Reviewer's report

Title: Pathogenesis of peroxisomal deficiency disorders (Zellweger syndrome) may be mediated by misregulation of the GABAergic system via the diazepam binding inhibitor

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Reviewer: myriam Baes

Reviewer's report:

General
This is a hypothesis paper that formulates a novel pathogenic mechanism for the neurodevelopmental defects in peroxisome deficiency conditions in man and in mice. It is indeed true that the molecular mechanisms causing neuronal migration defects, hypotonia and facial dysmorphisms in Zellweger syndrome and in peroxisomal multifunctional protein-2 deficient patients are still unknown. As mentioned by the author the observations in mouse models of peroxisomal disorders have not confirmed previously proposed hypotheses that the pathology is related to distinct metabolic changes. The presented hypothesis that altered GABAergic neurotransmission underlies the neurodevelopmental defects is attractive and it seems also worthwhile to test it in the available mouse models. However, certain arguments (in particular the microarray result) are not convincing and the hypothesis fails to explain at this point all observations from the mouse models.

Discretionary Revisions (which the author can choose to ignore)

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

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. In the section ‘Pathogenic mechanism of Zellweger syndrome’(page 3), several potential metabolic mechanisms causing Zellweger syndrome that were previously reported by other investigators are mentioned. However, the second mechanism concerning disturbances of membrane microdomains refers to a paper which does not discuss the pathogenesis of Zellweger syndrome. Therefore it seems that this is rather a conclusion of the author of this paper than a previously suggested mechanism.
   The fifth argument refers to the analysis of the Pex5 knockout mouse in which impairment of glutamatergic signalling was observed. However, it is incorrectly cited that this impairment is due to reduced plasmalogen levels. Rather, in the paper by Gressens et al. reduced levels of PAF are proposed as potential cause of the reduced signalling at the NMDA receptor.

2. On page 4, it is mentioned that disruption of multifunctional protein type 2 or 3-oxoacyl-CoA thiolase leads to a Zellweger syndrome like phenotype. However, it was recently reported that the single case of thiolase deficiency was wrongly diagnosed and appeared to be a MFP-2 deficient patient (Ferdinandusse et al., Am J Hum Gen, 70, 1589-93, 2002). The text should therefore be adapted.

3. It is an exaggeration that the 3 mouse models of Zellweger syndrome are an exact phenocopy of the human disease. Several important pathologies including hepatomegaly, renal cysts and bone abnormalities are not recapitulated in the mouse models.
4. The idea that the Diazepam Binding Inhibitor (DBI) could be involved in Zellweger pathology based on the described microarray analysis is not convincing. In the first place it is not clear why the candidate gene has to be coregulated with lipid biosynthesis genes. What is the evidence that the expression of lipid biosynthetic genes are altered in Zellweger syndrome? Secondly, because DBI is involved in lipid metabolism as an acyl CoA binding protein, it is not surprising that it is coregulated with lipid metabolising enzymes. Thirdly, the use of microarray data derived from carcinomas seems to be irrelevant for the pathogenic mechanisms in brain of Zellweger patients. Fourthly, from the title of table 1 it is not clear what is meant by the expression profiles that are ‘most similar to DBI’.

5. According to the further presentation of the hypothesis, only a downregulation of DBI is relevant because this would lead to an overactivation of the GABA(A) receptor and the non-GABA(A) receptor. Is the author aware of any conditions in which DBI is suppressed in brain? It would be worthwhile to mention this in the text.

6. Although the DBI hypothesis is attractive, it is not clear whether it can explain all observations of the mouse models with peroxisome deficiencies. If the increase in metabolite X is the primary cause (which are most likely acyl-CoA derivatives), how can it explain that no migration disturbances were found in MFP2 and in MFP1/MFP2 knockout mice, whereas severe impairments were observed in Pex11beta knockout mice?

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: Acceptable

Statistical review: No

Declaration of competing interests:

No to all