Editorial

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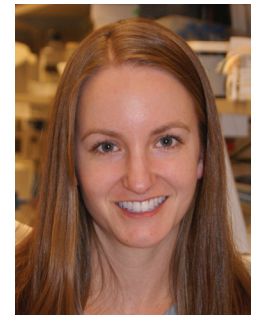
Biomarkers in Medicine

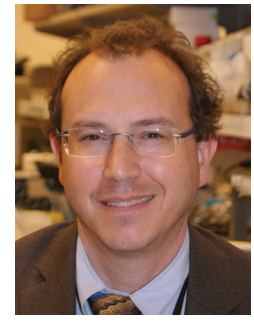
Progress in the identification of subgroups in ALK-negative anaplastic large-cell lymphoma

"…ALK-negative anaplastic large cell lymphoma is a clinically and genetically heterogeneous entity."

Keywords: *ALK* • anaplastic large cell lymphoma • chromosomal rearrangement • *DUSP22* • lymphoma genetics • T-cell lymphoma • *TP63*



Rebecca L Boddicker
Department of Laboratory Medicine & Pathology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA



Andrew L Feldman
Author for correspondence:
Department of Laboratory Medicine & Pathology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA
Tel.: +1 507 284 4939
Fax: +1 507 284 5115
feldman.andrew@mayo.edu

Classification of anaplastic large cell lymphoma: historical background

Anaplastic large cell lymphoma (ALCL) represents a group of non-Hodgkin lymphomas of mature T-cell origin (peripheral T-cell lymphomas [PTCLs]) that share common pathologic features, especially the presence of large lymphocytes that often involve lymph node sinuses and express the Ki-1 antigen, now designated CD30 [1]. A chromosomal rearrangement in a subset of these cases, t(2;5)(p23;q35), was found to involve the nucleophosmin gene, *NPM1*, and a novel tyrosine kinase gene, designated anaplastic lymphoma kinase or *ALK* [2]. Immunohistochemical staining for ALK allowed recognition that cases with several histologic patterns as well as cases with variant, non-*NPM1* partner genes could be unified into a common clinicopathologic entity, ALK-positive ALCL [3]. An additional group of cases lacked *ALK* rearrangements, and these ALK-negative ALCLs occurred in older patients and had inferior outcomes compared with ALK-positive ALCLs [4]. The fourth edition of the WHO classification of lymphomas provisionally classified ALK-negative ALCL as a distinct entity separate from ALK-positive ALCL [5], and this provisional status is likely to be dropped in a forthcoming WHO update. Nevertheless, diagnostic criteria for ALK-negative ALCL still are evolving, particularly to distinguish it from other CD30-positive PTCLs [5–7]. Primary cutaneous ALCL is recognized separately by the WHO and represents ALCLs that present in the skin and typically have excellent long-term outcomes [5]; these tumors share some genetic features with systemic ALCLs, as discussed below.

The pathogenic role of ALK fusions in ALK-positive ALCL has been studied extensively; however, the pathobiology of ALK-negative ALCL remains incompletely understood [6]. Gene expression profiling studies have identified a molecular signature for ALK-positive ALCL and another signature common to all ALCLs [7]. This latter signature can help distinguish ALCL from other PTCLs, but identifying a signature specific for ALK-negative ALCL has proved challenging. This difficulty likely relates in part to intrinsic molecular heterogeneity within the category of ALK-negative ALCL.

Heterogeneity within ALK-negative ALCL

Recent data have indicated that ALK-negative ALCL is a clinically and genetically heterogeneous entity. Our group has identified rearrangements in the *DUSP22-IRF4* gene region on chromosome 6p25.3 in a subset of peripheral T-cell lymphomas [8]. These rearrangements were associated with downregulation of *DUSP22*, which encodes a dual-specificity phosphatase and putative tumor suppressor, and subsequently are referred to as *DUSP22* rearrangements [9]. *DUSP22* rearrangements occurred in both systemic ALK-negative ALCL and primary cutaneous ALCL, and were distinct from rearrangements involving *IRF4* and the T-cell receptor-α gene, *TRA*, in rare CD30-negative PTCLs [8]. We also found recurrent rearrangement of *TP63* in

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ALK-negative ALCL, most commonly with the partner gene *TBL1XR1* [10]. *TP63* encodes the p53 family member, p63, and the rearrangements encode p63 fusion proteins homologous to DNp63 isoforms that have putative oncogenic function.

To characterize these rearrangements further, we studied the histologic, phenotypic, genetic and clinical features of 73 systemic ALK-negative ALCLs [11]. Thirty-two ALK-positive ALCLs were included for comparison. *DUSP22* and *TP63* rearrangements were seen in 30 and 8% of ALK-negative ALCLs, respectively, and were mutually exclusive; neither rearrangement was seen in ALK-positive ALCL. ALK-negative ALCLs lacking *DUSP22* and *TP63* rearrangements were designated 'triple negative' ALCLs. Five-year overall survival in *DUSP22*-rearranged ALCL was excellent (90% at 5 years) and similar to survival in ALK-positive ALCL (85%), but was poorer in triple-negative ALCL (42%) and very poor (17%) in *TP63*-rearranged ALCL.

