World Scientific Research Journal Volume 9 Issue 4, 2023
ISSN: 2472-3703 DOI: 10.6911/WSRJ.202304_9(4).0030

Progress in The Mechanism of Focal Adhesion Kinase in Leukemia

Yuling Kan[1, *]

[1]Central Laboratory, Binzhou People's Hospita, Binzhou, 256601, Shandong, China

[*]Corresponding author. E-mail: kanyuling@163.com

Abstract

Focal adhesion kinase plays a role in cell cycle regulation, cytoskeletal assembly, adhesion, migration, motor ability, and growth regulation through a variety of signal pathways, and regulates tumor proliferation, apoptosis, invasion, metastasis, and angiogenesis. It has become a new target of tumor therapy at present. The role of focal adhesion kinase in the genesis and development of leukemia is reviewed as follows.

Keywords

Focal adhesion kinase; Leukemia; Overview.

1. INTRODUCTION

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase, which is an intermediary molecule of signal transduction pathways such as integrin, growth factor and cytokine. It plays an important role in cell cycle regulation, cytoskeleton assembly, adhesion, migration, mobility, growth regulation, survival and other aspects through a variety of signal pathways, thus affecting tumor proliferation, apoptosis, invasion Metastasis and angiogenesis also play an important regulatory role, and have gradually become a new target of tumor therapy. This article discusses the role of FAK in the occurrence and development of leukemia, and clarifies the role of FAK in hematopoiesis, leukemia, bone marrow microenvironment and signal transduction mechanism.

2. FAK AND BONE MARROW HEMATOPOIETIC MICROENVIRONMENT

Hematopoietic development regulation occurs locally in the bone marrow and constitutes a specific hematopoietic microenvironment The hematopoietic microenvironment of bone marrow is mainly composed of three parts: bone marrow stromal cells, extracellular matrix, and a variety of regulatory factors.

2.1. FAK and bone marrow stromal cells

Studies have shown that the proliferation of bone marrow stromal cells is related to integrin, and FAK plays a key role in integrin-mediated signal transduction pathway. When hematopoietic stem cells adhere to fibronectin in the extracellular matrix, they can induce the phosphorylation of FAK, further activate mitogen-activated pro-tein kinase (MAPK), and change gene expression, thus mediating cell adhesion and migration, regulating cell proliferation and survival, and play an important biological role [1]. FAK can also promote the expression of cyclin D in hematopoietic cells, reduce the expression of P21, and accelerate the transformation of cells from G to S phase [2]. MAPK is the most important growth signal regulatory protein found at present, which is widely distributed in the cytoplasm. Its member extracellular signal regulated kinase (ERK, mainly P44 and P42) is most closely related to the regulation of cell

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202304_9(4).0030

growth, differentiation and proliferation. The extracellular signal can induce a series of tyrosine phosphorylation reactions in the cell by interacting with the corresponding receptors, activate ERK to undergo nuclear translocation, and then phosphorylate a series of transcription factors to regulate cell growth[3].

2.2. FAK and regulatory factors

A large number of regulatory factors that play a role in the regulation of bone marrow hematopoiesis have been reported. They are divided into three categories, namely cytokines, adhesion factors and chemokines [4].

Cytokines mainly refer to chemical molecules that regulate the growth and proliferation of cells. They can be divided into two categories according to their roles in different stages of blood cell differentiation. The ones that regulate the differentiation of hematopoietic cells include SCF, IL-1, IL-3, IL-6, IL-11 and FL, and the ones that act in the late stage of differentiation include EPO, G-CSF, M-CSF, IL-5, etc. Sometimes they can affect different stages of differentiation of hematopoietic cells at the same time. Stimulating factors such as GM-CSF can promote the mobilization of hematopoietic stem/progenitor cells in bone marrow to peripheral blood, and its mechanism is related to breaking the balance of cytokines in bone marrow microenvironment. Some studies have shown that the expression of FAK mRNA and protein levels in bone marrow cells after cytokine stimulation significantly increased, resulting in the enhancement of cell proliferation and differentiation ability and exercise ability, indicating that FAK plays an important role in the maturation and exercise process of hematopoietic stem/progenitor cells in bone marrow microenvironment.

