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Review

Research progresses in the pathogenesis of anaplastic large cell lymphoma

Xiao-Lan Shi, Xiao-Wen Tang and De-Pei Wu

Abstract

Anaplastic large cell lymphoma (ALCL) is a distinct subset of T-cell non-Hodgkin's lymphoma. As a consequence of its low incidence, general pathogenic consideration of ALCL is lacking. In this review, we summarize the pathogenesis, epidemiology, clinical manifestations, and treatment of ALCL, so as to better understand key stages of the development of this disease and provide valuable information for future treatment.

Key words Anaplastic large cell lymphoma, anaplastic lymphoma kinase, pathogenesis

Anaplastic large cell lymphoma (ALCL), an aggressive non-Hodgkin's lymphoma (NHL), is classified as a type of peripheral T-cell lymphoma by the World Health Organization (WHO) and accounts for 2% to 7% of diagnosed NHL cases. ALCL has several distinct characteristics: tumor cells are anaplastic and strongly CD30 (Ki-1)-positive, tending to grow in clusters and invade lymph nodes; about half of the patients with ALCL have abnormal oncogenic anaplastic lymphoma kinase (ALK) fusion proteins. ALCL tumors are divided into ALK-positive (ALK^+ ALCL) and ALK-negative ALCL (ALK^- ALCL), according to the expression of ALK. Because of a low incidence of ALCL and poor understanding of the pathogenesis, clinical awareness of ALCL is limited and the disease is commonly misdiagnosed. This review focuses on the research progresses of its pathogenesis and briefly covers ALCL epidemiology, clinical features and treatment.

Epidemiology

According to the U.S. epidemiological survey, from 1992 to 2001, ALCL accounted for about 0.8% of all lymphomas and 13.9% of T/NK cell lymphomas; the annual incidence was 0.25 per 100 000 people, which was higher among Caucasians and African Americans (0.34 and 0.38 per 100 000 people, respectively) over Asian Americans (0.17 per 100 000 people). The incidence ratios of male to female were 1.9 (Caucasians), 2.0 (African Americans) and 1.3 (Asian Americans). According to the WHO classification, ALCL accounts for 3% of adult lymphomas and 10% to 30% of child lymphomas. In Asia, ALCL has a lower overall incidence.

Pathogenesis

ALK^+ ALCL

Recent advances in clinical and basic researches showed that ALK^+ ALCL may originated from transformed T lymphocytes and the pathogenesis was mainly associated with ALK-related chromosomal translocation[1]. However, the causes for chromosomal translocation (such as DNA damage, especially double-stranded DNA breaks, and DNA repair, in particular those involving non-homologous DNA recombination) and the exact origin of tumor cells are still poorly understood.

Molecular structure and physiological function of ALK In the 1980's, ALK (CD246), as a new receptor tyrosine kinase (RTK) belongs to the insulin receptor superfamily, was identified through studies of ALCL chromosomal translocation [2,3]. In human beings, the *ALK* gene (GenBank accession No.U62540, U66559) is localized at 2p23 and has 26 exons; the 6222 bp cDNA

