News Release

Title

Significance of perivascular tumour cells defined by CD109 expression in progression of glioma.

Key Points

- **We found that CD109, a GPI-anchored membrane protein, is a prognostic marker of glioma through the use of human samples and the RCAS/tv-a mouse glioma model.**
- **High expression of CD109 in BTSCs is involved in tumour progression.**
- **We hypothesised that CD109-positive cells were resistant to TMZ.**

Summary

In the progression of glioma, tumour cells often exploit the perivascular microenvironment to promote their survival and resistance to conventional therapies. Some of these cells are considered to be brain tumour stem cells (BTSCs); however, the molecular nature of perivascular tumour cells has not been specifically clarified because of the complexity of glioma. Here, we identified CD109, a glycosylphosphatidylinositol-anchored protein and regulator of multiple signalling pathways, as a critical regulator of the progression of lower-grade (World Health Organization grade II/III) glioma by clinicopathological and whole genome sequencing analysis of tissues from human glioma. The importance of CD109-positive perivascular tumour cells was confirmed not only in human lower-grade glioma tissues, but also in a mouse model that recapitulated human glioma. Intriguingly, BTSCs isolated from mouse glioma expressed high levels of CD109. CD109-positive BTSCs exerted a proliferative effect on differentiated glioma cells treated with temozolomide. These data reveal the significance of tumour cells that populate perivascular regions during glioma progression, and indicate that CD109 is a potential therapeutic target for the disease.

Research Background

For therapeutic targeting of human glioma, the most difficult challenges are incomplete tumour excision and tumour resistance to conventional radio- and chemotherapies. Extensive studies have revealed mechanisms for the refractory nature of glioma, including the existence of brain tumour stem cells (BTSCs) that exhibit high resistance to therapies. However, a critical issue in understanding the biology of BTSCs is how they exploit tumour microenvironments where many types of cell communicate via the production of soluble cues, such as growth factors and chemokines, which foster a supportive environment for BTSCs.

The aim of the present study was to investigate the role of CD109, a glycosylphosphatidylinositol (GPI) membrane-anchored and secreted protein that is highly expressed in various human malignancies in a environment for BTSCs.

Research Results

In the present study, we found that CD109, a GPI-anchored membrane protein, is a prognostic marker of glioma through the use of human samples and the mouse glioma model. It was interesting to find that CD109-positive cells preferentially localised in the perivascular area of human glioma and mouse tumours. Taken together with our in vitro analysis showing that high expression of CD109 in BTSCs is involved in tumour progression, it is tempting to hypothesise that CD109 is a marker of BTSCs that reside in the perivascular microenvironment. In addition, we found that CD109-positive cells survived in tumour tissues after Temozolomide treatment

Research Summary and Future Perspective

The plasticity between BTSCs and non-BTSCs in terms of CD109 expression is another concern that was not addressed in the present study. Our findings indicate that the net effect of CD109 inhibition may be more complex than that predicted by the simple view that CD109 mediates the proliferation of glioma tumour cells. To address this requires further sophisticated studies involving CD109 inhibition in animal glioma models. Furthermore, Our goal is to provide evidence that CD109 is a therapeutic target for the development of anti-glioma therapies.

Publication

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