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.

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Comment on Tesi et al, page 2266

I am SAMD9L: 7q regulator I am

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The SAMD9L gene and its paralog SAMD9, sitting head to tail on chromosome 7q, are among the notable absences in −7/−7q− myelodysplastic syndromes (MDSs). As with many other genes harboring somatic mutation in neoplasia, germ line variants often provide critical insights into the mechanisms of dysfunction. In this issue of Blood, Tesi et al provide tantalizing new details to the story of SAMD9L mutation and familial −7/−7q− syndromes.1 This widely expressed protein normally functions to inhibit proliferation and is therefore a potential tumor suppressor gene. The authors find 2 novel gain-of-function (GoF) variants that are associated with cytopenias, immunodeficiency, and neurological dysfunction and show how these can be ameliorated by coinherited loss-of-function alleles, or by somatic reversion of the mutated alleles in the bone marrow. When the progenitor ecosystem fails to select benign revertant clones,
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 $SAMD9L$ function is well-tolerated when inherited in the germ line, and recurrent $SAMD9L$ mutation is not observed in sporadic MDS (see figure). Although knockout mice are predisposed to develop acute myeloid leukemia, these results imply that additional loss of genes such as EZH2, CUX1, MLL3, or DOCK4 contribute to the $7q$ syndrome in humans. The curious observation is therefore that $SAMD9L$ 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.” In the case of hematopoiesis, however, the appearance of such $-7/7q$ clones foreshadows the development of a high-risk malignancy.

Germ line $SAMD9L$ mutation was recently identified in 2 pedigrees of ATXPC, including the index family, by Chen et al. 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 $SAMD9L$ 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 $SAMD9L$ was more important for maintaining these lineages and indirectly supporting the concept of lineage-primed stem cells.

The stage is now set to develop GoF models to explore the stress response of

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**Hypothetical model of the pathophysiology of germ line $SAMD9L$ GoF mutations in relation to hematopoietic stem and progenitor cell proliferation and differentiation.** Healthy individuals, with 2 wild-type $SAMD9L$ 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 $SAMD9L$ 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 $SAMD9L$ expression, with $SAMD9L$ GoF mutants acting as potent suppressors of cell proliferation, dramatically impairing hematopoiesis and immunity. The ensuing hematopoietic crisis can facilitate (3) selection and expansion of revertant mutants, by uniparental disomy (UPD) of $7q$. $SAMD9L$ loss-of-function (LoF) mutations in cis, or monosomy 7. Whereas UPD(7q) and in cis $SAMD9L$, LoF mutations can support clonal hematopoiesis and recovery from cytopenia, monosomy 7 is associated with development of myelodysplastic syndrome. Finally, carriers of combined $SAMD9L$ 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 $SAMD9L$ GoF mutations may be balanced by $SAMD9L$ LoF mutations.
progenitors and potential role of \textit{SAMD9L} in lineage specification.

Although many familial cases of MDS remain without a genetic etiology, \textit{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 \textit{GATA2} mutation, which may appear first as immunodeficiency, similar to at least 1 \textit{SAMD9L} pedigree with viral illness, intracellular infections, and pulmonary alveolar proteinosis. However, although deafness may occur with \textit{GATA2} mutation, advanced neurological deficit was not expected. The authors also noted that CD56\(^{bright}\) immature NK cells were preserved and Fms-like tyrosine kinase-3 ligand was only modestly elevated, in contrast to \textit{GAT}A2 mutation. The high frequency of reversion mutation adds further complexity to the diagnosis of \textit{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 \textit{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 \textit{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 \textit{SAMD9L}: Would you? Could you?

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\textbf{THROMBOSIS AND HEMOSTASIS}

\textbf{Comment on Simão et al, page 2280}

\textbf{Making thrombolysis safer in stroke}

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Thrombolytic 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 \textit{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 (PKal).\(^3\)

\textbf{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.}
I am **SAMD9L**: 7q regulator I am

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