Reviewer #1 comment

Specific Comments to Authors: FIGURA1. I recommend that the signs on all figures be larger so that they can be easily read. FIGURA Supplementary 1. In the network of proteins obtained by the Stream program, it is not observed which of them is the JOSD2 deubiquitinase. FIGURES 4 AND 5. It would be convenient to put in these figures the data that correspond to the control cells, without transfecting any plasmid, both in the relative amount of messenger RNA, cell viability, similar to the formation of colonies. FIGURE 6. Discuss the differences observed in cisplatin tumor growth between different cell lines. FIGURE 7. Western blot assays are very good, it would be convenient to graph these results to see more clearly the difference between the cells that have the empty vector and the one that has FLAG-JOSD2. **Describe the meaning of proteins like USP47, IGVZD-2, PRMT5 etc.

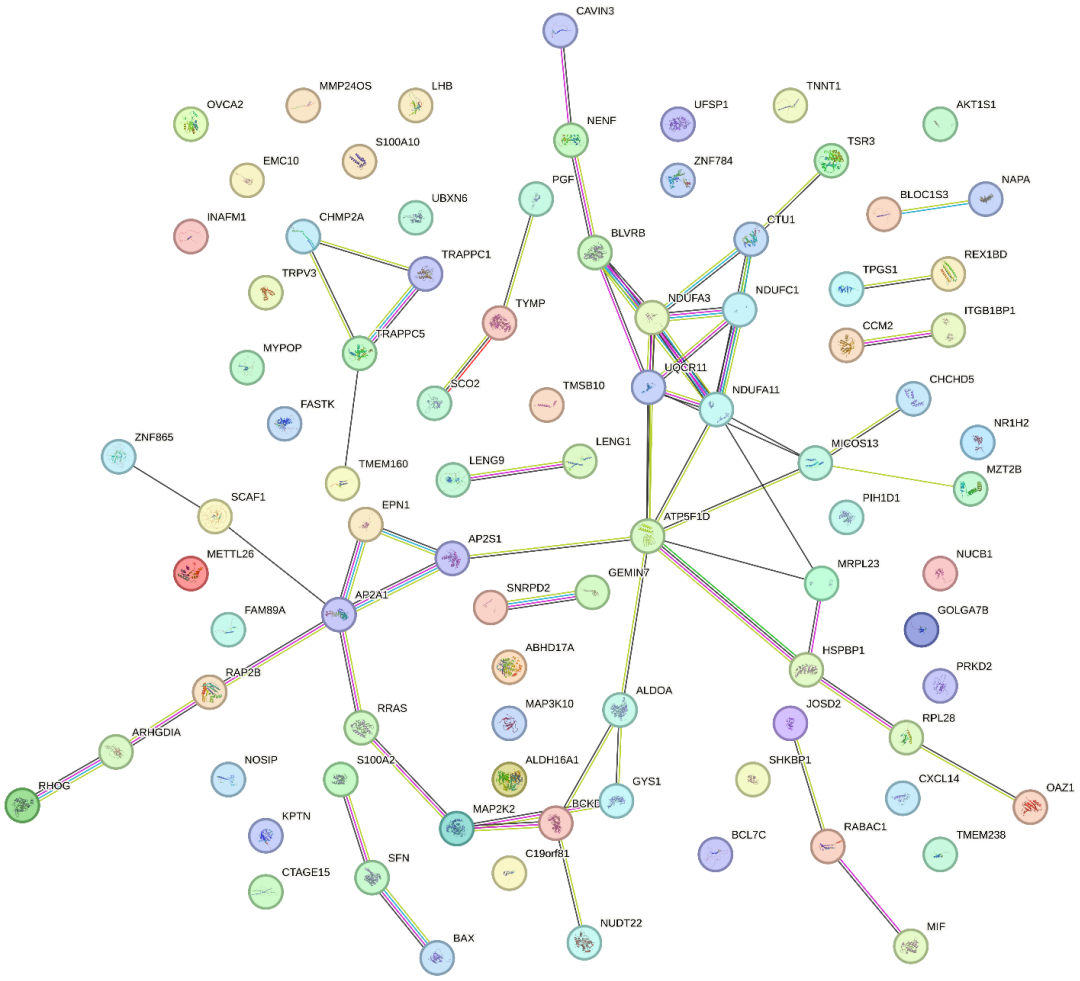
Answers

1. **FIGURA1. I recommend that the signs on all figures be larger so that they can be easily read.**

   Thank you for your advice. We have made every effort to adjust the Figure 1 labels to the best of our ability. However, due to some images being generated by online database websites or limitations in R language code, it is still not possible to make all labels equally conspicuous.

2. **FIGURA Supplementary 1. In the network of proteins obtained by the Stream program, it is not observed which of them is the JOSD2 deubiquitinase.**

   We divided the samples into two groups based on the high and low expression levels of the JOSD2 gene. Transcriptomic differential gene analysis was conducted for the two groups. The top 100 genes most correlated with JOSD2 were subjected to Protein-Protein Interaction (PPI) network visualization using the STRING database. In response to the suggestions from the reviewing expert, we included JOSD2 among the 100 differentially expressed genes and re-drew the PPI network.



