novel mutation (T595I), only present at the
time of AML.

Like Good’s immunodeficient children
whom he called “experiments of nature,”36 key
insights in human biology emerge from mo-
olecular and cellular study of a single patient.
While multistep clonal pathogenesis of a can-
cer has long been suspected since Vogelstein’s
classic study of colorectal tumors,7 the facility
of sampling hematopoietic clonal descendents
coupled to new advances in exome or whole
gene sequencing has now provided the
most compelling evidence. Comparable work
recently reported by Walter et al demonstrated
that progressed to AML.8

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Touw’s group has continued to reveal the
complex role played by the GCSFR in the
pathogenesis of SCN. While this group sought
to recapitulate the transformation with a
knock-in of the mutated GCSFRd715, the
mice did not develop MDS/AML even after
superpharmalogic doses of GCSF was
administered.9 A similar disappointment
occurred when Link’s laboratory created mice
with the knock-in of a mutated form of
neutrophil-expressed elastase (ELANE),
commonly affected in both SCN and cyclic
neutropenia.10 The mice did not develop neu-
	
tropenia. One important lesson from these
studies is that murine myelopoiesis and pa-
thology do not provide a precise model for
human myelopoiesis and disease. Clinical in-
vestigation trumps, even when it is on a single
patient.

Several unanswered questions remain in
the famine-to-feast story of SCN. (1) Which
came first: the sick stem cell11 or the super-
pharmalogic dose of filgrastim that pro-
moted genetic instability? The connection
between dose of filgrastim and risk of MDS/
AML was suggested by the French and
American studies.4,5 Indeed, the patient de-
scribed here required a higher-than-average
dose. (2) What is the initiating genetic lesion
of SCN? Mutations in multiple genes have
been identified in patients with SCN. The
genes encode a protease (ELANE), a mito-
chondrial protein (Hax-1), a transcription
factor (Gfi-1), a metabolic enzyme (G6PC), a
cytoskeletal protein (WASP), and the
GCSFR. No bone marrow samples from the
time of diagnosis or at the start of filgrastim
therapy were available to be interrogated.
Thus, we cannot be certain that mutations of

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Comment on Khandros et al, page 5265

Do not super-excess me!

Stefano Rivella  WEILL CORNELL MEDICAL COLLEGE

I have always been puzzled by the ability of normal erythroid cells to produce a stoici-
ometric amount of α- and β-globin chains in the absence of cross-talk me-
chanisms that would control and normalize the relative rate of expression of the genes
encoding these proteins.

The fact that carriers of β-thalassemia with a mutation in 1 of the 2 β-globin alleles
would have almost normal hemoglobin levels and could perform well in many sports was
even more puzzling. Pete Sampras, the leg-
denary tennis player, has thalassemia minor,1
and could perform well in many sports was
not preclude him from being one the most
successful tennis players ever. The seminal
article by Khandros and colleagues in this is-

sue of Blood provides an explanation for this
apparent paradox.2 They show that erythroid
cells are equipped with a series of protein qual-
ity control responses that can eliminate, to a
certain extent, the excess of α-chains pro-
duced in β-thalassemia.2-4 The authors show
that detoxification of free α-globin involves
activation of the ubiquitin proteasome system,
autophagy, and heat-shock response. These
observations place β-thalassemia in the cat-
egory of protein aggregation diseases such as
Parkinson, Alzheimer, Huntington, amyotro-
phic lateral sclerosis, and α-1-antitrypsin
deficiency.

Having characterized the protein quality
control mechanism used by the erythroid cells

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to eliminate the excess of α-chains, we can now address fascinating questions, both old and new. In β-thalassemia, the role of apoptosis has been well established as the main cause of reduced production of red cells. Formation of hemichromes (α-chain/heme aggregates) has been clearly associated with erythroid cell death. However, the extent of this phenomenon and whether the erythroid cells might be armed with additional tools to limit the damage associated with the excess of α-chains in the attempt to maximize red cell production are still debated. The data from Khandros et al suggest that these mechanisms play an important role in mitigating the phenotype of this disorder. Their results also suggest that these mechanisms are likely responsible for preventing any serious problem in β-thalassemia carriers. Furthermore, we can also speculate that the relative ability of these mechanisms to eliminate the excess of α-chains from the erythroid cells might also play an important role in the phenotypic variability observed in this disorder. 

Beta-thalassemia is another disorder in which these mechanisms likely play a major role. Additional studies will clarify these points.

The new observations from Khandros and colleagues also suggest a strong correlation between the excess of globin chains, their detoxification from the erythroid cells, and the degree of ineffective erythropoiesis. Therefore, it will be very interesting to investigate whether these responses modulate the phenotypic outcome in thalassemia disorders. If these mechanisms are shown to play a major role in limiting the effect of hemichromes on the ineffective erythropoiesis, new potential pharmacologic approaches might aim at increasing the elimination of these supernumerary molecules.

Recent data support the notion that modulation of the formation of hemichromes can profoundly alter ineffective erythropoiesis in β-thalassemia. Both administration of transferrin and increased expression of hepcidin can decrease erythroid iron intake, with subsequent reduction of hemichrome formation and amelioration of red cell morphology, production, and lifespan. In both cases, this was associated with increased hemoglobin levels. These observations support the data and the model proposed by Khandros and colleagues, in which elimination of some of the α-chains in excess allows production of better-quality red cells, while inhibition of the detoxification process increases the ineffective erythropoiesis. Interestingly, in animals in which transferrin or hepcidin were used as potential therapeutic tools, reduction of hemichrome formation was associated with diminished heme synthesis. This suggests that, potentially, the α-chains in excess might be disposed even more efficiently if they have fewer chances to aggregate with heme. Even this notion could be used to further enhance the ability of the detoxifying pathways to ameliorate the erythropoiesis in this disorder.

Moreover, the observation by Khandros et al might also prove useful in gene therapy for sickle cell anemia. It has been proposed that insertion of a normal β-globin gene into the hematopoietic stem cells of sickle cell patients might reduce the formation of the abnormal tetramers and prevent the formation of sickle red cells and the pathophysiologic sequelae associated with this phenomenon. However, the main concern associated with this approach is that, after gene transfer, the total amount of β-chains (sickle + normal) might exceed the amount of α-chains, leading to an α-thalassemia-like phenotype. The data from Khandros and colleagues suggest that a moderate excess of globin chains might be tolerated and eliminated efficiently by the erythroid cells. In conclusion, these novel findings will modify understanding of β-thalassemia and suggests new approaches to alleviate the symptoms of this disorder.

Conflict-of-interest disclosure: S.R. is a consultant for Novartis, Isis, and Biomarin Pharmaceuticals. In addition, he is coinventor on patents US8058061 B2 C12N 29/11115 and US75741179 B2 C12N 209062. The consulting work and intellectual property of S.R. did not affect in any way the design, conduct, or reporting of this editorial.
Do not super-excess me!

Stefano Rivella