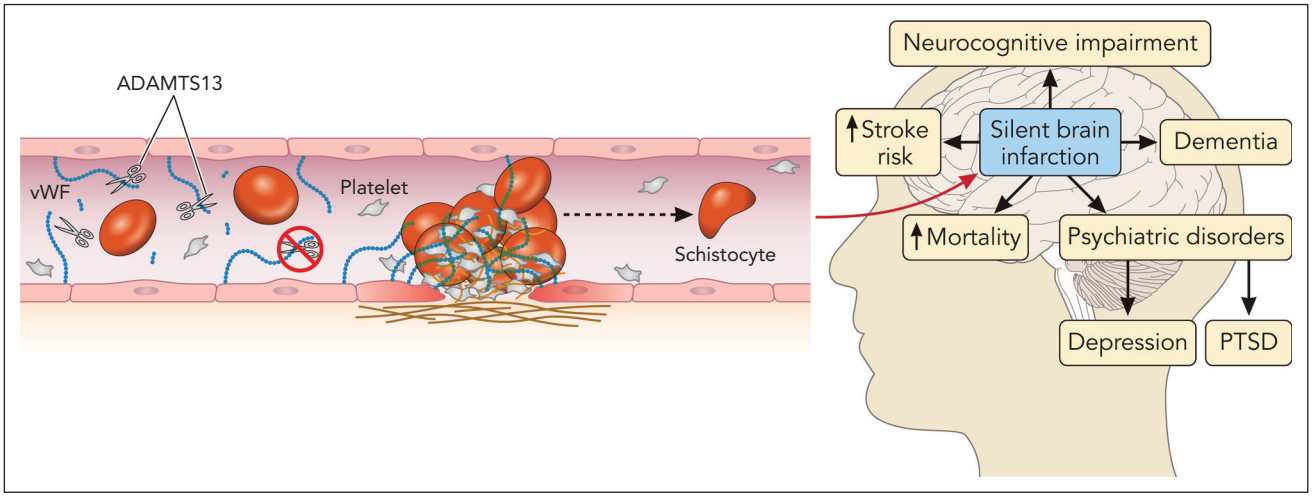

Thrombotic microangiopathy and the brain. In iTTP, autoantibodies against ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) prevent the cleavage of VWF multimers, leading to microthrombus formation and endothelial damage and resulting in ischemic end-organ damage, particularly in the central nervous system. SCIs are common in patients with iTTP while in remission and carry significant risks of associated morbidity and mortality. PTSD, posttraumatic stress disorder. Professional illustration by Patrick Lane, ScEYEnce Studios.

Conflict-of-interest disclosure: The author is on the advisory boards of and is a consultant for ArgenX, Sanofi, and Takeda. ■

REFERENCES

1. Chaturvedi S, Yu J, Brown J, et al. Silent cerebral infarction during immune TTP remission: prevalence, predictors, and impact on cognition. *Blood*. 2023;142(4):325-335.
2. Deford CC, Reese JA, Schwartz LH, et al. Multiple major morbidities and increased mortality during long-term follow-up after recovery from thrombotic thrombocytopenic purpura. *Blood*. 2013;122(12):2023-2029. quiz 142.
3. Saultz JN, Wu HM, Cataland S. Headache prevalence following recovery from TTP and aHUS. *Ann Hematol*. 2015;94(9):1473-1476.
4. Kennedy AS, Lewis QF, Scott JG, et al. Cognitive deficits after recovery from thrombotic thrombocytopenic purpura. *Transfusion*. 2009;49(6):1092-1101.
5. Kelley RA, Cheney MK, Martin CM, et al. Health following recovery from immune thrombotic thrombocytopenic purpura: the patient's perspective. *Blood Adv*. 2023;7(9):1813-1822.
6. Reeves SM, Llaneza AJ, Vesely SK, et al. Fatigue and cognition during remission in adults with immune thrombotic thrombocytopenic purpura [abstract]. *Blood*. 2022;140(suppl 1):1228-1229.
7. Sukumar S, Brodsky M, Hussain S, et al. Cardiovascular disease is a leading cause of mortality among TTP survivors in clinical remission. *Blood Adv*. 2022;6(4):1264-1270.
8. Upreti H, Kasmani J, Dane K, et al. Reduced ADAMTS13 activity during TTP remission is associated with stroke in TTP survivors. *Blood*. 2019;134(13):1037-1045.
9. Sonneveld MA, de Maat MP, Portegies ML, et al. Low ADAMTS13 activity is associated with an increased risk of ischemic stroke. *Blood*. 2015;126(25):2739-2746.
10. Denorme F, Kraft P, Pareyn I, et al. Reduced ADAMTS13 levels in patients with acute and chronic cerebrovascular disease. *PLoS One*. 2017;12(6):e0179258.

