



REVIEW

Cell of Origin and Immunologic Events in the Pathogenesis of Breast Implant—Associated Anaplastic Large-Cell Lymphoma



Suzanne D. Turner,^{*} Giorgio Inghirami,[†] Roberto N. Miranda,[‡] and Marshall E. Kadin^{§¶}

From the Division of Cellular and Molecular Pathology,^{*} Department of Pathology, University of Cambridge, Cambridge, United Kingdom; the Department of Pathology and Laboratory Medicine,[†] Weill Cornell Medicine, New York, New York; the Department of Hematopathology,[‡] The University of Texas MD Anderson Cancer Center, Houston, Texas; and the Department of Dermatology,[§] Roger Williams Medical Center, Providence, Rhode Island; and the Department of Dermatology,[¶] Boston University School of Medicine, Boston, Massachusetts

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Address correspondence to
Suzanne D. Turner, Ph.D., Di-
vision of Cellular and Molecular
Pathology, Department of Pa-
thology, University of Cam-
bridge, Lab Block Level 3, Box
231, Addenbrooke's Hospital,
Cambridge CB20QQ, United
Kingdom. E-mail: sdt36@cam.ac.uk.

Breast implant—associated anaplastic large-cell lymphoma (BIA-ALCL) is a CD30-positive, anaplastic lymphoma kinase—negative T-cell lymphoma. Nearly all cases have been associated with textured implants. Most cases are of effusion-limited, indolent disease, with an excellent prognosis after implant and capsule removal. However, capsular invasion and tumor mass have a more aggressive course and a fatal outcome risk. This review summarizes the current knowledge on BIA-ALCL cell of origin and immunologic factors underlying its pathogenesis. Cytokine expression profiling of BIA-ALCL cell lines and clinical specimens reveals a predominantly type 17 helper T-cell (Th17)/Th1 signature, implicating this as its cell of origin. However, a Th2 allergic inflammatory response is suggested by the presence of IL-13, with infiltration of eosinophils and IgE-coated mast cells in clinical specimens of BIA-ALCL. The microenvironment-induced T-cell plasticity, a factor increasingly appreciated, may partially explain these divergent results. Mutations resulting in constitutive Janus kinase (JAK)—STAT activation have been detected and associated with BIA-ALCL pathogenesis in a small number of cases. One possible scenario is that an inflammatory microenvironment stimulates an immune response, followed by polyclonal expansion of Th17/Th1 cell subsets with release of inflammatory cytokines and chemokines and accumulation of seroma. *JAK-STAT3* gain-of-function mutations within this pathway and others may subsequently lead to monoclonal T-cell proliferation and clinical BIA-ALCL. Current research suggests that therapies targeting JAK proteins warrant investigation in BIA-ALCL. (*Am J Pathol* 2020, 190: 2–10; <https://doi.org/10.1016/j.ajpath.2019.09.005>)

In 1997, a case of CD30-positive, anaplastic lymphoma kinase (ALK)—negative T-cell lymphoma in proximity to a breast implant was first reported.¹ Other cases of this uncommon malignancy (estimated US incidence, 2.03 per million person-years for textured implants)² were subsequently reported, with nearly all confirmed cases either associated with textured (versus smooth) implants or occurring in patients who had previously had textured implants.^{2–4} In 2016, the World Health Organization recognized breast implant—associated anaplastic large-cell lymphoma (BIA-ALCL) as a provisional entity distinguished from other ALK-negative ALCLs.⁵ Similar numbers of BIA-ALCL cases have been reported among

patients with implants for breast reconstruction for breast cancer or prophylaxis and for cosmetic purposes.^{2–4,6} Most patients with BIA-ALCL present with seroma without capsular invasion.^{3,6,7} Time of seroma occurrence after initial implantation or reimplantation ranges from 0.2 to 27 years in retrospective studies.^{6,8} In these cases, BIA-ALCL follows an indolent course, with patients having a favorable

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prognosis after complete surgical excision.⁹ However, patients with tumor mass infiltration of capsule and adjoining tissue face a more aggressive disease.^{9–11} The spectrum of cytologic and histologic changes encountered in BIA-ALCL is illustrated in [Figure 1](#). The purpose of this review is to summarize what is known about the BIA-ALCL cell of origin and immunologic factors underlying the pathogenesis of BIA-ALCL and to identify key areas where we believe future research is needed.