Adhesion factors (Adherins) are a class of regulatory factors that mediate the specific recognition and adhesion between cells and cells and between cells and matrix. They mainly include selectins, integrins and cadherins. FAK is the key molecule in integrin signal transduction pathway. After activating FAK, integrin can participate in many physiological functions and pathological changes of cells through multiple signal transduction pathways ex: FAK-Ras-MAPK pathway, FAK-STAT pathway, etc.

Chemokines are signal molecules that guide and drive the directional movement of cells. The most important factor in hematopoietic regulation is CXCL-12, which is a stromal cell-derived factor secreted by stromal cells. Its receptor CXCR4 plays an important role in the proliferation, differentiation, migration, homing of hematopoietic cells and the formation of immune organs. Studies have shown that it mainly regulates the homing or mobilization of hematopoietic stem/progenitor cells through the role of FAK.

3. FAK AND AML

The adhesion of AML cells to bone marrow stromal cells is a necessary condition for their survival and proliferation, and it can also avoid chemotherapy-induced apoptosis. The localization of AML cells in the bone marrow microenvironment is a multi-step process. First, adhesion molecules VLA4 and VLA5 support the transient adhesion of AML cells to fibrin. Then, the chemokine CXCL12 induces a stronger adhesion reaction, and FAK plays an important role in the signal pathway related to this adhesion reaction.

Christian Recher et al. tested 60 AML patients to evaluate the expression and phosphorylation level of FAK in AML cells and its function in adhesion flow and cell tolerance to drugs. The results showed that the expression of RNA and FAK protein was detected in 25 patients with AML, and its main phosphorylation site was Tyr397, which was an important functional region for the occurrence of FAK. In addition, the number of cells with FAK expression increased, the death time advanced, and the survival rate decreased. Previous studies have shown that normal CD34+cells do not express FAK, but this study found that 46% of AML patients have FAK

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202304_9(4).0030

expression in CD34+cells, and FAK+cells have a higher migration rate than FAK - cells, and the resistance to daunorubicin is also increased. In addition, using RNA interference technology, we found that FAK plays an important role in cell migration and drug tolerance in KG1 cell line of FAK+. This study is the first time to prove that FAK gene and protein, including CD34+AML cells, are detected in nearly half of AML patients.

In addition, Sonoda et al. found that FAK can activate Akt pathway and the expression of NF-KB-induced apoptosis inhibitor IAPs (cIAP-1, cIAP-2, XIAP) when treating HL-6O cells transfected with FAK cDNA with hydrogen peroxide and etoposide, resulting in cell resistance and cell insensitivity to radiotherapy. Lark et al. [5] found that FAK could increase the drug resistance of the CD34+acute myeloid leukemia cell line KG1 treated with daunorubicin.

4. FAK AND ALL

The maturation process of B cells in the blood system is also related to FAK. Research shows that immature B cells are mainly distributed in bone marrow hematopoietic tissue and interact with bone marrow microenvironment through CXCLl2-CXCR4 axis. CXCLl2/CXCR4 axis is very important for hematopoietic function and B lymphocyte production. The research found that FAK is the downstream signal molecule of CXCLl2-CXCR4 axis. It has been reported previously that CXCLl2 can induce the activation of FAK in various hematopoietic cell lines, mainly the tyrosine phosphorylation reaction of FAK. During the differentiation of primitive B cells, CXCL12 induces the sustained adhesion reaction, immature B lymphocytes have the sustained activation and phosphorylation reaction of FAK, while mature B cells only have the transient activation of FAK, This ensures that immature B cells continue to stay in the hematopoietic niche of bone marrow, while mature B lymphocytes are mainly in the peripheral blood circulation. Therefore, CXCL12 plays an important role in the residence and homing of hematopoietic stem cells in the hematopoietic microenvironment by mediating FAK.

Glodek et al. attempted to evaluate the role of FAK in cytokine-controlled human proB-ALL and migration and adhesion reactions, using two cell lines: human REH cells and mouse hematopoietic progenitor cells. The results showed that the activation of GTPase induced by CXCL12 in REH cells without FAK expression also decreased, indicating that FAK plays an important role in CXCL12-mediated signal transduction. In mouse hematopoietic progenitor cells, Cre-mediated FAK deletion resulted in CXCL12-induced damage of chemotaxis and adhesion. This indicates that FAK plays an important role in the signal pathway controlling the storage of hematopoietic cells and the development of various cell lines.

5. FAK AND CHRONIC MYELOID LEUKEMIA

Chronic myelocytic leukemia (CML) is a malignant clonal disease that occurs in hematopoietic stem cells. More than 95% of patients have ph chromosome and most of them express P120 fusion protein, a product of bcr-abl fusion gene. CML ph+cells escape the monitoring of normal cell proliferation and apoptosis control system, and the continuous proliferation and apoptosis tolerance is the fundamental reason for their survival in bone marrow and massive influx into peripheral blood.

It has been found that FAK has sustained activation and tyrosine phosphorylation in BCR/ABL gene transfected cells, but its role in leukemia cell generation is still unclear. Yi Le et al. used BCR-ABL-Ba F3 cell line (which is a pre-B lymphocyte transfected with BCR-ABL gene) and found that FAK gene silencing technology reduced cell proliferation and cloning, while increased cell apoptosis. In addition, it also prolonged the median survival period and the progression of leukemia, and increased the efficacy of imatinib BCR-ABL cells. This indicates that FAK is very important for the production of leukemia cells and may be a potential therapeutic target for leukemia. This mechanism is not completely clear. Some studies have

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202304_9(4).0030

reported that FAK is one of the downstream signal molecules of BCR-ABL, so FAK gene silencing may inhibit the leukemia response induced by BCR-ABL. For the study of apoptosis, some studies have found that FAK gene silencing can induce the apoptosis of AML cells dependent on caspase-8, but Yi Le et al. found that the apoptosis is dependent on caspase-3, so the specific mechanism still needs further study.

6. THE MECHANISM OF FAK IN THE OCCURRENCE AND DEVELOPMENT OF LEUKEMIA

6.1. Mediate cell adhesion and migration

Focal adhesion kinase can regulate the adhesion of cells to ECM. Together with integrin, FAK mediates the signal transduction pathway of cell and ECM adhesion. Current research shows that both FAK-Ras-MAPK and FAK-PI-3K pathways can regulate the reorganization of cytoskeleton, thus regulating cell adhesion and migration. It has been proved that Paxillin and Cas are directly connected with FAK. In vitro experiments show that both can be phosphorylated by FAK or Src. So as to regulate the cytoskeleton and then affect cell migration. The products of FAK-PI.3K pathway PI (3,4) P2 and PI (3,4,5) P3 are both related to cytoskeletal reorganization, thus regulating cell adhesion and migration.

Some studies have shown that the application of FAK inhibitors (anti-FAK pY397 antibody or FRNK) can significantly reduce cell movement. Shen et al. directly combined the adhesion spot localization region (FAT) with some signal molecules, and found that Src-FAT, P85-FAT and Grb7-FAT can stimulate cell migration when studying the regulatory role of FAK in cell migration and cell cycle.

6.2. Regulate cell proliferation and survival

Cell proliferation is closely related to ECM anchoring. The integrin-activated FAK-mediated MAPK pathway is responsible for this anchoring mechanism. Some cells in the body must be fixed to the surface of the matrix to proliferate, and also need growth factors and integrins to transmit signals. The activated MAPK can activate a variety of transcription factors, mediate the activity of FAK regulating gene expression, thus regulating cell proliferation and survival, and the enhanced Bcl-2 transcription caused by FAK-PI-3K pathway can also mediate this function.

From the analysis of the molecular structure of FAK, after its activation, tyrosine at the 397th position undergoes self-phosphorylation and becomes the binding site of Src family kinase with high affinity. The combination of the two forms the FAK/Src complex, further promoting its self-phosphorylation, and then activates Ras protein through complex signal transmission, which activates mitogen-activated protein kinase (MAPK). MAPK is a kind of protein kinase that widely exists in eukaryotic cells and has the double phosphorylation ability of serine and tyrosine. After being activated, the expression of c-fos and c-jun genes can be significantly enhanced. It can be seen that FAK, as a key signal molecule upstream of MAPK, plays an important role in cell adhesion, proliferation and migration. Some studies have found that FAK plays a decisive role in cell survival and death. Recently, it was found that the FAK pathway interacts with the extracellular matrix to activate ERK1/2, and then phosphorylates the Run2/cbfa-1 transcription factor, which regulates the expression of osteogenic genes, and finally induces the differentiation of human mesenchymal stem cells (hMSC) osteoblasts.