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LYMPHOID NEOPLASIA

Comment on Kameda et al, page 352

Targeting iron import to treat ANKL

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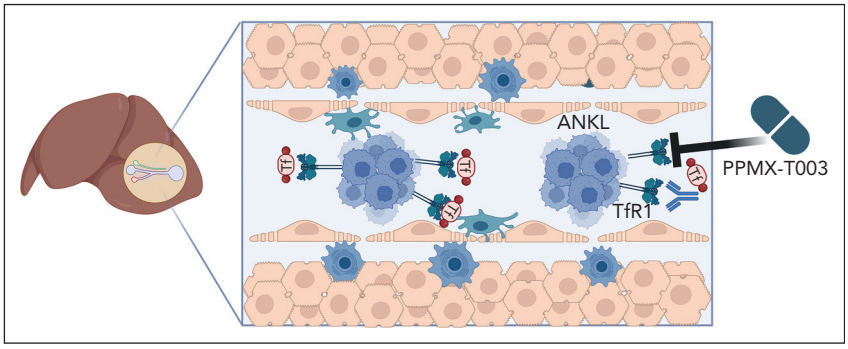
In this issue of *Blood*, Kameda et al show that aggressive natural killer cell leukemia (ANKL) cells primarily engraft and proliferate in the liver and suggest that the transferrin–transferrin receptor 1 (TfR1) axis may be a new therapeutic target.[1]

ANKL is a rare hematological malignancy characterized by a short-term clinical course and a particularly poor prognosis. It has a higher prevalence in Asia and South America than in western countries. It is frequently associated with reactivation of Epstein-Barr virus, in addition to the abnormal expansion of mature natural killer cells.[2,3] Although the ontogeny of the disease is poorly understood, 3 major groups of molecular abnormalities are found: (1) activating mutations of the JAK/STAT pathway, (2) mutations resulting in epigenetic dysregulation, and (3) impairment of DNA repair or alterations in *TP53*. Chemotherapy is the standard treatment but only affords a median survival of 2 to 7 months. Allogenic stem cell transplantation extends the survival of some patients, but the overall success is limited.[2-4] There is an urgent need for novel therapies and for preclinical models to test their efficacy.

Kameda et al established patient-derived xenograft (PDX) mouse models that have infiltration of ANKL cells in the



Targeting iron uptake as a new therapeutic option for ANKL. ANKL cells primarily engraft and proliferate in the liver sinusoid. The liver stores iron, and ANKL cells upregulate the TfR1 to take up iron-loaded transferrin. Inhibiting TfR1 by the monoclonal blocking antibody PPMX-T003 lowers iron import and deprives ANKL cells of their iron content, reducing their survival and/or proliferation. Figure created with BioRender.com.

bone marrow, spleen, and liver. In vivo imaging and flow cytometric analysis of the PDXs revealed that the ANKL cells primarily engraft and proliferate in the liver sinusoids and in the periportal areas of the liver before spreading to the spleen, blood, and bone marrow. They confirmed the sinusoid and/or periportal distribution of ANKL in the liver both in the mouse model and in patients.[1] Hepatosplenomegaly and liver dysfunction are also frequently observed in patients with ANKL.[3,4] Liver-derived ANKL cells also showed a particularly aggressive phenotype when compared with spleen-derived ANKL from the PDXs, and this was associated with a high expression of *MYC* and Myc-regulated genes. Analysis of RNA-sequencing data and an interactome analysis between liver cells and ANKL revealed an upregulated expression of the Myc-regulated TfR1 gene in ANKL cells and suggested that iron uptake via the transferrin-TfR1 axis might represent a potential therapeutic vulnerability (see figure).[1]

