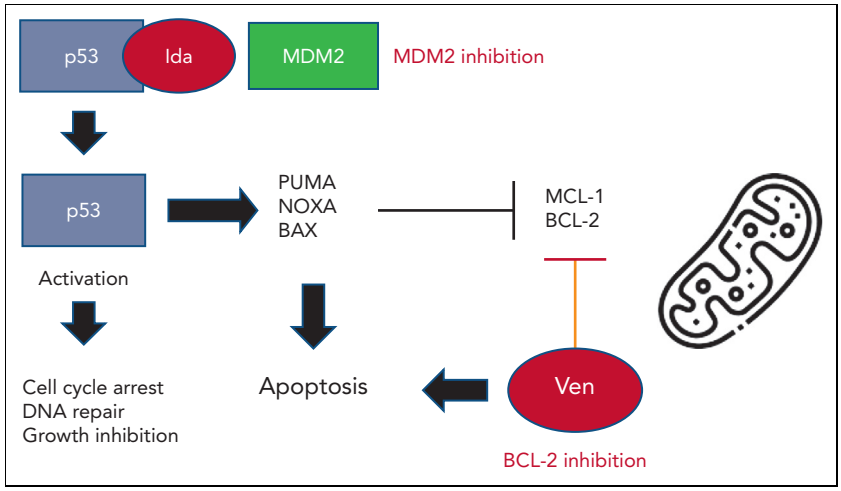


Proposed mechanism of action of combined MDM2 (idasanutlin) and BCL-2 (venetoclax) inhibition on AML cells.

VAF or led to the resolution of these aberrant clones. It is reasonable to assume that the dual antagonism of BCL-2 and MDM2 may have preferentially expanded the pool of *p53* mutant clones given the known resistance of these cells to venetoclax therapy.[9] Whether adding a third agent (such as azacitidine) to BCL-2 and MDM2 inhibition would mitigate this issue is unknown.

While idasanutlin is no longer being clinically developed for AML,[10] alternative MDM2 inhibitors (eg, KRT-232, APG-115, siremadlin) remain under active investigation for myeloid malignancies. Data from this phase 1b trial of venetoclax and idasanutlin provide important insights into the potential benefits and pitfalls of MDM2 inhibition in AML patients to further optimize these and future clinical studies.

Conflict-of-interest disclosure: E.S.W. has served in an advisory capacity for AbbVie/Genentech and on data safety monitoring committees for AbbVie clinical trials. ■

REFERENCES

1. Daver NG, Dail M, Garcia JS, et al. Venetoclax and idasanutlin in relapsed/refractory AML: a nonrandomized, open-label phase 1b trial. *Blood*. 2023;141(11):1265-1276.
2. Megias-Vericat JE, Martinez-Cuadron D, Sanz MA, Montesinos P. Salvage regimens using conventional chemotherapy agents for relapsed/refractory adult AML patients: a systematic literature review. *Ann Hematol*. 2018;97(7):1115-1153.
3. DeWolf S, Tallman MS. How I treat relapsed or refractory AML. *Blood*. 2020;136(9):1023-1032.
4. Ding Q, Zhang Z, Liu JJ, et al. Discovery of RG7388, a potent and selective p53-MDM2 inhibitor in clinical development. *J Med Chem*. 2013;56(14):5979-5983.
5. Lehmann C, Friess T, Birzele F, Kiialainen A, Dangl M. Superior anti-tumor activity of the MDM2 antagonist idasanutlin and the Bcl-2 inhibitor venetoclax in p53 wild-type acute myeloid leukemia models. *J Hematol Oncol*. 2016;9(1):50.
6. Pan R, Ruvolo V, Mu H, et al. Synthetic lethality of combined Bcl-2 inhibition and p53 activation in AML: mechanisms and superior antileukemic efficacy. *Cancer Cell*. 2017;32(6):748-760.e746.
7. Konopleva M, Pollyea DA, Potluri J, et al. Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia. *Cancer Discov*. 2016;6(10):1106-1117.
8. Yee K, Papayannidis C, Vey N, et al. Murine double minute 2 inhibition alone or with cytarabine in acute myeloid leukemia: results from an idasanutlin phase 1/1b study small star, filled. *Leuk Res*. 2021;100:106489.
9. Nechiporuk T, Kurtz SE, Nikolova O, et al. The TP53 apoptotic network is a primary mediator of resistance to BCL2 inhibition in AML cells. *Cancer Discov*. 2019;9(7):910-925.
10. Konopleva MY, Röllig C, Cavenagh J, et al. Idasanutlin plus cytarabine in relapsed or refractory acute myeloid leukemia: results of the MIRROS trial. *Blood Adv*. 2022;6(14):4147-4156.

