chimeric protein with strong tyrosine kinase activity **(2).**

Classification of CML according to WHO 2016:

The essential clinic pathological characteristics of Ph*(+) CML in the 2016 WHO classification is defined as follows.

Chronic phase (CP):

Most patients with CML are diagnosed in CP, which usually has an insidious onset. Nearly 50% of newly diagnosed cases are asymptomatic and discovered by routine examination when the white blood cell (WBC) count is found to be high**.** Common findings at presentation include fatigue, malaise, weight loss, night sweats, anemia, and about 50% of patients have palpable splenomegaly. Typical peripheral blood findings in CP are characterized by leukocytosis (12-1000 x 10^9/L with a median: 80 x 10^9/L) due to neutrophils in various stages of maturation, with peaks in the proportions of myelocytes and segmented neutrophils. granulocytic dysplasia is absent, Blasts typically account for < 2% of the WBCs **(3).**

Absolute Significant basophilia and eosinophilia are common, Absolute monocytosis may be present usually <3% except in rare cases with the p190 BCR-ABL1 isoform, which often mimic chronic myelomonocytic leukemia **(3).**

Platelet counts are normal or increased to1000 x 10^9/L **(3).**

Most cases of CML can be diagnosed based on peripheral blood findings combined with detection of the Ph chromosome and/or BCR-ABL by cytogenetic and molecular genetic techniques.

However, bone marrow aspiration is essential to ensure sufficient material for a complete karyotype, for morphological evaluation and to confirm the phase of disease. Bone marrow biopsy is not required to diagnose CML in most cases, but should be done if the findings in the peripheral blood are atypical or if a bone marrow aspirate is hypercellular. Megakaryocytes may be normal or slightly decreased in number, they may be smaller than normal and have hypo segmented nuclei; they are referred to as 'dwarf' megakaryocytes, but are not true micro megakaryocytes such as those seen in myelodysplastic syndromes. 40-50% of cases exhibit moderate to marked megakaryocytic proliferation**.** Pseudo-Gaucher cells are also common finding in bone marrow of CML patient in which a layer of immature granulocytes (5-10 cells in thickness) is common around the bone trabeculae, in contrast to the normal thickness of 2- 3 cells **(4).**

Moderate to marked reticulin fibrosis, which correlates with increased numbers of megakaryocytes. Splenic enlargement is reported in 30- 40% of biopsies at diagnosis due to infiltration of the red pulp cords by mature and immature granulocytes**. Accelerated phase (AP):**

Accelerated phase (AP) definition proposed by the World Health Organization**,** with anemia, increasing basophils or eosinophils, thrombocytopenia (or occasionally thrombocytosis), or increasing proportion of blasts being the most common findings**.** Clinical features suggesting "acceleration" supplement these laboratory findings and commonly include fever, night sweats, weight loss, bone pain, increasing splenomegaly despite therapy, and development of extramedullary disease (chloromas).

Failure to achieve a hematologic response to initial therapy with a TKI, hematological, cytogenetic, or molecular resistance to two sequential TKIs, or the development of two mutations in BCR-ABL1 during TKI therapy, is also a worrisome feature, in the absence of the findings listed above

Table (1): Criteria used in defining phases of disease in CML WHO criteria for accelerated phase 2016 (**5).**

WHO criteria for accelerated phase 2016 [17]
• >10–19% blasts in blood or marrow
Persistent or increasing WBC (>10 × 10⁹/L), unresponsive to therapy
• >20% basophils in blood
• Thrombocytopenia (<100 × 10⁹/L) unrelated to therapy
• Persistent thrombocytosis (>1000 × 10⁹/L) unresponsive to therapy

Blast crisis (BC):

