These patients have gastrointestinal polyps in a setting of chronic inflammation, STAT3 activation, and increased expression of inflammatory factors associated with cancer progression. Somatic variants in *STK11* are seen in skin, lung and other cancers. Deficiency of LKBP1 results in downregulation of MAPK, dysregulating metabolism toward an anabolic, proinflammatory state (see figure), and is implicated in the Warburg effect observed in cancer where anaerobic glycolysis is activated in normoxic conditions.[6] Ni et al studied myeloid-derived suppressor cells (MDSC) which down-regulate immune responses in ITP patients and controls in vitro and in an animal model of severe ITP. This group has previously shown that MDSC were deficient in ITP patients and improved by dexamethasone therapy. They now present evidence for a role of LKB1 deficiency in MDSC in ITP patients and demonstrate that low dose decitabine therapy restores LKB1 levels, energy balance and MDSC function.

The body of work by these investigators demonstrates that low dose decitabine has multiple salutary effects on restoration of immune regulation and energy balance in ITP. In addition to broadening our understanding of the pathophysiology of ITP and illuminating additional therapeutic choices (eg, AMPK agonists) this work provides a compelling rationale for further clinical trials to define the use case for low dose decitabine therapy for ITP.

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

REFERENCES

1. Ni X, Wang L, Wang H, et al. Low-dose decitabine modulates myeloid-derived suppressor cell fitness via LKB1 in immune thrombocytopenia. *Blood*. 2022;140(26):2818-2834.
2. Wang J, Yi Z, Wang S, Li Z. The effect of decitabine on megakaryocyte maturation and platelet release. *Thromb Haemost*. 2011;106(2):337-343.
3. Zhou H, Hou Y, Liu X, et al. Low-dose decitabine promotes megakaryocyte maturation and platelet production in healthy controls and immune thrombocytopenia. *Thromb Haemost*. 2015;113(5):1021-1034.
4. Zhou H, Qin P, Liu Q, et al. A prospective, multicenter study of low dose decitabine in adult patients with refractory immune thrombocytopenia. *Am J Hematol*. 2019;94(12):1374-1381.
5. Han P, Hou Y, Zhao Y, et al. Low-dose decitabine modulates T-cell homeostasis and restores immune tolerance in immune thrombocytopenia. *Blood*. 2021;138(8):674-688.
6. Zhang Y, Meng Q, Sun Q, Xu Z-X, Zhou H, Wang Y. LKB1 deficiency-induced metabolic reprogramming in tumorigenesis and non-neoplastic diseases. *Mol Metab*. 2021;44:101131.

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THROMBOSIS AND HEMOSTASIS

Comment on van Moorsel et al, page 2844

A novel VWF-associated thrombolytic agent

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In this issue of *Blood*, van Moorsel et al report the first results on Microlyse, a novel agent with treatment potential that uses a new target to lyse pathologic thrombi in acute ischemic stroke.[1] In a brief report, they present their mouse studies of experimentally induced stroke treated with either Microlyse, recombinant human tissue-plasminogen activator (rtPA), or vehicle. They show that Microlyse degraded thrombin-induced fibrin-rich thrombi in the middle cerebral artery (MCA), with results comparable to those obtained by rtPA infusion.

For decades, thrombolysis via rtPA has been the mainstay of treatment of acute ischemic stroke in humans.[2] Timely infusion of rtPA leads to a better functional outcome and less morbidity in ischemic stroke in humans.[3] However, a significant number of rtPA-treated patients have thrombi that are resistant to treatment. Another important downside of rtPA-induced thrombolysis is the induction of bleeding or hemorrhagic transformation. Therefore, new treatment options for patients suffering from acute ischemic stroke are still needed. Others have already shown that ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) has potential as a therapeutic agent for ischemic stroke, degrading von Willebrand Factor (VWF) within the VWF-containing thrombi in cerebral arteries in a mouse model.[4]

Microlyse is a VWF-targeting plasminogen activator that was recently developed by fusing anti-VWF VhHs (single variable domain on a heavy chain; nanobodies) directed to the C-terminal cystine knot (CT/CK) domain of VWF and the protease domain of human urokinase plasminogen activator (mini-uPA).[5] Upon binding to VWF, which is abundantly present in a thrombus, Microlyse activates plasminogen to plasmin. Plasmin can degrade, among other coagulation factors, both fibrin and VWF. In a previous study, the same research group showed that Microlyse can be used to degrade microthrombi in mouse thrombotic thrombocytopenic purpura (TTP) models by plasmin destruction of platelet VWF complexes.[5]

