Reviewer's report

Title: Suppression of Mcl-1 via RNA interference sensitizes human hepatocellular carcinoma cells towards apoptosis induction

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Reviewer: Roberto R. Rosato

Reviewer's report:

General

This is an interesting study where the role of Mcl-1 down-regulation by using siRNA interference is investigated as a possible addition to other established therapeutic alternatives. Several drugs either alone or in combination are tested in this regard. Although in general this manuscript may appear as mostly descriptive, the overall impression is favorable; moreover, it provides some interesting data that may constitute the basis for future studies. Some specific comments follow:

- Analysis of several signaling pathways revealed no changes in the expression or regulation of Mcl-1. Some relevant observations included:
  a- The synergistic interactions between LY294002 and either Epirubicin or 5-FU; these potential activities may be of clinical relevance and are worth of further experimental studies.
  b- One of the inhibitors used in these experiments was the Raf-I kinase inhibitor sorafenib. The concentrations used ranged from 0.1 to 1 ?M. Recent studies have shown that one of the mechanisms by which sorafenib was able to induce cell death was through translational modifications of Mcl-1. However, these effects were achieved at higher concentrations of the drug, i.e. ? 5?M and in models of leukemia cells (Yu et al, 2005, Oncogene 24:6861; Rahmani et al., 2005, JBC 280:35217). It would be interesting to determine whether an increase in the concentrations of sorafenib may result then in Mcl-1 down-regulation and enhanced lethality or sensitivity to other drugs in hepatocellular carcinoma cells.

- Experiments tending to investigate the potential role that Mcl-1 down-regulation may have in the mechanisms of drug-induced cell death are relevant, notably because they analyzed a panel of diverse drugs which lethality may be greatly enhanced. At the same time, they give some perspectives of those whose activities will not be modified, providing some clues of the mechanisms that may be involved and setting the stage for further investigations.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

None

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

Some parts in the Discussion section may be suppressed or reduced (for example, the description of the different types of siRNA; this has become a relatively expanded technique and pretty well known in its concepts and application).

Discretionary Revisions (which the author can choose to ignore)

None

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No
Declaration of competing interests:

'I declare that I have no competing interests'