Reviewer's report

Title: Rapamycin delays growth of Wnt-1 tumors in spite of suppression of host immunity

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Reviewer: Lu-Hai Wang

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BMC Cancer Svirshchevskaya et al

This paper describes a study examining the potential underlying basis for the anti-tumor effect of rapamycin. The study focused on discerning the immunosuppressive effect of rapamycin versus that on the pathway of m-TOR as reflected in inhibition of growth and promotion of apoptosis. Wnt-1 transgenic tumor-derived cells in syngeneic C57/BL/6 mouse model was used for assessing the anti-tumor and immune suppressive effect of rapamycin. The authors conclude that immune suppressive effect does not affect the tumor inhibition of rapamycin, and that the anti-tumor effect is not due to promotion of apoptosis or arrest of cell cycle by rapamycin. Rather, it is more likely due to inhibition of the m-TOR pathway and inhibition of growth. The experiments are well designed and executed and the data in general support the conclusion. The significance of the finding lying in discerning the immune suppressive effect of rapamycin from others in the observed anti-tumor efficacy of rapamycin. However, there are a number of issues that need to be addressed before the conclusion can be clearly made. In disregarding the role of immune suppressive effect, there should be a positive control demonstrating that the injected T1Rapa cells are immune competent. The selection and nature of the T1Rapa cells should be more clearly described and rationalized why they are suitable for the experiment. Some of the conclusion based on "data not shown" can be better evaluated if those data are provided as supplemental materials. These include data on the effect of Wnt-1 tumor implantation on immune system and the expression of Fas in Wnt-1 versus activated splenocytes.

Minor comments:

1. Fig.2A: The number of mice used for each experimental group should be indicated and the data should be presented with standard errors.

2. It is paradoxical that there was no significant difference in the proportion of various splenic cells at day 7 and day 20 of rapamycin treatment, yet there was a significant difference of the cells at the two time points (Fig.2A). Similarly, there was 25 to 52% of apoptosis with splenocytes at day 20, yet the cell number was not significantly different from that of control, which had only 10 to 18% of apoptosis.

3. Why Fas was singled out among many potential regulators of apoptosis for the analysis was not explained and rationalized.
4. Fig.5: Data on the inhibition of the signaling components of the AKT/m-TOR pathway by rapamycin appear not to be consistent within each individual cell cultures and tumor line. Namely inhibition of p-AKT, p-4E-BP1, p-p70S6K and p-S6 was not consistent qualitatively and quantitatively within each sample or cell line. This should be explained.

Rapamycin apparently does not inhibit tumor growth via promotion of apoptosis or cell cycle arrest, the authors should explain better their hypothesis how ra