Molecular biological characteristics of ALK-positive anaplastic large cell lymphoma

E.V. Chernyshova, D.S. Abramov, D.M. Konovalov, S.S. Larin, N.V. Myakova

Federal Research Centre of Pediatric Hematology, Oncology and Immunology named after Dmitriy Rogachev;
1 Samory Mashela St., Moscow 117997, Russia

Contacts: *Абрамов Дмитрий Сергеевич abramovd_s@bk.ru*

ALK-positive anaplastic large cell lymphoma (ALK+-ALCL) is a heterogeneous group of mature T-cell non-Hodgkin's lymphoma, and is characterized by CD30/Ki-1 expression. Recently, value of various prognostic factors is investigated. These include clinical, histological and molecular genetic changes associated with different signaling pathways activation. Some features of the mechanism of action of anaplastic lymphoma kinases and targeted therapies possibilities addressed in this review.

Key words: *ALK-positive anaplastic large cell lymphoma, children, anaplastic lymphoma kinase, prognostic factors, signaling pathways, tyrosine kinase inhibitors*

Background

ALK-positive anaplastic large cell lymphoma (ALK⁺-ALCL) is a heterogeneous group of mature T-cell non-Hodgkin's lymphomas expressing CD30/Ki-1 antigen. ALK⁺-ALCL was recognized as independent nosological entity in the late 1980s, when the t(2;5)(p23;q35) recurrent translocation with subsequent aberrant expression of tyrosine kinase (later called anaplastic lymphoma kinase) was described in the group of CD30-positive anaplastic large cell lymphomas. 9 Among children with non-Hodgkin's lymphomas the frequency of this form accounts for approximately 10−20 %. The disease usually affects children and young people under 30 y. o., but there were some cases when the disease onset was observed in patients over 60 y. o.[1,2]

Clinical course of ALK-positive anaplastic large cell lymphoma is characterized by the lesions in lymph nodes with extranodal involvement of the skin, soft tissues, bones, lungs, liver, and brain. Most of the patients are diagnosed with ALK+-ALCL at stages III and IV with peripheral and abdominal lymphadenopathy, bone marrow lesions.[8]

ALK-positive anaplastic large cell lymphoma has a favorable prognosis. At the same time, there are some patients, who are refractory to therapy; 10−20 % of the patients relapse. Thus, searching for new molecular targets for therapy as well as identification of new markers for disease prognosis is still relevant.

Morphological and clinical factors of the ALK⁺-ALCL prognosis

The histological picture of ALK⁺-ALCL is variable; according to WHO classification, there are two morphological types of the disease: common type (fig. 1) and non-common type (fig. 2). Non-common type has several histological variants (ranked by their frequency): histiocytic, small cell, mixed cell (with several variants in the one affected area), giant cells (resembling Hodgkin's lymphoma), sarcomatoid.[6−8]

Tumor cells are characterized by mandatory expression of ALK, CD30, TIA-1 cytotoxic granule associated proteins, granzymes B and/or perforins; in most of the cases by expression of epithelial membrane antigen (EMA), and variable expression of T-cell antigens (CD2, CD3, CD4, CD8, CD5, CD7).[4, 5] Expression of pan-T-cell markers is usually not detected in the tumor cells at immunohistochemical analysis.[3]

Non-common histological variants of ALK⁺-ALCL can be associated with worse prognosis of the disease. For example, in one of the studies 361 patients with ALK⁺-ALCL were divided into two groups depending on the histological picture of the disease: the first one comprised patients with common morphological type (65 % from the total number of patients), the second one − those with
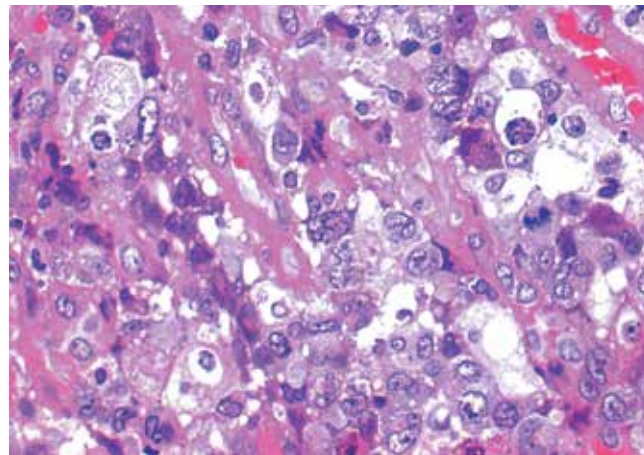

Fig. 1. *Common type ALK+-ALCL, hematoxylin and eosin staining, 60x magnification. Tumor cells are large, form solid structures, have intersinusoidal and parafollicular spread in the lymph node. Tumor cells have abundant cytoplasm, large bean-shaped or kidney-shaped nucleus; there are multinucleated cells, where nuclei are arranged in a wreath- or horseshoe-shaped pattern. The cells are characterized by high mitotic activity and large number of atypical mitosis figures.*
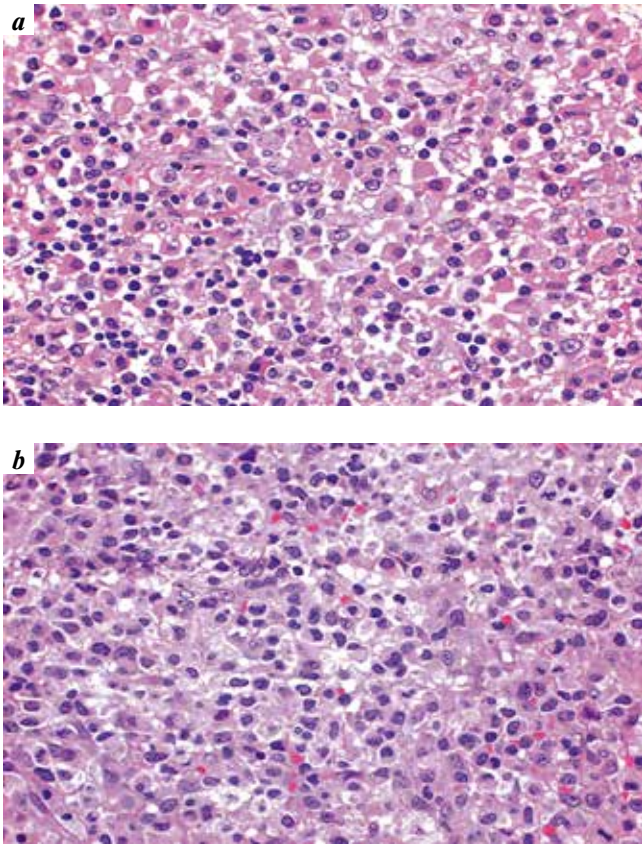
Fig. 2. *Non-common type ALK+-ALCL, hematoxylin and eosin staining, 60x magnification. Lymphohistiocytic varint (A), small cell variant (B). Lymphohistiocytic (LH) variant is a polymorphic neoplastic infiltrate, composed of scattered tumor cells mixed with a large number of histiocytes. Small cell (SM) variant is morphologically similar to other malignant lymphoproliferative diseases; tumor cells are located diffusely, their size does not exceed the size of a normal lymphocyte; there is no apoptotic activity, abnormal mitoses are present.*

non-common morphological type, mostly presented by lymphohistiocytic (LH) and small cell (SC) variants, together accounting for 32 % from the total number of cases. Patients with non-common morphological type were found to have a significantly worse prognosis. Moreover, this morphological type is associated with lesions of skin and mediastinum. The risk of lymphoma relapse was 4.7 times higher among patients with small cell histological variant ($n = 22$) comparing to those with common morphological variant. Patients with lymphohistiocytic variant ($n = 9$) had 1.5-fold increased risk of relapse.[25]

The following clinical factors are also associated with worse prognosis and increased risk of tumor relapse: lesions of mediastinum and skin, visceral involvement, increased concentration of lactate dehydrogenase (LDH), appearance of B-symptoms.[26–29]

The role of anaplastic lymphoma kinase in the disease pathogenesis

In the late 1980s several research groups have described a recurrent translocation in some CD30-positive anaplastic large cell lymphomas — t(2;5)(p23;q35).[9] The product was revealed in 1994; this was a recombinant protein of anaplastic lymphoma receptor tyrosine kinase (ALK) and nucleophosmin (NPM).[10] Further studies discovered more than 10 ALK translocation partners (table 1).[11–20]

Recombinant ALK proteins are involved in malignant transformation and were found in other types of cancer. Aberrant expression of ALK was described for the first time by Delsol et al. in diffuse large B-cell lymphoma, where neoplastic cells express plasma cell markers (CD138), CD4, but are negative for most B-cell markers and CD30-negative.[37] The discovery of recombinant TPM3-ALK and TPM4-ALK proteins in the myofibroblastic tumor cells (IMT) in 1999 confirmed the hypothesis regarding the involvement of ALK translocation in the development of this pathological condition. ALK expression is detected in 10 % of the cases in the cellular substrate of neuroblastomas, in glioblastoma and rhabdomyosarcoma cells.[45] Furthermore, tumor cells in patients with breast cancer were shown to express ALK with more aggressive course in case of pleiotrophin detection.[48] Recombinant TPM4-ALK protein can be found in patients with esophageal squamous cell carcinoma.[49] Finally, 6 % of the non-small cell lung cancer cases harbor EML4-ALK chimeric proteins.[15]

