Reviewer’s report

Title: Groucho recognizes an eh-1-like peptide motif in LEF-1 for HDAC-dependent repression

Version: 1 Date: 29 September 2008

Reviewer: Barbara Jennings

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In this manuscript, Arce et al. examine the physical interactions between Lef1 and Groucho, demonstrate that Lef1/Groucho repression is sensitive to the HDAC inhibitor TSA and survey the effectiveness of Groucho mediated repression in colon cancer cell lines.

Major Compulsory Revisions

1) The residual binding by 237-396 (that should include the Groucho Binding Motif (GBM) “FSHHMI”) is extremely weak, if significant at all (Figure 2a, lane 7). As the discovery of this GBM is a major finding of the paper, the authors must show direct binding of the FSHHMI peptide to a Groucho/TLE protein. If necessary, they could use GST-FSHHMI with in vitro translated/35S-methionone labelled full length Groucho.

2) The eh1 motif has been shown to interact with the WD domain in a very specific manner that accounts for the variations in eh1 sequences observed between protein families and across evolution (Jennings et al., 2006, Mol Cell., 22 p645-655). In what way does the sequence FSHHMI (6 residues, unlike the consensus for eh1, which is 8 residues) actually resemble a true eh1 motif other than starting with a phenylalanine? Does it form a short alpha-helical motif? Without further comparative work, using the term “eh1-like” is very misleading and must be omitted.

3) The authors overexpress a Groucho family protein in cell lines derived from colon cancers and assay repression of the TOPFlash reporter. The authors do not test/control for the levels of endogenous Groucho family proteins - thus it is not clear if the overexpression experiments are equivalent between cell lines.

4) The nomenclature used for Groucho family proteins is imprecise and ambiguous and must be revised. Which family member is being used in their assays? Human or mouse TLE1, Drosophila Groucho?

Minor Essential Revisions

i) The Background and Discussion sections are wordy and unclear and would benefit from being rewritten in a more succinct style.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests