

Review

Cytokines, Genetic Lesions and Signaling Pathways in Anaplastic Large Cell Lymphomas

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Simple Summary: This review summarizes the main features of anaplastic large cell lymphoma (ALCL) subtypes focusing on activated biological pathways that may have clinical significance for diagnosis, prognosis and personalized therapy.

Abstract: ALCL is a tumor of activated T cells and possibly innate lymphoid cells with several subtypes according to clinical presentation and genetic lesions. On one hand, the expression of transcription factors and cytokine receptors triggers signaling pathways. On the other hand, ALCL tumor cells also produce many proteins including chemokines, cytokines and growth factors that affect patient symptoms. Examples are accumulation of granulocytes stimulated by IL-8, IL-17, IL-9 and IL-13; epidermal hyperplasia and psoriasis-like skin lesions due to IL-22; and fever and weight loss in response to IL-6 and IFN- γ . In this review, we focus on the biology of the main ALCL subtypes as the identification of signaling pathways and ALCL-derived cytokines offers opportunities for targeted therapies.

Keywords: anaplastic large cell lymphoma; oncogenesis; cytokine; signaling pathways



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1. Main ALCL Subtypes

The different ALCLs represent about 16% of peripheral T cell lymphomas [1]. As summarized in Table 1, they form a heterogeneous group of CD30-positive T cell non-Hodgkin lymphomas according to their site of onset (systemic, cutaneous or breast implant-associated) and their genetic features, with several groups according to the presence of ALK rearrangement and subsequent ALK expression defining ALK-positive or ALK-negative ALCLs [2–4]. ALK-negative ALCL may carry DUSP22 rearrangements and/or TP63 rearrangements. ALK-positive and DUSP22-rearranged ALCLs have a better prognosis than triple-negative ALCL and TP63-rearranged ALCL, which have the worst outcome [2,3,5–7]. The site of origin is critical as illustrated by cutaneous ALCL (C-ALCL), which is commonly ALK-negative [8–10]. C-ALCL has a favorable prognosis with a 5-year disease specific survival of 90%, even in the presence of regional lymph node involvement or putative adverse genetic lesions such as the rare TP63 rearrangement [3,11,12].

1.1. Systemic ALK+ ALCL

Systemic ALK+ ALCL mainly occurs in children and young adults with a male predominance, affecting the lymph nodes as well as extranodal sites (Table 1). ALK+ ALCL presents with several morphological variants sharing the hallmark anaplastic cells (common, small cell, lymphohistiocytic, Hodgkin-like or composite), extensively reviewed elsewhere [4,13]. Tumor cells strongly express CD30, EMA, CD25, BCL6 and cytotoxic

molecules such as TIA1, granzyme B and perforin (Figure 1). The loss of several T cell markers including CD3, CD2, CD5, CD7 and the T cell antigen receptor (TCR) is a common feature of ALK+ ALCL cells, leading to an apparent “null cell” phenotype that may be used for the differential diagnosis with other CD30+ PTCL or CD30+ mycosis fungoides with large cell transformation [4,13,14]. ALK is localized at the nuclear/nucleolar or cytoplasmic level according to the partner gene involved in the fusion transcripts [15]. Although NPM1/ALK fusion transcripts are the most common, the other ALK partners are TPM3 (1q25), ATIC (2q35), TFG (3q21), TPM4 (19p13.1), MYH9 (22q11.2), RNF213 (17q25), TRAF1 (9q33.2), CLTC (17q23) and MSN (Xq11) [4,16–18]. The identification of the partner gene thus far has little impact on patient management, and ALK immunostaining is sufficient for diagnosis [14]. Monitoring of minimal residual disease by the detection of ALK transcripts has been mainly used in pediatric protocols and was recently implemented by a digital PCR technique based on a universal 3'ALK probe [16,19,20].

Table 1. Clinicopathological features of systemic, cutaneous and breast implant-associated anaplastic large cell lymphomas (systemic ALCL, C-ALCL, BIA-ALCL). ALK+ ALCL correspond to ALCL with *anaplastic lymphoma kinase* rearrangement.

Categories	Systemic ALK+ ALCL	Systemic ALK- ALCL	Cutaneous ALCL	BIA-ALCL
Patient age/gender	Children/adolescents	Adults	Elderly males	Women
Prognosis	Good	Poor	Excellent	Excellent
Treatment	Multiagent chemotherapy	Brentuximab-vedotin	Surgery, radiation, methotrexate	Capsulectomy
Extent of disease	Lymph nodes and frequent extranodal disease	Widespread	Skin with/without regional lymph nodes	Localized to breast
Pathology	Sheets of anaplastic cells, fibrosis in Hodgkin-like variant	Sheets of anaplastic cells	Sheets of anaplastic cells, frequent neutrophils	Individual and clusters of anaplastic cells often at capsule surface, frequent eosinophils

1.2. Systemic ALK- ALCL

Systemic ALK- ALCL frequently occurs in older patients and involves the lymph nodes and extranodal tissues, with a more aggressive course, B symptoms and advanced stages [21]. Absence of ALK expression combined with various morphologies may constitute a diagnostic challenge for differential diagnosis with either CD30+ PTCL or classic Hodgkin lymphoma (CHL) [1,4,14]. The key features are the cohesive pattern with sinus infiltration, the presence of hallmark cells, abundant cytoplasm, strong and uniform expression of CD30, frequent loss of T cell markers and expression of cytotoxic molecules (TIA1, granzyme B and perforin) or EMA. In contrast to CHL, ALK- ALCL does not express PAX5, EBV transcripts or LMP1 [4,18].

Genomic profiling of 32 clinical samples and 5 ALCL cell lines by microarray analysis identified overexpression of the BCL6, PTPN12, CEBPB and SERPINA1 genes in ALK-positive ALCL, whereas the CCR7, CNTFR, IL-22 and IL-21 genes were overexpressed in ALK-negative ALCL. High levels of interferon regulatory factor 4 (IRF4), which induces MYC expression, were observed in all ALCL subtypes [22]. Decreased expression of MYC-associated factor X (MAX), identified in both ALK+ and ALK- ALCLs, was associated with an uncommon morphology and expression of MYC and cytotoxic molecules in patients with adverse prognosis [23]. Others detected a high expression of MYC in 37% of ALK+ ALCLs, with a common morphology in older patients with a shorter survival [24].