3. **FIGURES 4 AND 5. It would be convenient to put in these figures the data that correspond to the control cells, without transfecting any plasmid, both in the relative amount of messenger RNA, cell viability, similar to the formation of colonies.**

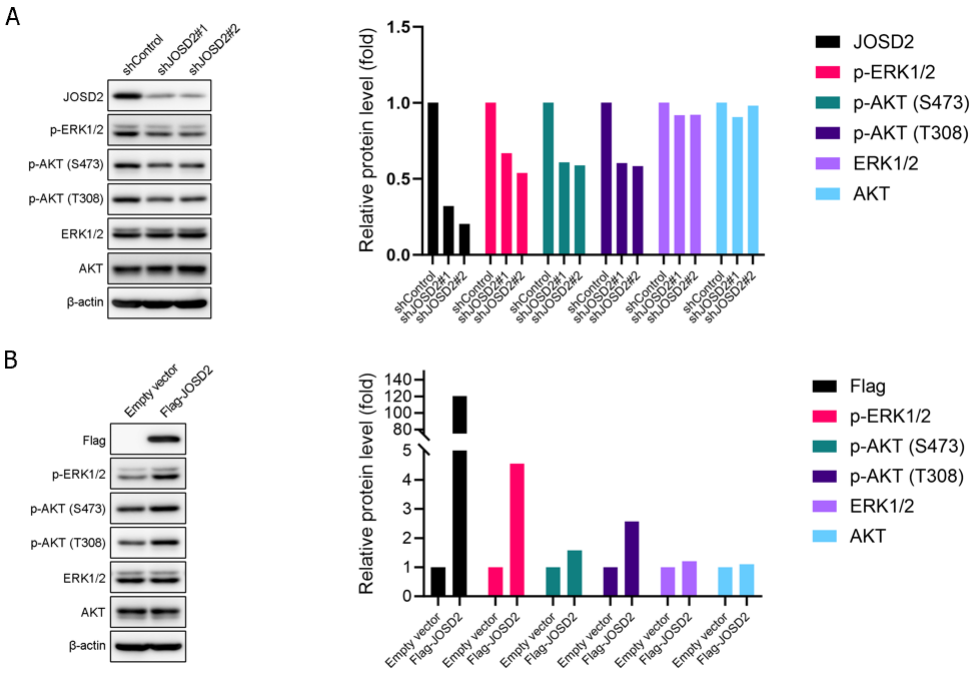
   Thank you for your suggestions. We have reviewed relevant literature, and the data pertaining to messenger RNA and cell viability are predominantly presented in bar charts and line graphs. If necessary, we would like to submit the data on messenger RNA and cell viability to the journal as supplementary material to enhance readers' understanding.

4. **FIGURE 6. Discuss the differences observed in cisplatin tumor growth between different cell lines.**

   According to the reviewing expert's suggestion, we discuss the differences observed in cisplatin tumor growth between different cell lines in **discussion section**. "Cisplatin is one of the primary chemotherapy drugs used in the treatment of ESCC. Our results in vivo confirmed that altering the expression of JOSD2, either by upregulation or downregulation, can modulate the resistance of ESCC to chemotherapy drugs, which highlights the significance of JOSD2 as a potential therapeutic target for overcoming cisplatin resistance in ESCC."

5. **FIGURE 7. Western blot assays are very good, it would be convenient to graph these results to see more clearly the difference between the cells that have the empty vector and the one that has FLAG-JOSD2.**

   In accordance with the recommendations of the reviewing expert, we have generated quantitative protein expression graphs based on Western blot results to better illustrate the findings.



6. Describe the meaning of proteins like USP47, IGVZD-2, PRMT5 etc.

In the discussion section, we elaborated on the four most likely protein substrates of JOSD2. “USP47, a DUB, has the ability to counteract the functions of E3 ubiquitin ligases, playing a role in cell growth and survival processes [32]. Several studies have provided evidence that USP47 is involved in the advancement of diverse cancer types [33-35]. There is limited research on the IGKV2D-29 gene. Polymorphism in the IGKV2D-29 gene was shown to lower the recombination frequency in B cells and was identified as especially crucial for immune responses to Haemophilus influenzae type b polysaccharide [36]. HSP90AB1 is a crucial participant in the activation of oncogenes and the preservation of cancer cell viability, which is due to the chaperone mechanism of HSP90AB1 within cancer cells, safeguarding significant amounts of mutated and excessively expressed oncogenic proteins from undergoing misfolding and degradation [37]. Among these proteins, PRMT5 plays a crucial oncogenic role in various malignancies and is a hot target in recent cancer therapies [38, 39]. However, there have been no studies reporting its deubiquitination modification. This implies that PRMT5 is likely a key substrate protein for JOSD2's oncogenic function, and the revelation of JOSD2's deubiquitination modification on PRMT5 holds significant innovative implications.”