The blastic transformation (also referred to as blast phase or blast crisis) is based on the presence of more than 20% blasts in the peripheral blood or bone marrow, or the demonstration of extramedullary infiltration by blast cells **.** In two-thirds of the cases, the blasts are myeloid with one-third of B-lymphoid lineage. The blasts are often undifferentiated morphologically and immunophenotyping is therefore recommended in all cases. It can be difficult to distinguish patients presenting initially with Ph-positive acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL) from those with blast crisis of CML**.** For patients with Ph + ALL, the presence of significant splenomegaly is more in keeping with preexisting, undiagnosed CML, whereas the presence of $p190^{BCR\text{-}ABL1}$ suggests de novo ALL while $p210^{BCR\text{-}ABL1}$ might suggest preexisting CML. It is possible, in both children and adults with CML, to develop blast transformation with mixed lineages, i.e., both lymphoid and myeloid surface markers detectable on the same cells or distinct subpopulations of blasts with either lymphoid or myeloid characteristics. T-lymphoid blast transformation is rare, but there are several cases showing both the *BCR-ABL1* fusion gene and T-cell receptor (TCR) gene rearrangements (**6).**

Cytogenetic and molecular changes are well recognized in 50–80% of the patients during transformation to accelerated or blast phase. So-called minor cytogenetic changes include monosomies of chromosomes 7 and 17, loss of the Y chromosome, and trisomies of chromosomes 17 and 21. Major cytogenetic changes, which suggest a more aggressive clinical course, include a double-Ph chromosome, trisomy 8, isochromosome i(17q), trisomy 19, and translocations of chromosome 3 with chromosome 21, t(3;21) (q26;q22). Alterations of the p53 gene on the long arm of chromosome 17 by deletion, rearrangement, or mutation, occurring predominantly with myeloid blast crisis, have been identified in up to 30% of CML patients entering the blast phase. Even before clinical manifestations, it is sometimes possible to detect these cytogenetic changes in the bone marrow, extramedullary masses, or splenectomy specimens **(7).**

In who classification 2022:

Chronic myeloid leukemia risk factors are refined, and accelerated phase is no longer required

The natural history of untreated CML before the introduction of targeted tyrosine kinase inhibitors was biphasic or triphasic: an initial indolent CP followed by a blast phase BP with or without an intervening accelerated phase AP. with TKI treatment and careful disease monitoring, the incidence of progression to advanced phase has decreased, and 10_ year overall survival rate for CML is 80-90%**.** The designation of AP has become less relevant, where resistance stemming from ABL1kinase mutation and additional cytogenetics abnormalities and the development of BP represent key disease attribute **(8)**

- **Cytogenetic analysis of CML patients:**

CML is diagnosed by detecting the Philadelphia chromosome. This characteristic chromosomal abnormality can be detected by routine cytogenetics. Karyotyping requires cells to be in the metaphase of the cell cycle. Therefore, it is necessary to cultivate and synchronize cells prior to cytogenetic analysis. Usually, bone marrow aspiration is required. Only if significant number of myeloblasts are present in the peripheral blood (typically in the accelerated or blastic phase), or in cases of excessive leukocytosis or presence of immature

cells capable of dividing, karyotyping can be performed with peripheral blood cells. In about 5% of CML patients no Philadelphia chromosome is found by conventional karyotyping **(9).**