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encodes a 1620-aa type-I transmembrane protein with a predicted molecular weight of 177 kDa; after post-translational modification (mainly N-glycosylation), mature ALK has an apparent weight of 200 kDa. In mice, the *Alk* gene (GenBank accession No.D83002) is localized on chromosome 17 and encodes a 1621-aa protein Alk, sharing 85% homology with human ALK. ALK consists of a 1030-aa N-terminal extracellular segment, a 28-aa transmembrane segment, and a 562-aa C-terminal intracellular segment (Figure 1). The extracellular segment contains 1) a signal peptide (the hydrophobic 26-aa N-terminal) guiding transmembrane traffic; 2) a ligand-binding domain (residues 391–401) binding endogenous ligand pleiotrophin (PTN) or midkine (MK); 3) a low density lipoprotein-A (LDL-A) and MAM domain (residues 480–635, a homology domain of meprins, A-5 protein and receptor protein tyrosine phosphates mu), of which MAM domain may be involved in intercellular interactions; 4) a glycine-rich domain close to a transmembrane segment; and 5) 16 N-glycosylation sites (NXS/T) and 26 serine residues (residues 425–487 and 987–1021 forming two serine clusters). The intracellular segment includes 1) a membrane-peripheral region (residues 1059–1122) containing a binding site (residues 1093–1096) of insulin receptor substrate-1 (IRS-1), facilitating a tyrosine phosphorylation-dependent interaction; 2) a tyrosine kinase catalytic region (residues 1123–1376) containing the kinase activity loop that consists of three-tyrosine motif (Y1278, Y1282 and Y1283), and the tyrosine phosphorylation-dependent Src binding site; and 3) the C-terminal region (residues 1377–1620) containing tyrosine phosphorylation-dependent SH2 domain-containing transforming protein (Shc) and phospholipase C-gamma (PLCγ) binding sites (residues 1504-1507 and residues 1603–1606, respectively)[4].The three-tyrosine motif in the tyrosine kinase catalytic region is the major self-phosphorylation site of the insulin receptor superfamily. Tyrosine self-phosphorylation changes the conformation of the activity loop, facilitating the access of ATP into the ATP-binding pocket and activating ALK.

In normal tissues, spatiotemporal expression of ALK is restricted, peaking during the prenatal period and decreasing rapidly after birth. In human beings, *ALK* mRNA is predominantly transcribed in the brain and

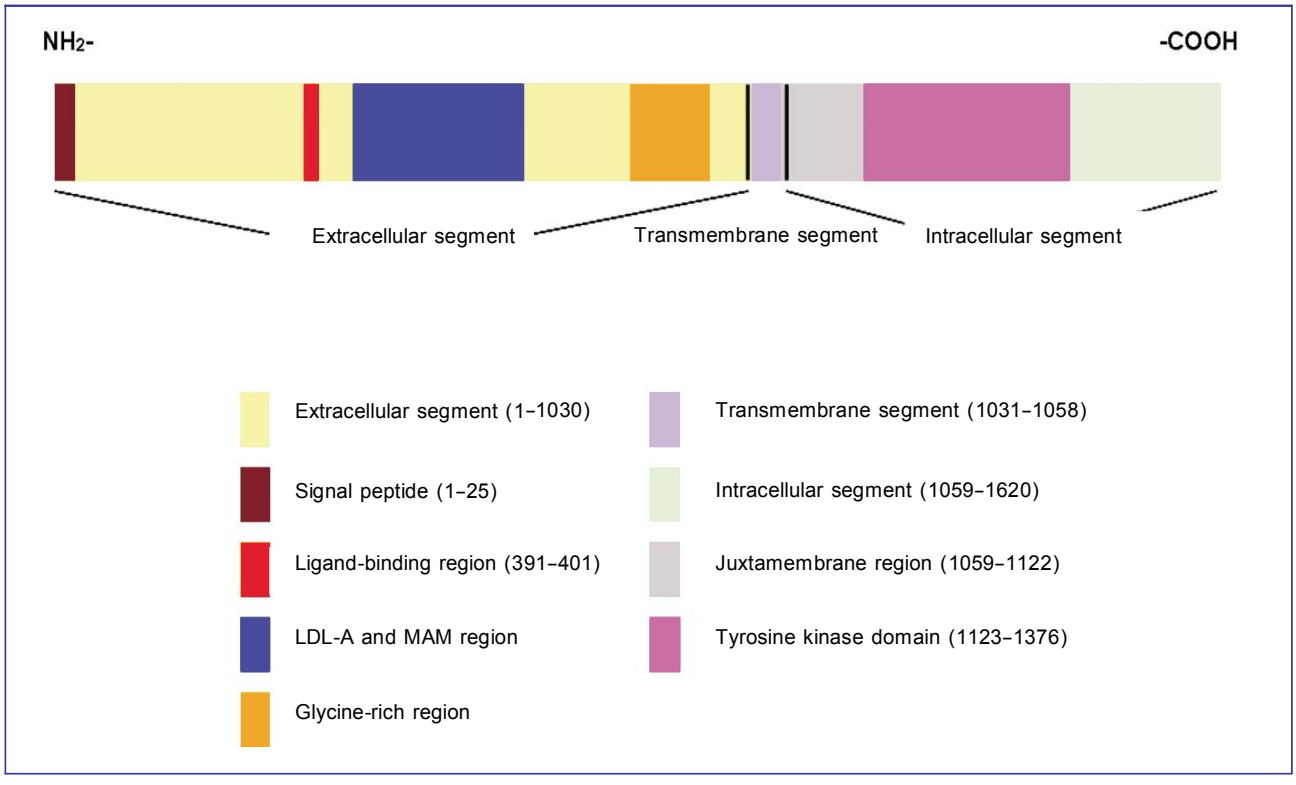

Figure 1. **Schematic representation of the full-length anaplastic lymphoma kinase (ALK) protein**. Full-length ALK is a single-pass transmembrane protein containing 1621 amino acid residues which can be divided into three parts: extracellular (N-terminal), transmembrane, and intracellular (C-terminal) segments. The extracellular segment mainly contains four functional domains: a signal peptide, a ligand-binding region, a LDL-A and MAM region, and a glycine-rich region (numbers in parenthesis represent the spanning amino acid residues of each region). The intracellular segment contains two major domains: a tyrosine kinase domain and a juxtamembrane region.

intestinal nervous tissues, scattering in the testis, placenta, and fetal liver; in mic e, *Alk* mRNA is predominantly transcribed in the brain and peripheral nervous system. Alk may function as a dependence receptor (inhibiting apoptosis at the presence of ligand and inducing apoptosis after ligand removal) regulating cell survival by interacting with PTN or MK, thus participating in the nervous system development. However, *Alk*-knockout mice show no obvious developmental defects in morphology or function, suggesting that ALK is not a key regulator in mammalian development[5].

ALK in ALK+ ALCL ALK is expressed in certain non-hematologic tumors (such as rhabdomyosarcoma, glioblastoma and breast cancer) and a few hematologic tumors (such as few diffuse large B-cell lymphoma)[4]. However, the high expression of ALK in ALK+ ALCL is due to the chromosomal translocation of *ALK* gene. Most breaks occur in the intron between exons 16 and 17. As exons 17 through 26 encode the intracellular segment of ALK, the C-terminal segment of the fusion/chimeric protein lacks the extracellular and transmembrane segments. Since all partner protein genes at the 5' end of the *ALK* fusion gene are widely expressed, the ALK fusion protein is constitutively expressed under the control of the 5' end partner protein gene promoter in ALK+ ALCL. In addition, some partner proteins at the N-terminus of the ALK fusion protein contain a coiled-coil domain (such as TFG and TPM), or a hydrophobic region (such as NPM), or are an inherent homodimer or multimer (such as ATIC and CLTC). Therefore, ALK fusion proteins can form homologous or heterologous oligomeric complexes. The MSN-ALK fusion protein is an exception, however. Although moesin has no oligomeric motif, it can attach ALK onto the cell membrane, facilitating ALK interactions with its partners. Although ALK fusion proteins lack the extracellular ligand-binding segment, oligomerization can lead to ALK activation and self-phosphorylation, thereby activating a series of downstream signaling pathways[6].

The prognosis of many patients with *ALK* chromosomal translocation is similar, indicating that ALK activation may be a key link in the pathogenesis of ALK+ ALCL. Thus *NPM-ALK* translocation, the most frequent translocation of *ALK*, has became the "molecular machine" model from which almost all chimeric ALK signaling pathways originate[1,6]. Studies showed that, through several intracellular signaling pathways, activated ALK regulates cell proliferation, apoptosis, morphology, migration, and invasion, regulates tumor cell phenotype and mediates tumor cell transformation. As a short-range positive feedback mechanism ensuring continuous activation of ALK, some downstream molecules (such as Src and Jak3) phosphorylate ALK.

Regulation of the cell cycle and apoptosis by ALK

Activated ALK regulates cell proliferation and apoptosis mainly through the Ras-extracellular signal-regulated kinase (Erk), Janus kinase 3 (JAK3)-signal transducers and activators of transcription 3 (STAT3), and phosphatidylinositol 3-kinase (PI3K)-Akt/protein kinase B (PKB) signaling pathways (Figure 2).

As mentioned, the tyrosine phosphorylation sites in the tyrosine kinase (TK) domain of activated ALK recruit Src; the tyrosine phosphorylation sites in the membrane-peripheral regions and C-terminal segment recruit IRS-1 and Shc, respectively, activating the Ras-Erk pathway[7,8]. However, recent studies suggest that the recruitment of IRS-1 and Shc is not the key step in activating the Ras-Erk pathway. Activated ALK can recruit and activate SH2 domain-containing tyrosine phosphatase 2 (Shp2), activate the Ras-Erk pathway by triggering growth factor receptor-bound protein 2-son of sevenless (Grb2-SOS) or Src[9,10]. In addition, the ALK C-terminus contains a PLCγ-binding site, facilitating PLCγ interaction and activation, stimulating the Ras-Erk pathway via PLCγ-DAG/IP3-Ca^{2+}-PKC[11]. Activated Ras-Erk can up-regulate cyclin A and cyclin D1, activate activated protein-1 (AP1)[12], and phosphorylate and activate Jun N-terminal kinase (JNK), which in turn phosphorylates c-Jun and activates AP1; activated AP1 can induce the expression of cyclin A and cyclin D3, and down-regulate p21 expression[13]. Mammalian target of rapamycin (mTOR) may also be activated by the Ras-Erk pathway, triggering its downstream effectors such as p70 ribosomal protein S6 kinase (p70S6K), S6 ribosomal protein (S6RP), and eukaryotic initiation factor 4E-binding protein 1 (eIF4EBP1)[14]. In summary, activated ALK facilitates Ras-Erk pathway activation, the up-regulation of cyclins (cyclin A, cyclin D1, and cyclin D3), the down-regulation of cyclin kinase inhibitor (p21), and the activation of protein translation-related regulatory factors (p70S6K, S6RP, eIF4EBP1), accelerating cell proliferation and inhibiting apoptosis.

Activated ALK can activate STAT3 directly by phosphorylation or indirectly by activating Jak3, which in turn phosphorylates and activates STAT3. Activated STAT can form a homodimer and functions as a transcription factor, inducing the transcription of some anti-apoptotic and pro-proliferation factors, such as Bcl-2, Bcl-X_L, myeloid cell leukemia sequence 1 (MCL1), and cyclin D3, while activating anti-apoptotic transcription factors, such as survivin and CEBPβ[15-18]. In addition, Jak2-STAT5B may induce cell proliferation and inhibit apoptosis by cooperating with Jak3-STAT3[19].