Genomic profiling showed that ALK+ ALCL displays a homogeneous cytotoxic/Th1 signature in contrast to ALK- ALCL that has either a cytotoxic profile or a Th2-associated signature. The TH2 group was enriched in cases displaying a *DUSP22* rearrangement [25]. The presence of *TP63* rearrangement in 12% of ALK- ALCLs defines a third ALCL category [2]. The different rearrangements such as *inv(3)(q26;q28)* or *t(3;6)(q28;p22.3)* generate

TBL1XR1-TP63 or *TP63-ATXN1* fusion transcripts, leading to expression of a dominant negative oncogenic p63 isoform [26]. In systemic ALK- ALCL, *TP63* rearrangement is associated with a poorer outcome. Exceptional C-ALCLs displaying both *DUSP22* and *TP63* rearrangements have been reported [2,3,7]. The absence of either *ALK*, *DUSP22* or *TP63* rearrangement defines a “triple-negative” subset of ALK- ALCL with a 5-year OS rate of 42% [2].

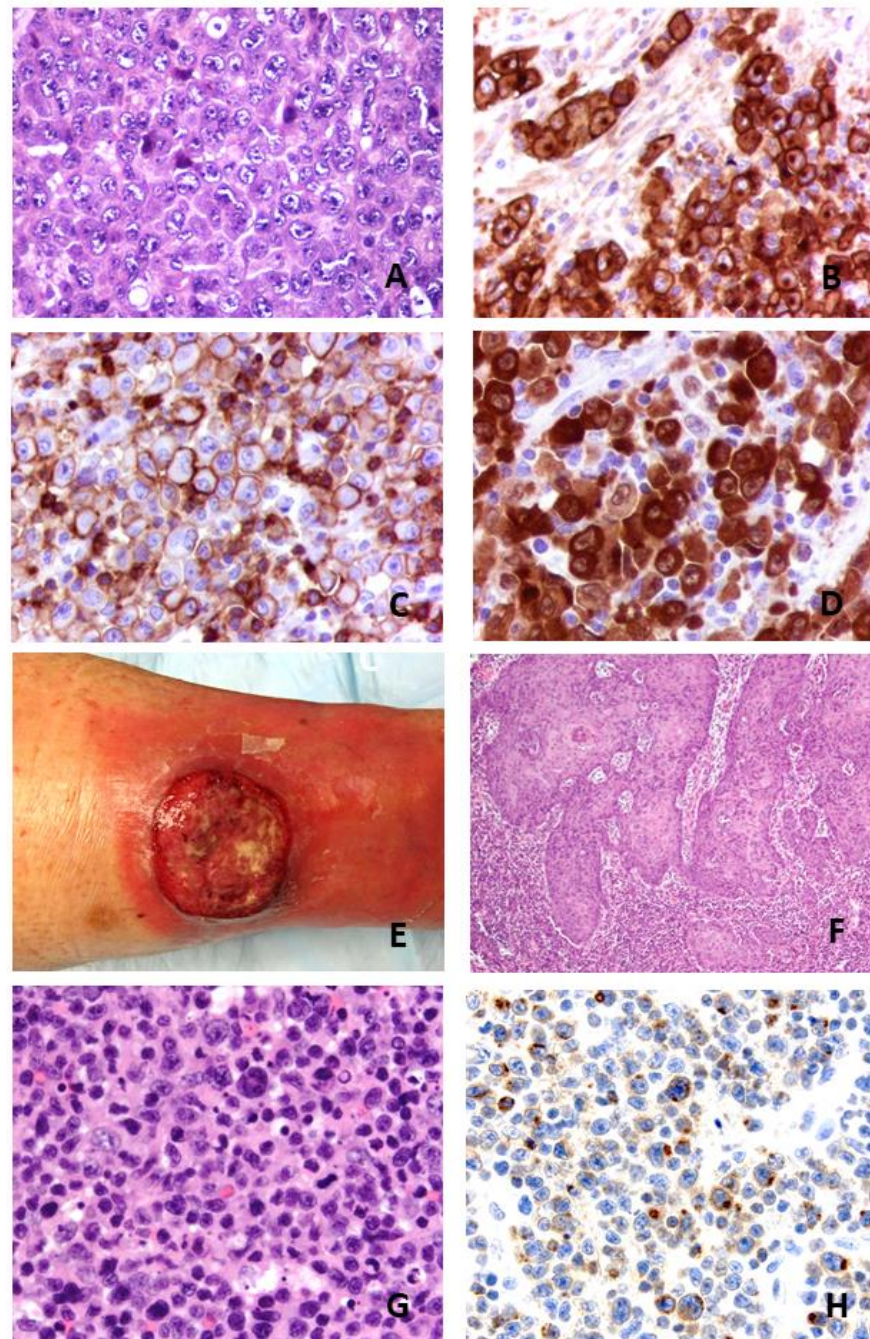


Figure 1. Morphological features of systemic ALK+ anaplastic large cell lymphoma. (A): HE: hematein and eosin staining $\times 400$. Common morphological variant with hallmark cells. (B–D): CD30, EMA and ALK immunostainings ($\times 400$). Courtesy of Dr Marie Parrens, CHU de Bordeaux, Pessac, France. Clinical and pathological features of a cutaneous anaplastic large cell lymphoma. (E): Tumor of lower leg. (F): Pseudoepitheliomatous hyperplasia on HE stain ($\times 200$). (G): Cytomorphology on HE stain ($\times 400$). (H): IL-17A immunostain of tumor cells ($\times 400$).