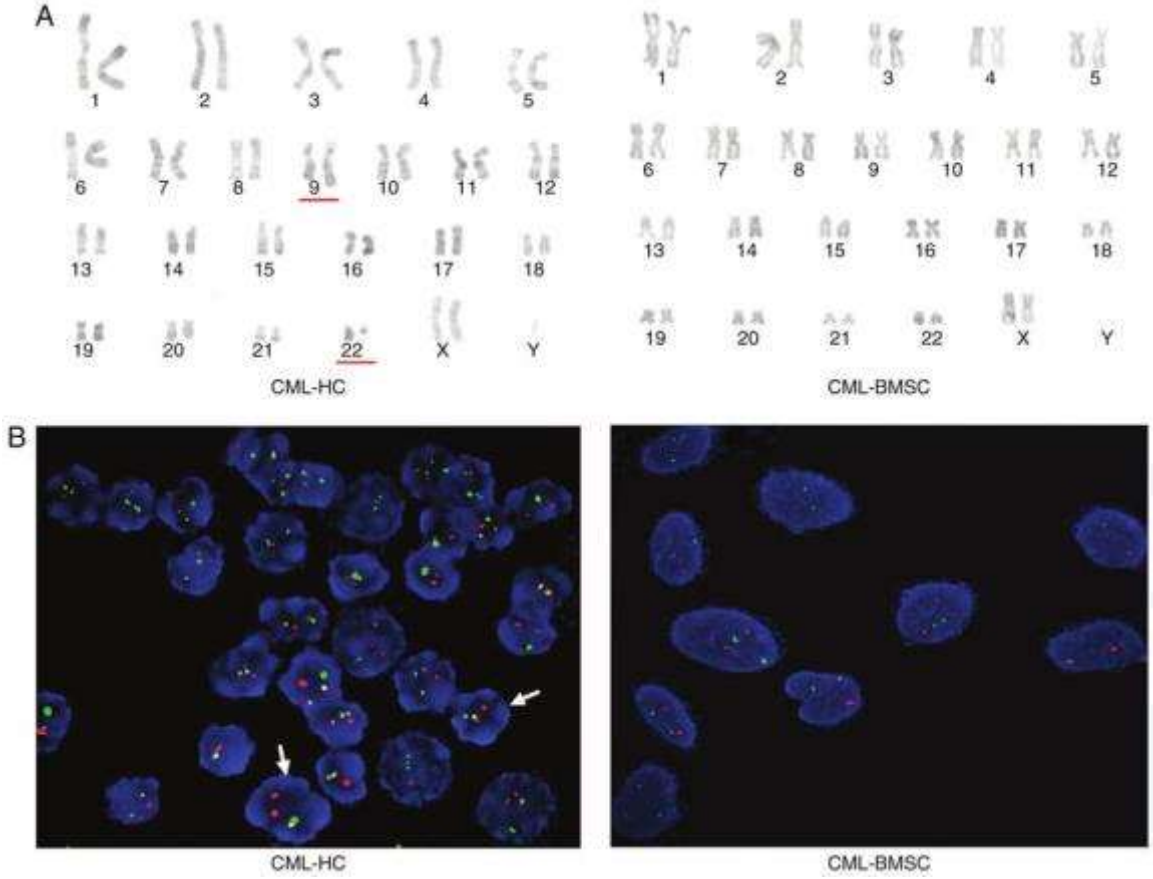

Figure (1): Cytogenetics of patients with CML. **(10).**
(A) Conventional cytogenetic analysis identified the philadelphia chromosome in CML-HCs (left panel) and a normal karyotype in CML-BMSCs (right panel). (B) Fluorescent in situ hybridization analysis revealed yellow signals in CML-HCs, which represented the BCR-ABL fusion gene (left panel). The yellow signal was negative in CML-BMSCs (right panel). CML, chronic myelogenous leukemia; BMSCs, bone mesenchymal stromal cells; HCs, hematopoietic cells.
(10).

- **Molecular cytogenetic analysis by (FISH):**

FISH can be used to detect the BCR-ABL gene rearrangements in metaphase or in interphase cells. Thus in contrast to karyotyping, a bone marrow aspiration is not absolutely required. FISH can also prove atypical gene rearrangements, which are missed by conventional cytogenetics. With FISH generally more cells are analyzed compared to karyotyping (usually >100 interphase cells with FISH versus 20 metaphase cells with karyotyping), so that the method has a greater sensitivity **(11).**
Locus specific identifier probes are used for detection of BCR_ABL fusion gene in CML patients. FISH thus is suitable method both for diagnosis and monitoring and is used in many hematology centers as a standard diagnostic method in CML, together with cytogenetics and quantitative PCR **(12)**.

