Reviewer's report

Title: Modulation of SOCS Protein Expression Influences the Interferon Responsiveness of Human Melanoma Cells.

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Reviewer: Peter Lee

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In the manuscript entitled Modulation of SOCS Protein Expression Influences the Interferon Responsiveness of Human Melanoma Cells by Lesinski et al., the authors identify expression of JAK-STAT pathway inhibitors SOCS1 and SOCS3 in metastatic melanoma cell lines, and expression of SOCS proteins was upregulated in response to IFNa or IFNg in some of the cell lines. Overexpression of SOCS1 or SOCS3 in melanoma lines abrogated IFN responses, while siRNA targeting of SOCS1 or SOCS3 potentiated IFN responses. The authors conclude that melanoma cells may utilize SOCS expression to block IFN responses and that SOCS protein targeting may be a therapeutic option.

Major points:

1. The major problem with this manuscript is the lack of novelty. It is already well established that SOCS1/3 negatively regulate IFN signaling pathways, and that SOCS1-3 expression is induced by STATs. Thus it is no surprise that overexpression of SOCS or knock-down of SOCS expression would alter IFN pathway responses in any cell type including melanoma lines.

2. The authors conclude that SOCS expression may limit IFN effectiveness in melanoma cells. However, this is the normal function of SOCS proteins, and the data presented do not compare melanoma lines with other types of cells, or with melanoma lines from different stages, thus this conclusion is not well-supported. More solid evidence would be derived from assays that enhance IFN-resistance in cell lines or in vivo models coupled with demonstrations of the role of tumor-expressed SOCS proteins in such a setting.

3. The authors make the suggestion that targeting of SOCS proteins may be a therapeutic option for cancer patients in order to enhance the effectiveness of IFN therapy or endogenous IFN responses. However, as the authors mentioned in the discussion it has been shown that “loss of SOCS1 expression is a critical event leading to elevated STAT3 signaling and over-expression of factors that promote cellular invasion and angiogenesis”. Thus, demonstrating the positive versus negative effects of SOCS inhibition in the cancer setting should be done before making such a suggestion, particularly since STAT3 activity in both the tumor and immune compartments plays a key role in tumor progression.

Level of interest: An article of insufficient interest to warrant publication in a
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