1.3. Cutaneous ALCL

Cutaneous ALCL belongs to primary cutaneous CD30+ lymphoproliferative disorders together with lymphomatoid papulosis and borderline cases. C-ALCL is defined by the presence of more than 75% of large cells expressing CD30+ in patients without evidence or history of epidermotropic T cell lymphoma [12,27]. The disease is limited to the skin, affecting the trunk, face and extremities (Figure 1). Regional lymph node involvement may exist but does not affect prognosis [11]. Most cases express a CD4+ T cell phenotype with loss of CD2, CD3 or CD5 and frequent expression of cytotoxic proteins [28]. However, some cases are CD4-/CD8+ or CD4+/CD8+. Unlike systemic ALCL, C-ALCLs usually express CLA and CD158k but do not express EMA. C-ALCLs also express skin-homing molecules such as CCR4, CCR10 and CCR8. MUM1 encoded by the *IRF4* gene is strongly positive, and CD15 is expressed in about half of the cases [10,27].

C-ALCLs exhibit some privileged cytogenetic features with a *DUSP22* rearrangement in up to 30% of cases [5,6]. *DUSP22*-rearranged ALCLs not only arise at extranodal sites but also present with sheets of large hallmark cells admixed with smaller cells having both nuclear indentations sometimes giving rise to doughnut cells [2,5,29,30]. The phenotype is non-cytotoxic with absence of EMA expression [5,30]. Interestingly, expression of the lymphoid enhancing transcription factor (LEF1) predicts *DUSP22* rearrangement with high specificity and sensitivity [31]. Some C-ALCLs and other CD30+ lymphoproliferations were shown to harbor an *NPM1-TYK2* fusion gene, leading to STAT1/3/5 activation [32]. However, common TYK2 expression in ALCL cannot serve to identify such cases. Very few C-ALCLs were found to display a *TP63* rearrangement that does not affect their good prognosis [3,7].

1.4. Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL)

This rare disease, generally occurring 8–10 years after implantation, presents with either a peri-implant seroma elicited by chronic inflammation or a capsular invasion, sometimes as a tumor. It shares many features with ALK-ALCL including expression of EMA, cytotoxic proteins and phospho-STAT3 [33]. CD30+ immunostaining and T cell monoclonality are diagnostic criteria. In late seromas generated by infection or implant rupture, high levels of IL-10, IL-13 and Eotaxin and an elevated IL10/IL-6 ratio are features of the effusion milieu [34]. BIA-ALCL exhibits Th-2 differentiation as neoplastic cells express GATA3 and FOXP3 [34]. Nevertheless, bacterial biofilm infection of implants has been implicated in provoking chronic inflammation as a trigger for BIA-ALCL [35].

2. ALCL Oncogenesis

2.1. ALCL Cell of Origin

The detection of NPM-ALK transcripts in neonatal cord blood suggested that ALK+ cells may originate from either stem cells or early thymic progenitors (ETP) [36]. A transgenic mouse model with expression of NPM-ALK under the CD4+ promoter indicated that ALK+ ALCL could emerge from ETP. CD4/NPM-ALK expression functioning as a surrogate TCR permits cells to bypass thymic selection through upregulation of Notch1 expression [37]. However, malignant transformation of CD4+ lymphocytes by NPM-ALK also suggests that ALK+ ALCL may derive from rare peripheral mature CD4+CD30+ T cells [38]. Transduction of NPM-ALK into mature CD4+ peripheral T cells after CD3/CD28 co-stimulation produced NPM-ALK-transformed lymphocytes displaying an early thymic precursor gene expression signature [39]. NPM-ALK induced lymphocyte survival and spreading but also reversed the mature T cell phenotype into an ETP phenotype associated with expression of pluripotency-associated transcription factors such as OCT4, SOX2 and NANOG under the control of HIF2A [39]. HIF2A silencing abrogated NPM-ALK and STAT3 activity, suppressing the cell growth of NPM-ALK-transformed CD4+ lymphocytes. Whether the above transgenic mice or preclinical models reflect a real difference between pediatric and adult ALCL is still a matter of debate. In a subset of ALCL (14%), a germline TCR also supports lack of thymic maturation [4,16,37].

2.2. ALK+ ALCL

The hallmark of ALCLs is the expression of the CD30 antigen, a member of the tumor necrosis factor (TNF) receptor superfamily normally expressed in peripheral T cells after antigen stimulation of the CD3/TCR complex [40,41]. Malignant transformation of CD4+ lymphocytes by NPM-ALK was shown to mimic physiological cytokine signals and/or TCR triggering [37,38,42]. The prototype of ALK+ ALCL is associated with NPM1-ALK fusion transcripts resulting from t(2;5)(p23.2;q35.1) translocation [43]. In ALK+ ALCL, the N-terminal domain of the partner activates the catalytic domain of the ALK protein through homo- and hetero-dimerization [4,16]. NPM-ALK triggers several intracellular signaling pathways involving PLCgamma, PI3K-AKT, Ras ERK, JAK3-STAT3 and STAT5 [13,17,44]. The MAPK-ERK pathway is mostly associated with proliferative effects, whereas the JAK3-STAT3 pathway and the PI3K-AKT pathway promote cell survival and phenotypic changes (Table 2) [42].

Table 2. Predominant features of the different anaplastic large cell lymphoma subtypes. ALCL, anaplastic large cell lymphoma. BIA-ALCL, breast implant-associated ALCL. * Exceptional ALK+ cutaneous ALCLs exist.

ALCL Subtype	Predominant Phenotype	Differentiation	Gene Rearrangement	Mutations	Signaling Pathways	Therapeutic Targets
Systemic ALK+ ALCL	CD30+ ALK+, EMA+, CD3+, CD4+, CD3-CD4- CD5-Cytotoxic	T-cytotoxic Th17/Th22,	ALK with NPM1 80%		STAT3	CD30, ALK, JAK
Systemic ALK- ALCL	CD30+ ALK-, CD3+, CD4+, CD3-CD4-CD5-, Cytotoxic	T-cytotoxic	TP63 (12.5%) DUSP22 rare	JAK-STAT	STAT3 ERBB4	CD30, JAK, HER
Cutaneous ALCL	CD30+, ALK-, EMA-, CD4+, CD2-CD3-CD5-, CLA+, Cytotoxic LEF1	Th2 /Th17	DUSP22 (30%) TP63 (10%) ALK * exceptional	MSC ^{E116K} DUSP22 rare	CD30-IRF4-MYC Th2 signaling	CD30 pSTAT6
		Th2	NPM-TYK2	TYK2	STAT1 STAT6	TYK
BIA-ALCL	CD30+, ALK-, EMA+, TCR-CD4+ > CD8+ Cytotoxic	Th2	-	JAK-STAT and epigenetic modifiers	STAT3 STAT6	CD30, JAK pSTAT6

2.3. STAT3 a Pivotal Transcription Factor in Most ALCL Subtypes

Many of the biological features of ALK+ ALCL result from epigenetic deregulation triggered by STAT3 activation. This applies to both ALK+ and ALK- ALCL, except for the ALK- ALCL subtype bearing DUSP22 rearrangement [5,45]. NPM-ALK triggers STAT1 phosphorylation and degradation and promotes STAT3 upregulation. STAT3 also induces the expression of DNA methyl transferase 1 that promotes epigenetic reprogramming of ALK+ cells that frequently lack expression of CD3+, TCRs and related molecules, including CD3ε, zeta-chain-associated protein kinase 70 (ZAP70), linker for activation of T cells (LAT) and lymphocyte cytosolic protein 2 (LCP2) [46]. Then, STAT3 induces immune escape mediated by expression of TGF-beta, IL-10, ICOS and PDL1 (Figure 2). NPM-ALK, through binding of STAT3, was shown to promote Notch1 deregulation which can be inhibited by γ-secretase inhibitors (GSIs), leading to apoptosis [47]. In ALK+ ALCL, several miRNAs including three members of the miR-17-92 clusters are aberrantly overexpressed, while miR-155 is >10-fold overexpressed in ALK- ALCL [48]. Alternatively, other miRNAs such as miR-101, miR-29c and miR-26 are down-regulated in ALK+ and ALK- ALCL cell lines

and primary human samples [48]. MiR-29a down-regulation is also driven by NPM-ALK activity and contributes to apoptosis blockade through epigenetic deregulation of MCL-1 expression [49]. A recent exome sequencing study also underscored the interplay between the STAT3 and Notch pathways in both ALK+ and ALK- ALCLs. A point mutation of T349P *NOTCH1* was detected in 12% of ALK+ and ALK- ALCL patient samples [47].

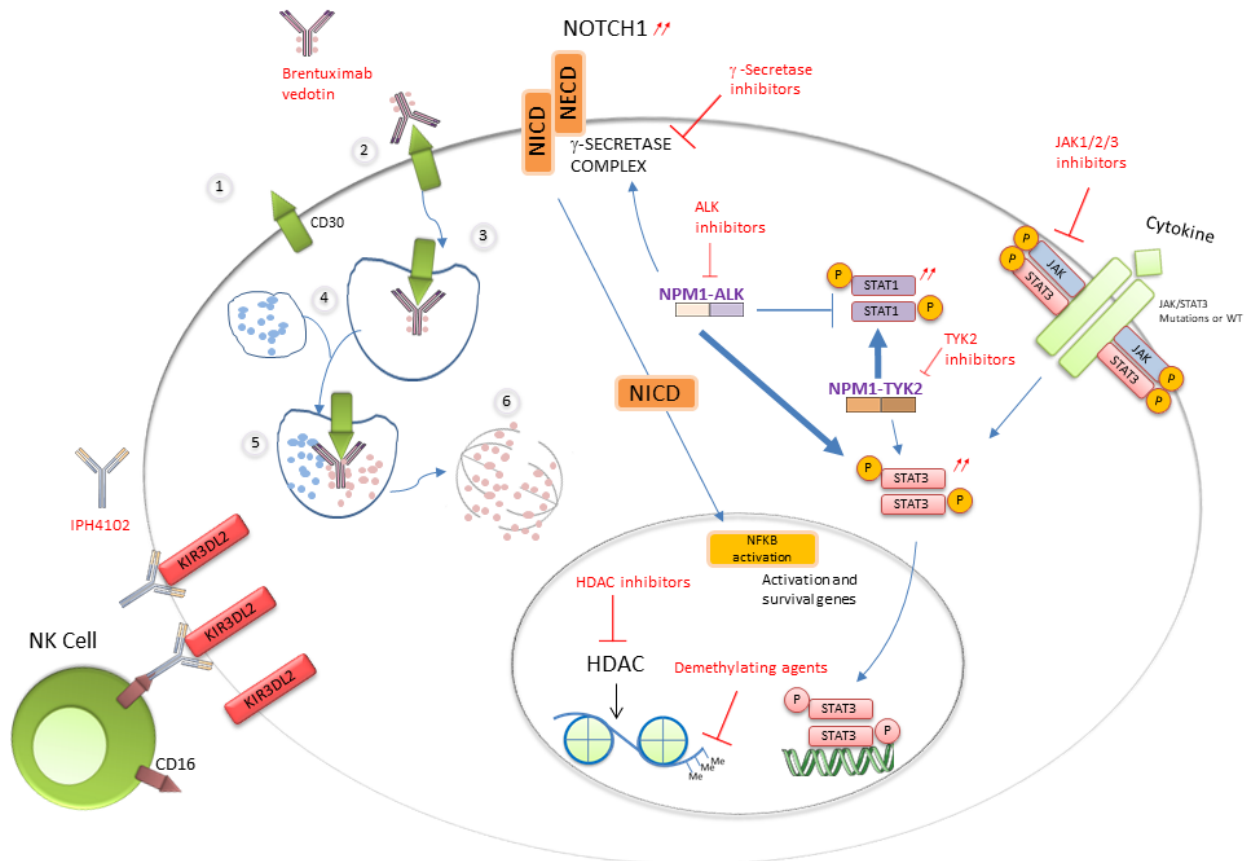


Figure 2. Activated pathways and therapeutic targets in ALCLs.

STAT3 activation occurs in ALK- ALCLs through different mechanisms (Figure 2). Activating point mutations of *STAT3* and/or *JAK1* have been identified in 18% of nodal ALK- ALCLs and in 5% of C-ALCLs [50]. Another study of PTCL identified in ALK- ALCLs the highest rate of *STAT3* mutations (38%) that may combine with *JAK* mutations (15%), while some ALK+ ALCLs (13%) presented *STAT3* mutation alone [51]. The highest pY-STAT3 phosphorylation level is present in ALK- ALCL displaying a typical CD3-CD5-CD7- CD30+ phenotype [51]. Whatever the *JAK* gene status, ALK- cells are addicted to cytokine receptor signaling, and JAK inhibitor sensitivity correlates with STAT3 phosphorylation [52]. About 60% of BIA-ALCLs have mutations in at least one member of the JAK/STAT pathway including *STAT3*, *JAK1* and *STAT5B* and in negative regulators such as *SOCS3*, *SOCS1* and *PTPN1* [53]. In addition, a majority of BIA-ALCL cases (74%) displayed recurrent mutations of epigenetic modifiers such as *KMT2C*, *KMT2D*, *CHD2* and *CREBBP* [53]. In rare ALK- ALCL subsets, chromosomal rearrangements creating chimeras combining a transcription factor (*NFKB2* or *NCOR2*) with a tyrosine kinase (*ROS1* or *TYK2*) were found to elicit STAT3 phosphorylation independent of *JAK1* or *STAT3* mutations [50].

2.4. STAT3-Independent ALK- ALCLs

ALK- ALCLs with 6p25.3 rearrangement are associated with *DUSP22* silencing and conserved *IRF4* expression, while inactivation of the second allele by *DUSP22* mutation is uncommon [54]. Interestingly, *DUSP22*-rearranged ALCL is characterized by a

unique global DNA demethylation profile associated with lack of STAT3 activation and overexpression of CCR8, HAND1, a developmental transcription factor and a group of cancer/testis-associated proteins. This profile includes upregulation of different costimulatory CD58 and HLA class II molecules and down-regulation of PD-1 that may contribute to the good prognosis of *DUSP22*-rearranged ALCL [55]. Among PTCL, recurrent mutations of the musclin gene (*MSC^{E116K}*) encoding a basic helix-loop-helix transcription factor were found to be specific for 35% of *DUSP22*-rearranged ALCLs [45]. The dominant negative *MSC^{E116K}* protein promotes the growth of normal and neoplastic T cells by blocking the expression of the cell cycle inhibitor E2F2. This leads to upregulation of the CD30–IRF4–MYC axis in an autocrine feedback loop and confers susceptibility to the BET inhibitor JQ1 [45]. About 24% of ALK- ALCLs are characterized by ectopic co-expression of truncated *ERBB4* transcripts and *COL29A1* transcripts [56]. Such *ERBB4*-positive ALCLs frequently display a Hodgkin-like morphology and express MMP9. Two oncogenic truncated *ERBB4* transcripts arise from an intronic transcription start site and promote tumorigenesis partially blocked by the pan-HER inhibitor neratinib in experimental models [56].

3. Cytokines in ALCLs

3.1. Detection and Monitoring of Cytokines

CD30/TNFRSF8 is a co-stimulatory molecule expressed on activated T and B cells commonly used as a marker for neoplastic cells of cHL, systemic ALCL and CD30+ CLPD [41,57]. Serum levels of soluble CD30 (sCD30) correlate with tumor burden and normalize following successful treatment of cHL and ALCL [58,59]. Similarly, serum levels of the soluble truncated γ -chain of the IL-2 receptor (sCD25) expressed by activated immune cells correlate with disease activity and prognosis in HL [58–60] and mycosis fungoides (MF) [61]. Hanson et al. adapted a commercially available enzyme-linked immunoassay (ELISA) (R&D Systems, Minneapolis, MN, USA) to measure sCD30 in malignant and benign seromas and plasma of patients with breast implants [62]. sCD30 could be detected at concentrations of >1800 pg/mL in seromas of nine patients with BIA-ALCL but not in their plasma or serum and in none of the seven patients with non-neoplastic effusions [62].

Serum CD30 levels were prognostically significant in 116 patients with CD30+ CLPD, including CALCL, and 96 patients with early mycosis fungoides (MF) followed up to 20 years [63]. A significant positive correlation was found between sCD30 levels and sCD25, CD40L, IL-6 and IL-8. CD30+ CLPD-derived cell lines secrete sCD30, sCD25, IL-6 and IL-8. CD30+ CLPD patients with above normal sCD30 and sCD25 levels had worse overall and disease-related survivals. High sCD30 also identified patients with worse survival in early MF. Increased IL-6 and IL-8 levels correlated with poor disease-related survival in CD30+ CLPD patients [63].

3.2. Cytokines in ALK+ ALCL

Savan et al. analyzed circulating cytokine levels in ALK+ ALCL patients and detected elevated levels of IL-22, IL-17 and IL-8 in untreated patient samples. IL-22 and IL-17 were undetectable in all patients who were in complete remission after chemotherapy [64]. Knörr et al. analyzed sera of 119 uniformly treated pediatric ALK+ ALCL patients and 15 patients in remission, while 11 low-stage B cell lymphoma patients served as controls [65]. Concentrations of IL-9, IL-10, IL-17A, hepatocyte growth factor (HGF), sIL-2R and sCD30 were significantly elevated in initial sera of ALCL patients when compared to control groups, indicating an ALCL-type cytokine signature. Levels of IL-6, IFN- γ , IP-10 and sIL-2R correlated with the stage, initial general condition, minimal disseminated disease, ALK antibody titers and risk of relapse among ALK+ ALCL patients. Only IL-6 showed an independent prognostic value in multivariate analyses [65]. Aberrant upregulation of interleukin 10 receptor subunit alpha (IL10RA) is observed in both ALK+ and ALK- ALCL and triggers STAT3 phosphorylation independently of NPM-ALK1 in ALK+ ALCL [66].

3.3. Signaling through IL-2R Activates the JAK/STAT Pathway in Cutaneous ALCL

Activation of JAK/STAT proteins was found to be involved in the signal transduction pathway mediated by the receptor for interleukin 2 in malignant T lymphocytes derived from cutaneous ALCL and Sézary syndrome [67]. Interaction of cytokine receptors such as IL-2R with their ligands induces activation of intracellular tyrosine kinases [68]. The high-affinity IL-2R is composed of three chains: α which is specific for IL-2, β and common γ . The cytoplasmic domain of the γ chain is associated with the tyrosine kinase Jak3, whereas the β chain is associated with Jak1 [69]. Binding of IL-2 to IL-2R results in the tyrosine phosphorylation of several substrates, including Jak3 and Jak1 themselves, as well as the IL-2R β and γ chains [69]. Soluble IL-2 receptor (sIL-2R) also correlated with tumor burden in SCID mice xenografted with the ALCL line JB6 and was detected in the urine of JB6-transplanted mice [70].

3.4. Cytokines in BIA-ALCL

In contrast to ALK+ ALCL, neither IL-17A nor IL-17F was detected in 48 h cell cultures of established BIA-ALCL lines nor in any of the eight malignant effusions (seromas) around breast implants, although one malignant effusion contained the Th17/Th22 cytokine IL-22 [71]. Instead, four out of the eight malignant effusions contained the Th2 cytokine IL-13, and one contained IL-5. More importantly, seven out of the eight malignant effusions contained >500 pg/mL IL-9 (attributed to Th2 or, more specifically, to Th9 cells), and six out of the eight malignant effusions contained IL-10. IL-9 was not detected in any benign effusions. In contrast, IL-6 was detected in both malignant and benign peri-implant effusions [71].

3.5. Cytokines Modify the Microenvironment and Pathology

3.5.1. BIA-ALCL

A pathologic feature of infiltrative BIA-ALCL that distinguishes it from most systemic ALCLs is the presence of numerous eosinophils [33]. Influx of eosinophils into tissues is promoted by IL-13, Eotaxin and IL-9, which are produced by anaplastic cells in BIA-ALCL [34,71,72]. IL-13, independently and in coordination with IL-4, promotes immunoglobulin heavy chain class switching of B cells to become IgE-producing plasma cells [73]. Numerous plasma cells are often observed in capsules affected by BI-ALCL [72]. IgE binding to high-affinity receptors of mast cells (Fc ϵ R1) triggers the release of vasoactive and chemotactic factors including histamine and prostaglandin D2 (PGD2) that recruits Th2 cells, basophils and eosinophils. Indeed, one of the authors of this review (MEK) has found that anaplastic cells in BIA-ALCL often express the PGD₂ receptor, CRTH₂ (Figure 3). Another feature of BIA-ALCL is thickening of involved capsules due to fibrosis which can be mediated by IL-13 signaling to stimulate fibroblasts through their PDGFR [74,75].

3.5.2. C-ALCL and CD30+ CLPD

Cytokines released by anaplastic cells in cutaneous lymphomas can dramatically affect the growth of keratinocytes. A noteworthy feature of CD30+ CLPD is pseudoepitheliomatous hyperplasia (PEH) of keratinocytes which can be mistaken for squamous carcinoma (Figure 1). In a study of 25 patients, two patterns of PEH were noted: (1) a follicular pattern was observed in 14 cases, commonly associated with a neutrophil-rich infiltrate ($p = 0.21$), and (2) an epidermal pattern was observed in 11 cases and commonly associated with eosinophil-rich infiltrates ($p = 0.03$) [76]. PEH in CD30+CLPD was associated with Th17/Th22 cytokine expression detected in tumor cells in 81% of cases tested. All 14 cases tested had a strong expression of cytokeratin 17 (CK17), a myoepithelial keratin not found in a healthy epidermis, but this was induced in a dose-dependent manner by IL-17 through the signal transducer and activators of transcription STAT1 and STAT3 [76,77]. IL-22 inhibits the maturation of keratinocytes and stimulates their migration, causing epidermal remodeling and often leading to psoriasiform/PEH-like lesions [78–80]. Transgenic overexpression of IL-22 in mice results in psoriasis-like skin alterations including hyperpro-

liferation, acanthosis and hypogranularity. IL-22 is produced by Th17 cells and, in a more restricted manner, by Th22 cells. While PEH lesions were associated with spontaneous regression and an indolent course, some patients developed a generalized process with tumor progression [76].

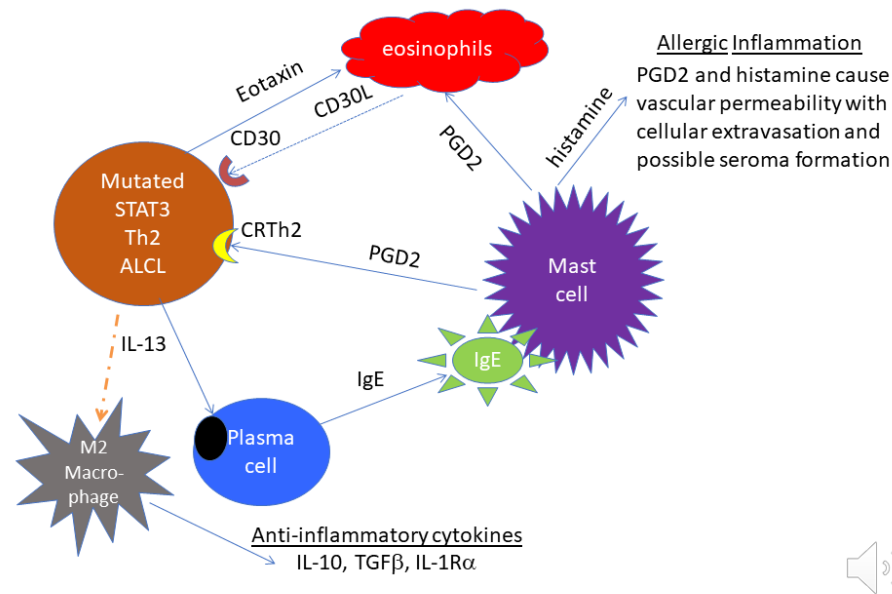


Figure 3. Proposed relationship between tumor cells and microenvironment in BIA-ALCL. On the left, tumor cells with mutated STAT3 release Eotaxin which attracts eosinophils. Eosinophils are known to express the CD30 ligand, which can support the proliferation of CD30+ tumor cells. At the lower left, tumor cells release IL-13 that polarizes macrophages to produce anti-inflammatory cytokines and induces plasma cells to produce IgE. In the center and upper right, IgE activates mast cells to release PGD2 to attract Th2 cells and eosinophils. PGD2 and histamine from activated mast cells cause vascular permeability, which may contribute to seroma formation.

SATB1, a thymocyte-specific chromatin organizer, helps to classify CD30+ CLPDs with different clinicopathological behaviors. SATB1 expression was identified in CD30+ anaplastic T cells in 11 of 12 (91.7%) lymphomatoid papulosis cases and in 16 of 42 (38.1%) C-ALCL cases. SATB1+ cases showed Th17 polarization, together with more prominent epidermal hyperplasia and granulocytic infiltration, consistent with the above-mentioned PEH [81]. SATB1+ lesions responded better to combined treatment with low-dose (5–20 mg/weekly) methotrexate and interferon γ 2b. In clinical samples of C-ALCLs, genes of the IL-13 signaling pathway, including IL13, IL13R α 1, IL13R α 2 and IL4R α , were enriched in SATB1+ cases, compared to SATB1- cases [82]. All SATB1+ CD30+ CLPDs were found to highly express pSTAT6, and most were IL-13+. A specific inhibitor of pSTAT6 (AS1517499) reduced cell viability in Mac1/2A cutaneous ALCL cell lines in a dose-dependent manner, as described previously for Sézary cells [82], indicating that blocking the IL-13/STAT6 signaling pathway may be a potential therapeutic regimen for SATB1+ CALCLs. In systemic ALCLs, ALK+ ALCLs strongly express SATB1, while ALK-negative cases lack SATB1, and STAT3, RORC and IL17A were highly expressed in SATB1+ cases [83].

3.6. Does Cytokine Profile Indicate the Cell of Origin or Maturation Stage of ALCLs?

3.6.1. Systemic ALCL

Several pieces of evidence suggest that tumor cells of systemic ALK+ ALCL display features of Th17 and/or ILC3 innate lymphoid cells. Schleussner et al. suggested some ALCLs could derive from innate lymphoid cells type 3 (ILC3) [84]. They demonstrated constitutive activation of AP-1 and IRF-4 in both ALK+ and ALK- ALCLs with AP-1 motifs bound to BATF and BATF3. The gene expression profile of ALCL cells included Th17/group 3 innate

lymphoid cell (ILC3)-associated marker genes such as AHR, IL17F, IL-22, IL-26, IL-23R and ROR γ t. Elevated IL-17A and IL-17F plasma levels were detected in a subset of children and adolescents with ALK+ ALCL, supporting the proposed Th17/ILC3 phenotype for ALK+ systemic ALCL.

Matsuyama et al. demonstrated that NPM-ALK promoted expression of miR-135b and its host gene LEMD1 through the action of STAT3. Further, miR-135b suppressed Th2 regulators GATA3 and STAT6, and miR-153b blockade attenuated IL-17 production, leading to an ALCL phenotype overlapping with Th17 cells [85]. ALK+ ALCL cell lines express Th17-associated signature genes, including IL-17F, IL-22, IL-26, AHR and RORC [64].

Eckerle et al. performed gene expression profiling of microdissected lymphoma cells of five ALK(+) and four ALK(-) systemic ALCLs, seven cALCLs and sixteen cHLs, and of eight subsets of normal T and NK cells [83]. All ALCL types showed significant expression of NF κ B target genes and upregulation of genes involved in oncogenesis (e.g., EZH2).

Knörr et al. asked whether a Th subset-specific serum cytokine pattern could be identified in childhood ALCL patients [65]. Although some patients showed a pattern of elevated IFN- γ , IP-10 and MIG (both produced upon stimulation with IFN- γ), and levels of IL-17 and IL-23 suggested activation of Th17 cells, ALCLs of most patients did not show a conclusive Th subset pattern.

3.6.2. BIA-ALCL

The cell lineage or differentiation stage of BIA-ALCL appears to be variable. In cell lines derived from malignant seromas, two of four co-expressed the Th2 cytokine IL-13 and the Th1 cytokine IFN γ [71]. None expressed Th17 cytokines characteristic of ALK+ ALCL. Three of four cell lines secreted IL-9, which was detected in eight out of nine malignant effusions. IL-9 was originally assigned to Th2 cells but more recently to Th9 cells, which also produce IL-10, detected together with IL-9 in four out of eight malignant effusions. Such evidence points to a Th2-type cytokine profile with expression of IL-10, IL-13, IL-9 and Eotaxin and frequent expression of the GATA3 and FoxP3 transcription factors. Breast implants may elicit a Th2-type response with accumulation of T cells, mast cells and eosinophils, and, due to activation of the STAT3 pathway, IL-10-producing T regulatory cells are recruited or induced [34]. The plasticity between Th2 cells and iTregs is in accordance with such observation [86]. Di Napoli used gene expression profiling and immunohistochemical data to suggest either activation-induced FoxP3 expression or a T helper-like regulatory T cell status in a proportion of BIA-ALCLs with upregulation of the RORC and *IL17A* genes and of the FOXP3 protein [87].

