Correspondence

Letter by Ryan et al Regarding Article, “Do Hemochromatosis Mutations Protect Against Iron-Mediated Atherogenesis?”

To the Editor:

The presence of iron within atheromatous plaques is thought to contribute to the pathogenesis of atherosclerosis. The “hemochromatosis paradox,” as referred to in the recent article by Sullivan, originates from the observation that despite significant iron overload, patients with hereditary hemochromatosis (HH) are not at increased risk for atherosclerosis. A number of reasons for this have been proposed, not least is the finding of favorable lipid profiles in C282Y homozygotes compared with wild-type controls. The majority of patients with HH are homozygous for the C282Y mutation of the HFE gene. HFE-HH is characterized by the inability of iron to induce hepcidin, the chief iron regulatory hormone. Failure of hepcidin to degrade ferroportin, an iron export molecule, results in excessive iron release from duodenal enterocytes and macrophages, causing systemic iron overload. Reduced intramacrophage iron levels may lead to defective macrophage function and even diminished foam cell formation, potentially providing protection from atherogenesis. Although an attractive hypothesis, the mechanism underlying this finding remains unclear.

We recently reported that suppression of monocyte chemotactic protein-1 (MCP-1), a potent chemokine and important mediator of atherosclerosis development, occurs in untreated C282Y homozygotes. In brief, MCP-1 expression examined by using quantitative RT-PCR in liver tissue from 25 iron-loaded C282Y homozygote males, compared with 4 male wild-type controls with normal liver histology. MCP-1 significantly decreased in HH versus controls (P<0.001). Hepcidin expression was also significantly reduced in HH (P=0.01) and correlated closely with MCP-1 expression (r=0.52; P=0.004).

Although hepatic MCP-1 expression was the focus of this study, Lawless et al reported reduced serum MCP-1 levels in C282Y homozygotes, compared with individuals with other HFE genotypes and wild-type controls. Taken together, these studies suggest that reduced MCP-1 is a feature of C282Y HH. Furthermore, in vitro data suggest MCP-1 expression may be modified by HFE variants.

In the setting of foam cell formation in atherogenesis, hepcidin deficiency may disarm macrophages by reducing intramacrophage iron levels. As noted by Sullivan, macrophages from mouse models of HFE-HH display blunted inflammatory responses, which may, in part, explain the reduced levels of MCP-1 seen in patients with HH.

It is therefore tempting to speculate that the suppression of MCP-1 in HH plays a role in the hemochromatosis paradox, by conferring protection against atherosclerosis despite iron overload, and highlights the need for further investigation into this area.

Disclosures

None.

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References

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