- **Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR):**

Reverse transcriptase- Polymerase Chain Reaction (RT-PCR) is the most sensitive assay available for the BCR-ABL chimeric mRNA. The assay measures the level of BCR-ABL transcripts in the peripheral blood or in the bone marrow, and it can detect one CML cell in the background of ≥ 100000 normal cells. Qualitative RT-PCR techniques are reported as either positive or negative. In contrast a quantitative PCR assay reports the actual percentage of BCR-ABL mRNA transcripts.A major advantage of quantitative PCR testing is the strong correlation between results obtained from peripheral blood and bone marrow, allowing molecular monitoring without the necessity of obtaining bone marrow aspirations. Since therapies for CML

have improved, patients have been able to achieve responses at the molecular level. Therefore, more sensitive measurements are necessary to detect minimal residual disease (MRD). Real-time quantitative polymerase chain reaction (RTQ-PCR) assessment can detect deeper levels of response, up to a 5-log reduction **(13)**.

Fibroblast Growth Factor

Fibroblast growth factors (FGFs) belong to a large family of 22 structurally related peptides. FGFs are classified into seven subfamilies based on gene locus, mode of action, and phylogenetics. These subfamilies are divided into three groups based on their mechanism of action: canonical FGFs, intracellular FGFs, and hormone-like FGFs. FGF subfamilies, groups, and receptor-/ligand-binding specificity **(13)**.

FGFs play an important role in the development, homeostasis, and repair of many organ systems such as the lung, liver, kidney, and gastrointestinal tract. In humans, 20 members of the FGF family have been identified all of which are structurally related signaling molecules **(13)**.

The fibroblast growth factor (FGF) is a family of proteins includes signalling proteins secreted by tissues to regulate cell metabolism, proliferation, differentiation, and survival **(14).**

These proteins bind heparin and have broad mitogenic and angiogenic activities, including the regulation of normal cell growth in the epithelium, bone soft connective and nervous tissues **(14).**

Table (2): Summarizes the function of FGFs **(14).**

Function	Subfamily related to the function	Target cell	Ref.
Cell proliferation	FGF1, FGF2	Preadipocyte	[45–48]
		Endothelial cell, epithelial cell, fibroblast cell, neural stem cell	
	FGF4	Trophoblast stem cell	[49]
	FGF7, FGF10	Epithelial cell	[50, 51]
	FGF18	Osteoblast, chondrocytes, osteoclast	[52]
Cell migration	FGF2	Astrocyte, myogenic cell	[47, 54]
	FGF4	Myogenic cell	[54]
	FGF7	Epithelial cell, keratinocyte	[55]
	FGF8	Neural crest cell	[56]
Cell differentiation	FGF1, FGF2	Neuroepithelial	[48, 52]
	FGF7	Keratinocyte	[57]
	FGF20	Monkey stem cell	[42]
Angiogenesis	FGF1, FGF2	Endothelial cell	[61]

Fibroblast growth factor 2:

FGF-2 binds to and activates the FGF receptors mainly via the RAS/MAP kinase pathway to regulate cell proliferation, migration and differentiation, as well as angiogenesis, in a variety of tissues, including skin, blood vessel, muscle, adipose, tendon/ligament, cartilage, bone, tooth and nerve (**15).**

FGF-2 Structure and Stability:

The crystal structure of FGF-2 suggests that it is a globular protein with an approximate folded diameter of 4 nm. It has a β barrel tertiary structure consisting of 12 antiparallel β strands connected by β turns. Hydrophobic residues line the core of the barrel while a large number of charged residues are present on the protein surface. A cluster of positively charged residues to one side is thought to constitute the heparin binding region of the protein. The latent instability of FGF-2 has been attributed to the significant amount of structural energy associated with the heparin binding site; binding with heparin or similar

glycosaminoglycans at a ratio as low as 0.3:1 w/w (heparin: FGF-2) has been shown to stabilize the FGF-2 against trypsin heat acid and protease-mediated inactivation (**16).**

In vivo, the interactions of FGF-2 with other endogenous molecules (e.g., heparan sulphate proteoglycan, Heparin, fibrinogen/fibrin), presented in soluble form or bound to cell membrane, are known to control its receptor interactions, stability, and concentration in an extracellular microenvironment **(17).**

