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REFERENCES

1. Jibril A, Hellmich C, Wojtowicz EE, et al. Plasma cell–derived mtDAMPs activate the macrophage STING pathway, promoting myeloma progression. *Blood*. 2023;141(25):3065-3077.
2. Cowan AJ, Green DJ, Kwok M, et al. Diagnosis and management of multiple myeloma: a review. *JAMA*. 2022;327(5):464-477.
3. Sun J, Park C, Guenthner N, et al. Tumor-associated macrophages in multiple myeloma: advances in biology and therapy. *J Immunother Cancer*. 2022;10(4):e003975.
4. Kopinski PK, Singh LN, Zhang S, Lott MT, Wallace DC. Mitochondrial DNA variation and cancer. *Nat Rev Cancer*. 2021;21(7): 431-445.
5. Samson N, Ablasser A. The cGAS-STING pathway and cancer. *Nat Cancer*. 2022;3(12): 1452-1463.
6. Cheng N, Watkins-Schulz R, Junkins RD, et al. A nanoparticle-incorporated STING activator enhances antitumor immunity in PD-L1-insensitive models of triple-negative breast cancer. *JCI Insight*. 2018;3(22): e120638.
7. Ruiz-Heredia Y, Ortiz-Ruiz A, Samur MK, et al. Pathogenetic and prognostic implications of increased mitochondrial content in multiple myeloma. *Cancers*. 2021;13(13):3189.
8. Gulla A, Morelli E, Samur MK, et al. Bortezomib induces anti-multiple myeloma immune response mediated by cGAS/STING pathway activation. *Blood Cancer Discov*. 2021;2(5):468-483.
9. Sokolowska O, Rodziewicz-Lurzynska A, Pilch Z, et al. Immune checkpoint inhibition improves antimyeloma activity of bortezomib and STING agonist combination in Vk*MYC preclinical model. *Clin Exp Med*. Published online 31 August 2022. https://doi.org/10.1007/s10238-022-00878-1

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MYELOID NEOPLASIA

Comment on Guo et al, *page 3078*

Getting to the core of ADAR2 activity in AML

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In an insightful article in this issue of *Blood*, Guo et al[1] identify the RNA editing enzyme ADAR2 (adenosine deaminase acting on RNA2) as a core tumor suppressor in core binding factor acute myeloid leukemia (CBF AML).[1] The ADAR family of RNA editases includes (1) ADAR1, which exists as a constitutively active ADAR1p110 isoform and an inflammatory cytokine-inducible ADAR1p150 isoform, which is commonly deregulated in advanced malignancies; (2) ADAR2, which is primarily expressed in the brain; and (3) ADAR3, which is catalytically inactive and thought to function as an ADAR2 antagonist.[2] Over the last decade, cumulative studies have shown that epitranscriptomic disruption of RNA integrity by ADAR1 fuels therapeutic resistance in a broad array of malignancies, including hematologic malignancies like acute myeloid leukemia (AML).[2-7] Although ADAR1 is essential for the maintenance of normal adult hematopoiesis[8] and transcriptomic integrity,[9] deregulation of adenosine-to-inosine RNA editing by ADAR1 has been linked to malignant reprogramming of progenitors in hematopoietic malignancies.[2-5] Moreover, inflammatory cytokine-mediated ADAR1 activation in tumor microenvironments has been linked to immune silencing and immune checkpoint inhibitor resistance.[6,7] Conversely, relatively little is known about deregulation of ADAR2 in therapy-resistant malignancies like AML.

Although patients with CBF (core binding factor) AML are initially sensitive to cytarabine chemotherapy, they have a relatively high rate of chemotherapeutic resistance after relapse, resulting in a median overall survival rate of only 5 years.[10] Specifically, CBF AML represents ~10% of all AML cases and is typified by *t(8;21) (q22;q22)* or *inv(16) (p13q22)/t(16;16)* translocations that generate *RUNX1/RUNX1T1 (AML1/ETO)* and *CBFB/MYH11* fusion genes, respectively.[10] Moreover, AML1/ETO displaces c-Jun from PU.1, thereby inducing a myeloid maturation arrest that, with additional genetic and/or epigenetic changes, promotes leukemic transformation.[10] Patients with CBF AML have a relatively low mutational burden compared with patients with intermediate or high-risk AML, which suggests that epigenetic (eg, *TET2, ASXL1*, and *ASXL2*) or epitranscriptomic (posttranscriptional) alterations may be important contributors to therapeutic resistance and relapse.

