Reviewer's report

Title: Metabolic phenotype of methylmalonic acidemia in mice and humans: the role of skeletal muscle

Version: 1 Date: 11 June 2007

Reviewer: Carlos Mello

Reviewer's report:

General
In this interesting manuscript Chandler and colleagues show that methylmalonyl-CoA mutase mutant mice present a general increase in MMA levels. In addition, the authors show that two methylmalonic acidemic patients subjected to combined liver and kidney transplantation present plasma MMA levels similar to patients treated with dietary therapy. The authors conclude, based on the murine model, that a large portion of circulating MMA has an extra-hepatorenal origin and likely derives from the skeletal muscle. The methods used are appropriate and the results are interesting. However, the authors do not specify the statistics applied to their data, and this is my major concern regarding this study. Overall, the study provides relevant data for the understanding of the mechanisms underlying tissue accumulation of MMA in methylmalonicacidemias, if supported by proper statistical analysis.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The authors should show the statistical analysis of each experiment: F values, degrees of freedom and p values. This is a relevant matter of concern, given the small “n” in each group. The authors conclude that combined transplantation does not alter the metabolic phenotype of the patients by comparing them with non-transplanted patients. The transplant-induced change in the metabolic phenotype would be more efficiently evaluated if the authors compared MMA levels before and after the transplant. This is particularly important because plasma MMA levels in the group subjected to dietary treatment vary from 150 to 500 µM (Figure 5). Therefore, the authors are encouraged to perform such a comparison and discuss the results.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Page 4, 18th line: remove “recent” from the sentence.
Please use “?” instead of “u” to define “?M” or other units (?l, etc…) throughout the manuscript.
Please standardize the x- and y-axis titles in all figures and add a marker indicating statistically significant differences between means.

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Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests.