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LYMPHOID NEOPLASIA

Comment on Heward et al, page 370

Epigenetic balance in DLBCL

Elisa Oricchio | Swiss Institute for Experimental Cancer Research; Swiss Cancer Center Leman

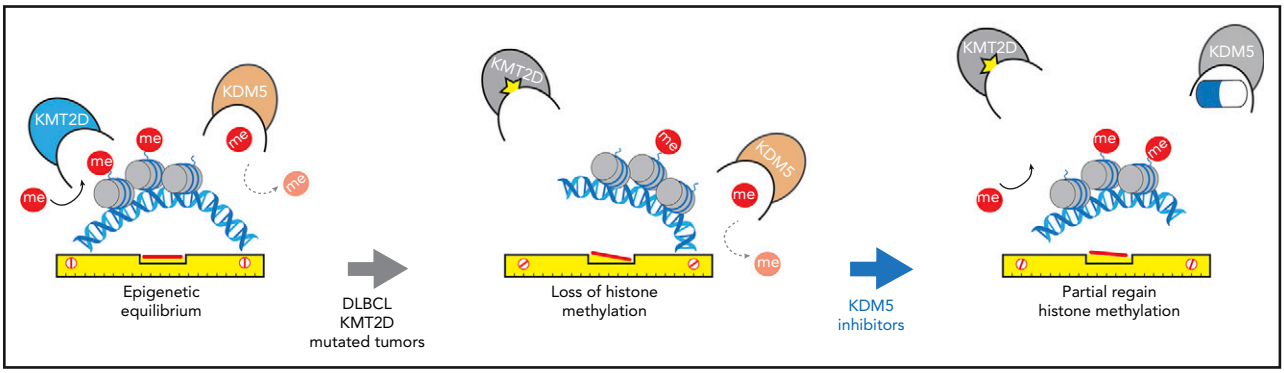
In this issue of *Blood*, Heward and colleagues show that inhibition of KDM5 can, in part, rescue the epigenetic and transcriptional phenotype related to the loss of KTM2D and reduce tumor growth.[1]

Cancer therapies are usually designed to directly target and block the activity of oncogenic drivers. Loss of tumor suppressors contributes equally to tumor development, but they are almost impossible to target therapeutically. Understanding which molecular changes derive from altered tumor-suppressor activity provides opportunities to identify indirect therapeutic targets where inhibition will counterbalance and "correct" these changes. In diffuse large B-cell lymphoma (DLBCL), it is possible to partially correct the epigenetic phenotype derived from the loss of histone-methyl transferase (HMT) KMT2D activity by inhibiting the histone-demethylase (HDT) KDM5.

Histone posttranslational modifications are essential for regulating and modulating gene expression. The epigenetic status of coding and noncoding regions is defined by the relative presence of various posttranslational modifications of different lysines on the tail of histones. For example, histone-3 lysine-4 mono-di-tri methylation (H3K4me) or histone-3 lysine-27 trimethylation (H3K27me3) mark transcriptionally active and inactive regions, respectively.[2] Proteins, such as HMTs and HDTs, that control the methylation status at histone tails must act in concert to maintain the epigenetic status and identity of each cell.[3]

In non-Hodgkin lymphoma, such epigenetic regulators are among the most frequently mutated genes.[4] These include both gain-of-function mutations that enhance HMT activity, such as EZH2^{Y646X} (10% to 25% of patients, on average), and the more common, loss-of-function mutations of *KMT2D* (up to 70% of patients).[5,6] Pharmacological inhibitors have been developed to directly target EZH2, and they are currently tested in the clinic.[7] However, restoring the activity of tumor-suppressor genes such as *KMT2D* is more challenging. KMT2D contributes to maintenance of H3K4 methylation, whereas the histone demethylase KDM5 is responsible for H3K4 demethylation. Lack of KMT2D activity in lymphoma cells results in decreased H3K4 methylation. Although it is not possible to restore the activity of KMT2D directly, Heward and colleagues show that pharmacological inhibition of KDM5 proteins counteract this effect and levels of H3K4me3 were recovered in KMT2D-mutated cells (see figure). These epigenetic modifications were associated with gene expression reactivation of both KMT2D-dependent and -independent genes and with reduced tumor growth in vivo. In this study, the extensive molecular characterization of the effects of KDM5 inhibition and preclinical data in xenograft models lay the basis for possible applications of KDM5 inhibitors in the clinic.

