Review of: "Metabolic-scale gene activation screens identify SLCO2B1 as a heme transporter that enhances cellular iron availability"

Johannes Stöckl[1]

1 Medical University of Vienna

Potential competing interests: The author(s) declared that no potential competing interests exist.

Unlu et al. report in this paper that SLCO2B1 can act as alternative iron-carrier which allows sufficient iron-uptake of cells to support proliferation. The authors demonstrate that SLCO2B1 is rather selectively expressed on microglia cells and imports heme-analogs. Heme is then degraded by HMOX2 and iron is released and available in the cell.
This is a novel finding and mechanism and significantly contributes to a better understanding of cellular iron-import.

The experimental approach is excellent, the experiments are well-done and the results are clearly presented.

In my opinion three improvements should be added or included by the authors:

1) the authors convincingly demonstrate that SLCO2B1 is required for the uptake of heme but do not directly analyze if heme binds to SLCO2B1 or if SLCO2B1 is mainly required for the internalization?

2) it is widely accepted that free heme is rare in our body, particularly at homeostatic conditions. Heme is typically bound to proteins such as hemopexin and albumin. The authors should demonstrate whether SLCO2B1 binds and internalizes also heme-loaded proteins or only free heme molecules. Could it be that SLCO2B1 is able to scavenge heme from plasma proteins?

3) The Discussion is its current form is rather an Abstract and not informative enough. The authors should offer and discuss a model or physiological situation where SLCO2B1-mediated iron uptake is or could be relevant in more detail.