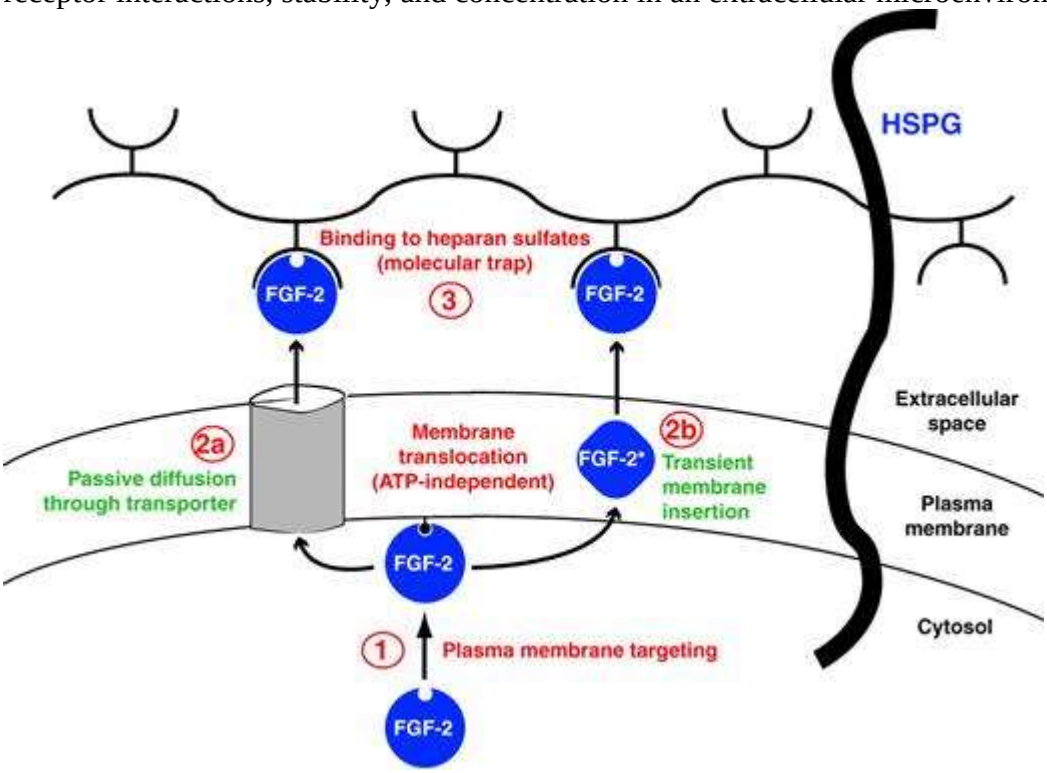

Figure (2): Schematic model for FGF-2 secretion. (1) Plasma membrane targeting; (2) membrane translocation; and (3) extracellular trapping by binding to HSPGs. FGF-2 membrane translocation does not depend on ATP hydrolysis or a membrane potential but rather is a diffusion-controlled process. **(17).**

FGF2 Gene Expression:

FGF2 is expressed in a developmental and tissue specific manner. Differentiating populations of cells also have shifting levels of FGF2 protein content. Cell phenotype and environment can affect the length of the FGF2 mRNA and isoform expression by posttranscriptional regulation of polyadenylation. In contrast to primary cells that predominantly express the LMW FGF2, the shorter FGF2 mRNA transcripts in stressed and transformed cells translate from the upstream CUG initiation codons to generate HMW FGF2 isoforms (**18).**

FGF2 protein expression has been classified into two distinct patterns. The first, characterized by high levels of the AUG-initiated LMW isoform accompanied by low/undetectable levels of CUG-initiated HMW isoforms, is observed in normal cells such as skin fibroblasts, retinal pigment epithelial cells and aortic endothelial cells. In contrast, the second pattern, defined by high levels of HMW isoforms and low/undetectable levels of LMW, is seen in transformed cells including uterus carcinoma (HeLa cells), liver adenocarcinoma (SK-Hep-1 cells), pancreatic carcinoma (MIA PaCa-2 cells), epidermoid carcinoma (A-431 cells), breast adenocarcinoma (MCF-7 cells) and colon adenocarcinoma (HT-29). Fluctuations in FGF2 protein expression and localization occur in response to cell density, cell cycle and differentiation **(19).**

Function:

FGF2 is a pleiotropic signaling molecule involved in many biological processes including angiogenesis, embryonic development (brain, limb, lung, heart, muscle, bone, blood, eye and skin) and wound healing. Despite complex involvement in any aspects of embryogenesis FGF2 knockout mice are viable, functioning and do not display any apparent neurological deficit. FGF2 deficient mice have impaired brain development, blood pressure regulation, wound repair and bone formation **(19).**

LMW FGF2 stimulates cell growth, proliferation, migration and differentiation via FGFR signaling and ligand receptor complex internalization. The FGF2 mitogenic response is controlled by direct and indirect regulation of nuclear kinase and transcription factor activity essential for ribosome biogenesis during cell proliferation and growth **(17).**

The effects of HMW are dependent on isoform, expression level and cell type. The majority of HMW FGF2 functions require nuclear localization. The HMW nuclear forms of FGF-2 have been reported to interact with a 55 kDa nuclear protein, FIF (FGF-2-interacting factor), which interacts specifically with FGF-2 but not with FGF-1, FGF-3, or FGF-6. Some of the biological effects of FGF-2 may be mediated by interaction with FIF, which has anti-apoptotic activity. High levels of HMW FGF2 induce proliferation in a variety of cells including aortic endothelial, fibroblasts, glioma, pancreatic tumor and liver adenocarcinoma cells. Low levels of HMW FGF2 inhibit cell proliferation in glioma and fibroblast cells (**20).**

Role of FGF2 in hematological tumors:

The role of FGF2 in hematopoiesis starting at early stages of development through adulthood. In early stages of development, FGF2 has an important role in the proliferation of hemangioblasts, which are common progenitors of hematopoietic and endothelial cells that play a central role in hematopoietic and angiogenic differentiation **(21).**

In addition, FGF2 plays a role in self-renewal, cell survival, and cell adhesion of human embryonic stem cells. In adult hematopoiesis, FGF2 induces proliferation of stromal cells of bone marrow. FGF2 also induces the production of interleukin-6 (IL-6) and counteracts the suppressive effect of transforming growth factor beta (TGF-β) on myeloid progenitor cells. Myeloid precursor cells can be induced by FGF2 to give rise to erythroid progenitors **(17).**

The involvement of FGF2 in various stages of hematopoiesis suggests that its dysregulation can result in hematological cancers **(17).**

Clinical prognostic value of FGF2 in hematological tumors:

High serum FGF2 levels were significantly correlated with tumor bulkiness, Therefore, the levels of serum FGF2 may have prognostic significance in these cancers, and quantification of FGF2 may provide an indirect, non-invasive way to monitor patients with high risk of relapse from hematological tumors **(17).**

Role of FGF2 in CML

WBCs recovered from CML patients contained only small amounts of the 24 kDa isoform of FGF-2, although the level of soluble FGF-2 in plasma was significantly increased **.** While searching for the potential source of FGF-2 in the blood of these patients, with exclusion of the possibility of a concomitant occurrence of solid tumors and noncancer diseases. Nevertheless, other possible sources of FGF-2 in plasma of CML patients should be considered. One of them is the rapidly proliferating blasts that are present in bone marrow, while being rare in peripheral blood. During progression of CML, especially in its terminal stages, large numbers of proto-differentiated blasts are released into the bloodstream (**23).**

The FGF-2 must be present at very high concentrations in order to activate MEK and ERK in CML-derived cells, which certainly also express the MAP kinase cascade-activating BCR-ABL fusion proteins p190 and p210 (**24).**

Menzel et al. (27) demonstrated that exogenously added FGF-2 acts as a survival factor that protects cells from, for example, fludarabide-induced cell death.