https://doi.org/10.1182/blood.2022018739

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on van Halteren et al, page 1277

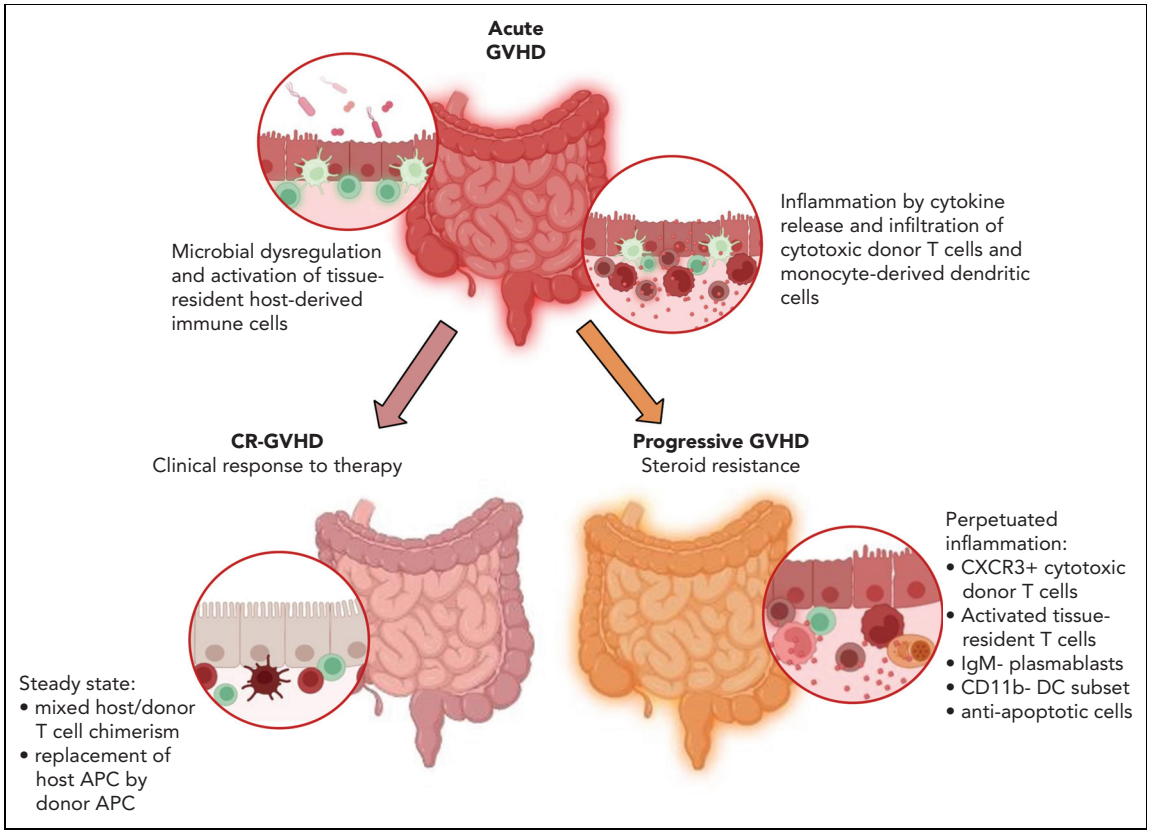
Good or bad cops: immune cells in aGVHD

Georg Stary | Medical University of Vienna; Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases; and CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences

In this issue of *Blood*, van Halteren et al have identified an immune cell signature associated with the onset of acute graft-versus-host disease (aGVHD) and with the treatment response to first- and second-line therapy.[1]

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative treatment option for many advanced hematopoietic malignant diseases. Its success in curing these disorders relies on the synergistic effect of eradicating malignant host leukocytes by pretransplant treatment regimens, such as chemotherapy and radiation, and full reconstitution of a donor-derived immune system mediating posttransplant graft-versus-leukemia effect (GvL) against remaining malignant cells.[2,3] Alongside desired GvL, unwanted acute GVHD may result from complex interaction of tissue-resident host immune cells and newly engrafted donor cells.[4,5] Acute GVHD is a major complication of HSCT that limits its broader application. Despite significant progress in prophylactic and therapeutic strategies, GVHD remains a major cause of morbidity and mortality after HSCT, occurring after 30% to 40% of transplants and accounting for up to 15% of deaths. Remarkably, relapse rates are significantly lower in patients who develop GVHD,[6] indicating a link between GVHD and GvL.