Anaplastic lymphoma kinase, also known as CD246, belongs to the superfamily of insulin receptors. ALK molecule consists of an extracellular ligand-binding domain (which contains glycine-rich repeats, LDL and MAM), transmembrane domain, and cytoplasmic domain, possessing catalytic activity. Pleiotrophin and midkine are considered as ALK ligands, their expression ensures embryonic development of the nervous system, neuronal migration and angiogenesis.[31] Physiological role of the ALCL kinase in adults is still unclear; however the patients, receiving tyrosine kinase inhibitors (crizotinib), were observed to have unexplained side effects, such as bradycardia, decreased testosterone level in men, visual impairments.[32–34]

Oligomerization of the kinase domains of recombinant proteins imitates binding of a ligand to tyrosine kinase; this is a trigger for activation and conduction of the key signals for cells growth and proliferation. So, Ras-ERK signaling pathways are required for proliferation, while JAK3-STAT3 and PI3K/Akt pathways define phenotype changes and immortalization of ALCL cells.[8,30] Schemes of the main intracellular cascades, involved in malignant transformation of cells, are described below.

JAK3-STAT3 signaling pathway[30]

Immortalization of tumor cells is ensured by the activation of signal-transducing proteins and transcription activators STAT3. STAT-proteins are phosphorylated by JAK kinases, afterwards they dimerise and translocate to the nucleus in order to initiate the transcription of anti-apoptotic factors and cell cycle regulators — BCL2, BCL2BL1, CEBPB, MCL1, cyclins (figure 3).

RAS-ERK signaling pathway 30

Docking of several adaptors (IRS-1, SHC1, SRC) on the specific tyrosine residues of ALK is necessary to trigger

Table 1. *Translocations involving ALK gene 4,8*

Translocation	Partner protein	Frequency, %	Recombinant protein (kDa)	Cellular localization	Tumor type
t(2;5)(p23;q35)	NPM (nucleophosmin)	70—80	NPM-ALK (80)	Nucleus, nucleoli, and cytoplasm	ALK+ ALCL; ALK+ DLBCL
t(1;2)(q25;p23)	TPM3 (tropomyosin 3)	12—18	TPM3- ALK (104)	Cytoplasm	ALK+ ALCL; IMT
t(2;3)(p23;q21)	TRK-fused gene (TFG)	2	TFG-ALK (113, 97, 85)	Cytoplasm	ALK+ ALCL;
inv (2)(p23;q35)	ATIC	2	ATIC-ALK (96)	Cytoplasm	ALK+ ALCL; IMT
t(2;17)(p23;q23)	CLTC1 Clathrin heavy chain-like 1	2	CLTC1-ALK (250)	Granular cytoplasmic	ALK+ ALCL; ALK+ DLBCL; IMT
t(2;X)(p23;q11—12)	MSN (moesin)	< 1	MSN-ALK (125)	Cell membrane	ALK+ ALCL;
t(2;19)(p23;p13)	TPM4 (tropomyosin 4)	< 1	TPM4-ALK (95—105)	Cytoplasm	ALK+ ALCL; IMT
t(2;17)(p23;q25)	ALO17	< 1	ALO17-ALK (−)	Cytoplasm	ALK+ ALCL
t(2;2)(p23;q13) orinv(2)(p23;q11−13)	RANBP2 (RAN binding protein 2)	< 1	RANBP2-ALK (160)	Nucleoli	IMT
t(2;22)(p23;q11.2)	MYH9 (non-muscle myosin heavy chain)	< 1	MYH9-ALK (220)	Cytoplasm	ALK+ ALCL
t(2;11;2)(p23;p15;q31)	CARS (cysteinyl-tRNA synthetase)	< 1	CARS-ALK (130)	−	IMT
ins (3'ALK)(4q22−24)	−	< 1	−	Granular cytoplasmic	ALK+ DLBCL
t(2;4)(p23;q21)	SEC31L1 (SEC31 homologue)	< 1	SEC31L1-ALK (−)	Cytoplasm	IMT
inv(2)(p21;p23)	EML4	6	EML4-ALK (−)	−	NSCLC

ALK, anaplastic lymphoma kinase; ALCL, anaplastic large cell lymphoma; IMT, inflammatory myofibroblastic tumor; DLBCL, diffuse large B-cell lymphoma; NSCLC, non-small cell lung cancer

Ras-ERK signaling cascade. After that, this complex of molecules interacts with SHP2-GRB2, causing Ras activation, which in turn phosphorylates ERK1 and ERK2 transcription factors (figure 3). As a result of ERK1 and ERK2 phosphorylation, p21 protein is inactivated, the activity of cyclins D3 and A increases, which eventually leads to unregulated cell cycle and growth. Moreover, activation of the Ras-ERK pathway induces phosphorylation of mTOR targets: ribosomal protein S6 kinase (p70S6K), S6 ribosomal protein (S6RP), inactivation of 4E-binding protein (EIF4EBP), which leads to ribosomal biogenesis and protein synthesis. Direct binding of phospholipase C with a tyrosine residue of ALK also occurs. Phospholipase C catalyzes the hydrolysis of phosphatidylinositol into two important second messenger molecules: diacylglycerol (DAG) and inositol triphosphate (IP3). Inositol triphosphate, binding to Ca^{2+}-channels of the endoplasmic reticulum, induces Ca^{2+} release, increasing the concentration of this ion in cytoplasm. In the presence of Ca^{2+}, diacylglycerol activates protein kinase C (figure 3).

PI3K-Akt signaling pathway[30]

NPM1-ALK binds p85 regulatory subunit of PI3K, which effectors are AKT1 and AKT2. They inactivate proapoptotic factor BAD and block FOXO3 molecules by phosphorylation of amino acid residues Tyr24, Ser256, Ser319. The targets of FOXO3 are the genes transcribing the molecules that mediate apoptosis, blockers of the cell-cycle at G1 phase and metabolic blockers (figure 3).

JunB − signaling pathway[36]

The start of RAS-ERK and PI3K-akt signaling cascades acts as a trigger for the Junb family proteins, which create a transcription factor AP-1 by forming homo- and heterodymers. The targets for AP-1 factor are the genes, responsible for the synthesis of proteins, involved in the regulation of proliferative activity and apoptosis. Activation of JunB-signaling pathway initiates the expression of CD30 antigen and GzB protein in ALK+-ALCL cell cultures, this indicates the involvement of GzB in pathogenesis of ALK-positive anaplastic large cell lymphoma (figure 3).

Clinical value of anaplastic lymphoma kinase

Anaplastic lymphoma kinases are an attractive target for the therapy (use of inhibitors) since they are widely spread in the tumor tissues, but their expression and functioning are limited in the normal tissues. Crizotinib (PF-02341066) seems to be among the most interesting drugs for clinical practice. Its pharmacological action
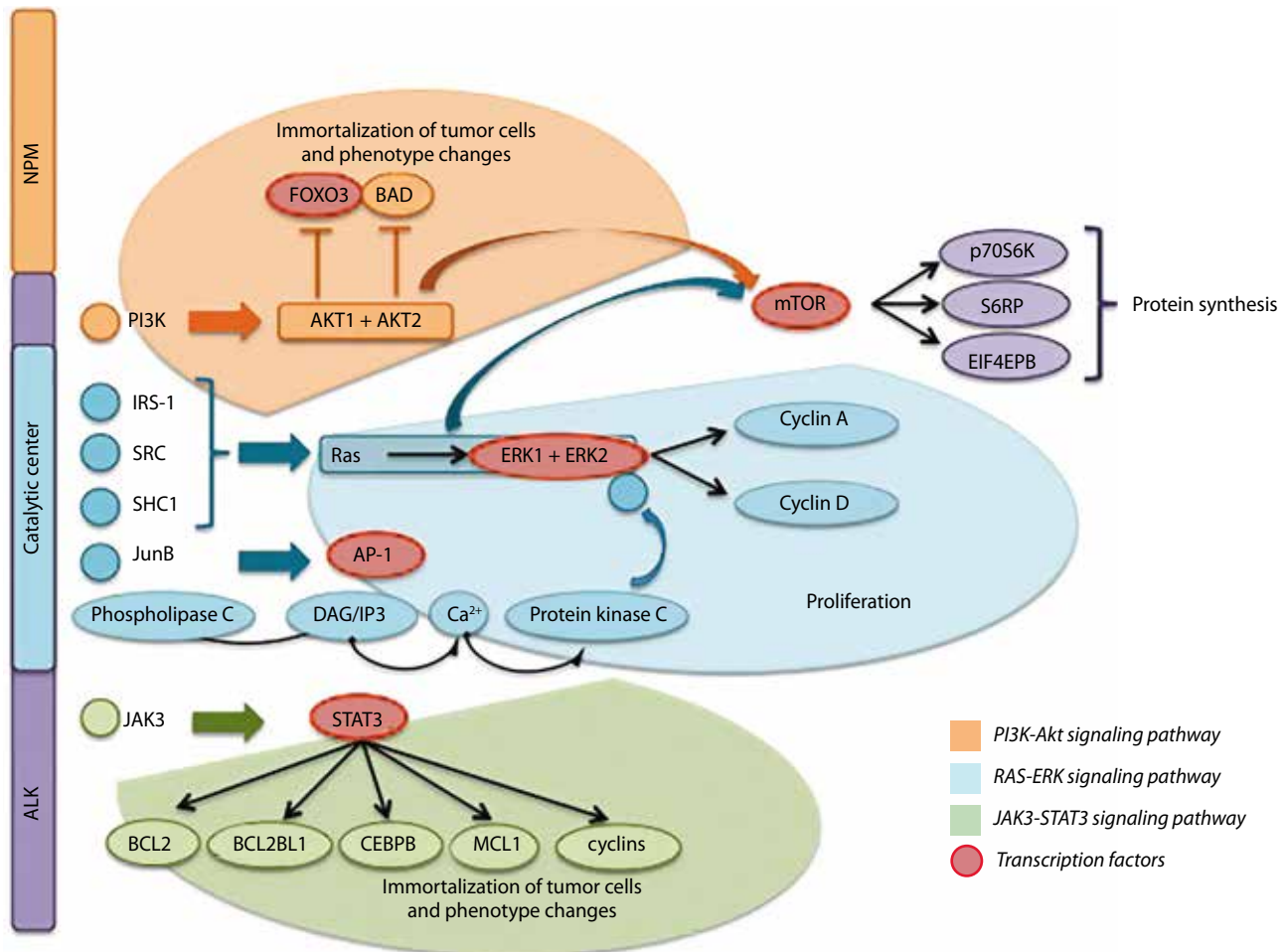
Fig. 3. *General scheme of intracellular signaling cascades of anaplastic lymphoma kinase recombinant proteins.*

