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Preview

Adhesion GPCRs in glioblastoma revisited

Tobias Langenhan[1,2,3,*]
[1]Rudolf Schönheimer Institute of Biochemistry, Division of General Biochemistry, Medical Faculty, Leipzig University, Leipzig, Germany
[2]Comprehensive Cancer Center Central Germany (CCCG), Germany
[3]Institute of Biology, Faculty of Life Sciences, Leipzig University, Leipzig, Germany
*Correspondence: tobias.langenhan@gmail.com
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Glioblastoma is a devastating brain malignancy that has remained intractable to modern cancer treatments. Ravn-Boess et al.[1] have discovered that the adhesion G protein-coupled receptor CD97/ADGRE5 contributes to glioblastogenesis and makes for an excellent molecular surface marker flagging the tumor cells.

Immunobiological approaches have been revolutionizing cancer therapy without an end in sight. The advent of therapeutic antibodies, checkpoint inhibition of T cell activation, chimeric antigen receptor expressing T (CAR-T)/natural killer (CAR-NK) cells, and personalized cancer vaccines offer a striking weaponry that exploits a tumor's alien antigen profile to muster a therapeutic attack at neoplastic tissue.[2] Although hematopoietic and some solid tumor entities are now successfully treated with immune therapeutics, for glioblastoma multiforme, a malignant brain tumor type and one of the most devastating cancers, no such treatment exists.

Help is coming from a study that analyzed the select expression profile of the family of adhesion G protein-coupled receptors (aGPCRs) in glioblastoma.[1] aGPCRs are a class of over 30 human surface receptors that interact with adhesive ligands embedded in the extracellular matrix or affixed on juxtaposed cell membranes.[3] Through these interactions, mechanical stimuli can be sensed and converted into biochemical messages inside the cell.[4] Akin to other adhesion molecules, many aGPCRs display extensive extracellular regions with eclectic combinations of protein domains. aGPCRs, therefore, offer two opportunities for immunooncology. Due to their often cell-specific expression profile, the receptors are formidable cell markers with ample epitope space to provide information on cell identity for cancer immunotherapies, a property that has started to be utilized.[5] Second, the biological activities of aGPCRs could control aspects of tumorigenesis or progression. Interference with aGPCR signals could thus aid in slowing down tumor growth, control its invasiveness, or curtail metastatic spread.[6]

In a recent paper published in *Cell Reports*, Ravn-Boess et al. studied the expression profile of all aGPCRs in patient-derived glioblastoma samples by using an unbiased transcriptomic survey. Intriguingly, about a third of all aGPCR members appeared upregulated in the tumor tissue, confirming the group's previous scientific focus on the role of another aGPCR, GPR133/ADGRD1, in glioblastoma.[7] When matching the transcriptional expression with proteomic datasets in glioblastoma, and after comparing healthy brain with glioblastoma samples, another receptor, CD97/ADGRE5, then emerged as the frontrunner. CD97 was very highly expressed in glioblastoma, while it is not or only lowly present in normal brains, lending itself to speculations on the receptor's involvement in glioblastoma pathogenesis. The authors continued to test the causality of CD97 and glioblastoma emergence with genetic approaches. Both CRISPR/Cas9-directed removal of *CD97* and shRNA-mediated knockdown of *CD97* mRNA resulted in substantial retardation of tumor growth owing to the reduced emergence of tumor clones, tumor stem cell renewal, and proliferation of glioblastoma cells. Revisiting the outcome of *CD97* knockdown in patient-derived glioblastoma cells, the authors uncovered a severe reduction in pathways that support anaerobic metabolism, implicating CD97 in glycolytic energy sourcing under oxygen-free conditions. This situation, epitomized as the Warburg effect, commonly occurs in glioblastoma tissue masses due to their fluctuating vascularization. Combined biochemical and pharmacological analyses further showed how CD97 controls the expression of glycolysis genes. Interestingly, although the receptor did not seem to signal through Gαi and Gα12/13 routes as previously shown, it instructed the intracellular Ras-Raf-MEK-ERK path, alternatively known as the mitogen-activated protein kinase (MAPK) pathway. The authors went on to delineate that CD97 is phosphorylated at its intracellular terminus by a set of GPCR kinases (GRKs) which resulted in the recruitment of β-arrestin, an adaptor protein involved in GPCR internalization and a MAPK pathway stimulator. Compellingly, when Ravn-Boess et al. expressed a mutant CD97 variant, which was resistant to phosphorylation, production of the MAPK component p-ERK was curtailed. In addition, phosphorylation-resistant CD97 was unable to stimulate the formation of glioblastoma tumorspheres *in vitro*. The authors confirmed that the previously identified CD97 ligand Thy-1/CD90 was also interacting with the receptor in glioblastoma. This finding was corroborated when CD97 exposure to Thy-1 resulted in higher MAPK pathway activity.

Finally, Ravn-Boess et al. turned to the antigenic potential of CD97 as an immune marker for glioblastoma cells. After isolating a monoclonal α-CD97 antibody recognizing an epitope in the extracellular receptor portion from a synthetic antibody library, the authors observed increased internalization of CD97-antibody complexes. They utilized this effect by conjugating the antibody with a cytostatic drug that exerts a stalling effect on cell

proliferation upon internalization. Reassuringly, glioblastoma cells from patients exposed to the α-CD97-toxin conjugate displayed largely reduced cell viability in *in vitro* assay.

CD97 is no stranger to the field of molecular oncology; it was described as a dedifferentiation marker in thyroid carcinoma more than 25 years ago and, thus, was the first aGPCR associated with cancer.[8] Other aGPCRs have been added, underlining the developmental roles of the aGPCR family.[9,10] The current study by Ravn-Boess et al. demonstrates the potential of exploiting the human aGPCR repertoire for understanding how individual tumor types arise and thrive.

On the flip side and irrespective of the individual biological activity of aGPCRs in cancer cells, their exposed extracellular regions constitute an untapped reservoir of well-characterized molecular markers. The glioblastoma omics results of Ravn-Boess et al. provide a valuable resource to the community, as a couple of other aGPCRs displayed increased abundance in the neoplastic tissue, although not such as marked as CD97. Following up on some of these candidates can widen the window for viable molecular glioblastoma targeting strategies. A recent study on the aGPCR EMR2/ADGRE2, a close homolog of CD97, demonstrated the power and promise of this endeavor by functioning as a molecular surface marker of leukemic stem cells in acute myeloid leukemia.[5] In the study, a tailored ADGRE2-CAR allowed for the efficient targeting and subsequent eradication of cancer stem cells in a humanized mouse model of this neoplasia when combined with an independent chimeric co-stimulatory receptor. The deeper our understanding of the combinatorial aGPCR expression code of cancer cells, the better we can devise ways to combat them.

DECLARATION OF INTERESTS

The author declares no competing interest.

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