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DUSP22-rearranged ALCLs appear to represent a distinct group with unifying pathologic findings in addition to their favorable outcomes. These cases showed less histologic variability than other types of ALCL, nearly always demonstrating the so-called 'common' histologic pattern [3]. These features were characteristic and reproducible, including sheets of tumor cells with minimal inflammatory background and occasional cells with doughnut-like nuclei containing cytoplasmic pseudoinclusions [12]. *DUSP22*-rearranged ALCLs also tended not to express cytotoxic granule-associated proteins, which are expressed frequently in other ALCLs [11,12].

DUSP22 rearrangements occur in primary cutaneous ALCL at a frequency similar to systemic ALK-negative ALCL [13]. Although primary cutaneous ALCLs have been considered ALK-negative by definition [5], recent data have shown that some cases express ALK and have a clinical course similar to that of other primary cutaneous ALCLs [14]. Thus, ALCLs with *ALK* rearrangements and those with *DUSP22* rearrangements share several features: they have similar and characteristic histologic appearances; they can present as systemic or cutaneous disease and the systemic forms have similarly favorable prognoses. As such, ALK-positive ALCLs and *DUSP22*-rearranged ALCLs can be considered prototypical ALCLs, while *TP63*-rearranged ALCLs and triple-negative ALCLs are less well characterized and require further study.

Rearrangements of *DUSP22* or *TP63* are not the only genetic abnormalities that can be used to segregate ALK-negative ALCLs into subgroups. For example, ALK-negative ALCLs with copy number losses at 17p13 (including *TP53*) or 6q21 (including *PRDM1*) have poorer overall survival rates than cases without these lesions [15]. Mutations involving *JAK1* or *STAT3* and kinase gene fusions involving *TYK2* or *ROS1* activate STAT3 in ALK-negative ALCL; 43% of cases express nuclear phospho-STAT3, suggesting a possible therapeutic target [16]. Integrating these findings with the distribution of *DUSP22* and *TP63* rearrangements will be critical to understand the molecular heterogeneity of ALK-negative ALCL in greater depth.

Current clinical implications & future directions

We currently test for *DUSP22* and *TP63* rearrangements in ALK-negative ALCL in our routine clinical hematopathology practice. In our opinion, the differences in survival among the genetic subtypes of ALK-negative ALCL are of sufficient magnitude to be important to clinicians and patients. The results also may impact the role of autologous stem-cell transplantation (SCT). Institutions that favor early SCT for PTCLs often include patients with ALK-negative ALCL but not ALK-positive ALCL because of the generally favorable outcomes following combination chemotherapy alone for the latter [17]. Because our data indicated no outcome differences between *DUSP22*-rearranged ALCL and ALK-positive ALCL, *DUSP22* status might play a role in the decision to employ early SCT. Although *TP63*-rearranged ALCLs require further study because of their rarity, early SCT might have limited utility in these patients as well, since most patients either did not achieve remission or died shortly after SCT. These patients might be candidates for alternative or experimental up-front approaches.

The implications of the new genetic findings in ALK-negative ALCL on diagnostic criteria remain unclear. The presence of *DUSP22* rearrangements might, in the appropriate clinicopathologic setting, be useful to support a diagnosis of ALK-negative ALCL. However, since these rearrangements tend to occur in histologically typical cases in which there is not significant diagnostic doubt, this may prove useful in only a minority of cases [12]. A more challenging question is whether *DUSP22*-rearranged ALCL represents a clinicopathologic entity distinct from either ALK-positive ALCL or other ALK-negative ALCLs. The finding of unique histologic, phenotypic, genetic and clinical fea-

tures is compelling, but this decision likely will depend on results of additional series and other approaches such as gene expression profiling.

Molecular stratification of ALK-negative ALCL to guide selection of targeted therapies is an area of intense interest. The finding of convergent genetic events contributing to STAT3 activation raises the possibility of therapies directed at this target [16]. Ongoing studies of the functional impact of *DUSP22* and *TP63* rearrangements may indicate roles for specific therapies directed at overactive kinase pathways or p63 signatures, respectively [18,19]. Further work is also needed in evaluating triple-negative ALCLs, to determine whether these represent a true genetic subset of ALK-negative ALCL or contain further heterogeneity. Finally, the molecular heterogeneity of ALK-negative ALCL likely will extend beyond genetics to encompass such factors as micro-RNAs, epigenetics and the microenvironment.

The ongoing task of lymphoma classification presents a paradox. With increasing molecular understanding, tumors with a spectrum of histologic findings can be unified into new disease entities [20]. At the same time, this increased understanding unveils previously unrecognized heterogeneity within known entities. The ongoing molecular dissection of ALCL, from ALK to the new genetic findings discussed here, represents a paradigm for the evolving process of disease definition and underscores the challenge ahead in the era of new targeted therapies and personalized medicine.

Financial & competing interests disclosure

AL Feldman is supported by award number R01 CA177734 from the National Cancer Institute. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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