Reviewer's report

Title: Tuning of liver mitochondrial plasticity during brain tumor development

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Reviewer: Elliot Crouser

Reviewer's report:

General
Based on previous literature showing changes in liver function in the context of non-hepatic cancer, Pouliquen and colleagues hypothesized that the presence of a remote brain tumor would alter the dynamics of structured water in liver mitochondria, measured by NMR, which presumably equate with changes in mitochondrial functions. Liver mitochondrial changes in the context of brain tumor were compared to changes conferred by short-term fasting. Changes in the dynamics of structured water in animals with brain tumors were not attributable to changes in membrane fatty acid saturation, such as occurs during fasting, but may relate to elevated membrane cholesterol content. Changes in mitochondrial membrane characteristics associated with brain tumor were proposed to account for changes in mitochondrial ion content and enhanced liver caspase activity.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1) Brain tumors can be associated with systemic release of various hormones, including antidiuretic hormone (ADH), which may result in whole body water retention and hyponatremia. Is this model associated with water retention or changes in sodium balance? If so, how would this influence the experimental results, including the observed increase in mitochondrial volume, changes in ion concentration, and changes in structural water?
2) Essentially all of the data presented in the manuscript are derived from a post-hoc analysis of the data (i.e., subgroup analysis of the animals demonstrating the greatest change in mitochondrial NMR parameters). Comparisons of the NMR data from the entire experimental group should be included in the figures.
3) The size of each experimental group is not mentioned in the manuscript.
4) Caspase activity is increased in the livers of the T+++ animals. Is this related to increased hepatocyte apoptosis? As noted in the discussion, NMR characteristics of liver mitochondria in T+++ animals and mitochondria of apoptotic liver cells are very similar. It seems plausible that the observed changes in mitochondrial structural water in T+++ animals are primarily related to ongoing apoptosis.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1) There are a number of misspellings (e.g., page 7, line 9: "accelated" should be "accelerated"; page 9, 1st line of the discussion: "litterature" should be "literature"). The manuscript should be carefully reviewed for misspellings and grammatical errors.

Discretionary Revisions (which the author can choose to ignore)
1) The functional consequences of altered structural water in liver mitochondria is not directly evaluated. Instead, much of the discussion represents conjecture. It would be interesting to know if changes in structural water parameters, as reflected by NMR, equate with demonstrable changes in mitochondrial function (e.g., respiration, propensity to undergo the permeability transition, ion transport).

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

Level of interest: An article whose findings are important to those with closely related research interests
**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No

**Declaration of competing interests:**

I declare that I have no competing interests.