KDM4C in germinal center lymphoma: a new piece of the epigenetic puzzle

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In this issue of *Haematologica*, López *et al.*[1] report their findings from mining whole genome sequencing data from tumors of patients (n=183) with germinal center (GC) lymphoma, curated as part of the International Cancer Genome Consortium MMML-Seq (Molecular Mechanisms in Malignant Lymphoma by Sequencing) project, to add histone demethylase *KDM4C* (4% of cases) to a burgeoning list of epigenetic regulators recurrently altered in these diseases. Both *in silico* analyses and functional reconstitution studies, in a subset of cell lines, support a tumor suppressive role for *KDM4C* in contrast to previous reports of its having oncogenic activity,[2] underlining the important contribution of cellular and molecular context to the roles of epigenetic regulators.

It is now well established that chromatin deregulation is a hallmark of cancer, seen notably in the B-cell malignancies follicular lymphoma and diffuse large B-cell lymphoma, in which mutations arise early in the evolution of the disease, and typically affect multiple components of the chromatin machinery in the same patient. The introduction of targeted resequencing has highlighted a now familiar gamut of recurring gene mutations in *KMT2D*, *CREBBP*, *EZH2*, *ARID1A*, *EP300* and linker histones[3,4] and spurred efforts to understand the nature of cooperation occurring between these regulators, and their functional downstream consequences. The findings here regarding *KDM4C* (also called *JMJD2C*), on chromosome 9p24, represent a departure, focusing on copy number variation. The gene encodes a member of the Jumonji family of demethylases, which can remove methyl groups from histone residues H3K9 and H3K36 adding to the overall complexity of the epigenetic deregulation underlying GC lymphomas (Figure 1) and cautions against a tunnel vision focus on well-characterized marks such as H3K27 and H3K4. Indeed, the study by López *et al.* on *KDM4C* creates a heightened awareness of the existence of rare, and for the most part, largely inaccessible structural variants that are difficult to resolve using targeted or whole exome sequencing approaches.

Critically, it begs the questions of whether KDM4C or the corresponding chromatin marks H3K9 and H3K36 are deregulated by other recurrent genetic or epigenetic alterations. For instance, an increase in H3K27me3 is induced not only by perturbations of the methyltransferase *EZH2* a target of SET domain gain-of-function mutations and amplifications of chromosome 7 in GC lymphomas[5,6] but also by loss-of-function mutations and deletions of the corresponding demethylase *KDM6A* (also known as *UTX*) in other cancer types including leukemias.[7] Indeed, loss of linker histone proteins, frequent in GC lymphomas, has been shown to result in a distinct gain of H3K36 dimethylation.[8] It is safe to assume that the application of whole genome sequencing will uncover an increasing number of diverse alterations with converging mechanistic effects to those of already established mutations. The translational application of epigenetic targeting therapies is exemplified by the Food and Drug Administration's approval of the EZH2 inhibitor tazemetostat for relapsed/refractory follicular lymphoma. The enrichment of *EZH2*-mutant patients among responders (69% $EZH2^{mut}$ *vs.* 35% $EZH2^{WT}$),[9] represents the potential of predictive biomarkers, while also highlighting

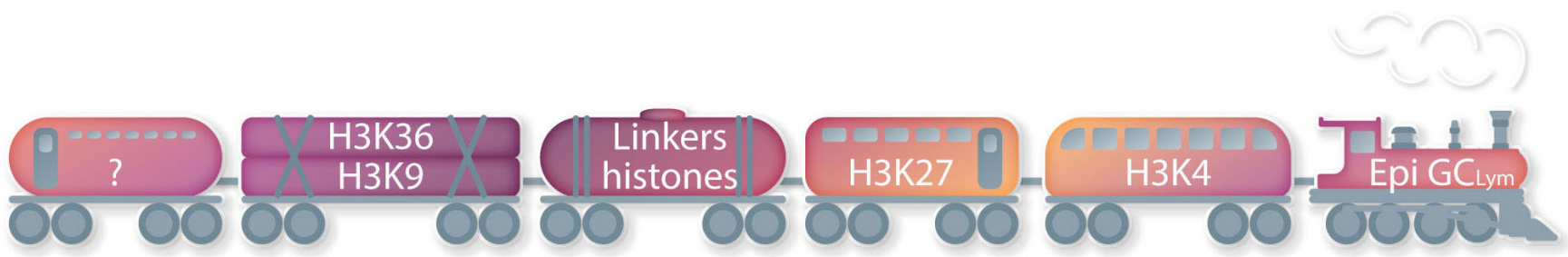

Figure 1. Epigenetic deregulation in germinal center lymphomas: a growing number of histone proteins and their tail residues are known to be altered in these diseases.

the lack of fidelity of a single genetic predictor of response and resistance to pleiotropically-acting treatments and the need to consider the modulating effects of other factors.

The contribution of epigenetic alterations to outcomes in follicular lymphoma is underlined by their inclusion in the clinico-genetic M7-FLIPI score, which has some predictive value for overall survival in patients treated with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone), and with five of the seven constituent genes (*EP300*, *CREBBP*, *MEF2B*, *ARID1A*, *EZH2*) representing epigenetic regulators, with either positive or negative predictive value. The holy grail, however, in an evolving treatment landscape, is a predictive model that performs independently of therapy choice, with the M7-FLIPI not being informative in patients treated with rituximab plus bendamustine.[10] In this regard, the study by López and colleagues[1] makes us cogent that we need to look beyond gene mutations and be as assiduous as possible in documenting the spectrum of lesions that may be contributing to the biology of the cancer. This certainly raises challenges for companion diagnostics, but progress is being made in the ability to assess genomic sequence, translocation, and copy-number data with the aim of classifying patients into higher fidelity subtypes that offer predictive value for treatment.[4]

This new addition of *KDM4C* alterations to the growing list of epigenetic deregulation occurring in these diseases suggests that other rarer events have been overlooked and need to be accounted for. Indeed, whether KDM4C plays a key role in the GC reaction and what contribution alterations have to malignant transformation or disease maintenance remains to be characterized. An attractive feature of leveraging epigenetic mutations for therapeutic intervention in follicular lymphoma is their early and clonally stable occurrence,[3] suggesting that this approach could conceivably target the common progenitor cell population that repopulates the tumor at relapse. It would therefore be valuable to establish whether *KDM4C* alterations occur early in disease evolution.

Despite advances with agnostic treatments such as chimeric antigen receptor T cells and bispecific antibodies, the use of epigenetic-targeting therapies and the profiling of epigenetic landscapes for potential biomarkers remain at the forefront of efforts to achieve precision medicine approaches for GC lymphomas. A key challenge is, therefore, the elucidation of a full picture of the heterogeneous drivers of the epigenetic deregulation frequent in these diseases.

Disclosures

No conflicts of interest to disclose.

Contributions

Both authors contributed equally.

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