Triggering Event

Much of the underlying etiology of BIA-ALCL remains to be elucidated, but multiple factors appear to be involved in its development, including host genetic factors.^{7,12} Various triggers, with varying degrees of evidence, have been proposed for the development of BIA-ALCL, including mechanical friction, implant shell particulates, implant components leaching into surrounding tissue, and bacterial biofilm.^{13,14} The evidence supporting the association of bacterial biofilm with a greater risk of BIA-ALCL is that the uneven surfaces of textured breast implants provide a sheltered environment for bacterial proliferation, supporting a higher biofilm load than is possible for smooth implants and explaining the higher rates of BIA-ALCL with textured implants.^{6,15} Another possibility for triggering a pathophysiological cascade is that a superantigen may be involved, as is the case in cutaneous T-cell lymphoma,¹⁶ although this remains speculative for BIA-ALCL at present. The discovery of ribosomal protein S10 in BIA-ALCL samples suggests that viral etiology is another possibility because ribosomal protein S10 contributes to formation of

the internal ribosome entry site by which viral transcripts gain entry to the ribosome.^{17,18}

Innate Immune Response

Cellular and cytokine studies suggest that an inflammatory milieu may be a necessary component of the pathobiology of BIA-ALCL.^{19–21} In response to bacteria or other yet undefined antigens, acute inflammation is initiated by innate immune cells (eg, mast cells, neutrophils, and macrophages).²² Through antigen presentation, these cells may activate adaptive immune cell responses via the release of cytokines and chemokines.²³

The lymphoma cells of most cases of BIA-ALCL lack T-cell receptors α/β or γ/δ or have gene mutations that may contribute to a defective T-cell receptor phenotype.^{11,21,24–27} Lack of adaptive T-cell functionality suggests that an innate immune response may significantly contribute to BIA-ALCL immunopathophysiology. This may be further supported by a study using human peripheral blood mononuclear cell cultures, which found that exposure to silicone breast implant surfaces did not induce T-cell activation. However, some implant surfaces resulted in increased expression of the proinflammatory cytokines IL-1 β , IL-6, and tumor necrosis factor- α , which play a role in macrophage activation.²⁸ Furthermore, eosinophils and mast cells with strongly bound cell-surface IgE, which are characteristic of allergic inflammation, have been found in BIA-ALCL tissue²⁰ ([Figure 2](#)).

IL-22, produced by group 3 innate lymphoid cells (ILC3), has been associated with malignancies, including T-cell lymphomas.^{29,30} Up-regulation of ILC3 genes and secretion of IL-22 have been observed in ALCL cell lines,