In this groundbreaking study, Guo et al demonstrate that ADAR2 deregulation is a key driver of CBF AML propagation.[1] In mouse models of t(8;21) CBF AML, RUNX1-driven transcription of ADAR2 was found to be repressed by the RUNX1-ETO AE9a fusion protein. Moreover, this dominant negative repression of ADAR2 could be reversed by overexpression of catalytically-active ADAR2 in both t(8;21) and inv16 AML cells. Furthermore, expression of COPA and COG3 ADAR2 RNA editing targets inhibited human t(8;21) AML cell line clonogenicity. As an important epitranscriptomic (posttranscriptional) process, RNA editing is usually regulated by inflammatory cytokine signaling. Thus, the role of the leukemia stem cell (LSC) niche in driving ADAR2 deregulation will need to be examined in murine models of CBF AML as well as in humanized LSC mouse models. Primate-specific Alu sequences represent key editing sites and therefore ADAR2-related editome analyses will need to be analyzed in human CBF AML samples and with lentiviral ADAR2 overexpression and short hairpin RNA (shRNA) knockdown studies. The role of ADAR2 in normal human hematopoietic stem and progenitor cell (HSPC) maintenance will also need to be investigated. Overall, this study provides novel mechanistic insights into the tumor-suppressive role of ADAR2-mediated RNA editing in CBF AML and sets the stage for investigating the cell type and tumor microenvironment specific roles of ADAR2 deaminase deregulation in human LSC propagation. Finally, the restoration of ADAR2-mediated tumor-suppressive activity may represent a

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core strategy for the development of therapies that effectively prevent CBF AML relapse.

Conflict-of-interest disclosure: C.J. is the cofounder of Aspera Biomedicines and Impact Biomedicines and receives royalties for patents related to CD47. K.S. declares no competing financial interests. ■

REFERENCES

1. Guo M, Chan THM, Zhou Q, et al. Core-binding factor fusion downregulation of ADAR2 RNA editing contributes to AML leukemogenesis. *Blood*. 2023;141(25):3078-3090.
2. Jiang Q, Crews LA, Holm F, Jamieson CHM. RNA editing-dependent epitranscriptome diversity in cancer stem cells. *Nat Rev Cancer*. 2017;17(6):381-392.
3. Zipeto MA, Court AC, Sadarangani A, et al. ADAR1 activation drives leukemia stem cell self-renewal by impairing Let-7 biogenesis. *Cell Stem Cell*. 2016;19(2):177-191.
4. Lazzari E, Mondala PK, Santos ND, et al. Alu-dependent RNA editing of GLI1 promotes malignant regeneration in multiple myeloma. *Nat Commun*. 2017;8(1):1922.
5. Jiang Q, Isquith J, Ladel L, et al. Inflammation-driven deaminase deregulation fuels human pre-leukemia stem cell evolution. *Cell Rep*. 2021;34(4):108670.
6. Ishizuka JJ, Manguso RT, Cheruiyot CK, et al. Loss of ADAR1 in tumours overcomes resistance to immune checkpoint blockade. *Nature*. 2019;565(7737):43-48.
7. Zhang T, Yin C, Fedorov A, et al. ADAR1 masks the cancer immunotherapeutic promise of ZBP1-driven necroptosis. *Nature*. 2022;606(7914):594-602.
8. Hartner JC, Walkley CR, Lu J, Orkin SH. ADAR1 is essential for the maintenance of hematopoiesis and suppression of interferon signaling. *Nat Immunol*. 2009;10(1):109-115.
9. Tan MH, Li Q, Shanmugam R, et al. Dynamic landscape and regulation of RNA editing in mammals. *Nature*. 2017;550(7675):249-254.
10. Borthakur G, Kantarjian H. Core binding factor acute myelogenous leukemia-2021 treatment algorithm. *Blood Cancer J*. 2021;11(6):114.

