Glioblastoma is the most common primary brain tumor in adults, which is associated with an extremely poor prognosis, with a median survival following diagnosis of 15 months. Glioblastoma are aggressive tumors, characterized by areas of rapid cell proliferation, angiogenesis, and necrosis, reflecting the aggressive nature of this disease. To date, standard treatment for glioblastoma involves surgical resection of as much of the tumor bulk as possible, followed by radiotherapy and chemotherapy to eliminate the remaining cells. However, these treatments are palliative in nature, and tumors fatally relapse within 7 to 10 months. As such, long-term survival rates for glioblastoma patients have not significantly improved over the past decade.

Glioblastoma are associated with significant inter- and intratumoral heterogeneity. Within glioblastoma exists a population of tumor-initiating cells also named as glioblastoma stem-like cells (GSCs) that have a proposed role in tumor initiation, resistance to current therapies, invasion, and angiogenesis. Although some debates on the origin and definition of GSCs remain, the presence of these cells within specific niches within tumors is unknown. Our laboratory conclusively demonstrated that brain endothelial cells positively control the expansion of GSCs. Notably, we found that GSCs are addicted to the hormonal peptide apelin (APLNR) secreted by surrounding endothelial cells, and identified the APLN/APLNR nexus as a promising druggable network in glioblastoma.

ABSTRACT: Glioblastoma multiforme are mortifying brain tumors that contain a subpopulation of tumor cells with stem-like properties, termed as glioblastoma stem-like cells (GSCs). These GSCs constitute an autonomous reservoir of aberrant cells able to initiate, maintain, and repopulate the tumor mass. A new approach to brain tumor therapy consists of targeting the GSC population. The GSCs are situated in perivascular niches, closely associated with brain microvascular endothelial cells thereby involved in bidirectional molecular and cellular interactions. In this scenario, the endothelium not only supplies oxygen and necessary nutrients but also seeds a protective microenvironment for tumor growth. Although GSC fate, plasticity, and survival are regulated by external cues emanating from endothelial cells, the nature of such angiocrine signals remains unknown. Our laboratory conclusively demonstrated that brain endothelial cells positively control the expansion of GSCs. Notably, we found that GSCs are addicted to the hormonal peptide apelin (APLNR) secreted by surrounding endothelial cells, and identified the APLN/APLNR nexus as a promoting druggable network in glioblastoma.

KEYWORDS: Glioblastoma, apelin, GPCR, endothelium

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An alternate argument is that the observed reduction in tumor volume associated with MM54 administration may be due to a reduction in angiogenesis. Apelin has previously been implicated in angiogenesis and is reported to induce vessel sprouting and stabilization of contacts between endothelial cells.\textsuperscript{15,16} Indeed, apelin has a proposed role in tumor angiogenesis and response to anti-angiogenic therapies, with apelin messenger RNA reported to be elevated in patients who do not respond to anti-angiogenic therapy.\textsuperscript{19} Moreover, apelin expression has been positively correlated with increased microvessel densities and subsequent tumor growth in human non–small-cell lung carcinoma.\textsuperscript{20} It is well established that tumors rely heavily on neo-angiogenesis to receive the nutrients they require to survive.\textsuperscript{21} Consequently, the observed effect on tumor growth by blocking apelin in vivo may also be associated with an anti-angiogenic effect rather than by directly targeting the GSCs. However, the weight of the in vitro data suggests that endothelial–derived apelin has a clear role in the maintenance of these human GSCs.\textsuperscript{1} Moreover, implantation of GSCs in which the apelin receptor has been silenced while left intact in host endothelial cells demonstrated a reduction in tumor size compared with shRNA control groups, a result which cannot be explained by apelin-mediated changes toward angiogenesis.

Although impressive results were obtained with the MM54 compound in xenografted mice, it is important to note that both genetic and pharmacological evidence for the role of APJ in glioma growth were established in immuno-compromised animals. In keeping with this idea, recent published data suggest that in melanoma, point mutations of the \textit{APLNR} gene are associated with a failure of targeted immunotherapies\textsuperscript{22} indicating that the interaction between APLNR and the immune system may warrant further investigation. Nonetheless, tumor growth in vivo is a complicated and multifaceted process that is rarely due to one factor or mechanism alone, and compounds that target multiple aspects of tumorigenesis may prove extremely beneficial. Together, the results of this study highlight the potential of endothelial–derived apelin as an exciting target for glioma growth (Figure 1).

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**Author Contributions**

EHW wrote the manuscript; JG edited the text and prepared the figure.

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