In the Van Moorsel et al study, the authors examined the use of VWF-targeted thrombolysis to overcome rtPA resistance in a mouse model of thrombotic stroke. The authors compared results with the use of the new thrombolytic agent Microlyse to those with rtPA and vehicle (as control) in experimental stroke, by inducing the formation of fibrin-rich and platelet-rich thrombi in the MCA. In the fibrin-rich thrombi stroke model, both rtPA and Microlyse were superior to vehicle in obtaining cortical reperfusion and reducing the volume of cerebral lesions. In the platelet-rich thrombi, neither rtPA nor Microlyse was better than vehicle in obtaining cortical reperfusion. However, a significant reduction of cerebral lesion volume was seen in Microlyse-treated animals, compared to those treated with vehicle or rtPA. Although this study was carried out in only a limited number of mice, these results are interesting and may

provide the basis for a new thrombolytic agent for ischemic stroke patients in the future. The authors conclude that their findings support the broad applicability of Microlyse in stroke treatment.

A remarkable finding is that both Microlyse and rtPA resulted in higher reperfusion levels, compared to vehicle, whereas in the platelet-rich model (induced by topical application of $FeCl_3$) for acute ischemic stroke, both treatments led to reperfusion comparable to that observed with vehicle. In addition, the degree of recanalization of the MCA was significantly less with Microlyse, compared to that with rtPA. Further studies are needed to better understand the variability in response to treatment with Microlyse. Also, histopathologic studies would be of interest to determine how the outcome is correlated with fibrin and VWF composition in thrombolysis-resistant thrombi. This issue is especially important because of the highly heterogeneous composition of thrombi, in terms of fibrin, platelets, and VWF content, in ischemic stroke.[6] No data are reported on the plasma levels of VWF in this model, either before or after treatment with Microlyse. This issue may be of interest, given the well-known association of VWF levels with risk of ischemic stroke and outcome of stroke.[7,8]

Bleeding is the major side effect of rtPA treatment, even though rtPA is fibrin-specific and is associated to only a small degree with plasmin-mediated fibrinogenolysis in the circulation. Bleeding did not occur in the mice treated with Microlyse in this study, but additional studies are needed to assess the safety of Microlyse in relation to hemorrhagic transformation of ischemic stroke and other signs of bleeding in these mouse models.

Despite the limitations of the first study results presented in this brief report in *Blood*, the novel approach of using VWF-associated plasminogen activation with Microlyse may be a new and promising thrombolytic option that deserves further study.

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REFERENCES

1. van Moorsel MVA, de Maat S, Vercruysse K, et al. VWF-targeted thrombolysis to overcome rh-tPA resistance in experimental murine ischemic stroke models. *Blood*. 2022;140(26):2844-2848.
2. del Zoppo GJ, Poeck K, Pessin MS, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Ann Neurol*. 1992;32(1):78-86.
3. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014;7:CD000213.
4. Denorme F, Langhauser F, Desender L, et al. ADAMTS13-mediated thrombolysis of t-PA-resistant occlusions in ischemic stroke in mice. *Blood*. 2016;127(19):2337-2345.
5. de Maat S, Clark CC, Barendrecht AD, et al. Microlyse: a thrombolytic agent that targets VWF for clearance of microvascular thrombosis. *Blood*. 2022;139(4):597-607.
6. Jolugbo P, Ariens RAS. Thrombus composition and efficacy of thrombolysis and thrombectomy in acute ischemic stroke. *Stroke*. 2021;52(3):1131-1141.
7. Wieberdink RG, van Schie MC, Koudstaal PJ, et al. High von Willebrand factor levels increase the risk of stroke: the Rotterdam study. *Stroke*. 2010;41(10):2151-2156.
8. Taylor A, Vendramin C, Singh D, Brown MM, Scully M. von Willebrand factor/ADAMTS13 ratio at presentation of acute ischemic brain injury is predictive of outcome. *Blood Adv*. 2020;4(2):398-407.

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