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Comment on Sharma et al, *page 3091*

Heme and macrophages: a complicated liaison

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In this issue of *Blood*, Sharma et al show that hepatic damage in sickle cell disease (SCD) is aggravated by the limited ability of phagocytes to clear apoptotic cells, a process known as efferocytosis, and to resolve inflammation.[1] Hemolysis plays a major role by reprogramming macrophages towards highly inflammatory and poorly efferocytic cells through the coordinated suppression of efferocytosis receptors and induction of a metabolic shift towards aerobic glycolysis.

SCD is a debilitating disorder with significant morbidity due to organ damage. The liver is affected by SCD, resulting in the so-called sickle hepatopathy. Sickle hepatopathy encompasses a wide range of acute and chronic liver pathologies, the pathogenesis of which have not been fully characterized. The clinical spectrum of liver disease ranges from mild abnormalities of liver function in patients who are asymptomatic to dramatic acute crises associated with liver failure and eventual cirrhosis. Although hepatic dysfunction affects up to 10% to 40% of patients with SCD, the molecular mechanisms promoting progressive liver injury in SCD remain poorly understood, and therapeutic approaches to prevent it are suboptimal.[2] Sharma et al provide novel insight into the cellular and molecular mechanisms underlying liver damage in SCD, showing that hepatic injury is aggravated by defective apoptotic cell clearance by resident and recruited macrophages.

Macrophages are responsible for the removal of senescent and/or damaged erythrocytes and for the clearance of free hemoglobin and heme through receptor-mediated endocytosis of hemoglobin/haptoglobin and heme/hemopexin complexes, respectively.[3,4] In SCD, the macrophages are stressed owing to the shortened half-life of red blood cells. Moreover, the macrophages are exposed to excess heme owing to the saturation of both haptoglobin and hemopexin binding capacity. In addition, both hepatic and recruited macrophages actively participate in the resolution of tissue damage by removing dead and dying cells.[5]

Sharma et al show that efferocytosis is impaired by hemolysis in SCD. Heme scavenging by the heme carrier hemopexin is sufficient to improve apoptotic cell removal by resident and recruited hepatic phagocytes, thus indicating that excess heme actively contributes to impaired efferocytosis. Importantly, heme was found to drive a complex functional reprogramming of macrophages, whereby cell efferocytic and reparative capacities are suppressed in favor of a marked proinflammatory profile. This effect is in line with heme action as a damage-associated molecular pattern (DAMP) and with its ability to promote sterile inflammation through inflammatory cytokine release and impaired resolution of tissue damage.[6]

Sharma et al show that heme reprograms macrophages through a coordinated functional and metabolic adaptation achieved via suppression of efferocytosis and mitochondrial remodeling. Normally, in the presence of apoptotic cells, macrophages enhance mitochondrial biogenesis to meet the metabolic needs of efferocytosis and catabolize, via mitochondrial fatty acid β-oxidation and oxidative phosphorylation, the excess membrane lipids of the ingested apoptotic cells. These events are all controlled by the transcription factors PPARγ and PGC1α, key regulators of the expression of efferocytosis receptors and mitochondrial biogenesis.[7] Heme-mediated suppression of PPARγ and PGC1α, via Toll-like receptor 4 (TLR4) activation, reduces efferocytosis receptors on the cell plasma membrane and alters mitochondrial dynamics. Thus, heme-induced mitochondrial remodeling acts as an adaptive metabolic response to reduced cell lipid load and apoptotic cell engulfment. As a result of diminished efferocytosis and mitochondrial remodeling, heme-activated macrophages do not increase mitochondrial respiration and adenosine triphosphate production upon apoptotic cell or lipid exposure (see figure).

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