responses were seen, even in rituximab refractory patients, and the durability of response to the combination appeared longer than the previous response to rituximab-based therapy, the systemic administration of IL-21 did not appear to significantly enhance the efficacy of rituximab.

In the study by Bhatt et al, they found that fusing IL-21 to rituximab to generate a fusokine molecule led to direct apoptosis of lymphoma cells, including those that were resistant to IL-21 treatment alone. Furthermore, they found that the fusokine enhanced NK cell activation, resulting in increased cytokine production by effector cells and greater antibody-dependent cytotoxicity. These findings strongly suggest that local action of IL-21 rather than systemic administration may clearly provide a significant therapeutic advantage.6

Unique molecules such as the anti-CD20-IL-21 fusokine molecule provide a proof of principle that local delivery of a cytokine such as IL-21 in the context of antibody binding to the malignant cell may have profound therapeutic advantages, and may be better than administering these components systemically. Clearly, additional studies will be necessary to assess whether the agent is safe and effective, and clinical trials are planned. However, these early preclinical studies suggest that a fusokine molecule such as this may be highly effective in treating lymphoma. The addition of IL-21 to an anti-CD20 antibody in this fashion is truly a case of “the tail wagging the dog.”

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

REFERENCES


DOI 10.1182/blood-2017-02-767541
© 2017 by The American Society of Hematology
a predisposition to −7/7q− MDS is observed, otherwise known as the familial condition of ataxia-pancytopenia syndrome (ATXPC; Mendelian Inheritance in Man no. 159550). Neurological consequences, although variable, are not remedial by reversion mutation.

As the authors observe, heterozygous loss of \( \text{SAMD9L} \) function is well-tolerated when inherited in the germ line, and recurrent \( \text{SAMD9L} \) mutation is not observed in sporadic MDS (see figure).\(^2\) Although knockout mice are predisposed to develop acute myeloid leukemia, these results imply that additional loss of genes such as \( \text{EZH2}, \text{CUX1}, \text{MLL3}, \) or \( \text{DOCK4} \) contribute to the 7q− syndrome in humans.\(^3\) The curious observation is therefore that \( \text{SAMD9L} \) mutation does not directly cause malignancy, as might be expected for deleterious mutation of a tumor suppressor gene. Rather, it is the GoF that causes disease by restricting hematopoiesis to the point that pathologically adapted clones emerge, a phenomenon previously described in other tissues as “compensatory aneuploidy.”\(^4\) In the case of hematopoiesis, however, the appearance of such −7/7q− clones foreshadows the development of a high-risk malignancy.

Germ line \( \text{SAMD9L} \) mutation was recently identified in 2 pedigrees of ATXPC, including the index family, by Chen et al.\(^5\) These authors speculated that GoF mutation and consequent suppression of cell proliferation might lead to the selection of 7q− clones. Evidence in favor of this mechanism is now presented by Tesi et al through in vitro experiments. In addition, these authors provide insightful comments about the potential role of viral infection and interferon production in driving the selection of beneficial revertant or pathological aneuploid clones. Induction of \( \text{SAMD9L} \) by interferon is proposed as a mechanism of feedback inhibition of emergency hematopoiesis that might explain the physiological transient suppression of hematopoiesis during infection. Carefully documented infections in the patients were followed by profound cytopenia and then remission, suggesting that reversion mutation had occurred at this point. Further nuances were observed in the lineages that harbor revertants. Higher reversion frequency was observed in B and natural killer (NK) cells, suggesting that escape from oversuppression by \( \text{SAMD9L} \) was more important for maintaining these lineages and indirectly supporting the concept of lineage-primed stem cells.\(^6\) The stage is now set to develop GoF models to explore the stress response of

