Reviewer's report

Title: Homeostatic response under carcinogen withdrawal. Heme oxygenase 1 expression and cell cycle association

Version: Date: 27 October 2006

Reviewer: Masato Noguchi

Reviewer's report:

General
Authors analyzed the HO-1 cellular localization and the expression of HO-1 and the cell cycle-related proteins such as cyclin E, cyclin-dependent kinases (CDK2 and CDK4), Bcl-2 and p21cip1/waf1 in the three mouse group, the control group that received a standard laboratory diet (SLD), the hepatocarcinoma (HC) group that received DAB for 89 days, and the homeostasis response (HR) group that received DAB for 77 days and then received SLD since day 78. The results they have obtained are:
1. The increases of p21cip1/waf1, a CDK inhibitor, and Bcl-2, an anti-apoptotic protein, were seen in the HC group, while the significant increases of CDK2 and cyclin E were observed in the HR group. Thus it was suggested that the hepatic cells of the HC group are in the deregulation state, while those of the HR group are in the process of regeneration.
2. The expression of HO-1, a stress response protein, was elevated in the HC group, while that in the HR group was normal. Thus it was thought that the oxidative stress was mitigated by quitting the DAB administration.
3. The immunohistological examination also suggested a possibility that HO-1 functions to mitigate the oxidative stress induced by the carcinogenic agent within cell.
Finally they concluded that their results provide a rationale for using HO-1 over expression as an alternative therapy to diminish tissue inflammation and deterioration in illnesses.
The reviewer thinks that data are original and consider that the interpretations are reasonable.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. The Abstract does not state the results of immunostaining at all.
2. The authors think that the expression level of HO-1 protein is related to the defense activity against oxidative stress during liver regeneration. The reviewer is interested in the differences of the HO-1 activities (heme degradation activity) among the control, HC, and HR groups.
3. Discussion is too easy; just describing mainly the amounts of protein expressed and histological findings. If the authors intend to generalize their results to cell reproduction in a precancerous state and change of apoptosis, more detailed literal retrieving would be desired whether some similar changes have been observed in other pathological conditions such as viral hepatitis etc, especially because the authors concluded their results provide a rationale for using HO-1 over expression as an alternative therapy to diminish tissue inflammation and deterioration in illnesses.

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

Minor Essential Revisions
1. The text contains many grammatical mistakes as well as typos. Because the English is clumsy as a whole, the reviewer felt difficulties to understand quite a few sentences. Some of the typos the reviewer noticed are:
   1) “bilirrubin” (page 2, line 5, and page 3, line 3) should be “biliverdin”. Bilirubin is not the direct product of heme oxygenase reaction.
   2) Fig. 1. “SDL” should be “SLD”
   3) Fig 3. There are no "oP" labels.
Discretionary Revisions (which the author can choose to ignore)
1. The reviewer wonders that much more information concerning the influence of DAB administration and the effect of its stoppage would be obtained if the authors took much more observation time points not but only day 89.
2. The rise of CDK4 level can also be seen in the HR group, though it is not much as that of CDK2 (Fig. 2). Text says that “…while no variation was detected in the CDK4 in any of the tested groups” (page 6, line 9 from bottom). In order to clarify this issue, how do the authors think to take the examination of cyclin D into consideration?

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: Not suitable for publication unless extensively edited

Statistical review: No

Declaration of competing interests:
I declare that I have no competing interests.