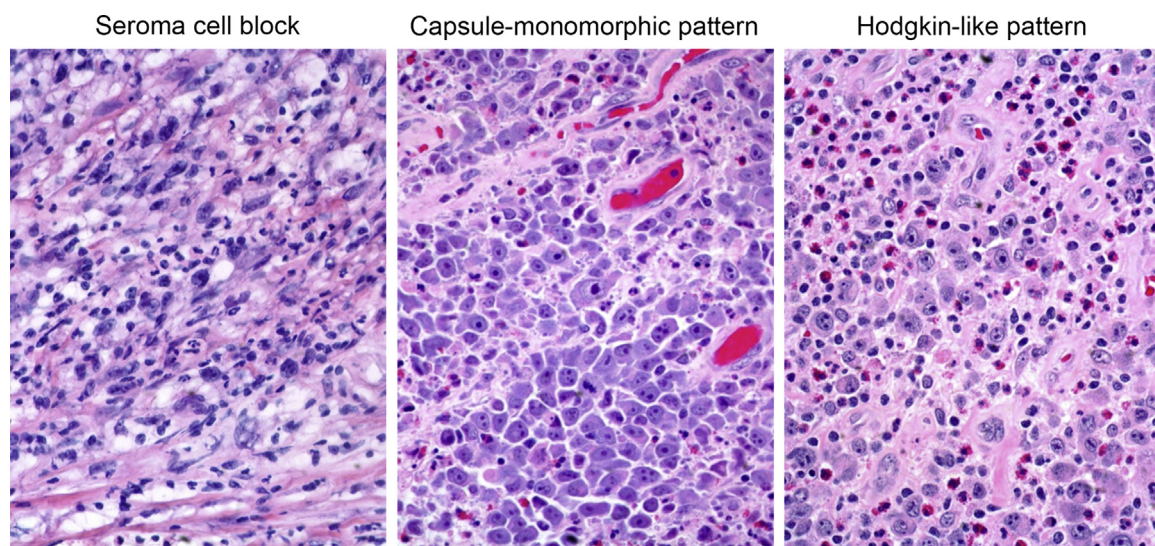


Figure 1 Spectrum of cytologic and histologic changes in breast implant–associated anaplastic large-cell lymphoma (BIA-ALCL). **Left panel:** The seroma cell block contains large anaplastic cells with an admixture of inflammatory cells and fibrin. Seroma cell blocks are helpful for the diagnosis of BIA-ALCL. **Middle and right panels:** The spectrum of morphologic changes that can be encountered when BIA-ALCL infiltrates the capsule and surrounding breast tissue. Original magnification, $\times 400$.

Mast cells coated with IgE in BIA-ALCL

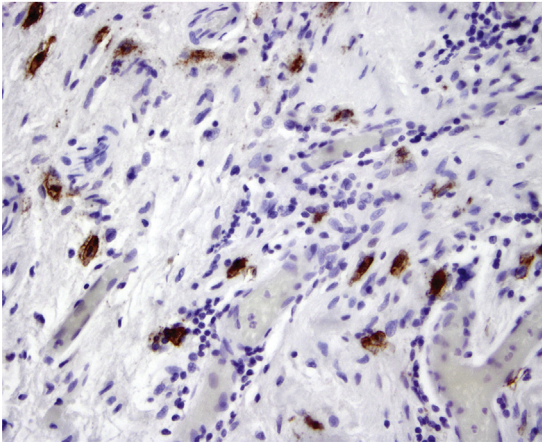


Figure 2 Mast cells in breast implant–associated anaplastic large-cell lymphoma (BIA-ALCL) show strong IgE surface expression (brown stain). Rabbit antibody (catalog number 75673; Abcam, Cambridge, UK) was used neat. Second-stage antibody was from R&D Systems (Minneapolis, MN; catalog number CTS005). Original magnification, $\times 400$.

pointing to ILC3 cells as a potential cell of origin for ALK-positive ALCLs.³¹

Cell of Origin

Thymic Progenitor Cells in ALCL

Because of the relatively recent recognition of BIA-ALCL as a clinical entity and its relative rarity, knowledge of its pathobiology is more limited than for the other types of ALCL, such as systemic ALK-positive ALCL (ALK-positive sALCL), systemic ALK-negative ALCL (ALK-negative sALCL), and primary cutaneous ALCL (pcALCL).³² Although ALCL subtypes are associated with divergent clinical presentations and prognoses, some aspects of their pathogenesis are shared.³³ All ALCL subtypes have common features, including variable expression of surface markers that support a T-cell origin. All are positive for CD30, which is a cell membrane protein of the tumor necrosis factor receptor family normally found on the surface of activated B and T cells.^{11,26,34–36} In addition, T-cell receptor gene rearrangements are seen and there is rare cell surface T-cell receptor expression and the frequent loss of CD3.^{11,21,26,27,35,37–39} All studied subtypes have anaplastic morphology⁴⁰ and strongly express antigen presentation–associated proteins (human leukocyte antigen-DR⁺CD80⁺CD86⁺).^{21,35,41} Malignant cells are commonly CD4 positive, less frequently CD8 positive, and rarely CD4/CD8 double positive.^{11,26,27,35,42,43} Some cases are CD4⁺/CD8⁻/CD3⁻ (triple negative; null cell phenotype), but are still T-cell derived, as evidenced by molecular T-cell receptor rearrangements.^{11,26,27,35,42,44} Nonetheless, ALCL often expresses perforin and/or granzyme B, irrespective of CD4/CD8 phenotype.^{11,26,42,43,45–47} BIA-ALCL has

similarities with pcALCL in terms of morphology, biomarkers, a typically localized disease with frequent absence of systemic symptoms, and a generally favorable prognosis.^{9,48}

