could help to change the current paradigm, in which large volumes of donated blood components (an increasingly scarce global resource) are routinely given to neonates and infants undergoing repair of CHD.

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

REFERENCES

1. Icheva V, Ebert J, Budde U, et al. Perioperative diagnosis and impact of acquired von Willebrand syndrome in infants with congenital heart disease. *Blood*. 2023;141(1):102-110.
2. Federici AB, Budde U, Castaman G, Rand JH, Tiede A. Current diagnostic and therapeutic approaches to patients with acquired von Willebrand syndrome: a 2013 update. *Semin Thromb Hemost*. 2013;39(2):191-201.
3. Ranucci M, Giamberti A, Baryshnikova E. Is there a role for von Willebrand factor/factor VIII concentrate supplementation in complex congenital heart surgery? *J Thromb Haemostasis*. 2018;16(11):2147-2149.
4. Guzzetta NA, Williams GD. Current use of factor concentrates in pediatric cardiac anesthesia. *Paediatr Anaesth*. 2017;27(7):678-687.
5. Avila M, Lee K, Bouskill V, Rand M, James P, Carcao M. Acquired von Willebrand syndrome in pediatric patients with congenital heart disease: challenges in the diagnosis and management of this rare condition. *Haemophilia*. 2015;21(1):e89-e92.
6. Vangenechten I, Mayger K, Smejkal P, et al. A comparative analysis of different automated von Willebrand factor glycoprotein Ib-binding activity assays in well typed von Willebrand disease patients. *J Thromb Haemost*. 2018;16(7):1268-1277.
7. Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. *Blood*. 2011;117(25):6777-6785.
8. Hashmi SK, Velasquez MP, Yee DL, Hui S-K, Mahoney D, Srivaths LV. Pediatric acquired von Willebrand syndrome in cardiopulmonary disorders: do laboratory abnormalities predict bleeding risk? *J Pediatr Hematol Oncol*. 2017;39(2):121-125.
9. Icheva V, Nowak-Machen M, Budde U, et al. Acquired von Willebrand syndrome in congenital heart disease surgery: results from an observational case-series. *J Thromb Haemost*. 2018;16(11):2150-2158.

https://doi.org/10.1182/blood.2022018184

IMMUNOBIOLOGY AND IMMUNOTHERAPY

Comment on Yakymiv et al, page 111

CD39-CD73-adenosine effects in Sézary syndrome

Sean Whittaker and Christine L. Jones | King's College London

In this issue of *Blood*, Yakymiv et al[1] provide evidence that malignant CD4+ T-cells derived from patients with Sézary syndrome (SS), the leukemic variant of cutaneous T-cell lymphoma (CTCL), express high levels of the CD39 and CD73 ectonucleotidases, which may contribute to an immunosuppressive microenvironment. Treatment of advanced stages of CTCLs remains challenging, reflecting a low rate of durable remissions despite recent approval of several targeted therapies, such as brentuximab and mogamulizumab. Unlike mature nodal T-cell malignancies, CTCLs derived from skin-homing memory CD4+ T-cells have very high tumor mutational burden due to ultraviolet radiation,[2] but responses to checkpoint inhibition remain modest.[3] This level of response reflects the difficulty of enhancing T-cell immune responses in T-cell malignancy, and so an understanding of the tumor microenvironment in CTCLs remains a critical need.

Specifically, Yakymiv et al show that SS patients with high expression of CD39 have higher plasma levels of adenosine monophosphate (AMP) in vivo, compared to those of healthy donors, and when these CD39+ tumor cells are co-cultured in vitro with human pulmonary microvascular endothelial cells, increased concentrations of adenosine are generated. Furthermore, they report that CD3/CD28-mediated proliferation of CD8+ T-cells from SS patients and healthy donors is inhibited in the presence of adenosine triphosphate (ATP). In contrast, when inhibitors of the adenosine receptor (A2AR) are added, ATP does not inhibit proliferation of CD8+ T-cells. Although Yakymiv and colleagues did not analyze the effects of ATP on the proliferation of CD4+ malignant T-cells, Sonigo et al showed that both anti-CD73 antibody and A2AR inhibition only partially restored proliferation of the CD4+ malignant T-cells from SS patients.[4] These results, albeit in a small cohort of SS patients, are compelling and suggest that the CD39/CD73/adenosine axis promotes immunosuppression in SS, enhancing our understanding of the tumor microenvironment in CTCL (see figure).

CD39 and CD73 are members of a family of ectonucleotidases that are expressed in a wide range of cancers to promote a favorable tumor microenvironment.[5] In both solid and hematologic malignancies, extracellular ATP accumulates at levels much higher than those observed in healthy tissues, owing to tumor cell death and metabolic stress.[6] Extracellular ATP acts as a danger signal, triggering proinflammatory responses, but CD39 hydrolyzes ATP to AMP, which is sequentially converted by CD73 into immunosuppressive adenosine, allowing the tumor to evade immune monitoring. Adenosine may affect the tumor microenvironment directly or by exosome-mediated cellular exchange of CD39. Other ectonucleotidases include CD38, CD157, and CD203a, which also generate adenosine via the sequential catabolism of NAD+. Although high expression of CD39 was initially characterized as a distinguishing feature of Treg cells, mediating their immunosuppressive abilities,[7] many immune effector cells express CD39, including memory CD4+ T-cells with an exhausted phenotype that is recognized as a feature of SS cells. The bioavailability of adenosine is regulated by adenosine deaminase, and the docking station for adenosine deaminase is CD26, which intriguingly is consistently lost on malignant CD4+ T-cells in SS.