The TfR1 is a ubiquitously expressed membrane glycoprotein that mediates the cellular uptake of iron from the plasma glycoprotein transferrin. Iron uptake involves the binding of transferrin to the transferrin receptor, followed by receptor-mediated endocytosis.[5] Iron is stored in the liver and is a critical element in several cellular functions, such as oxygen transport, DNA synthesis and repair, and, thereby, cell proliferation. There is accumulating evidence that iron metabolism plays a crucial role in cancer progression, and many tumor cells show a higher dependency on iron than healthy cells.[6,7] Kameda et al performed an in vivo CRISPR-Cas9 manipulation of the ANKL PDXs to confirm that ANKL cells are vulnerable to iron deprivation and that the transferrin-TfR1 interaction between liver cells and ANKL is a potential therapeutic target. Treatment of the ANKL PDXs with PPMX-T003, a humanized anti-TfR1 monoclonal antibody, resulted in a significantly enhanced disease latency and in eradication of the disease from the liver, although lesions remained in spleen and bone marrow.

Novel therapeutic approaches, such as immune checkpoint inhibitors and cellular immune therapy, and targeted approaches (eg, inhibiting the JAK/STAT signaling pathway) are currently being explored for the treatment of patients with ANKL.[3] PPPMX-T003 showed an acceptable safety profile in a phase 1 clinical trial.[8] The study by Kameda et al provides important insights into the iron metabolism of ANKL and provides justification for further clinical trials based on the idea of targeting iron uptake via the TfR1 receptor axis to treat this fatal disease.

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REFERENCES

1. Kameda K, Yanagiya R, Miyatake Y, et al. The hepatic niche leads to aggressive natural killer cell leukemia proliferation through the transferrin–transferrin receptor 1 axis. *Blood*. 2023;142(4):352-364.
2. Nazarullah A, Don M, Linhares Y, Alkan S, Huang Q. Aggressive NK-cell leukemia: a rare entity with diagnostic and therapeutic challenge. *Hum Pathol Case Rep*. 2016;4:32-37.
3. El Hussein S, Medeiros LJ, Khoury JD. Aggressive NK cell leukemia: current state of the art. *Cancers (Basel)*. 2020;12(10):2900-2916.
4. Sumbly V, Vest M, Landry I. Aggressive natural killer cell leukemia: a brief overview of its genomic landscape, histological features, and current management. *Cureus*. 2022;14(2):e22537.
5. Luria-Pérez R, Helguera G, Rodríguez JA. Antibody-mediated targeting of the transferrin receptor in cancer cells. *Bol Med Hosp Infant Mex*. 2016;73(6):372-379.
6. Abbaspour N, Hurrell R, Kelishadi R. Review on iron and its importance for human health. *J Res Med Sci*. 2014;19(2):164-174.
7. Morales M, Xue X. Targeting iron metabolism in cancer therapy. *Theranostics*. 2021;11(17):8412-8429.
8. Ogama Y, Kumagai Y, Komatsu N, et al. Phase 1 clinical trial of PPMX-T003, a novel human monoclonal antibody specific for transferrin receptor 1, to evaluate its safety, pharmacokinetics, and pharmacodynamics. *Clin Pharmacol Drug Dev*. 2023;12(6):579-587.

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MYELOID NEOPLASIA

Comment on Shao et al, page 365

ZDHHC21: a mitochondrial vulnerability in AML

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In this issue of *Blood*, Shao et al[1] reveal that ZDHHC21-mediated palmitoylation regulates oxidative phosphorylation and is essential for a subset of acute myeloid leukemia (AML) cells.

Oxidative phosphorylation is a mitochondrial metabolic process by which cells generate energy in the form of adenosine triphosphate (ATP). Electrons generated through the flux of metabolites through the tricarboxylic acid (TCA) cycle are transferred through a cascade of proteins termed respiratory chain complexes. The