Reviewer's report

Title: Iron behaving badly: inappropriate Iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases

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Reviewer: RICK WELCH

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Iron behaving badly: inappropriate Iron chelation as a major contributor to the aetiology of vascular and other progressive inflammatory and degenerative diseases, by Douglas B. Kell

I shall group my comments according to the following specific queries in the instructions to reviewers:

1. Does the review cover an area of importance in the field covered by the journal?

Absolutely, yes. I realize that BMC Medical Genomics only rarely considers narrative reviews. The paper by Prof. Kell certainly qualifies for such an exception. It is not simply a ‘review’. It is a grand, synthetic (and ultimately testable) hypothesis supported by a diverse and extensive body of scientific literature. Moreover, this opus constitutes one of the most integrative and well-conceived designs of the human physiome that I have seen in the systems biology literature. The biomedical significance of Prof. Kell's central idea bears far-reaching potential in our understanding of a fundamental cause (both primary and secondary), the treatment, and the prevention of inflammatory/degenerative diseases.

2. Does the review present a comprehensive, authoritative review of recent and existing work in this area?

Absolutely, yes. The scope and breadth of this story are most impressive. The sheer size of the reference list not only bespeaks the comprehensiveness of the review, but also supports authoritatively the hierarchical systems-level validity of the idea. Prof. Kell is a renowned expert in bioenergetics, cell biology, systems biology, bioanalytical methodology, inter alia. Aside from the mere(!) reference list, he brings to bear a highly logical and convincing argument in support of the basic premise/hypothesis. He has shown a keen eye for finding a commonality amongst a host of medical disease states, and the evidence for such a common thread seems far more than circumstantial or happenstance. I came away persuaded that this is real, and I only wish I were in a position to rush to the lab bench and begin testing the verity of the idea in relation to some of the cited
3. Is the review a substantial advance upon other reviews in this area, by the authors or others?

Yes, most definitely. ROSs are commonly thought to be part-and-parcel of a host of inflammatory and degenerative diseases. And there have been suggestions that iron is involved in some of these conditions. But I think that Prof. Kell has hit the nail on the head, in pinpointing a potentially definitive (and unifying) connection between the two aspects. His analysis should lead biomedical researchers to rethink, not only the cause of certain inflammatory/degenerative diseases, but also how those diseases are treated and, indeed, prevented. Many accepted nutritional practices (e.g., iron requirement, vitamin C usage, phytochemical [anti-oxidant] supplementation) may be called into question.

4. Have the authors avoided bias in their reporting of the literature, factual inaccuracies or misleading statements?

I think that Prof. Kell has exhibited great judgment, in dealing with these issues in a balanced and unbiased manner. It is apparent to me that he has spent considerable time and effort in reviewing and assessing the weight of the evidence under view.

5. Is the review well referenced, with all statements of fact accompanied by a reference?

Yes, indeed. One might say, at first glance, that the reference list is excessive. As you get into the review, though, you soon realize that the vast array of citations gives credence to a. the broad hierarchical systems-level nature of the concept and b. the wide range of medical conditions relating thereto. [A minor recommendation: I found the suggestion of the existence of mammalian siderophores tantalizing. Prof, Kell treats admirably this issue (and presents the evidence) at the organismal level. However, I would like to see, albeit speculatively, some indication of his thinking at the subcellular microenvironmental level. For example, in his discussion of Friedreich’s ataxia, I could not help but ponder the possibility that such entities as the reported mitochondrial iron chaperone proteins might be involved?]

6. Is the review written well enough for publication?

Absolutely! I strongly urge you to publish. This paper is far more than a simple ‘narrative review’. It is a powerfully synthetic and far-reaching hypothesis that is well supported by a wealth of evidence.

**Level of interest:** An article of outstanding merit and interest in its field

**Quality of written English:** Acceptable