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Comment on Nie et al, page 2428

"Iron mining" to inhibit tumor growth

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Control of tumor growth by new strategies remains a vital research goal. Nie and associates convincingly demonstrate that expression of mitochondrial ferritin leads to mitochondrial iron sequestration, which inhibits tumor growth in vivo. This work illustrates the potential importance of the mitochondrion in controlling iron metabolism and confirms that iron deprivation is an effective method to prevent cancer growth.

In recent times, the field of iron metabolism has undergone radical changes with the discovery of a range of new proteins that play important roles in the use of this critical nutrient. One of the more intriguing of these molecules is mitochondrial ferritin (MtFt).[1] As its name suggests, this protein is found in the mitochondrion and is closely related to the well-known iron storage molecule cytosolic ferritin. The role of MtFt remains unclear, although it appears to sequester iron in diseases such as sideroblastic anemia.[2]

In this issue of *Blood*, Nie and colleagues make the intriguing observation that overexpression of MtFt leads to marked mitochondrial iron uptake, which remarkably can be visualized by electron microscopy. Moreover, this enhanced mitochondrial iron sequestration capacity leads to inhibition of tumor growth. These observations are important for 2 reasons. First, they demonstrate that mitochondrial iron metabolism is highly significant and intimately associated with whole-cell iron trafficking. Second, the apparent deprivation of cytosolic iron resulting from high MtFt expression leads to inhibition of tumor growth.

With regard to the unexpected ability of MtFt to alter whole-cell iron metabolism, this finding elucidates a signaling pathway that was previously unknown. Overexpression of MtFt results in cytosolic iron deficiency, as demonstrated by increased RNA-binding activity of the iron regulatory proteins, which leads to increased transferrin receptor 1 and decreased cytosolic ferritin expression. At the same time, there is reduced expression of the mitochondrial protein frataxin. The decrease in frataxin is intriguing, as this protein is down-regulated in the severe neuro/cardiodegenerative disease Friedreich ataxia.[3] Decreased frataxin is associated with increased mitochondrial iron accumulation, although its precise role in iron trafficking remains unclear.[3] The fact that frataxin expression is altered upon mitochondrial iron uptake and storage adds further weight to the hypothesis that frataxin is integrally involved in iron metabolism.[3] At present, it remains unclear how the increase in MtFt signals the marked changes in cellular iron metabolism observed, nor is it known how the iron effectively bypasses the cytosol to result in specific trafficking to the mitochondrion. These questions await further investigation. However, the surprises derived from modulating MtFt suggest our understanding of cellular iron metabolism remains far from complete.

While such a powerful mode of controlling iron metabolism would be tempting to manipulate, the hyperexpression of MtFt cannot be readily achieved in patients to inhibit tumor growth. Recent studies exploring iron deprivation using chelators as a therapeutic strategy against cancer have shown it can be highly effective in vitro and in vivo.[4,5] It can be speculated that iron deprivation of the cytosol mediated by overexpression of MtFt prevents tumor growth by inhibiting iron-dependent enzymes such as the rate-limiting step of DNA synthesis, ribonucleotide reductase.[5] Moreover, iron depletion leads to increased transcriptional activity of the hypoxia-inducible factor that results in the increased expression of the proapoptotic molecule BNip1 and the metastasis suppressor Nmyc-downstream-regulated gene-1.[4,5] Hence, the report by Nie and colleagues confirms that cellular "iron mining" may be a useful strategy to inhibit tumor growth. ■

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Comment on Scott et al, page 2435

From 1 to 2 mutated JAK2: the road from ET to PV

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In this issue of *Blood*, Scott and colleagues give insight into myeloproliferative disorder heterogeneity induced by V617F JAK2 by showing that ET and PV are associated with mono- and biallelic mutations, respectively.

The discovery in 2005 by 4 different groups that a single JAK2 mutation (V617F JAK2) was observed in 90% of polycythemia vera (PV), 60% of essential thrombocythemia (ET), and 50% of idiopathic myelofibrosis represents a major advance in the understanding of these disorders (and validated the previous theory of the proximity of these myeloproliferative disorders),[1-4] but it has also raised a new major question: how can a single mutation give rise to several diseases? The paper by Scott and colleagues, from Green's group, in this issue of *Blood* represents one more step to validate the concept that the number of V617F

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JAK2 copies, as well as the overall intensity of the constitutive signaling, explains the phenotype heterogeneity. It has already been shown that about one third of patients with PV have a biallelic (homozygous) V617F JAK2 mutation associated with a 9p loss of heterozygosity (LOH).[5] This biallelic mutation appears to be due to a mitotic recombination. In contrast, this is extremely rare in ET. In this report, Scott and colleagues have taken a new step forward by demonstrating that some V617F JAK2 homozygous hematopoietic progenitors were present in all studied patients with PV and undetectable in patients with ET. Thus, this recent work from Green's team strongly suggests that differences between ET and PV are dependent only on this parameter.

V617F JAK2 is a subtle mutation that induces a low gain of function in JAK2. There is increasing evidence that its activity requires the presence of cytokine receptors to induce signaling.[6] In addition, we reported that mutated V617F JAK2 function was inhibited by the normal nonmutated JAK2.[2] Thus, duplication of the mutant allele with the loss of the normal allele will theoretically greatly increase signaling. However, the differences in phenotype between a biallelic and a monoallelic mutation suggest strongly that a biallelic mutation will essentially favor erythroid and granulocytic progenitor proliferation but will inhibit megakaryocytic differentiation. In contrast, a monoallelic mutation will give an advantage to the megakaryocytic lineage. This hypothesis explaining disease heterogeneity may underscore major differences in signaling through cytokine receptors and thus open new pathways for research.

Overall, this result suggests that a V617F JAK2 as a single genetic event will give rise to ET. A second genetic event, apparently a mitotic recombination, would be required to cause PV. This hypothesis will absolutely require knock-in mice to be validated. However, it seems likely that any other secondary genetic events synergizing with V617F JAK2 will also be implicated in PV pathogenesis. Thus, it is expected that some patients with PV will be also heterozygous when a larger cohort of patients will be studied. What about idiopathic myelofibrosis: is it related to the same mechanism (ie, the number of V617F JAK2 alleles)? Or are other events necessary to develop fibrosis? Another interesting point concerns the high frequency of mitotic recombination in PV. Does it mean that another event (previous to JAK2 mutation) is necessary to induce a genetic instability before the occurrence of a monoallelic mutation in PV? Indeed, it is expected that if the mono- to biallelic theory is true, all instances of PV will be preceded by ET. However, less than 15% of ETs transform into PV. Are differences between ET and PV thus related to genetic determinants regulating the ability to perform mitotic recombination in the hematopoietic stem cell compartment?

In conclusion, this elegant work from Green's group is a major step in the demonstration that "copy number" is the basis of the heterogeneity of the myeloproliferative disorders, which can explain differences between V617F JAK2 ET and PV, at least in part. ■

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