

proteins: Membrane (59%), Spike (26%), and Nucleocapsid (22%), differs from that identified by Grifoni et al,<sup>7</sup> who found Spike-specific T cells in all of the convalescent donors they examined. These differences underscore the potential for variables, such as the severity of infection and latency from infection to evaluation to impact the immune response. Furthermore, by identifying immunodominant areas of the M protein, this study suggests that vaccines combining more than Spike protein antigens may mediate durable protective immunity that more closely mimics natural protection.

Characterization of viral CTLs for not only the viral epitope recognized but also the HLA allele that presents that epitope is critical to the application of adoptive therapy with banked, third-party T cells.<sup>5</sup> For example, Keller et al demonstrate that SARS-CoV-2 CTLs recognizing membrane peptide 37 (AA 145 to 160) are restricted in recognition of this peptide through HLA DRB1\*1101. These T-cell lines can then be selected for use in recipients sharing this HLA allele. A bank of viral-specific T-cell lines restricted by a set of commonly inherited HLA alleles could support treatment of most of the world's population.

The isolation and expansion of T cells from individuals recovered from mild to moderate COVID-19 infections are an appealing way to mimic an adaptive rather than maladaptive immune response. Complicated questions remain, including whether adoptive transfer of CTLs will need to occur early after infection before a maladaptive immune response is established and which patients will need adoptive T-cell therapy. Although the presumption is that immunocompromised patients such as recipients of hematopoietic transplant are at high risk of COVID-19–related mortality, recent reports suggest that transplant recipients can have favorable outcomes.<sup>8</sup> In addition, although limited by small numbers, other reports suggest that in patients with specific immune deficiency disorders, the nature of the underlying defect may predict severity of infection, whereas in other disorders, the specific defect is not predictive.<sup>9,10</sup> Whether adoptive transfer of SARS-CoV-2–specific populations of well-characterized T cells will prevent or treat COVID-19 will need to be evaluated formally in clinical trials. However, answering these questions will be facilitated by the remarkably rapid addition of CTLs to the

potential armamentarium against a global pandemic.

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## LYMPHOID NEOPLASIA

Comment on Los-de Vries et al, page 2927

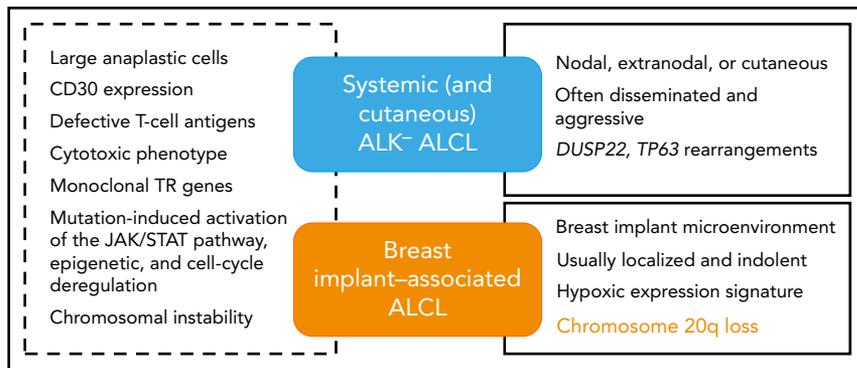
# Chromosomes in breast lymphoma

Laurence de Leval | Lausanne University Hospital; Lausanne University

**In this issue of *Blood*,<sup>1</sup> Los-de Vries and colleagues investigate genome-wide chromosomal copy gains and losses in breast implant-associated anaplastic large cell lymphomas (BIA-ALCLs) and identify that frequent losses at chromosome 20q13.13 are a characteristic genomic feature of this disease.**

BIA-ALCL is a very rare T-cell lymphoma categorized in the current World Health Organization classification of lymphoid malignancies as a provisional entity. It is defined as a subtype of anaplastic lymphoma kinase (ALK)<sup>−</sup> anaplastic large cell lymphoma (ALCL), which arises in patients with breast implants inserted for either cosmetic or reconstructive purposes.<sup>2</sup> The disease typically presents as a late-onset pericapsular effusion (seroma-associated or in situ lymphoma) and is usually cured by complete surgical excision. Less commonly, patients are diagnosed

with poor prognosis, advanced stage disease with an infiltrative tumor mass, or with regional lymph node involvement.<sup>3</sup> Since the first case was described in 1997, epidemiological studies have confirmed that there is a causal relationship to the presence of textured breast implants. Our current understanding of BIA-ALCL pathogenesis includes a chronic inflammatory/immune reaction elicited by the implant or bacteria adherent to it, with secondary genetic lesions mediating transformation, dependence on cytokine activation, and JAK-STAT pathway activation.<sup>3,4</sup>



Common and distinctive features of breast implant-associated vs other ALK<sup>-</sup> ALCLs.