6.3. Closely related to cycle regulation

FAK regulates cell cycle mainly through Grb2-MAPK-Cyclin D1 signal transduction pathway. The entry of cells from G1 phase to S phase is related to the cyclin-dependent protease Cylin D. It was found that phosphorylation of Tyr925 site of FAK structure can combine with Grb2, activate MAPK enzyme, and then activate the expression of Cylin D1. The high expression of FAK

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202304_9(4).0030

can accelerate the cells from G1 phase to S phase. In addition, FAK activates ERKL/2 through Ras-Raf-ERK, and activated ERKL/2 can participate in mTOR signal pathway and cell cycle regulation by inhibiting TSC2 and inducing the expression of cyclinD1 and Cdk, respectively.

6.4. FAK inhibits apoptosis

Normal cells will undergo apoptosis when they lose matrix and lack adhesion, which is called anoikis. Apoptosis contributes to the integrity of the tissue and prevents the cells that lose the matrix connection from adhering to the position that is not suitable for growth. Overexpression of FAK in cancer cells can make the cells go beyond this growth inhibition, even in the absence of cell adhesion, turn to non-anchored growth, so that cancer cells lose growth inhibition and continue to proliferate. FAK plays an important role in cell and ECM survival signal transduction.

The exact way of preventing cells from apoptosis is still unclear, but FAK may play an important role in the activation of anti-apoptotic protein Bcl-2 by PI-3K. In addition, it can also inhibit apoptosis through FAK-P53 pathway. FAK can bind to p53 through its N-terminal FERM domain, and then inhibit the transcription of downstream genes activated by p53, including p21, Mdm2, etc. The products of these genes are important regulatory proteins of p53 induced apoptosis. FERM mediates the transport of FAK into the nucleus and binding with p53, and then binding with Mdm2, making p53 degrade and prevent apoptosis through ubiquitination pathway. It has been reported that the mechanism of FAK preventing cells from apoptosis may be the activation of PI-3 kinase-mediated protein kinase B/Akt apoptosis signal pathway.

6.5. FAK is closely related to angiogenesis

Tumor angiogenesis is a complex process of degradation and remodeling. Its steps include the degradation of vascular endothelial basement membrane and the migration and proliferation of endothelial cells to tumor tissue. MMPs are more important in the degradation enzyme system of ECM, and MMP-2 is considered as a regulator of tumor "angiogenesis switch". The study of MMP gene knockout showed that the growth of blood vessels and tumor in mice with MMP-2 gene deletion was slow. MMP-9 can bind to the cell surface through CD44 to promote angiogenesis, while FAK can affect the expression of MMP-2 and MMP-9 through FAK/Src-RAC-JNK signal pathway to affect tumor angiogenesis. VEGF combined with receptor Flk-l (total life kinase-1) can activate MAPK system through protein kinase C (PKC) or FAK-ras signal transduction pathway, causing endothelial cell proliferation and promoting angiogenesis.

Previous studies have proved that the overexpression or activation of FAK plays an important role in the occurrence, development, invasion and metastasis of tumors, which suggests that FAK may be a very good new target for tumor treatment. Because FAK is the upstream molecule of multiple signal pathways, inhibiting the function of FAK may block multiple tumor-related signal pathways, which may be a treatment strategy closer to the essence of leukemia.

ACKNOWLEDGMENTS

This paper was funded by Hospital level project of Binzhou People's Hospital (YBKTZR202117).

REFERENCES

[1] Gianeotti FG, Ruoslahti E. Integrin signaling. Science, 1999; 285: 1028-1032.

[2] Zhao JH, ReiskeH, Guan JL, et a1.Regmlation ofthe cell cycle by focal adhesion kinase. J Cell Biol, 1998; 143: 1997-2008.

ISSN: 2472-3703 DOI: 10.6911/WSRJ.202304_9(4).0030

[3] Sun Lan, Liu Wenli, Sun Hanying. Effect of ligustrazine on the expression of vascular endothelial growth factor in bone marrow stromal cells of irradiated mice. Chinese Journal of Experimental Hematology 2004,12 (1): 86-89.

[4] YANG M, LI K, LAM A C, et a1.Platelet-derived growth factor enhances granulopoisis via bone marrow stromal cells.[J].1nt J Hematol, 2001, 73(3): 327-334.

[5] Lark AL,et al.Overexpression of focal adhension kinase in primary colorectal carcinomas and colorectal liver metastases:immunohistochemistry and real-time PCR analyses.Clin Cancer Res, 2003, 9(1):215-222.