

Review report

Thank you for the opportunity to review “Sema4D/Plexin-B1 is involved in anti-PD-1 resistance 1 in melanoma via PI3K/AKT signaling pathway” by Zhang et al. The authors attempt to study the role of Sema4D/Plexin-B1 interaction in regulating PD-1 resistance in melanoma.

Even though, the biology question addressed in this article appears to be relevant in the field, this article should be rewritten. Overall, the sentence structures are too long and the vocabularies are poorly used to communicate clear messages. There are many grammatical and spelling mistakes. The result section is not sufficiently described. No rationale for the experiments was stated and experiment designs were absent or poorly explained. The discussion section seems to be more of the result section since it only contains the interpretation of the data.

The main finding of this article is that PD-1 resistance in B16-F10R can be the result of Sema4D upregulation and knock down this protein can rescue the sensitivity of these cells to PD-1 treatment. Thus, the title is not accurate. Author did not show the interaction between Sema4D and Plexin-B1. Author did not investigate the source of Plexin-B1 that interacts with Sema4D on the tumor cells, mediating PD-1 resistance effect. It is intriguing that both Sema4D and Plexin-B1 are upregulated in B16-F10R taking into account that it is the interaction between these two molecules that involves in cancer progression. Sema4D is more described to be expressed on immune cells. Can author explain the decision to only investigate Sema4D and not Plexin-B1? Did author look at the effect of Plexin-B1 knock down? The whole study was conducted with only one cell line, authors should validate this finding at least partially using one more cell line.

In all the figure legends, author should briefly describe the method, experiment design, and the types of data which are presented.

Figure 1: Can author show PDL-1 expression in B16-F10 and in B16-F10R? And, the responsiveness of both cell lines to anti-PD-1 treatment evaluated by at least cell viability or cell death.

In the figure title, author used terms that I think is not accurate:

1. “Sema4D/Plexin-B1 expression in cell” should be “Sema4D and Plexin-B1 expression in melanoma cell lines”
2. “divided” should be “derived”
3. “Sema4D/Plexin-B1” should be “Sema4D and Plexin-B1”

Figure 2: Can author show how silencing Plexin-B1 will affect PD-L1 expression?

Author used terms that I think is not accurate:

“Sema4D deficiency inhibit PD-L1 expression” should be “Sema4D silencing downregulates PD-L1 expression in B16-F10R”

Figure 3: Can author overexpress Sema4D in B16-F10 and see if that could reverse the responsiveness of this line to PD-1 treatment. In 3B, what is the X axis of the dot plot? Author has to be consistent with the way he or she presents the datasets in the graph. In 3C, the Sema4D-NC group is in grey, not black as shown in 3A and 3E.

In the figure title, author used terms that I think is not accurate:

1. "Sema4D deficiency potentiates anti-PD-1 treatment efficacy" should be "Sema4D deficiency renders B16-F10R cells sensitive to PD-1 treatment"

Figure 4: What is the experiment design? Were the cells treated with anti-PD-1? The title is not reflecting the finding in that figure. Author did not show that PD-1 treatment inhibited cell invasion and migration, but knock down Sema4D decreases the ability of the cells to migrate. What is the experiment conducted in 4C?