Activated ALK can activate PI3K by binding to the p85 subunit of PI3K; activated PI3K phosphorylates and activates Akt1/Akt2, and then insulates Bad and suppresses p27 by phosphorylation[20-22]. In addition, forkhead box transcription factor O3A (FOXO3A) can be

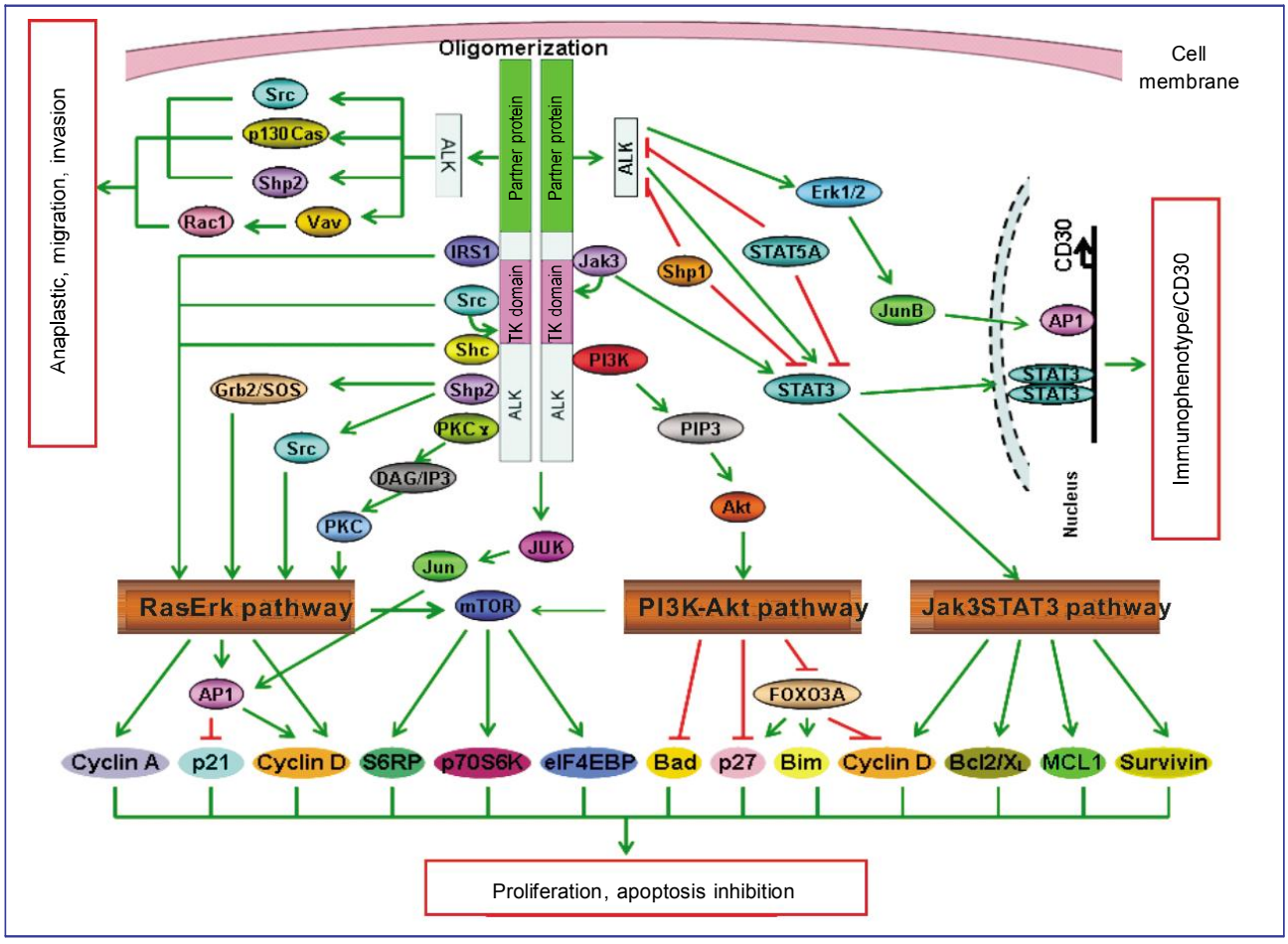

Figure 2. **Roles of ALK in the pathogenesis of ALK$^+$ anaplastic large cell lymphoma (ALCL)**. After spontaneous oligomerizaton or induction by cytoplasmic factors, the activation of chimeric ALK triggers transforming events, such as proliferation and apoptosis inhibition, cellular immunophenotyping (CD30 up-regulation), and abnormal morphological changes (anaplasia), migration and invasion. Following ALK activation, the recruitment of IRS-1, Src, and Shc and the subsequent stimulation of Shp2-Grb2/SOS, Shp2-Src, and PLCγ-DAG/IP3-PKC could synergistically activate the RAS-Erk pathway, up-regulating the expression of cyclin A and cyclin D, and down-regulating the expression of p21, which could also be a target of the JUK-Jun-AP1 pathway triggered by ALK activation. In addition, the PI3K-PIP3-Akt and Jak3-STAT3 pathways also could be triggered by the activation of ALK. As a result, cyclin D expression would be abnormally regulated, the expression of Bcl2/Bcl-X_L, Bim, MCL1, survivin would be up-regulated, whereas the expression of p27 and Bad would be down-regulated. Consequently, these abnormally regulated cell cycle- and apoptosis-related molecules could stimulate cell proliferation and inhibit apoptosis. Moreover, Ras-Erk and PI3K-PIP3-Akt activation could target mTOR to stimulate certain translation-associated factors (such as p70S6K, S6RP, and eIF4EBP1) and enhance cell proliferation. Stimulating the Ras-Erk and Jak3/STAT3 pathways could induce JunB phosphorylation and AP1 up-regulation, and STAT3 dimerization in the nucleus, respectively. As a result, the transcriptional activity of *CD30* gene would increase. The simulation of Src, Shp2, p130Cas, and Vav-Rac1 could be induced by ALK activation. As a consequence, cytoskeletal arrangement and dynamics would be abnormally regulated, inducing changes in morphology (anaplasia) and transformation (migration and invasion). Green arrows represent activation or up-regulation; red semi-bars represent inhibition or down-regulation.