Compared with other targeted anticancer therapies, epigenetic inhibitors change the epigenetic and transcription status of the cells genome wide. Targeted therapies blocking the activity of signaling proteins induce specific modifications of a signaling cascade. Conversely, inhibition of the activity of



KDM5 inhibitors reequilibrate the epigenetic spirit level. Inhibition of KDM5 limits H3K4me3 loss in patients with DLBCL expressing mutated KMT2D.

epigenetic modifiers can induce modifications of chromatin structures and simultaneously influence the expression of multiple genes.[8] Indeed, treatment with KDM5 inhibitors reactivated the expression of multiple genes, beyond those that were silenced by *KMT2D* loss. In addition, several epigenetic modifiers have noncatalytic functions.[9] Thus, inhibition of KDM5 proteins, on the one hand, can rescue the oncogenic phenotype acquired by KMT2D-mutated lymphoma cells, but, on the other hand, it induces additional epigenetic and transcriptional changes.

It is clear that inhibition of KDM5 results in accumulation of H3K4me3 and reactivation of gene expression, but how this culminates in an antiproliferative phenotype is more complex. For example, Heward et al observed downregulation of BCL2 upon treatment with KDM5 inhibitors, which is an indirect consequence of KDM5 inhibition. The dynamic and functional interactions between multiple epigenetic regulators makes it difficult to anticipate how the modification of one element will influence the activity of the others. Moreover, different targets could be reactivated in different tumors, as their expression will be influenced by the presence or absence of other genomic alterations, the stage of the tumor, and the composition of the tumor microenvironment. Thus, heterogenous epigenetic and transcriptional changes may limit the identification of direct targets that could serve as biomarkers of response to KDM5 inhibitors.

Overall, treatment with epigenetic inhibitors offers the possibility of broadly modulating cancer cell transcriptional activity and, although their therapeutic benefit as single agents may present some limitations, their ability to promote the expression of previously silenced genes can favor the presentation of new antigens; thus, their application in combination with immunotherapies could be promising.[10]

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MYELOID NEOPLASIA

Comment on Sorror et al, page 387

Fitness for intensive chemotherapy: a continuing conundrum

Andrew H. Wei | The Alfred Hospital

In this issue of *Blood*, Sorror et al[1] address an important issue: Does reducing the intensity of induction therapy in acute myeloid leukemia (AML) improve outcomes in the elderly. A multicenter retrospective and prospective nonrandomized cohort study was conducted to examine outcomes with intensive or nonintensive chemotherapy (NIC) among patients stratified by a multimodal AML composite risk score (with higher scores given to older age, increased comorbidity burden, and adverse cytogenetic risk). In addition, the authors examined the impact of chemotherapy intensity on quality of life, patient, and physician perceptions of outcome.

The median age of AML at diagnosis is 68 years; therefore, most patients are considered "elderly" and face the complex decision of whether to choose intensive or NIC for their initial treatment. From a population registry perspective, the proportion receiving intensive chemotherapy (IC) declines with age: 60 to 69 (83%), 70 to 74 (67%), 75 to 79 (39%), and 80 to 84 years (12%) (Swedish Registry 2014-2019; Gunnar Juliusson, Lund University Cancer Centre, written communication, 23 February 2021).[2] Among older adults with AML, complete remission after IC declines with age: 60 to 69 (78%), 70 to 74 (68%), 75 to 79 (62%), and 80 to 84 years (48%), but early death increases: 60 to 69 (6%), 70 to 74 (9%), 75 to 79 (13%), and 80 to 84 years (13%). Two-year survival also declines with age: 60 to 69 (~40%), 70 to 74 (~30%), and 75 to 84 years (~20%). As a result, there is reduced enthusiasm to administer IC to older patients, with the assumption that lower intensity options may spare the patient a prolonged stint in hospital, while maintaining quality of life (QOL) and lowering the risk of early death. In the United States, Surveillance, Epidemiology, and End Results data from 2000 through 2009 indicate that 60% of patients with AML older than 65 years receive no chemotherapy and have a median survival of only 1.5 months.[3]