Reviewer's report

Title: Topical Rapamycin Inhibits Tuberous Sclerosis Tumor Growth in a Nude Mouse Model

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Reviewer: Aristotelis Astrinidis

Reviewer's report:

This study by Raukty A. and colleagues addresses the question whether topical application of rapamycin (as an ointment) decreases tumor growth formation in nude mice injected subcutaneously with tuberin-null Tsc2-/-/Tp53-/- MEFs. Direct application of 0.4% and 0.8% rapamycin significantly reduced tumor size and increased survival compared to vehicle control. Mice treated with 0.16mg rapamycin IP (corresponding to the dose of the 0.8% rapamycin ointment), had the greatest reduction in tumor growth, and increase in survival. Because there was no significant difference in tumor growth when the 0.8% rapamycin was applied directly to the tumor, compared to indirect application of 0.8% rapamycin, the authors conclude that the effect on tumor growth is caused by transdermal absorption of rapamycin, and a systemic increase in rapamycin levels. Indeed, rapamycin levels in whole blood of mice treated with 0.8% rapamycin were significantly increased at 24h and 48h post-treatment, compared to 0.4% rapamycin. However there was no difference in tumor rapamycin levels between the 0.4% and 0.8% groups.

Although this study clearly indicates that topical rapamycin application can cause reduction of tumor growth in the TSC xenograft mouse model, the practical application for the treatment of TSC-associated skin manifestations is uncertain, mainly because this study indicates that topical use of rapamycin in this mouse model causes a systemic increase for the drug. With ongoing rapamycin clinical trials for TSC, it would be interesting to see the outcome on skin lesions. However, the topical application of rapamycin might be useful for a subset of patients.

* Major Compulsory Revisions

None

* Minor Essential Revisions

None

* Discretionary Revisions

1. Based on work from other groups does topical application of rapamycin cause a systemic increase in the blood?
2. At what extend is mTOR inhibited in the rapamycin-treated tumors
(immunohistochemistry or immunoblotting with phospho-S6 antibody)?
3. Are there other evidence correlating with tumor growth (proliferation, apoptosis, angiogenesis) on rapamycin-treated tumors?

What next?: Accept after discretionary 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, the manuscript does not need to be seen by a statistician.

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