It is widely accepted that progenitor stem cells are the origin and initiators of different types of cancer that exhibit self-renewal, multipotency, and aggressive properties (1,2). This concept represents a different approach compared with previous theories, and the idea that cancer may be primarily driven by a small population of stem cells has important implications. For example, shrinking a tumor without killing the cancer stem cells may not be sufficient, since the remaining tumor cells are capable of re-growing, often with modified properties and resistance to previously used therapies. Furthermore, for the purpose of personalized therapy it is important to identify molecular traits that are specific to cancer stem cells, in comparison with normal stem cells, and this is a timely and achievable task.

Gliomas comprise the vast majority of malignant brain tumors. Low-grade (LG) forms (WHO grade II) are less malignant, but these slow-growing and infiltrating tumors can become more aggressive, evolving into glioblastoma multiform (GBM) (WHO grade IV), the most frequent and lethal glial neoplasm. High-grade (HG) gliomas include a panel of brain pathologies that includes oligodendroglioma and anaplastic astrocytoma (WHO grade III), as well as GBM (WHO grade IV). Current treatment modalities are rather limited, only modestly improving the survival of these patients (6). This is mainly due to resistance of gliomas to both radiotherapy and chemotherapy, as well as the rapid invasion properties of the glioma cells in brain tissue. The BBB poses an additional challenge, making delivery of effective drug doses for therapies to tumor cells is quite challenging. These characteristics have led to research focused on identification of specific molecular traits of the glioma progenitor cells.

Mammalian protease-activated receptors (PARs) are a subgroup of G protein-coupled receptors (GPCRs) that form a subfamily of PARs (7-11). PAR1 and PAR2 play a central role in epithelial tumor growth in a variety of epithelial malignancies (12-15). Whereas PAR1 is not considered a thrombin receptor (unlike PAR1, PAR3 and PAR4), the PAR1-tethered ligand SFLLRN is capable of transactivating PAR2 (16,17). Increasing evidence supports the notion that PAR1 and PAR2 exist in a close proximity and act as a functional unit while forming heterodimers (16-18). Consistently, PAR2 plays a dominant role, conferring function in tumor development while forming PAR1-PAR2 heterodimers, as well as in atherosclerotic plaque formation (19).
Auvergne et al. successfully isolated glial progenitor cells (GPCs) by applying a monoclonal antibody; A2B5+, and sorting these cells from human gliomas (20). mRNA profiling identified a gene signature (including F2R PAR) that distinguishes A2B5+ tumor progenitor cells from A2B5+ progenitor cells isolated from the normal brain white matter. In a recent Oncogene publication (21), this group demonstrated that shRNA silencing or pharmacological inhibition of PAR, effectively attenuated glioma tumor expansion, in vivo. 

Our understanding of PAR, and its signaling pathway has vastly expanded. As PAR, and PAR, have a central task in tumor etiology, signal-binding motifs within their C-tails have been identified as critical sites for epithelial malignancies, and have been linked specifically to breast cancer growth. This is manifested via the association of Akt/ PKB pleckstrin-homology (PH)-domain as a key signaling event of PARs. Other PH-domain signal-proteins such as Etk/Bmx and Vav, also associate with PAR, and PAR, through their PH-domains (22). These PH-domain binding sites may provide a powerful platform for future therapeutic medicaments in cancer. Furthermore, PH-binding motifs may be utilized to identify powerful targets in cancer-driver GPCRs. Actually, peptides are more amenable efficient crossing of the BBB since a wide range of non-natural modifications may be applied, and a plethora of functional groups for site specific conjugation to a designated peptide or protein may be introduced (23-25). In addition, they are less immunogenic. Thus peptide shuttles may provide an efficient delivery mode, and may also be as a potent drug substance, following suitable modifications to optimize lipid solubility and hydrophilicity.

Pepducins are cell-penetrating peptides that act as intracellular modulators of PARs (26). They are comprised a short peptide derived from a GPCR third intracellular loop (e.g., PARs) tethered to a hydrophobic moiety. This structure allows pepducin lipopeptides to anchor in the cell membrane lipid bilayer and target the PAR/G protein interface. These peptides are also available as antagonists of PAR.

Much attention has also been given to the involvement of serine proteases in brain injuries and other pathologies. In addition to tissue plasminogen activator (tPA), which is significant due to its therapeutic use in ischemic stroke, accumulating data have indicated that the serine protease thrombin, a major protease in the coagulation cascade, has important effects in brain injury (27). Once blood enters into the brain after injuries such as primary intracerebral hemorrhage and brain trauma, thrombin is immediately generated by cleavage from the circulating prothrombin in the blood. However, many traumatic and ischemic brain injuries that are associated with BBB disturbance occur without hemorrhage. In fact, it appears that the brain itself is a source for prothrombin production. Prothrombin mRNA is expressed in the cells of the nervous system (28), and upregulated following brain-related injuries (27,29,30). Taken together with the fact that mRNA for factor X is also generated in the brain (31), this implies that thrombin can be formed within the brain tissue with no breach in the BBB (Figure 1).

Other proteases that are centrally involved in the remodeling of tumor microenvironment stromal cells and with degradation of the extracellular matrix (ECM) are the zinc-dependent endopeptidases and matrix metalloproteinases (MMPs). Among these are MMP-1, as well as MMP-11 and MMP-19, which are highly upregulated in various malignancies, including gliomas (32). MMP-1 is produced by stromal cells rather than the tumor cells (33). Both thrombin and MMP1 are physiological activators of PAR, (11,34).

Overall, advances in sequencing technology, gene array analysis, and bioinformatic tools, as well as the availability of sensitive and efficient means to isolate progenitor cancer stem cells, enable the identification of specific cancer progenitor molecular traits. These delicate means hold great promise in the fight against gliomas.

Acknowledgements

The authors acknowledge support by grants from the Israel Academy of Sciences and Humanities and Nofar Chief Israeli Scientist, Trade and Industrial Office to RB-S.

Footnote

Provenance: This is a Guest Commentary commissioned by the Section Editor Ning Huang (Department of Neurosurgery, the Second Affiliated Hospital of Chongqing Medical University, Chongqing, China).

Conflicts of Interest: The authors have no conflicts of interest to declare.

References


Figure 1 PAR1 is highly expressed in gliomas. PAR1 activating proteases are found localized within the vicinity of the brain tumor microenvironment including: MMP1, factor X, prothrombin and thrombin. PAR1, protease-activated receptor 1; MMP, matrix metalloproteinase.