Assigning a cell of origin to any ALCL has proved challenging, although all ALCLs fall under the umbrella of peripheral T-cell lymphomas and, thus, by definition, are of post-thymic origin. In one study, gene expression profiling (GEP) of a subpopulation of ALK-positive and ALK-negative ALCL cells reflected an early thymic progenitor origin.⁴⁹ Yet, in another study of ALK-positive ALCL, ALK-negative ALCL, and pcALCL, GEP was unable to clearly assign a pattern of CD4⁺ helper T cell, CD8⁺ cytotoxic T cell, or CD30⁺ activated T cell of origin to ALCLs.⁵⁰ However, in this study, the GEP of subsets of helper and cytotoxic T cells was not considered. In the case of ALK-positive sALCL, *in vivo* studies have provided evidence of an early thymocyte origin with T-cell receptor expression, which is necessary for thymic egress.³⁹ In addition, DNA methylation fingerprints in both ALK-positive and ALK-negative ALCL samples were found to be consistent with a thymic origin, although epigenomic reprogramming at a later stage could not be ruled out.⁵¹

Th17/Th1 Phenotype

A different cell of origin was recently suggested by a GEP study of several ALK-positive and ALK-negative cell lines.³¹ These cells demonstrated a GEP characteristic of type 17 helper T cells (Th17) and, in some cases, ILC3 cells, with AP-1-BATF and AP-1-BATF3 playing a crucial role in Th17/ILC3 skewing.^{31,52} Further supporting a Th17 phenotype, the IL-17A and IL-17F cytokines were secreted by these cells and were detectable in patients with ALCL. These findings were consistent with a previous study in which IL-17A and IL-17F were shown to be associated with ALCL.⁵² Although these studies did not include BIA-ALCL, the origin of these ALCL subtypes is of more than academic interest because eradication of clinical disease depends on elimination of any reservoirs that might cause relapse.⁵³

In considering cellular origin and phenotype, CD4⁺ helper T-cell plasticity must be kept in mind.⁵⁴ Differentiation of naïve CD4⁺ T cells into discrete Th1, Th2, Th17, regulatory T cells, and other subsets is not only context dependent, but the polarization states reached in some cases maintain context-dependent late plasticity governed by epigenetic regulation that is, in turn, influenced by secondary stimulation.⁵⁵ Specifically, Th17 cells are known to be capable of acquiring functional characteristics associated with Th1 cells, although the reverse does not seem to occur,⁵⁶ and cells producing both IL-17A and interferon- γ have been reported. Thus, Th17 cells recruited in response to extracellular antigens may initiate an inflammatory response via IL-17A and IL-17F before transitioning into