is based on binding intracellular kinase domain. 8,51 *In vitro* studies have shown a dose-dependent decrease of ALK autophosphorylation. Crizotinib induces apoptosis in the cell lines, containing ALK gene translocation products, particularly Karpas-299 (NPM-ALK), SU-DHL-1 (NPM-ALK), NCI-H3122 (EML4-ALK). The use of crizotinib in clinical trials demonstrated a dramatic improvement of the prognosis in patients with ALK-positive non-small cell lung cancer. Median progression-free survival was 7.7 months in the group of crizotinib, while among patients receiving standard chemotherapy it was only 3 months. Objective response rate was 60 % and 20 % in the group of crizotinib and standard chemotherapy respectively. The use of crizotinib for treatment of ALK⁺-ALCL relapses and inflammatory myofibroblastic tumors has also shown a convincing effect.

Despite the brilliant results of clinical trials of crizotinib in ALK-positive tumors, most of the patients have early relapses during the first year and develop resistance to the drug. There are two main mechanisms of crizotinib resistance. The most common cause is ALK-gene mutation and amplification, leading to the decline in inhibition efficiency. The detection of F1174 and I1171 mutations in the kinase domain during the treatment of ALK⁺-ALCL

should be considered as a sufficient reason for use of next generation tyrosine kinase inhibitors. The second mechanism of drug resistance development implies starting of alternative intracellular cascades by the tumor cells. Activation of STAT3 and EMT signaling pathways in the cells of non-small cell lung cancer leads to escape of the tumor from immune surveillance. Combined therapy with crizotinib and STAT3-inhibitors restores the sensitivity of crizotinib-resistant cells. New inhibitors of the PI3K/AKT/mTOR signaling pathways induce apoptosis and autophagy of neuroblastoma cell lines.

Conclusion

ALK-positive anaplastic large cell lymphoma is a group of mature non-Hodgkin's T-cell lymphomas, which tumor cells contain tyrosine kinase recombinant proteins. Malignant transformation is driven by aberrant activation and strengthening of key intracellular signaling cascades. The discovery of ALK recombinant proteins and their role in the pathogenesis of the disease has lead to growth of interest to tyrosine kinase inhibitors, including crizotinib and next generation ALK-inhibitors. At the same time, there is a group of patients, who have early relapses and develop the resistance to tyrosine kinase inhibitors. Simultaneous use

of crizotinib and other inhibitors of intracellular signaling cascades may be more rational. Thus, further investigation of the malignant transformation mechanisms along with searching and implementation of the new inhibitors of transcription factors, activated in ALK signaling cascades, is a promising direction in the development of new drugs.

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