Reviewer’s report

Title: Methylthioadenosine (MTA) inhibits melanoma cell proliferation and in vivo tumor growth.

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Reviewer: Rosa Maria M Pascale

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This manuscript deals with the potential therapeutic effect of MTA on melanoma. To investigate this proposal were performed in vitro proliferation and viability assays using six different mouse and human melanoma cell lines wild type for RAS and BRAF or harboring different mutations in RAS pathway. It was also tested the therapeutic MTA capabilities in in vivo experiments using a xenograph mouse melanoma model and a variety of molecular techniques to investigate MTA anti-proliferative and pro-apoptotic properties.

By in vitro experiments MTA treatment inhibited melanoma cell proliferation and viability in a dose dependent manner, and BRAF mutant melanoma cell lines appear to be more sensitive. MTA was effective inhibiting in vivo tumor growth. The molecular analysis and in vitro experiments indicated that MTA induces cytostatic rather than pro-apoptotic effects, inhibiting the phosphorylation of Akt and S6 ribosomal protein and inducing the down-regulation of cyclin D1. At the end the authors concluded that MTA inhibits melanoma cell proliferation and in vivo tumor growth particularly in BRAF mutant melanoma cells, suggesting a naturally occurring drug, Methylthioadenosine potentially useful for melanoma treatment.

This work has been made by expert in the field and it is experimentally sound. The manuscript is intelligible, the results are clearly illustrated and commented. The questions posed by the authors are clear and well defined.

Minor points:
1. pag 9, line 6: on the bases of results in Fig3 the pathways affected by MAT should be the PI3K/Akt/mTor and Ras/Erk,
2. pag 10, line 5: the authors should add the word “mutant” speaking of BRAFV600E cells
3. pag 10, line 7: the P values of the inhibitory effects of MTA on G1 phase should be mentioned.

Level of interest: An article of importance in its field

Quality of written English: Acceptable
**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

'I declare that I have no competing interests'