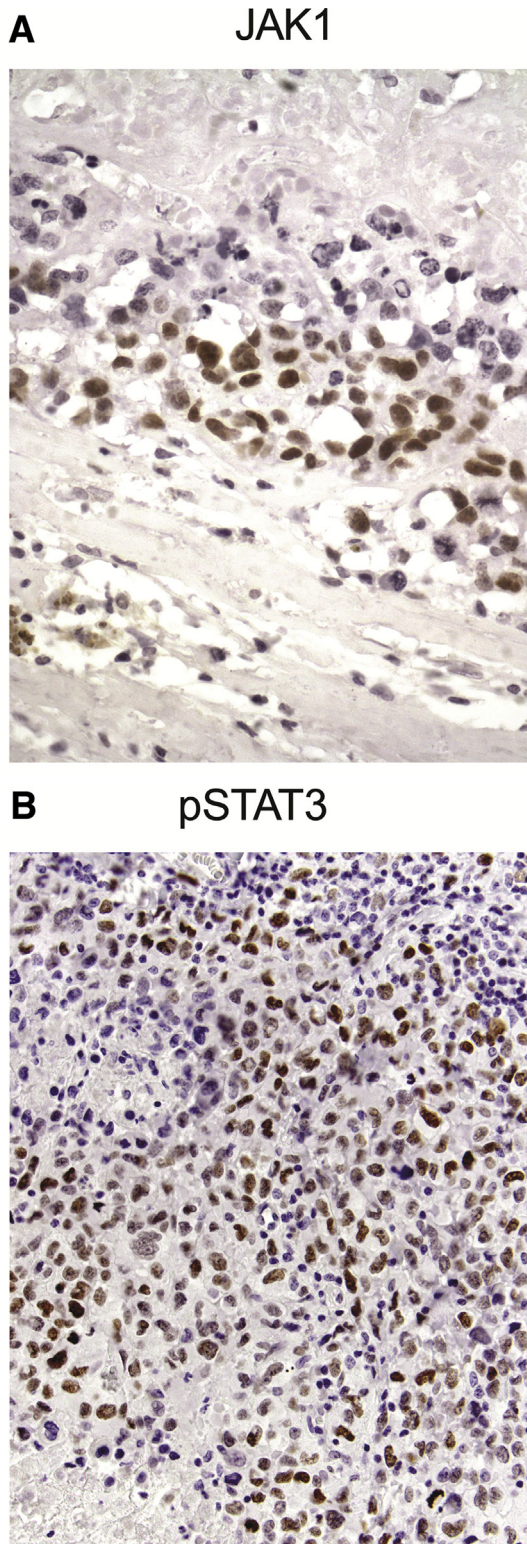


Figure 3 **A:** Anaplastic cells in breast implant–associated anaplastic large-cell lymphoma (BIA-ALCL) express Janus kinase 1 (JAK1; nucleus, brown stain). Rabbit monoclonal antibody (mAb) IgG number 3344 (Cell Signaling Technology, Danvers, MA) was used at 1:100 dilution. **B:** Anaplastic BIA-ALCL cells express phospho-STAT3 (pSTAT3) in the nucleus (brown stain). (Tyr705)(D3A7) rabbit mAb IgG number 9145 (Cell Signaling Technology) was used at 1:200 dilution. Original magnification: $\times 600$ (A); $\times 400$ (B).

Th1-like cells, thereby providing characteristics of both cell types.⁵⁵

A study of BIA-ALCL GEP was performed on cell lines derived from patient samples as well as pcALCL cell lines.⁴⁸ BIA-ALCL cells displayed moderate to high expression levels of the Th1 signature cytokine interferon- γ as well as IL-17A and IL-17F. Interestingly, high expression of suppressor of cytokine signaling 3, which has been proposed to play a role in ALCL pathogenesis via the Janus kinase 3–signal transducer and activator of transcription 3 (JAK3-STAT3) pathway,⁵⁷ was also characteristic of BIA-ALCL cells. BIA-ALCL cells and pcALCL cells had similar cytokine and transcription factor profiles, including high levels of suppressor of cytokine signaling 3, SATB1, and JunB, which may promote lymphoma development through transcriptional regulation of platelet-derived growth factor receptor- β .^{48,58,59} Expression of IL-17F and interferon- γ was confirmed in BIA-ALCL tumor cells and surrounding capsule from clinical samples, with stronger IL-17F expression in capsular infiltrates.⁴⁸

Collectively, these results suggest that breast implants may, by still undefined mechanisms, trigger a local Th17/Th1 immune response, leading to subsequent cytokine-promoted fibrosis and the formation of the peri-implant capsule.⁴⁸ Given the extremely low incidence rate of BIA-ALCL, in the vast majority of cases, this must not have downstream malignant sequelae, although it may be a factor in the capsular contracture sometimes encountered. Accepting the hypothesis of a predominantly Th17/Th1 phenotype, what then remains to be elucidated are the additional hits and downstream transformational processes necessary for the development of BIA-ALCL in this milieu.

Immunologic Pathways in BIA-ALCL Pathogenesis

The Role of Inflammation

Several lines of evidence point to the role of an inflammatory environment with chronic T-cell stimulation in BIA-ALCL pathogenesis. In clinical specimens from patients with BIA-ALCL that was invasive through the peri-implant capsule, malignant cells were associated with an inflammatory background with a large number of eosinophils (Figure 1).¹¹ BIA-ALCL cell lines and 14 of 14 clinical BIA-ALCL capsule specimens were found to secrete or express IL-13, the Th2-associated signature cytokine of allergic inflammation, which was only infrequently expressed in ALK-negative sALCL, ALK-positive sALCL,⁶⁰ or benign capsular tissue specimens.²⁰ In this study, BIA-ALCL tissue samples contained numerous eosinophils and mast cells with surface-expressed IgE, also characteristic of allergic inflammation. In contrast, few ALK-negative or ALK-positive sALCL samples contained eosinophils, and ALK-positive ALCL has been associated with predominantly Th17 cytokines.⁶¹ These results suggest

