Reviewer's report

Title: MRP3: A molecular target for human high-grade glioma immunotherapy

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Reviewer: Hilko Ardon

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Description: This is a well written and easy to read manuscript on MRP3 as potential target for human high-grade glioma (HGG) immunotherapy. The authors describe that MRP3 is overexpressed at both mRNA and protein levels in HGG, and that this overexpression is correlated with higher risk of death. From these data Kuan et al. conclude that the tumor-associated antigen MRP3 has a potential use as a prognostic predictor for malignant gliomas and might be useful in immunotherapeutic strategies for treating malignant glioma patients.

Comments

Major Compulsory Revisions:

1. Relative MRP3 mRNA expression levels, IHC, and age were considered as possible predictors of survival and survival analyses were made based on these three factors. As one could expect age was a strong predictor of survival, as were high levels of mRNA expression. However, it is unclear from the reported data if other known prognostic factors, such as RPA classification, Karnofsky Performance Score and grade of resection, were taken into account. Also, it is unclear if all patients received the same postdiagnostic treatment, since differences in survival might be due to differences in treatment. Therefore, it is mandatory to see the demographic and treatment details of the different patients before conclusions can be drawn on the prognostic value of MRP3 mRNA expression.

2. Based on the legend of Fig.1 it can be concluded that all the results for normal brain tissue (MRP3 mRNA levels) come from 1 sample (NWB (normal whole brain) n = 1) (?). A bigger sample size would strengthen the claims of the authors.

Minor Essential Revisions

1. It would be interesting to see MRP3 IHC results for normal brain, since expression is expected to be absent.

2. The legend of Fig. 2 should be changed; quantitative FACS analysis should point to Fig. 2 (C) and (D).

3. It is unclear whether the Results of the Statistical analyses are based on uni- or multivariate models (as described in Methods). This should be clarified.
4. The Conclusions section of the Abstract should be rewritten (incorrect sentence).

Discretionary Revisions

1. The first paragraph of the Discussion starts with a description of the ideal antigens for immunotherapy. Besides the three characteristics already mentioned, the immunogenic potential of an antigen (especially in the case of active immunotherapy) is also a key-feature of an ideal antigen. Moreover, tumor-associated antigens (TAAs) for immunotherapeutical use should be present on the tumor cells that are responsible for recurrence of the tumor (since HGG are very heterogeneous it can be expected that not all tumor cells will express the same TAAs).

2. Table 2 does not seem to add much to the manuscript and a description in the text would be sufficient.

3. In the first alinea of the Background it is stated that ‘mean postdiagnostic survival for HGGs remains less than one year’. More recent studies point to a longer median overall survival: 14.6 months since Temozolomid (TMZ) was introduced in the postoperative treatment (surgery – radiochemotherapy (TMZ) – maintenance TMZ chemotherapy) (Stupp et al., N Eng J Med 2005).

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