Some CD30+ CLPDs are derived from a novel subset of CD4+Th2 cells that produce inflammatory Th17 cytokines [88]. This subset of Th2 cells was reported to promote exacerbation of chronic allergic asthma [89]. These results are consistent with our recent report linking atopy to the pathogenesis of lymphomatoid papulosis [90].

4. Therapy of ALCLs

4.1. Front-Line Treatments

In adult systemic ALCL, several combined chemotherapy regimens obtain a high event-free survival rate, especially for local or regional disease [19,21,91]. The addition of etoposide improved prognosis, with a 3-year survival of 100% [92]. However, relapse occurred in 20–30% of patients, requiring reinduction by high-dose chemotherapies before autologous or allogenic hematopoietic stem cell transplantation [21,91].

In pediatric patients, adapted protocols with reduced cumulative doses of toxic drugs obtained a 92% overall survival at 2 years. A risk-stratified strategy restricted autologous HCST for pediatric ALCL high-risk relapses and vinblastine for intermediate or low-risk relapses [19,93].

C-ALCL can be cured by complete surgical excision and/or local radiotherapy as first-line treatment [94]. For multifocal lesions, low-dose methotrexate is the first-line treatment, and vinblastine was also proposed at relapse [95,96].

About 80% of BIA-ALCL patients are cured by surgical resection of implants and the surrounding capsule. Adjuvant localized radiation is performed when excision is incomplete. For patients with tumors and/or regional lymph node involvement, adjuvant chemotherapy or targeted therapy is available [97].

4.2. Targeted Therapies

Patients with advanced or refractory/relapsing ALCL, BI-ALCL or CALCL obtain their first benefit from targeted therapies directed against CD30, ALK, NOTCH1 or JAK (Tables 1 and 2). Some of them are now also used in combination therapy in front-line treatment [97–99].

The anti-CD30 brentuximab-vedotin is a monoclonal anti-CD30 antibody fused to a microtubule inhibitor. The latter is delivered after endocytosis and lysosome fusion (Figure 2) [99,100]. It has been approved by US and European agencies for the treatment of relapsing systemic ALCL or C-ALCL either as a single-agent therapy or in combination with chemotherapy [99,101]. The limited durability of response together with significant toxicity including neuropathy and cytopenia has led to considering other therapies such as anti-CD30 CAR T cells [102].

A new anti-CD158k antibody primarily developed for the treatment of Sézary syndrome can also be employed in C-ALCL [103,104].

ALK inhibition by first-generation inhibitor crizotinib provided promising results, especially in pediatric ALK+ ALCL, with an objective response rate ranging from 54% to 90% [19]. Resistance to ALK inhibition may be acquired by the emergence of specific ALK mutations that may be counteracted by new-generation inhibitors such as alectinib or ceritinib [105]. IL-10 autocrine synthesis and aberrant upregulation of the IL-10 receptor subunit also bypass NPM-ALK inhibition and contribute to single-ALK inhibitor resistance [66].

Given the resistance mechanisms arising after single-agent therapies, combination therapy associating chemotherapy with either anti-CD30 targeting or ALK inhibition is proposed for patients with relapsing disease [106].

Blocking the IL-9/Jak3 pathway has potential for treatment of both ALK+ ALCL and BIA-ALCL where tumor cells express IL-9 in an autocrine loop [71,107].

In a model of alternative activation of NF- κ B in ALCL revealed by CRISPR screening, Wang et al found that in NF- κ B-inducing kinase (NIK)-positive ALK- ALCL cells, common JAK/STAT3 mutations promote transcriptional activity of STAT3 which directly regulates NFKB2 and CD30 expression [108]. Endogenous expression of CD30 induced constitutive NF- κ B activation through binding and degrading of TRAF3. In ALK+ ALCL, the CD30 pathway is blocked by NPM-ALK oncoprotein, but STAT3 activity and resultant NFKB2 expression can still be induced by NPM-ALK, leading to minimal alternative NF- κ B activation. The study suggests combined NIK and JAK inhibitor therapy could benefit patients with NIK-positive ALK- ALCL carrying JAK/STAT3 somatic mutations [108].

ALK+ ALCL expresses a high level of PD-L1 because of the constitutive activation of multiple oncogenic signaling pathways downstream of ALK activity. In a novel model using CRISPR screening, Zhang et al discovered that PD-L1 induction was dependent on NPM-ALK activation of STAT3, as well as a signalosome containing GRB2/SOS1, which activates the MEK-ERK and PI3K-AKT signaling pathways [109]. These signaling networks, through STAT3 and the GRB2/SOS1, induce PD-L1 expression through the action of transcription factors IRF4 and BATF3 on the enhancer region of the *PD-L1* gene. IRF4 and BATF3 are essential for PD-L1 upregulation, and IRF4 expression was correlated with PD-L1 levels in primary ALK+ ALCL tissues. Targeting this oncogenic signaling pathway in ALK+ ALCL largely inhibited the ability of PD-L1-mediated tumor immune escape when cocultured with PD-1-positive T cells and natural killer cells.

In preclinical models of ALK- ALCL, JAK 1/2 inhibition by ruxolitinib proved to be more efficient than STAT3 inhibitors [52]. Targeting the Th2 signaling pathway with a specific pSTAT6 inhibitor, AS1517499, also has potential for the treatment of C-ALCL

and other CD30+ CTCLs [82,88]. Recent whole-genome sequencing of 12 C-ALCLs also underscored the potential value of PI3K-AKT inhibition for patients who are resistant to skin-directed therapy and/or with extracutaneous progression [110].

5. Conclusions

The four main types of ALCL differ according to the age of patients, site of onset, prognosis, tumor cell phenotype and genetic lesions.

Translational studies have revealed key cytokine pathways and epigenetic modification regulating tumor cell growth.

Besides directly targeting tumor cells by cytotoxic drugs or antibodies, cytokine pathways may represent potential targets for personalized therapy according to the specific profile of each ALCL case.

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