phosphorylated by activated Akt, which can block its entry into the nucleus, thereby inhibiting the expression of p27 and Bim while up-regulating cyclin D2[23]. These signals synergistically orchestrate the inhibition of apoptosis and abnormal cell cycle progression. Moreover, Akt activation can also activate the mTOR pathway, but its effect is weaker than Ras-Erk pathway[14,24].

Regulation of cell immunophenotype by ALK The activation of ALK stimulates the Ras-Erk pathway, then phosphorylates JunB and up-regulates AP1. In addition, activation of the Jak3/STAT3 pathway leads to the dimerization of STAT3 after being phosphoryled, resulting in the up-regulation of CD30 transcription[18,25].

Regulation of cell transformation, migration, and invasion by ALK Activated ALK activate several downstream effectors (Src, Shp2 and p130 Crk-associated substrate) which can cause the

rearrangement of cytoskeletal proteins, such as filamentous actin, whose abnormal assembly can lead to cell deformation [8,10,26]. In addition, activated ALK can phosphorylate guanine nucleotide exchange factors (GEFs) from the Vav family, which in turn can activate GTPase (such as Rac1) from the Rho family and induce cell migration and invasion[27].

Other mechanisms underlying the pathogenesis of ALK⁺ ALCL Recent studies have shown that Shp1 and STAT5A promoters are hypermethylated in ALK⁺ ALCL, inhibiting their transcriptional activity. Shp1 can inhibit the activity of ALK and STAT3, and STAT5A also represses ALK activity, therefore, the suppression of Shp1 and STAT5A may promote the tumorigenesis of ALCL [28,29], supporting the hypothesis that epigenetic suppression plays a role in the pathogenesis of ALK⁺ ALCL.

In addition to being a cell surface antigen in ALK⁺ ALCL, CD30 is involved in the pathogenesis. Although the underlying mechanism is not clear, CD30 is closely related to ALCL staging. At early onset, CD30 expression and activation can induce cell apoptosis, then CD30 participates in a series of regulatory steps involving the cell cycle and apoptosis by activating the NF-κB pathway (both canonical and non-canonical)[1,18,30].

