Reviewer’s report

Title: CXCR7 is induced by hypoxia and mediates glioma cell migration towards SDF-1alpha

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Reviewer: peter canoll

Reviewer’s report:

This is a very interesting paper that addresses an important topic of great clinical relevance. Specifically, the paper explores the role of SDF-1 and CXCR7 signaling in hypoxia induced glioma migration. This study builds on the authors’ previous studies characterizing the role of SDF-1 and CXCR4 signaling in glioma migration, and advances the story. The paper is well written and the results are straight forward and of high quality. The conclusions are clearly supported by the results. The relevant literature is appropriately cited and discussed. There are just a few minor issues that I feel should be addressed

Minor Revisions:

1) The methods should provide a bit more information on how the Western blot data was quantified and how the fold changes were calculated. Specifically, for the data shown in figure 1 were the measurements normalized to loading control? In figures 4 and 5, was the signal for the phospho-AKT normalized to loading control or to total AKT?

2) For the shRNA knockdown studies, the authors state the following: “The efficiency of knockdown was confirmed by Western blot analysis.” They should either present this data or state “data not shown”

Discretionary Revisions

1) A graph showing the results of the quantitative measures of the Western blots would be helpful to illustrate the trends shown in figures 1, 4, and 5.

2) In figure 5, the effects of AMD3100 without CXCR7 knockdown are not shown. It would be helpful if the authors discussed if what is known about CXCR4 signaling. Is it known if CXCR4 induces phosphorylation of ERK or ARK? If so, does AMD3100 inhibit this?

3) It is a very interesting finding that both CXCR4 and CXCR7 are required for SDF-1 induced migration of hypoxic glioma cells, but blocking both CXCR4 and CXCR7 does not provide an additive effect, either with regards to transfilter migration or phosphorylation of ERK and AKT. It is also very interesting that CXCR7 can be co-immunoprecipitated with CXCR4-HA. It would be nice if the paper included a little more discussion on how the authors might interpret these findings. For example, does SDF-1 induced migration require cross-talk between...
CXCR4 and CXCR7? Or do they have another potential mechanism in mind.

4) It would be interesting if the authors expanded the discussion to include some mention of SDF-1, CXCR4 and CXCR7 expression in the different subtypes of glioblastoma. For example, they could query the TCGA database to see if there is any subtype specific differences in the expression. Do the levels of these signaling molecules tend to correlate with each other, as one might expect since they are all upregulated by hypoxia.

**Level of interest:** An article of outstanding merit and interest 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 declare that I have no competing interests