Elevated levels of FGF2 have previously been measured in the serum of CML patients**,** where it was reported to function as an autocrine promotor of proliferation. FGF2 expression was increased in CML and AML stroma during the development of resistance to kinase inhibitors, indicating that FGF2 expression is a regulated autocrine growth factor for stroma (**25).**

This is consistent with the role of FGF2-FGFR1 autocrine expansion of stroma in stress-induced hematopoiesis and suggests that leukemia cells are able to hijack the FGF2 stress response for survival. The regulation of FGF2-FGFR1 signaling is also supported by the positive correlation in expression of both

FGF2 and FGFR1 in a subset of primary AML marrow samples, indicating that this pathway can be selectively activated. FGFR inhibitors not only inhibit autocrine growth of stroma, but reduce exosome secretion and significantly alter the protective ability of stromal cells. Since exosomes contain a complex mixture of proteins, cytokines, lipids and microRNAs (all of which potentially contribute to leukemia cell protection), inhibiting secretion of exosomes is a promising approach to blunting this complex mechanism of resistance.

In stress hematopoiesis (highly complex and dynamic process that involves crosstalk between HSPCs, bone marrow stromal cells, and nonhematopoietic tissues to sense apathogenic organism and convert the signal of an infection into the signal for myeloid differentiation), FGF2 stimulates expansion of both supportive marrow stromal cells and hematopoietic stem/progenitor cells to regenerate the marrow. There is evidence that stress hematopoiesis is a frequent event in CML, because up to 35% of CML patients treated with Imatinib (IM) and newer agents develop transient cytopenias (**26).**

It Was showed that a certain percentage of patients suffering from CML (but not from MDS, AML, ALL and HCL) contain abnormally high amounts of FGF-2 in their blood plasma, similar to levels found previously in individuals suffering from B-CLL (**27).**

Moreover, It Was provided that data showing that peripheral WBCs in both subtypes of leukemic disease are capable of synthesizing FGF-2. There is still, however, a major difference between B-CLL and CML WBCs in the spectrum of molecular mass isoforms of FGF-2 that they contain.

In study carried out by **Traer et al** (**25)** found that FGF2 in the marrow of newly diagnosed CML patients treated with IM and found a highly variable, but consistent increase in FGF2 from marrow biopsies taken 6-18 months after initiation of IM suspect that FGF2 likely decreases in most patients as they return to normal marrow homeostasis and has no clinical impact. However, they proposed that in some patients a sustained feed-forward FGF2 expression can promote FGF2 expression in stromal cells in an autocrine manner and survival of CML cells in a paracrine manner (the CML cells themselves may induce FGF2 expression), eventually leading to overt IM resistance. In this proposed model, the normal regeneration of the marrow after IM treatment is hijacked by CML cells, similar to what has been described in other malignancies**.** Ponatinib overcomes FGF2-mediated resistance and also interrupts the feed-forward FGF2 loop in the stroma, leading to a normalization of FGF2 expression.

The development of IM resistance took about 1 month, suggesting that either a small subpopulation of cells was capable of using FGF2 as a growth molecule and/or a genetic/ epigenetic event was required to resume growth in the presence of FGF2 (**25).**

Traer et al. (25) found that FGF2 was significantly increased in the bone marrow of patients without KD mutations who subsequently responded to ponatinib treatment. Most of the increased FGF2 in these patients was localized in stromal cells and thus it is likely that FGF2 acts in a paracrine manner, similar to other reported models of ligand induced resistance **(28).**

The leukemic cells use FGF2 to survive the effects of the kinase inhibitors. However, it was not clear how the FGF2 signal reaches the leukemia cells from the bone marrow stromal cells. Leukemic cells that had taken up FGF2 were better able to respond to kinase inhibitor treatment than leukemia cells that had not **[29]**. FGF2 also affects the bone marrow stromal cells themselves, causing them to grow faster, produce more FGF2 and release more exosomes. Blocking the effects of FGF2 on the stromal cells slowed their growth and caused fewer exosomes to be released. This suggests that taking advantage of drugs that prevent bone marrow stromal cells from releasing FGF2 in exosomes might improve treatments for leukemia **[29].**

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