Because of the rarity of the disease and usually limited availability of tumor cells or tissues, only a small number of cases have been evaluated by genomic and molecular techniques. Previous studies have focused on characterizing the mutational landscape of BIA-ALCL or on searching for structural variants known to occur in other ALK<sup>-</sup> ALCLs.<sup>5</sup> In the paper published in this issue, the authors used shallow (low-coverage) whole-genome sequencing in order to evaluate chromosomal copy number aberrations in BIA-ALCL and compare the results to systemic ALK<sup>-</sup> ALCL. Shallow whole-genome sequencing is a recently described technique of copy number variation sequencing, which requires a depth of genome coverage <1 time. It uses shortread sequencing, making it particularly suitable for analyzing DNA from routinely processed formalin-fixed samples and is based on the counts of reads aligned to chromosomal windows or bins after exclusion of problematic genomic regions.<sup>6</sup> Limitations of the method include that it does not identify structural chromosomal aberrations or polyploidy. Genome-wide DNA profiling of BIA- and systemic ALCLs detected a broad range of genomic imbalances in the vast majority of cases, both gains and losses, distributed along all chromosomes, indicating that chromosomal instability already documented in systemic ALCLs is a shared feature of both entities. This is also in line with cytogenetic data from the few BIA-ALCL cell lines consistently showing complex karyotypes.<sup>7</sup> There was substantial overlap and few significant differences between the 2 entities, but strikingly the most frequent aberration in BIA-ALCL (ie, 20q loss peaking at 20q13.13-13.2 present in two-thirds of the cases) was detected in only 13% of the systemic ALK<sup>-</sup> ALCLs analyzed.

Moreover, 20q loss has been very rarely found in other ALCLs and peripheral T-cell lymphoma-not otherwise specified. Therefore, this finding qualifies 20q deletion as a genomic marker unique to BIA-ALCL. This feature is important for disease definition and classification because it supports the concept that this a separate entity distinct from other ALK<sup>-</sup> ALCLs (see figure). Indeed, besides the unique clinical context being 1 major defining feature of the disease, BIA-ALCL is otherwise indistinguishable from other ALK<sup>-</sup> ALCLs by morphology and immunophenotype. Moreover, the pattern of mutations observed in BIA-ALCL, preferentially distributed among effector and regulators of the JAK/STAT pathway, epigenetic modifiers, and regulators of cell cycle is overlapping with that of other T-cell lymphoma entities, especially other ALK<sup>-</sup> ALCLs.<sup>4</sup> Of note, in line with the novel findings reported here, 2 studies have also documented specificities in terms of the gene expression signature of BIA-ALCL, notable for an hypoxic signature, which likely reflects the peculiar confined microenvironment in which this lymphoma develops.<sup>8,9</sup>

An interesting finding reported by Los-de Vries et al is that in situ (seroma-type) BIA-ALCL comprises a more aberrant and more heterogeneous genome compared with invasive tumors, whereas an inverse relationship was described for mutations, more numerous in tumor-type BIA-ALCL.<sup>4</sup> This brings a meaningful insight into BIA-ALCL progression, which seems to be associated with a change in oncogenic signatures<sup>10</sup> and a selection of subclones.

Whether shallow whole-genome profiling represents a useful adjunct in the

assessment of periprosthetic seroma fluid requires prospective evaluation. Feasibility can be inferred from the conclusive results on circulating free DNA, but the major obstacle lies in the availability of the technique. It is not yet widely used in diagnostic laboratories. A systematic analysis of seroma fluids, assuming sufficient samples can be obtained, would contribute interesting insights into currently poorly characterized early stages of BIA-ALCL development.

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