Reviewer's report

Title: Assessment of cellular cobalamin metabolism in Gaucher disease

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Reviewer: Jean-Louis Gueant

Reviewer's report:

The authors address a question that is clinically relevant. Patients with Gaucher Disease have abnormalities in plasma transport of vitamin B12 that are not explained at the cellular level. Vitamin B12 is decreased along with a paradoxical increase in holoTC.

To answer this question, the authors carried out a study in patient fibroblasts, which shows very interestingly the absence of dramatic modification of the key substrates of the remethylation pathway. They do not observe a difference in detection of cellular transcobalamin, in western blot.

However, several remarks can be made in relation to the question asked:

- Manifestations of GD involve the liver, the spleen and the reticuloendothelial system. The metabolism of vitamin B12 has specificities in each of these organs and tissues, with a prominent role of the liver in B12 storage and transport. It is not sure that fibroblasts are the most appropriate model for this study.

- The mass spectrometry assays are very convincing. However, cell incorporation tests of radiolabelled vitamin B12 should also be carried out to study its subcellular distribution and its possible accumulation in lysosomes.

- Moreover, it is essential to look for potential abnormal intracellular distribution of the lysosomal transporters of vitamin B12, LMBRD1 and ABCD4 and also to check whether these two proteins have interactions that are preserved.

- It would also be desirable to have additional data on plasma transport in patients for whom these cell studies were made, including the saturation percentage of vitamin B12 on haptocorrin and the saturation percentage of vitamin B12 on transcobalamin.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes

Are the conclusions drawn adequately supported by the data shown?
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No

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