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Model of heme-iron recycling and tissue iron redistribution in HO-1-deficient mice. Splenic macrophages and liver Kupffer cells that phagocytose senescent red blood cells die in HO-1−/− mice. The contents released from dying macrophages include nonmetabolized heme iron. Reproduced from Figure 7 in Kovtunovych et al.6
These findings underscore the homeostatic importance of detoxifying and clearing hemoglobin and heme. The day-to-day recycling of iron and detoxification of heme is critical for hematopoiesis. The cytoprotective aspects of HO-1 in hemolysis can be seen in sickle cell disease, where gene therapy augmenting HO-1 can modulate microvascular occlusion in murine models of sickle cell disease and where HO-1 polymorphisms are associated with acute chest syndrome.  

Could bone marrow transplants be used to treat children with HO-1 deficiency? Certainly these data suggest this possibility. In addition, gene therapy, induced pluripotent stem cells, and possibly gene editing of CD34 hematopoietic stem cells, followed by autologous transplants, may be on the horizon. HO-1 deficiency also may be more common than previously documented. The triad of intravascular hemolysis, high haptoglobin, and low bilirubin certainly should alert clinicians regarding HO-1 deficiency.

How the Hmox1−/− mouse livers become so efficiently repopulated with homing wild-type Kupffer cells is still a mystery. This niche is “open” in the Hmox1−/− mice, as liver macrophages are absent and the wild-type macrophages may just move in. Could the engraftment of wild-type macrophages nurse the bone marrow in these Hmox1−/− mice to correct the anemia? When “Mac” the macrophage is back in town, heme is detoxified and iron is recycled.

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REFERENCES

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THROMBOSIS & HEMOSTASIS

Comment on Omarova et al, page 1531

Primetime for γ′

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In this issue of Blood, Omarova et al show that fibrinogen, particularly the γ′ variant, increases the anticoagulant effect of activated protein C in plasma.  

Whether γ′ (pronounced gamma prime) fibrinogen is prothrombotic or antithrombotic is a somewhat contentious issue. The concentration of γ′ fibrinogen and the ratio of γ′ fibrinogen to total fibrinogen is associated with both arterial and venous thrombosis, but not always in the same direction.  

Fibrinogen is a 6-chain protein containing 2 copies each of the Aα, Bβ, and γ chains.γ′ fibrinogen arises from an alternative messenger RNA (mRNA) processing event in the γ chain pre-mRNA (see figure). Approximately 7% of total fibrinogen contains a γ′ chain, although the concentration range is quite broad, unlike most coagulation factors, with a reference interval of 8.8 to 55.1 mg/dL.  

Although epidemiology studies of arterial thrombosis demonstrate consistently that elevated levels of γ′ fibrinogen are associated with cardiovascular disease, the same cannot be said of epidemiology studies of venous thrombosis and thrombotic microangiopathy. Some studies show an association with γ′ fibrinogen levels, whereas other studies

![Gene Processing](image)

Alternative processing of the FGG gene pre-mRNA. The FGG 10 034C>T SNP (rs2066865) results in lower levels of γ′ fibrinogen. This SNP may affect the relative rate of spliceosome activity that cleaves out the ninth intron to form the γA isoform vs polyadenylation and cleavage activity that polyadenylates within the intron and cleaves the mRNA at the 3′ end of the polyadenylation site to form the γA isoform. Professional illustration by Xavier Studio.
Look out heme, Mac is back in town

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