For decades, high dosages of glucocorticosteroids such as prednisone or methylprednisolone have remained a pillar of frontline treatment in HSCT recipients who develop grade 2 to 4 GVHD, despite GVHD prophylaxis. The broad immunosuppression induced by



Pathological mechanisms of aGVHD. (Top) Microbial products and cytokines from resident cells (eg, effector T cells, $CD163^+$ monocyte-derived macrophages) are believed to induce GVHD. (Bottom) While complete response to first-line therapy usually induces an equilibrium of host/donor tissue-resident T cells and replacement of host macrophages by donor APCs in barrier tissues, steroid resistance is now shown to be related to the occurrence of $CXCR3^+$ donor T cells, activated tissue-resident T cells, plasmablasts, and dendritic cells. APC, antigen-presenting cells; DC, dendritic cells; IgM, immunoglobulin M. Figure designed by Johanna Strobl and created with BioRender.com.

glucocorticosteroids is associated with severe side effects. GVHD is not resolved in roughly half of the patients receiving such treatment, and their disease is considered steroid refractory (SR-GVHD). Additional treatment options exist today, with JAK inhibition, tumor necrosis factor blockade, extracorporeal photosynthesis, or mesenchymal stem cells being used as second-line therapy.[7,8] Nevertheless, overall survival in SR-GVHD is less than 50% at 6 months, and overall survival in response to second-line therapies is also poor (<30%).[8]

The underlying mechanisms accounting for SR-GVHD and biomarkers associated with response to therapy are currently unknown. Therefore, it is important to identify mechanisms underlying GVHD development and clinical response to glucocorticosteroids and second-line therapies. In addition, the identification of markers that predict individual patient response to first- and second-line therapy will be crucial to implementation of personalized targeted treatment.

van Halteren et al analyzed patient cohorts that were defined by their response to therapy. By doing so, they found in a broad analysis using mass cytometry that various immune cell compartments were changed even prior onset of clinical symptoms at early stages of aGVHD. By applying high-dimensional CYTOF profiling (an application of mass cytometry in which antibodies are labeled with heavy metal ion tags rather than fluorochromes) of blood samples of aGVHD patients, the authors found higher numbers of $CD163^+CD11b^+$ monocytes and T-cell subsets expressing skin- and gut-homing molecules in the peripheral blood of aGVHD patients even before there were clinical manifestations of the disease. When examining aGVHD cohorts with different responses to first- and second-line therapy by mass cytometry, the authors found higher numbers of effector and regulatory T cells with skin- and gastrointestinal-homing receptors, certain dendritic cell subsets, and plasmablasts to be associated with therapy refractory GVHD (see figure). Importantly, findings in peripheral blood samples were corroborated with tissue samples of gastrointestinal tract or skin affected by GVHD. As the sample size of the different patient cohorts was rather small in the present study, validation will be needed to assess the utility and reproducibility of the findings for use as prognostic markers for treatment response. Equally important, this study identifies the contributions of several immune cell compartments to SR-GVHD. Uncovering the cellular interactions between T cells, dendritic cells, and B cells that contribute to treatment response will be quite important. The unique approach of high-dimensional immune cell profiling in well-defined patient cohorts will provide new perspectives of the immune cell network in complex diseases in future well beyond the specific context of GVHD.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

REFERENCES

1. van Halteren AGS, Suwandi JS, Tuit S, et al. A unique immune signature in blood separates therapy-refractory from therapy-responsive acute graft-versus-host disease. *Blood*. 2023; 141(11):1277-1292.
2. Nakasone H, Remberger M, Tian L, et al. Risks and benefits of sex-mismatched hematopoietic cell transplantation differ according to conditioning strategy. *Haematologica*. 2015; 100(11):1477-1485.
3. Alho AC, Kim HT, Chammas MJ, et al. Unbalanced recovery of regulatory and effector T cells after allogeneic stem cell transplantation contributes to chronic GVHD. *Blood*. 2016;127(5):646-657.
4. Strobl J, Pandey RV, Krausgruber T, et al. Long-term skin-resident memory T cells proliferate in situ and are involved in human graft-versus-host disease. *Sci Transl Med*. 2020;12(570):abb7028.
5. Divito SJ, Aasebo AT, Matos TR, et al. Peripheral host T cells survive hematopoietic stem cell transplantation and promote graft-versus-host-disease. *J Clin Invest*. 2020;130: 4624-4636.
6. Weisdorf D, Zhang MJ, Arora M, Horowitz MM, Rizzo JD, Eapen M. Graft-versus-host disease induced graft-versus-leukemia effect: greater impact on relapse and disease-free survival after reduced intensity conditioning. *Biol Blood Marrow Transplant*. 2012;18(11):1727-1733.
7. Zeiser R, von Bubnoff N, Butler J, et al. Ruxolitinib for glucocorticoid-refractory acute graft-versus-host disease. *N Engl J Med*. 2020; 382(19):1800-1810.
8. Friend BD, Schiller GJ. Beyond steroids: a systematic review and proposed solutions to managing acute graft-versus-host disease in adolescents and young adults. *Blood Rev*. 2022;52:100886.

https://doi.org/10.1182/blood.2022018226

LYMPHOID NEOPLASIA

Comment on Flerlage et al, page 1293

Unraveling family ties in Hodgkin lymphoma

Lucy C. Fox | Peter MacCallum Cancer Centre and Royal Melbourne Hospital

In this issue of *Blood*, Flerlage et al[1] expand our understanding of genetic factors which contribute to a predisposition to the development of Hodgkin lymphoma (HL). Comprehensive genetic analysis with whole genome sequencing was performed on individuals with and without HL from families in which at least 2 or more first-degree relatives had experienced the disease. Risk variants for HL were identified and the description of these variants by Flerlage et al provides the rationale and a starting point for further interrogation of these variants in other cohorts of patients with HL and their families.

In recent years, many advances have been made in understanding genetic predisposition to some forms of myeloid malignancy, particularly myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Although there remain aspects of familial MDS and AML that are understood incompletely, sufficient evidence has been obtained to permit inclusion for the first time, in the 2017 World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues,[2] a category entitled "Myeloid neoplasms with germline predisposition." Consideration of whether one of these monogenic predisposition conditions exists is now deemed to be an essential part of new acute leukemia evaluation, regardless of the age of the patient. Since the 2017 iteration of the World Health Organization Classification, more evidence in the setting of predisposition to lymphoid malignancy has been obtained, leading to an alteration in the International Consensus Classification category title from "myeloid neoplasm predisposition" to "hematologic neoplasms with germline predisposition."[3] However, these recent developments have largely been in the area of predisposition to lymphoblastic leukemia, and the current classifications do not specifically describe a germline predisposition to HL.

Although we remain unable to include a HL predisposition within contemporary hematologic malignancy predisposition classifications, clustering of HL within some families has long been recognized.[4] In 1959, Razis et al[5] commented that "we do not know whether the reported cases of familial Hodgkin's disease in the medical literature signify medical curiosities, or whether they carry weighty environmental and genetic implications." Evidence obtained since this time indicates that the latter was correct, namely, that multiple extrinsic and intrinsic factors are likely to contribute to HL development (see figure). There is an increased risk of approximately 3-fold described in first-degree relatives of patients with HL compared with the general population risk and siblings (as opposed to parents or offspring) experience a higher risk.[6] Although some rare monogenic causes have been suggested, the majority of HL pedigrees have remained largely unsolved, with current thinking that the observation of HL clustering in some families is due to a combination of polygenic and environmental factors.[7] A well-described association between specific human leukocyte antigen alleles and risk of both Epstein-Barr virus (EBV)-positive and EBV-negative HL development provides evidence of a genetic susceptibility to this disease.[8]

Flerlage et al analyzed individuals from 36 HL pedigrees. To increase the probability of analyzing a family with an underlying germline predisposition, the pedigree selection criteria included that at least 1 patient from the pedigree had onset of HL before the age of 22 years. The EBV status of patients and tumor tissue in this cohort was unknown. This factor is a limitation acknowledged by the authors and was partly mitigated by the deliberate selection of kindred in which a young person had developed HL (the group with lowest rates of EBV-associated HL). The authors described 44 HL risk variants among 28 of the HL pedigrees analyzed, including both coding and noncoding risk variants. Variants were considered recurrent if present in more than 1 pedigree. However, of the 4 variants deemed recurrent, they were observed in only 2 or 3 families. Of these 4 recurrent risk variants, 3 were noncoding, including one variant in the 5′ untranslated region of *KLHDC8B* and 2 were intronic variants