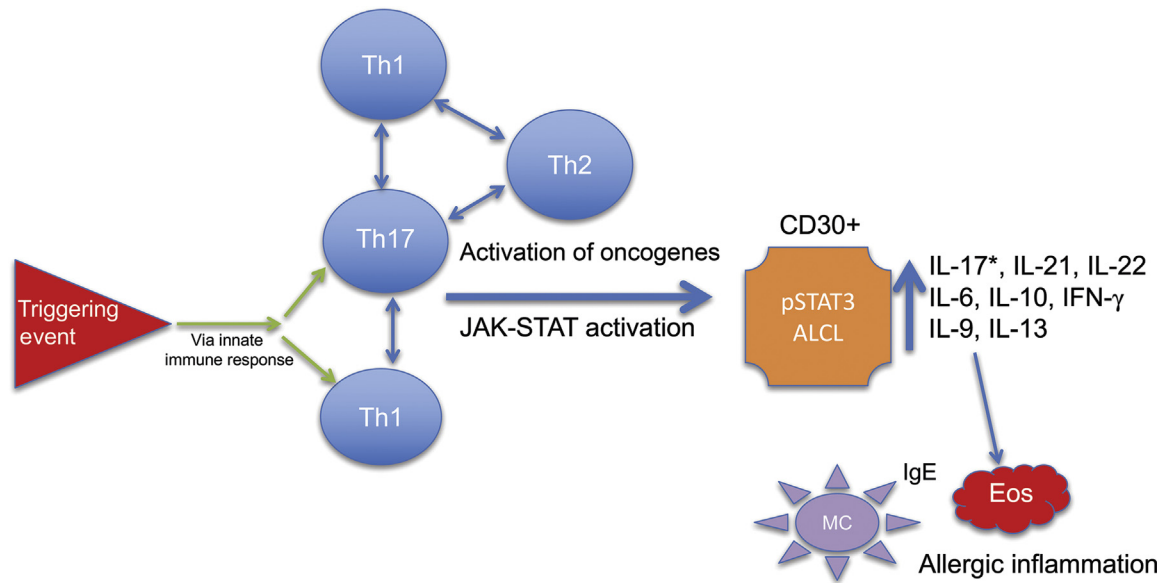


Figure 4 Proposed hypothesis for progression of immune T-cell infiltrates to breast implant–associated anaplastic large-cell lymphoma (BIA-ALCL). In this proposed model, a triggering event elicits both innate and adaptive [type 17 helper T-cell (Th17)/Th1/Th2] immune responses. Oncogenic events, including critical mutations leading to constitutive Janus kinase (JAK)–STAT activation and/or other oncogenic drivers, result in the emergence of monoclonal, CD30-positive BIA-ALCL cells capable of amplifying the inflammatory environment through plasticity and secretion of cytokines, leading to infiltration of eosinophils (Eos) and IgE-coated mast cells (MC). *Variable reports of IL-17 expression in the literature. IFN- γ , interferon- γ ; pSTAT3, phospho-STAT3.

that IL-13 is a functional biomarker of BIA-ALCL and imply that allergic inflammation may be a unique component of its pathogenesis. Furthermore, allergen-bound IgE causes mast cell activation, resulting in the release of cytokines, such as IL-9, IL-13, and the inflammatory mediator histamine, and chemokines, including prostaglandin D₂.^{62–64} Histamine, in turn, promotes microvascular permeability; its release from mast cells may contribute to the pathogenesis of BIA-ALCL.⁶⁵

The presence of numerous eosinophils is also characteristic of most Hodgkin lymphomas.⁶⁶ It was found that these express functionally active CD30 ligand on their surfaces, which acts to transduce proliferative signaling in CD30⁺ cells, including Reed-Sternberg cells, thereby representing an important element in Hodgkin lymphoma pathology.⁶⁶ In a subsequent investigation, multivariate analysis revealed that eosinophilia was the strongest prognostic factor in nodular sclerosing Hodgkin lymphoma, predicting poor outcomes for freedom from treatment failure ($P < 0.001$) and overall survival ($P < 0.001$) in a stage-stratified model.⁶⁷ Although CD30 ligand is known to be expressed in several B- and T-cell malignancies,⁶⁸ its expression and potential role in BIA-ALCL, although intriguing, remain to be elucidated.

The apparent divergence with the IL-17F– and interferon- γ –producing Th17/Th1 phenotype that evidence suggests comprises the cell of origin may be explained, in part, by several factors. In a chronically inflamed milieu, subsets of Th2 cells would be expected to be present. The known plasticity of helper T-cell subtypes could also factor into this difference. Multiple subtypes, including regulatory

T cells, appear to be capable of differentiation into Th17-producing cells.⁶⁹ In addition, CD30-mediated IL-13 production from CD4⁺ T cells that is entirely independent of T-cell receptor signaling has been reported in a murine model.⁷⁰ Thus, it is conceivable that neoplastic BIA-ALCL cells, which, as previously noted (*Innate Immune Response*), generally lack surface T-cell receptor expression, may still serve as a source of this inflammatory cytokine.