Furthermore, other studies suggest that heat shock protein 90 (HSP90), Suc-associated neurotrophic factor-induced phosphorylated target/fibroblast receptor substrates (SNT/FRS), and nuclear interacting partner of anaplastic lymphoma kinase (NIPA) are also involved in the cell transformation of ALK⁺ ALCL, but the underlying mechanisms need further clarification[1].

Current studies on ALK⁺ ALCL pathogenesis are limited to the functions of ALK. Little is known about its partner proteins, with understanding restricted to their effects on ALK subcellular localization. Note that many studies on signaling pathways are based on experiments *in vitro* or with cell lines and may not reflect the scenario *in vivo*. For example, many studies have shown that *NPM-ALK* transgenic mice and cells do not necessarily develop into ALCL. Therefore, the exact mechanism of pathogenesis of ALK⁺ ALCL requires further research and clinicians need to be very cautious before using particular signal molecules for targeted therapy.

ALK⁻ ALCL

ALK⁻ ALCL is classified as a CD30⁺ T cell lymphoma, possessing morphologic characteristics similar to ALK⁺ ALCL. Its epidemiological characteristics and clinical manifestations are highly heterogeneous and in general, ALK⁻ ALCL has a poorer prognosis than ALK⁺ ALCL. As a consensus on immunophenotype, cytogenetics, and molecular characterization is not established, there are no internationally accepted diagnostic criteria for ALK⁻ ALCL. In the 2008 WHO classification, ALK⁻ ALCL is classified as a separate disease, possessing a similar morphology to ALK⁺ ALCL[31].

In absence of exact etiology, specific genetic mutation, and characteristic genetic markers, the pathogenesis of ALK⁻ ALCL is poorly understood. However, when comparing indicators of clinical treatment and prognosis with the abnormal expression of molecules associated with ALK⁻ ALCL, investigators found that apoptotic dysregulation may be involved in ALK⁻ ALCL pathogenesis. The infiltration of activated cytotoxic T lymphocytes (CTLs) has been observed in ALK⁻ ALCL [32]. Granzyme B, which is released from CTLs, can induce cell apoptosis directly by activating Caspase-3 or indirectly by activating Bid, leading to the release of cytochrome C from mitochondria [33,34]. ALK⁻ ALCL cells have been shown to express protease inhibitor 9 (PI9), which functions as an intracellular serine proteinase inhibitor that inhibit tumor cell apoptosis by inhibiting the activity of CTL-released granzyme B [35,36]. Meanwhile, due to a feedback regulatory mechanism, increased tumor infiltration by activated CTLs enhances cell apoptosis in the surrounding normal tissues. Furthermore, ALK⁻ ALCL cells have a higher expression of Bcl-2 and other anti-apoptotic proteins, which can inhibit the mitochondria-mediated apoptosis pathway, and lower expression of caspase-3 precursor, which also can inhibit apoptosis [37]. However, the above pathways involving in the inhibition of apoptosis are not unique to ALK⁻ ALCL; on the contrary, many tumors use similar mechanisms to suppress apoptosis. Therefore, some investigators suggest that ALK⁻ ALCL may represent the end-stage pathology of various T-cell lymphomas[38].

Clinical Manifestations

Clinical symptoms of ALK⁺ ALCL are as follows: (1) early onset, most patients are less than 30 years old[39,40]; (2) male predominance, with a male to female ratio of 1.2–2:1; (3) superficial and abdominal lymphadenectasis often appears, large tumors are very common, accounting for 30%–54%, accompanied by inguinal lymphadenectasis in about 40% of the pediatric cases; mediastinal invasion is rarer in ALCL than in Hodgkin disease (HD); 25% of the patients have splenomegaly; (4) most patients are already in the late stage (stage III–IV) at diagnosis and are often accompanied by B symptoms (75%), especially a high temperature[40,41]; (5) extranodal invasion is common (60%) and about 40% of the patients have 2 or more extranodal lymphomas; (6) bone marrow metastases are detected in 11% of the patients by HE staining and in 30% of the patients by

immunohistochemical staining (expression of CD30 and p80 in bone marrow cells).