Functional studies have established a role for the CD39/CD73/adenosine pathway in other hematologic malignancies, notably chronic lymphocytic leukemia, which includes a plethora of effects on regulation of cellular components of the immune system to ensure maintenance of

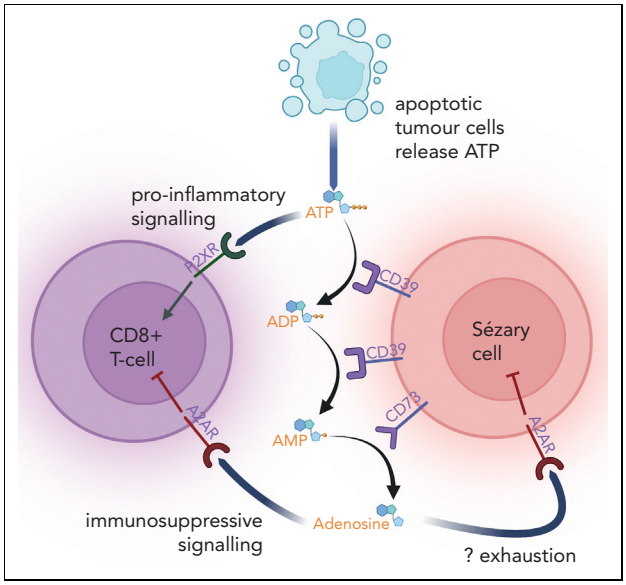

Diagram illustrating the CD39/CD73/adenosine pathway in Sézary syndrome, whereby malignant T-cells expressing CD39 and CD73 hydrolyze ATP to adenosine to create an immunosuppressive environment.

tolerance as well as effects on chemotaxis to enable tumor cells to be retained in growth-supportive niches.[8] Other effects include upregulation of anti-apoptotic mediators, inhibition of cytotoxic T-cell activation and proliferation, and enhanced expression of checkpoint inhibitors such as programmed death 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).[5]

The reports of Yakymiv et al[1] and Sonigo et al[4] have shown that increased expression of CD39 is found on the malignant CD4+ T-cells in SS patients, but larger studies are now required to clarify whether CD39 expression could represent a prognostic biomarker. Important to note is that these studies need to correlate expression of CD39 with genotype, as the A allele of the single-nucleotide polymorphism rs7096317 has been shown to be permissive for CD39 expression in healthy CD4+ T-cells,[9] and CD39 expression also increases with age.[10] Also important is an understanding of the spatial expression and function of CD39/CD73 in the skin as the tumor niche, as well as the direct effects of adenosine on the malignant T-cells, and specifically, whether adenosine contributes to the development of an exhausted phenotype in SS.

The CD39/CD73/adenosine pathway represents a promising therapeutic target, and indeed, clinical trials are in development using antibodies against both CD39 and CD73 and small molecule inhibitors of CD73.[5] Trials assessing use of these novel agents in combination with chemotherapy, with radiotherapy, and with checkpoint inhibitors are also being considered.[5] Mogamulizumab targeting the skin-homing chemokine receptor CCR4 expressed in CTCL was recently approved and provides a further potential combination approach targeting the malignant T-cell in CTCL with enhanced immune responses in the tumor microenvironment.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

REFERENCES

1. Yakymiv Y, Marchisio S, Ortolan E, et al. CD39/CD73 dysregulation and adenosine metabolism contribute to T-cell immunosuppression in patients with Sézary syndrome. *Blood*. 2023;141(1):111-116.
2. Jones CL, Degasperi A, Grandi V, et al. Spectrum of mutational signatures in T-cell lymphoma reveals a key role for UV radiation in cutaneous T-cell lymphoma. *Sci Rep*. 2021; 11(1):3962.
3. Khodadoust M, Rook A, Porcu P, et al. Pembrolizumab in relapsed and refractory mycosis fungoides and Sézary syndrome: a multicenter phase II study. *J Clin Oncol*. 2019;38(1):20-28.
4. Sonigo G, Bozonnat A, Dumont M, et al. Involvement of the CD39/CD73/adenosine pathway in T-cell proliferation and NK cell-mediated antibody-dependent cell cytotoxicity in Sézary syndrome. *Blood*. 2022; 139(17):2712-2716.
5. Moesta AK, Li X-Y, Smyth MJ. Targeting CD39 in cancer. *Nat Rev Immunol*. 2020; 20(12):739-755.
6. Di Virgilio F, Adinolfi E. Extracellular purines, purinergic receptors and tumor growth. *Oncogene*. 2017;36(3):293-303.
7. Deaglio S, Dwyer KM, Gao W, et al. Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. *J Exp Med*. 2007;204(6):1257-1265.
8. Serra S, Vaisitti T, Audrito V, et al. Adenosine signaling mediates hypoxic responses in the chronic lymphocytic leukemia microenvironment. *Blood Adv*. 2016;1(1):47-61.
9. Roederer M, Quaye L, Mangino M, et al. The genetic architecture of the human immune system: a bioresource for autoimmunity and disease pathogenesis. *Cell*. 2015;161(2): 387-403.
10. Fang F, Yu M, Cavanagh MM, et al. Expression of CD39 on activated T cells impairs their survival in older individuals. *Cell Rep*. 2016;14(5):1218-1231.

https://doi.org/10.1182/blood.2022018185