JAK-STAT Pathway Centrality

Cytokine signaling predominantly uses the JAK-STAT pathway, which is, therefore, central in converting extracellular signals into changes in cellular protein expression.⁷¹ Acquired mutations in JAK-STAT signaling have been associated with oncogenesis in T-cell lymphomas.^{72,73} *JAK1* and/or *STAT3* mutations were found in 37.5% of ALK-negative sALCL specimens; fusion proteins involving the kinases TYK2 and ROS1, leading to constitutive STAT activation, were also identified, implicating STAT3 activation as a key oncogenic driver in this cancer type.^{12,74,75}

A study of whole exome sequencing on DNA extracted from effusion cytology fluid and germline DNA of two patients with effusion-limited BIA-ALCL revealed somatic, activating mutations in *JAK1* and *STAT3* as well as a germline *JAK3* mutation, the latter suggesting a possible genetic risk factor for the development of this lymphoma.¹² Clinical specimens from 12 of 12 patients with BIA-ALCL tested positive for phospho-STAT3 (pSTAT3) by immunohistochemistry.¹¹ Examination of capsular tissue from patients with BIA-ALCL by

immunohistochemistry found that all tested cases ($n = 27$) were positive for the presence of activated STAT3, which is found in only 38% to 47% of ALK-negative ALCLs⁷⁶ (Figure 3). BIA-ALCL cell lines expressed high levels of p-STAT3, which correlated with aggressiveness in xenografted mice.²¹ These cell lines also produce high levels of the cytokines IL-6 and IL-10, both of which transduce signals via STAT3; and investigators have proposed that autocrine signaling by IL-6 is necessary for survival of these cells.^{21,77,78} Two of the three BIA-ALCL cell lines tested (both having activating *STAT3* mutations) and most of other ALK-negative cell lines exhibited absolute JAK1-STAT3 dependence; in these cell lines, the JAK inhibitors ruxolitinib, tofacitinib, and AZ-3 as well as JAK1 and STAT3 knockdown by shRNA inhibited proliferation.⁷⁹ Cells that were p-STAT3 positive were susceptible to JAK inhibition regardless of the presence of *JAK-STAT* mutations, which implies that other mechanisms resulting in constitutive p-STAT3 expression are operative but that these cells still depend on JAK1-STAT3 signaling.⁷⁹

These findings have several noteworthy implications. Dysregulation of JAK-STAT signaling appears to play a central role in the development of BIA-ALCL. From a therapeutic standpoint, JAK-STAT dependence may, therefore, constitute an attractive target in BIA-ALCL, and could represent an additional targeted approach, with case studies currently reporting efficacy for the anti-CD30 antibody-drug conjugate brentuximab vedotin.^{80,81}

Conclusions

The existing data suggest that BIA-ALCL is a complex disease resulting from the interplay of several pathophysiological processes. It is likely that a triggering event stimulates an immune response, leading to the recruitment of lymphocytes and other inflammatory cells (Figure 4). However, much remains to be understood regarding its etiology and the mechanisms driving its progression, necessitating further investigation. The proposed role of bacterial biofilms and other possible triggers of the inflammatory immune cascade requires further studies. The presence of both a distinctly inflammatory phenotype with a Th17/Th1 cell of origin and a distinct Th2 phenotype characteristic of allergic inflammation must be reconciled, and it will need to be determined if this duality reflects T-cell plasticity and/or a downstream effect of Th17/Th1 inflammation. In addition, a thorough assessment of the impact of JAK-STAT pathway mutations may give additional insight into the mechanisms of disease, as well as direct therapeutic strategies for its management. Ongoing and future research on the molecular mechanisms underlying BIA-ALCL may provide still better options for its prevention and treatment in all patients.

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Author Contributions

M.E.K. co-authored the manuscript, provided illustrations, and introduced concepts of pathogenesis of breast implant-associated anaplastic large-cell lymphoma; S.D.T. developed concepts discussed in the manuscript and coauthored and edited the manuscript; all authors approved the manuscript.

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