Reviewer's report

Title: Profound tumor-specific Th2 bias in patients with malignant glioma

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Reviewer: silvano ferrini

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General observations
The manuscript by Shimato et al. shows that in vitro stimulation of PBMC from glioma patients stimulated in vitro with synthetic epitopes from MAGE-3A and IL-13Ra2 recognized by Th cells induce skewing of the cytokine profile towards a Th2-profile relative to PBMC from healthy donors.

The observation that in vitro antigen stimulation by Th epitopes induces Th2 skewing in PBMC from glioma patients is interesting, although a Th1/Th2 imbalance has been previously reported in glioma patients. This study has several major limitations which require revision.

Minor essential revisions
1) The HLA class II restriction profile of the peptides used should be indicated along with the HLA class II haplotype of the subjects included in the study. Otherwise, where the peptides promiscuous to multiple HLA-Class II alleles? In any case this aspect should be clearly defined.

2) Clinical characteristics of the patients should be provided in a summary table.

3) The conclusion that future vaccination strategies should consider the possibility “to reverse the profound Th2 skewing” is rather obvious and is presently addressed by the use of different adjuvants in clinical trials. The authors should further comment on this point and suggest which approach they would pursue to achieve this goal (TLR agonists? Cytokines such as IL-12?).

Major Compulsory Revision
The authors state that a Th2 profile has been induced by antigen stimulation on the basis of the IFN-g/IL-5 profile of secreted cytokines. This assay however is not sufficient to define a Th2 skewing. In particular, gliomas have been suggested to induce induction of Tr1 (regulatory type I) cells (Akasaki et al), which produce both IL-5 and high levels of IL-10 (reviewed in Wu et al).

Therefore further efforts to characterize the Th2 or Tr1 skewing of the response should be attempted by measuring IL-10 and IL-4 (the prototypic cytokine produced by Th2 cells). In this context, the protocol used for the evaluation of cytokine secretion by Th cell lines seems not optimal. It appears that PBMC were cultured for 14 days with a single antigen pulse at the onset of cultures. Usually a second short-term stimulation is used before cytokine assay to avoid consumption of cytokines such as IL-4.
Alternatively, attempts to assess the expression of the Th2-specific transcription factor GATA3 (mRNA or protein) in cultured T cells should be considered.

Induction of a CD4+ T regulatory type 1 response by cyclooxygenase-2-overexpressing glioma.

IL-10-producing type 1 regulatory T cells and allergy.
Wu K, Bi Y, Sun K, Wang C.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I have no conflict of interest to disclose.