ALK$^-$ ALCL usually occurs in an older population (mostly aged 45 to 60 years old). Hodgkin-like ALCL in a younger population and 85% of the patients are ALK$^-$ and are usually in stage IIA. About 60% of the patients have an enlarged mediastinum, but have no skin or bone metastasis. These clinical manifestations are significantly different from that of ALK$^+$ ALCL[42,43]. Secondary ALCL, derived from other lymphomas such as mycosis fungoides, peripheral T-cell lymphoma, HD, and lymphomatoid papulosis, often occurs in older people. ALK- typing predicts poor prognosis. In 2008, Savage *et al.*[44] showed that ALK$^-$ ALCL has a similar incidence of extranodal invasion as ALK$^+$ ALCL. ALK$^+$ ALCL frequently metastasizes to the bone marrow, bone, subcutaneous tissue and spleen, whereas ALK$^-$ ALCL frequently metastasizes to the skin, liver and gastrointestinal tract.

The ALCL involving peripheral blood and bone marrow metastasis was termed as the "leukemic phase" ALCL, and has a low incidence and poor prognosis, regardless of ALK expression[45].

Treatments

Because of a low incidence of ALCL, its treatment and prognosis have seldom been reported, and there were no standardized treatment protocols of ALCL. Most studies on ALCL treatment are retrospective, focusing on conventional chemotherapy or high-dose chemotherapy combined hematopoietic stem cell transplantation. Currently, most ALCL patients are treated with multidrug combination chemotherapy supplemented with radiotherapy. The patients with ALK$^+$ ALCL are sensitive to chemotherapy and have a higher long-term survival rate. The 5-year survival rate of ALK$^+$ ALCL patients is 71%–93%, significantly higher than that of ALK-ALCL patients (15%–40%). The 2010 NCCN Clinical Practical Guideline recommends that the selection of ALCL treatments should be based on staging and prognosis indices. Two options are clinical trials or combined chemotherapy with involved-field radiotherapy. High-dose chemotherapy with autologous stem cell transplantation (ASCT) can be used as a salvage therapy. A large series of retrospective studies on peripheral T-cell lymphoma have shown that most patients with ALCL received multidrug chemotherapy or anthracycline-based chemotherapy, 5 ALK$^-$ ALCL patients and 6 ALK$^+$ ALCL patients received ASCT as the initial treatment; the overall response rate of initial treatment was 88% in ALK$^+$ ALCL patients and 76% in ALK$^-$ ALCL patients, with the 5-year overall survival (OS) of ALK$^+$ and ALK$^-$ ALCL patients higher than failure-free survival (FFS) (in ALK$^+$ patients, 70% vs. 60%; in ALK$^-$ patients, 49% vs. 36%)[46], indicating that ASCT salvage therapy may be effective for certain cases.

Hence, the best strategy for the treatment of ALCL is still in question[47-49]. Most investigators recommend a preceding evaluation on ALK, IPI, and other prognostic factors before choosing a treatment strategy. For patients incurring drug resistance or relapse from first-line therapy, second-line therapy or new drugs can be applied to improve the prognosis. New ALCL targeted drugs include CD30 monoclonal antibody, CD25 monoclonal antibody, and denileukin2.

Summary

ALCL has a low incidence and its occurrence is a complicated multi-step process. Currently, no ideal treatment for ALCL caused by the abnormal activation of ALK and its downstream signaling pathways is available. In this review, we summarized key mechanisms underlying the pathogenesis, clinical manifestations, and treatment, provide insight for future therapy.

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