---

Hypothetical model of the pathophysiology of germ line \( \text{SAMD9L} \) GoF mutations in relation to hematopoietic stem and progenitor cell proliferation and differentiation. Healthy individuals, with 2 wild-type \( \text{SAMD9L} \) copies (top row), have (1) normal, steady-state hematopoiesis and (2) increased cellular output upon infection-induced, demand-adapted hematopoiesis. In contrast, carriers of heterozygous \( \text{SAMD9L} \) GoF mutations (middle row) may (1) display grossly normal (subclinical?) hematopoiesis for some time, but (2) experience cytopenias and immunodeficiency upon infections early in life. In this setting, interferons can promote \( \text{SAMD9L} \) expression, with \( \text{SAMD9L} \) GoF mutants acting as potent suppressors of cell proliferation, dramatically impairing hematopoiesis and immunology. The ensuing hematopoietic crisis can facilitate (3) selection and expansion of revertant mutants, by uniparental disomy (UPD) of 7q, \( \text{SAMD9L} \) loss-of-function (LoF) mutations in cis, or monosomy 7. Whereas UPD(7q) and in cis \( \text{SAMD9L} \), LoF mutations can support clonal hematopoiesis and recovery from cytopenia, monosomy 7 is associated with development of myelodysplastic syndrome. Finally, carriers of combined \( \text{SAMD9L} \) GoF mutation and rare LoF variants in trans (bottom row) are asymptomatic, suggesting they have normal (1) steady-state and (2) demand-adapted hematopoiesis. As such, pathogenic effects of \( \text{SAMD9L} \) GoF mutations may be balanced by \( \text{SAMD9L} \) LoF mutations.
progenitors and potential role of SAMD9L in lineage specification.

Although many familial cases of MDS remain without a genetic etiology, SAMD9L joins a growing list of germ line variants that predispose to cytopenia and malignant transformation.7 A differential diagnosis is likely to include severe forms of dyskeratosis congenita, which may also affect the nervous system,8 or heterozygous GATA2 mutation, which may appear first as immunodeficiency, similar to at least 1 SAMD9L pedigree with viral illness, intracellular infections, and pulmonary alveolar proteinosis. However, although deafness may occur with GATA2 mutation, advanced neurological deficit would not be expected. The authors also noted that CD56bright immature NK cells were preserved and Fms-like tyrosine kinase-3 ligand was only modestly elevated, in contrast to GATA2 mutation. The high frequency of reversion mutation adds further complexity to the diagnosis of SAMD9L GoF because, at the presentation of MDS, this allele will have been lost from the myeloid lineages in peripheral blood, requiring a sample of nonhematopoietic tissue for genetic screening.

Overall, the studies performed on these new cases of SAMD9L mutation illustrate the exquisite long-term balance in growth regulation that must be maintained within the human progenitor compartment. Much remains to be learned about how SAMD9L and its paralog SAMD9 are involved, including their interactions with each other. Recent evidence points to a role in endosome fusion and recycling of growth factor receptors.10 With apologies to Dr Seuss and his beloved character Sam-I-Am, the final question is of therapeutic potential. We would like to ask SAMD9L: Would you? Could you?

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

REFERENCES


DOI 10.1182/blood-2017-03-770198 © 2017 by The American Society of Hematology

THROMBOSIS AND HEMOSTASIS

Comment on Simão et al, page 2280

Making thrombolysis safer in stroke

David Gailani VANDERBILT UNIVERSITY MEDICAL CENTER

Thrombotic therapy with tissue plasminogen activator (tPA) was approved by the US Food and Drug Administration for treatment of acute ischemic stroke in 1996 and remains the only approved pharmacologic treatment for this condition.1 Although considered the standard of care, tPA is underused in stroke patients for several reasons, including the strict eligibility criteria, narrow treatment window, and risk of life-threatening bleeding.1,2 In this issue of Blood, Simão et al present findings using a mouse model of cerebral ischemia–reperfusion injury that indicate some adverse effects of tPA therapy in stroke patients may be mitigated by blocking the protease plasma kallikrein (PKa).3

tPA catalyzes conversion of plasminogen to plasmin (see figure, yellow arrow), a key mediator of fibrin clot degradation. Thrombolytic therapy for ischemic stroke was first proposed in the 1960s, but it became clear early on that the promising results obtained with this strategy in myocardial infarction would not be realized in stroke patients.2

Mechanism for tPA-mediated activation of plasma prekallikrein (PPK). A therapeutic dose of tPA converts plasminogen in plasma to plasmin (yellow arrow) in a suitably high concentration to facilitate generation of the protease factor XIIa (FXIIa) from its precursor FXII. FXIIa then initiates reciprocal activation of PPK to PKa, as indicated by the red arrows. PKa may contribute to the adverse side effects associated with tPA therapy through several mechanisms, including cleavage of high molecular weight kininogen (HK) to cleaved kininogen (HKa), liberating bradykinin (BK, green arrow), activation of the matrix metaloproteinase-9 (MMP-9) system (blue arrow), and sustained FXII activation. Professional illustration by Somersault18:24.
I am **SAMD9L**: 7q regulator I am

Matthew Collin