Reviewer's report

Title: BAG-1 haplo-insufficiency impairs lung tumorigenesis

Version: 1 Date: 19 August 2004

Reviewer: Andrew Christian B Cato

Reviewer's report:

General
Götz et al have submitted a manuscript showing that Bag-1 haplo-insufficiency impairs lung tumorigenesis. The message of the manuscript is interesting and the presentation is clear. However the discussion and conclusions are not well balanced and are not supported by the data.

Major compulsory revisions
1. The main weakness of this manuscript is that it describes reduced levels of Bag-1 but unfortunately these are not evident from the data presented. The difference in the level of Bag-1 must be re-examined by analysing more mice. From the immunoblot in Fig. 2a, it can be interpreted that the Bag-1 knock-down completely eliminates Bag-1L (p50) as well as Bag-1 (p32) expression. In this connection, it is very surprising that there is hardly a difference in the level of these proteins when extracts from (+/-) and (+/+ ) mice are compared. The apparent difference in the level of the Bag-1 proteins reported in the immunoblot in Fig. 2a also occurs in the control GAPDH signal.
2. Another point is that this manuscript describes the knock-out Bag-1 mice but hardly shows data on these mice. A brief statement was made to the effect that exons I and II were replaced by the neomycin resistant gene (details to be published elsewhere). One wonders why the present results are not put together with the original knock-out paper since the message is short and clear. A better description of the knock-out strategy and results is required.
3. As the reported interaction of Bag-1 with c-Raf and activation of c-Raf occurs via the C-terminal portion of the Bag-1 protein, one would expect Bag-1L (p50) to function in a similar way unless the amino terminus of this protein possesses a negative regulatory function. It would have been nice if more information had been presented to help understand which Bag-1 isoform is doing what. The problem of the Bag-1 isoforms was not at all tackled in this manuscript. The authors need to consider this in the interpretation of their results.
4. The scheme in Fig. 4 is a bit premature (in fact it does not provide any useful information) in view of the comments made in the conclusion on the uncertainty as to whether the survival of the adenoma cells requires Bag-1 interaction with c-Raf or Hsc70/Hsp70 or an additional protein.

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:
None